OUTPATIENT MANAGEMENT *of* HIV INFECTION

Third Edition

Joseph R. Masci, M.D.

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Dedication

To my wife, Elizabeth, and my son, Jonathan, for their enduring patience and constant encouragement and to my father for his lifelong inspiration.

Preface

The HIV/AIDS epidemic continues to advance on both old and new fronts. More than previously, however, two distinct epidemics can now be discerned. Because of great improvements in therapy, promising trends have emerged in the United States and other developed countries. New cases and death rates have fallen steadily since the mid-1990s. Where systems of care permit, countless patients have seen a reversal of HIV-related symptoms and significant reconstitution of their immune systems because of effective antiretroviral therapy. New childhood HIV infections have been reduced almost to the vanishing point in the United States, and the image of AIDS as a uniformly lethal disease has been largely transformed in the public mind to that of a chronic, but treatable, disorder. Unfortunately, this transformation has been so profound that, in some circles, it has fueled an increase in high-risk sexual activity.

In stark contrast is the situation in the developing world where an ever-increasing proportion of the world's AIDS occurs. As the number of infected individuals in Africa has exceeded even the most nightmarish predictions of a few years ago, the countries of South Asia, Central Asia, and Eastern Europe have witnessed an acceleration of their regional epidemics.

Why has the epidemic followed these two divergent paths? In developed countries possessing the resources to fund comprehensive systems of care, development and distribution of, and reimbursement for effective drugs to combat the disease, HIV/AIDS has, at least partially, retreated. But the enormous dedication of funds and the availability of a versatile and effective healthcare apparatus required to accomplish this are far out of reach for most of the countries of the world, including those most devastated by AIDS. Education regarding risk avoidance and, specifically, "safe sex" practices has met with much success in the developed world but, often, with cultural taboos and simple lack of resources to support behavioral change in the developing world.

In all this there is good news and there is very bad news. The good news is that with a concentrated effort, societies can effectively combat this terrible modern plague. The bad news is that such an effort is beyond the capacity of many individual governments and cooperative measures are in their infancy. As long as this situation prevails, the devastation will continue on a scale that was unimaginable 20 years ago when an unusual syndrome of immune deficiency was first described in a small number of homosexual men in New York and California and first dubbed the acquired immune deficiency syndrome.

The challenge of AIDS is complex and multifaceted. Knowledge is accumulating at a remarkable rate. An informed, compassionate practitioner remains the most important ally for the HIV-infected individual attempting to navigate the complex medical and social issues inherent in this disease. It is hoped that this book will be of assistance to those who have accepted this challenge and responsibility.

Author Biography

Dr. Joseph Masci graduated from New York University School of Medicine in 1976. After completing his training in internal medicine at Boston City Hospital and infectious diseases at Mount Sinai Medical Center in New York City, Dr. Masci started the AIDS clinic and program at Elmhurst Hospital Center, a municipal hospital in Queens, New York, in 1985 and has supervised its functions and expansion since that time. He is currently chief of infectious diseases and associate director of the department of medicine at Elmhurst, medical director for AIDS services of the Queens Health Network, and associate professor of medicine at Mount Sinai School of Medicine.

Dr. Masci is the author of two previous editions of this book (Mosby-Year Book, 1992, 1996) as well as numerous textbook chapters and scholarly papers on AIDS and other infectious diseases, and he lectures frequently to academic and lay audiences. His research has been in the areas of therapy and complications of HIV infection as well as behavioral aspects of HIV transmission. He sits on a variety of New York City and New York state committees and panels overseeing clinical care, quality assurance, and medication availability for AIDS programs throughout New York state. He currently lives in Manhasset, New York with his wife and son.

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1 Overview of the HIV/AIDS Epidemic

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I. HISTORICAL PERSPECTIVE

In the 20 years since it was first recognized, the HIV/AIDS epidemic has transformed medicine and has itself undergone several transformations. Initially identified as a rare syndrome affecting homosexual men in the United States in the early 1980s,[1] the acquired immunodeficiency syndrome (AIDS) was soon recognized to affect injection drug users, hemophiliacs who had received clotting factors and other recipients of blood products, heterosexual partners of infected individuals, and children of infected mothers. The apparent geographical scope of the epidemic steadily enlarged and soon included every continent, but was especially concentrated in sub-Saharan Africa. The causative agent was identified as a lymphotropic retrovirus[2] termed first the human T cell leukemia/lymphoma virus, type III (HTLV-3) and subsequently the human immunodeficiency virus, type I (HIV-1, HIV).[3]

A means of rapidly screening blood for antibody to the virus was developed and, beginning in 1985, donated blood in the United States was routinely screened.[4] This diagnostic test permitted a more complete picture of the epidemic to be drawn. Seroprevalence studies of large segments of the general population such as blood donors, military recruits, and applicants for marriage licenses indicated that less than 1% of the population was infected. However, individuals in the highest risk categories for HIV infection were found to have astonishingly high rates of infection, suggesting that HIV had been present as a human pathogen for at least several years before the recognition of the first AIDS cases. It rapidly became clear that most HIV-infected individuals had no symptoms of disease and that the number of symptomatic patients with worsening immune deficiency would be expected to increase steadily. This large group of asymptomatic people also represented a reservoir of infection that would further fuel the epidemic.

An intense, international search for effective antiretroviral agents led to the release of zidovudine (AZT) in 1986 after clinical trials suggested improved survival among some patients with HIV infection.[5] Simultaneously, strategies were developed to treat and prevent several of the major opportunistic infections which represented the great killers of infected individuals with critical immune deficiency. Measurements of cellular immune function, rarely evaluated in adults prior to the advent of HIV, became a key factor in managing HIV infection, and techniques to quantitate T cell subsets

rapidly became available as routine procedures in commercial and hospital laboratories. Additional therapeutic agents, also drugs of the nucleoside class, were developed and released in the late 1980s and early 1990s, but the actual efficacy of these agents either in monotherapy or multidrug regimens was questioned by many and side effects to therapy were common as refinements of dosing came only after widespread availability of several agents. A major breakthrough came with the demonstration that the risk of vertical transmission could be substantially reduced through the administration of zidovudine during pregnancy and delivery and during the postpartum period to the infant. By the mid-1990s systems of care to test for HIV infection and to provide antiretroviral therapy and preventive therapy for opportunistic infections were well established in many areas of the country, especially the urban centers of the east and west coasts which had been most hard hit by AIDS. Abruptly, in the mid-1990s a major therapeutic advance took place with the release of two new classes of antiretroviral drugs. First, the protease inhibitors and, soon after, the non-nucleoside reverse transcriptase inhibitors were shown to have activity against the virus and to suppress viral replication. Clinical trials established that circulating virus could be reduced, often to unmeasureable levels, by these agents but that resistant strains of the virus emerged quickly if only one drug or class of drugs was used at a time.

Multidrug combinations consisting of 3, 4, or even more agents were studied and found to suppress viral replication more durably and often to permit partial or complete restoration of immune function. Longitudinal studies had established that the amount of circulating virus correlated closely with overall prognosis, and blood tests of so-called "viral load" rapidly became available to enable more precise monitoring of response to therapy. Survival improved significantly and progression to AIDS became less common among HIV-infected patients who were treated with such combined treatment regimens, which were termed highly active antiretroviral therapy (HAART).

With the dramatic success of this new form of therapy came unexpected problems, however. Viral resistance emerged more rapidly than anticipated and a large proportion of patients showed no or only temporary responses to HAART. Peculiar side effects, such as a unique syndrome of fat redistribution and hypertriglyceridemia, were seen with several agents especially the protease inhibitors, and lactic acidosis with hepatic steatosis emerged as a complication of nucleoside therapy. The large pill burden and minor, but vexing, side effects such as diarrhea, drug rashes, nightmares, and other disorders made HAART difficult or impossible for some. Adherence to these treatment regimens often became inadequate, even among motivated patients, leading to more rapid emergence of viral resistance was seen. Underserved communities of individuals in the United States at high risk of HIV infection continue to have inadequate access to care and assistance in maintaining themselves on appropriate treatment. Globally, the HIV epidemic has proceeded essentially unchecked with the majority of cases in the impoverished countries of sub-Saharan Africa where neither prevention nor treatment has had a significant impact (see Figure 1.1).

As the third decade and the next century of the HIV/AIDS epidemic begin, many questions and challenges remain. Among these are:

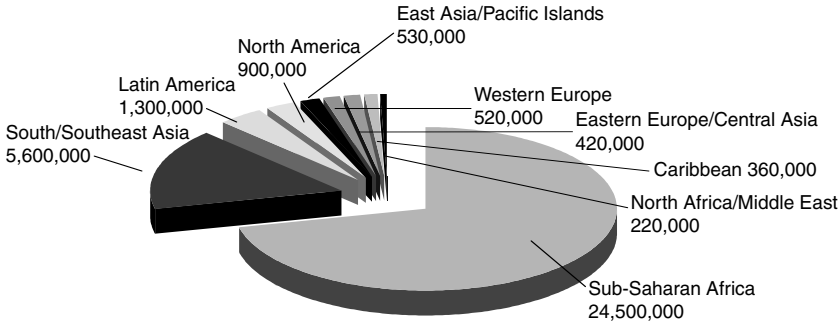

FIGURE 1.1 Global estimated HIV/AIDS cases by region through 1999. (Adapted from Gayle, H., *AIDS*, 14 (suppl 2), S8, 2000.)

What lessons have been learned to help the developing countries most affected by AIDS combat the epidemic?
How will the massive number of "AIDS orphans" in developing countries be cared for?
When should antiretroviral therapy be instituted to provide the greatest long-term benefit and to minimize the risk of resistance?
How can immune reconstitution be accomplished and maintained?
What is the potential for an effective vaccine?
What new pharmaceuticals hold the most promise to further reduce the impact of HIV infection and how should they be developed most efficiently and, if effective, gotten to those in need in time?
How will those traditionally out of reach of the healthcare system be afforded the benefits of advances in therapy?
How will the medical community in the United States respond to the challenge of further changes in therapeutic strategies and goals? How will the constantly changing body of knowledge about HIV infection and its management be communicated rapidly to the practitioners who must apply science to the clinical setting?

II. TRENDS IN THE EPIDEMIC

A. Overview

Approximately 34 million individuals were living with HIV infection or AIDS at the end of 1999. The distribution by region was as follows:[6]

Sub-Saharan Africa: 24,500,000
South and Southeast Asia: 5,600,000
Latin America: 1,300,000
North America: 900,000
East Asia and Pacific Islands: 530,000
Western Europe: 520,000

Eastern Europe and Central Asia: 420,000
Caribbean: 360,000
North Africa and Middle East: 220,000
Australia and New Zealand: 15,000

The epidemic has differed somewhat from region to region not only in the number of individuals affected and, therefore, the strain on the healthcare system, but also on the segment of the population hardest hit. Some features, however, are common worldwide: HIV/AIDS has affected the young, otherwise healthy individuals first; efforts to limit spread have met with only partial success; and providing access to effective therapy has been difficult in developed countries and nearly impossible in the developing world. For this reason, it is almost certain that the worst days of the HIV/AIDS epidemic lay ahead, especially in the developing countries of Africa, Asia, and South America.

B. United States

It is estimated that between 650,000 and 900,000 persons in the United States are infected with HIV.[7] Through the end of 1999, a total of 733,374 AIDS cases had been reported from the United States since the beginning of the HIV/AIDS epidemic, including 99% adults and adolescents and 1% children under the age of 13. Through the first 9 months of 2000, an additional 30,346 cases had been reported.[8] The gender distribution of the cumulative total cases has been unequal with more than 4 times as many men as women reported so far (see Figure 1.2). The distribution of reported cases by race and ethnicity has been as follows: 43% of cases have been in whites, 37% in blacks, and 18% in Hispanics, with fewer than 1% each among Asians and Pacific Islanders, Native Americans, and Alaskan Natives[9] (see Figure 1.3). The proportionate number of cases among blacks and among women of all races has increased steadily, with blacks exceeding whites in both reported AIDS cases and deaths since 1996. The proportion of women has also risen steadily in recent years,

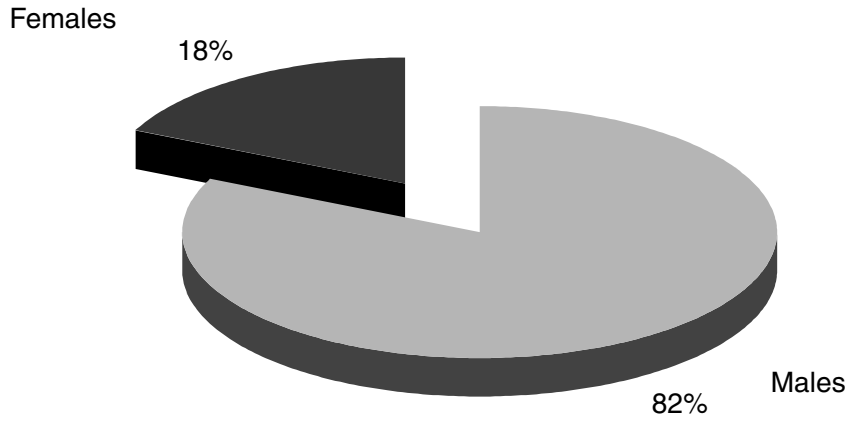

FIGURE 1.2 Gender distribution of U.S. adult AIDS cases through mid-2000. (Adapted from CDC, *HIV/AIDS Surveillance Report*, 12, 2000.)

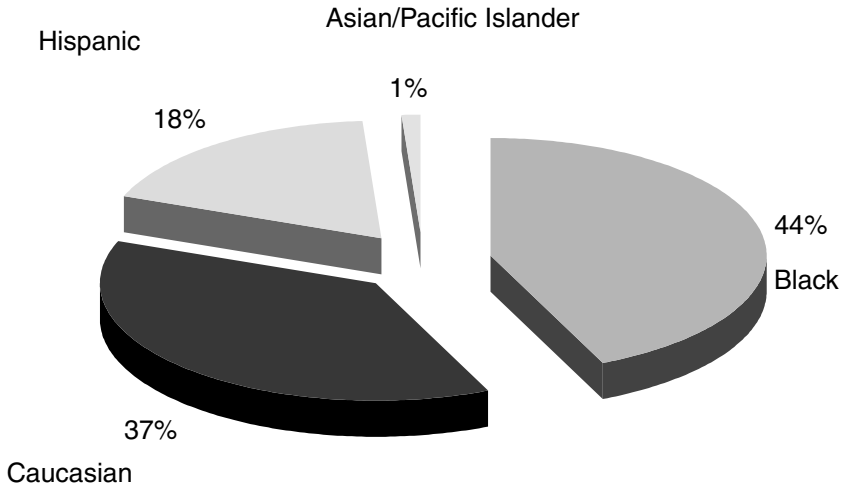

FIGURE 1.3 Ethnic categories of U.S. AIDS cases through mid-2000. (Adapted from CDC, *HIV/AIDS Surveillance Report*, 12, 2000.)

reaching 23% of reported cases in 1999, the majority now being infected through the heterosexual route rather than by injection drug use. On the positive side have been two major advances in therapy: the widespread use of potent antiretroviral therapy beginning in 1996 and the use of zidovudine to reduce perinatal transmission and pediatric AIDS since the early 1990s. Approximately 10,000 deaths were reported in 1999, down from over 49,000 in 1995, the year before protease inhibitors became available for antiretroviral therapy. Only 93 pediatric AIDS cases were reported in 1999, down from a high of 947 in 1992.

1. HIV Seroprevalence

Reported AIDS cases represent only a fraction of the number of individuals infected with HIV. With improved care and delayed progression to AIDS and with prolonged survival of patients with AIDS, the natural history of HIV infection has changed dramatically since the mid-1990s. Progression to AIDS previously signaled the terminal phase of disease consisting of steady and irreversible decline in immune function and increasingly symptomatic illness, disability and, within months to a few years, death. Potent antiretroviral therapy has slowed this progression for many individuals and significantly reversed the deterioration of immune function in a substantial proportion so that many individuals previously meeting the AIDS case definition on the basis of severity of immune dysfunction no longer do. Despite such ambiguities, HIV seroprevalence data can give a more complete picture of the status of the AIDS epidemic and can give valuable insights into likely future trends.

As of the end of 1999, in 31 states and the U.S. Virgin Islands, persons (adults and children) testing positive for HIV infection were reported by name to public health authorities. Data from these areas have been used to formulate a picture of the HIV epidemic that goes beyond data extracted from reports of persons with AIDS, which

all states and areas tabulate. The picture obtained this way is incomplete, particularly since several states and areas (New York, California, District of Columbia) from which a large proportion of AIDS cases had been reported did not (until recently in the case of New York) have reporting mechanisms for HIV-infected persons without AIDS.

2. General Population: United States

Through 1999, of the 733,374 AIDS cases reported in the United States since the beginning of the epidemic,[10] 82% were men, 18% women, and 1% children. It was estimated that 850,000 adults and children in the United States were living with HIV infection. More than 28% of these individuals are thought to have minor children, half of whom live with an infected parent.[11] Twenty thousand deaths were attributed to AIDS in 1999 and 70,000 children had lost either their mother or both parents to the disease since the beginning of the epidemic.

3. Gender

The HIV/AIDS epidemic was initially recognized as a disease primarily and disproportionately affecting men. As the global epidemiology of HIV infection has been elucidated, however, it has become clear that women are equally, if not more often, affected. Twenty-three per cent of newly reported AIDS cases and nearly 40% of newly reported HIV infections occurred in women,[10] continuing a trend of a steadily rising proportion of women among reported cases since the early days of the epidemic.

4. Race/Ethnicity

The African-American and Hispanic communities have borne a disproportionate burden of the AIDS epidemic. Overall, 43% of AIDS cases have been reported in whites, 37% in blacks, and 18% in Hispanics, with less than 1% among Asians and Pacific Islanders.[10] However, in 1999, 42% of newly reported AIDS cases occurred among blacks, 20% in Hispanics, and 36% in whites (see Figure 1.4).

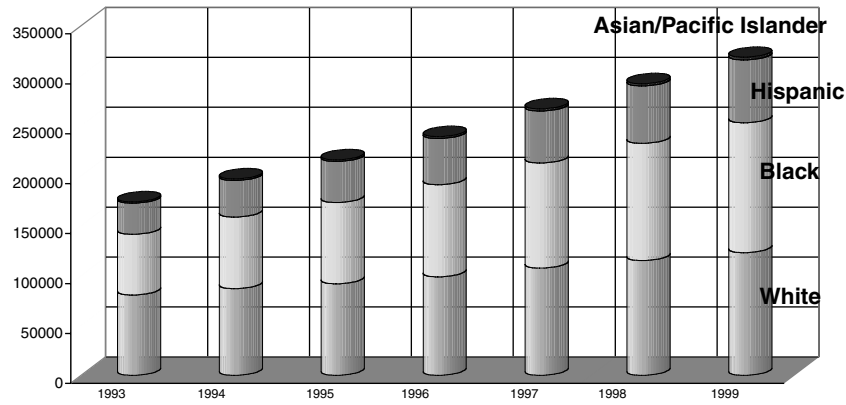

FIGURE 1.4 Estimated persons in U.S. living with AIDS by race/ethnicity, 1993–99. (Adapted from CDC, *HIV/AIDS Surveillance Report*, 12, 2000.)

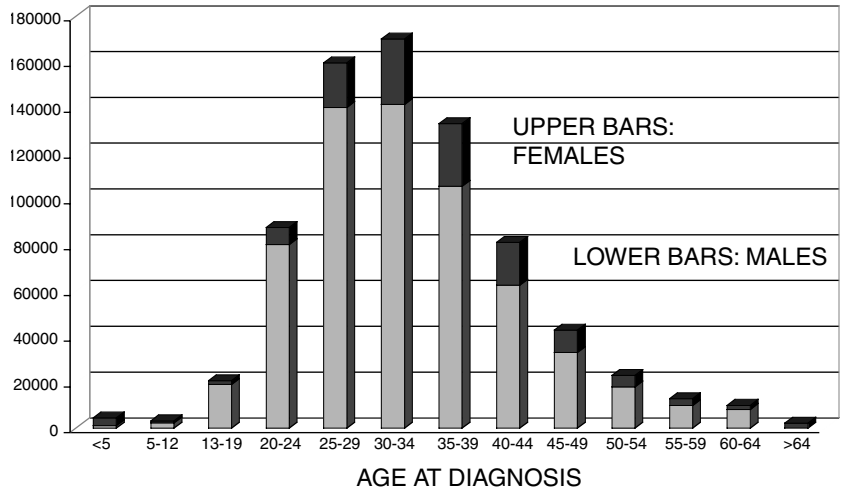

FIGURE 1.5 Age distribution of cumulative U.S. AIDS cases.

5. Age

HIV infection has traditionally been a disorder primarily affecting adults during their reproductive years. Recent data indicate an aging of the HIV/AIDS population, in part because of longer survival among patients receiving combination antiretroviral therapy. Nevertheless, more than 86% of newly diagnosed and reported HIV infections occurred in individuals between the ages of 20 and 50 (see Figure 1.5).

6. Geographical Distribution

In the United States, the HIV/AIDS epidemic has had its greatest impact in large urban centers, although spread into suburban and rural areas has increased steadily. All regions of the country have been affected (see Figure 1.6). New York, New Jersey, California, Texas, Florida, and the District of Columbia have been hardest hit. The epidemic has shown a pattern of spread from urban centers into adjacent suburbs as well as rural communities. The highest rates of AIDS per 100,000 population in 1999 were in New York (75.5), Florida (65.7), Georgia (40.9), South Carolina (46.6), Arizona (41.5), Louisiana (38.7), and California (36.3). The lowest rates were seen in North Dakota (1.9), Montana (3.0), and Idaho (3.8).[10]

7. Risk Behavior

Since the beginning of the epidemic, men who acquired infection through homosexual contact have accounted for the majority of reported AIDS cases (56%).[10] However, the proportion represented by this group has declined in recent years and reached 44% in 1999. In contrast, the proportion infected through heterosexual contact, accounting for 10% of all cases since reporting began, rose to 15% overall and 40% of female cases in 1999 (see Figures 1.7, 1.8, 1.9).

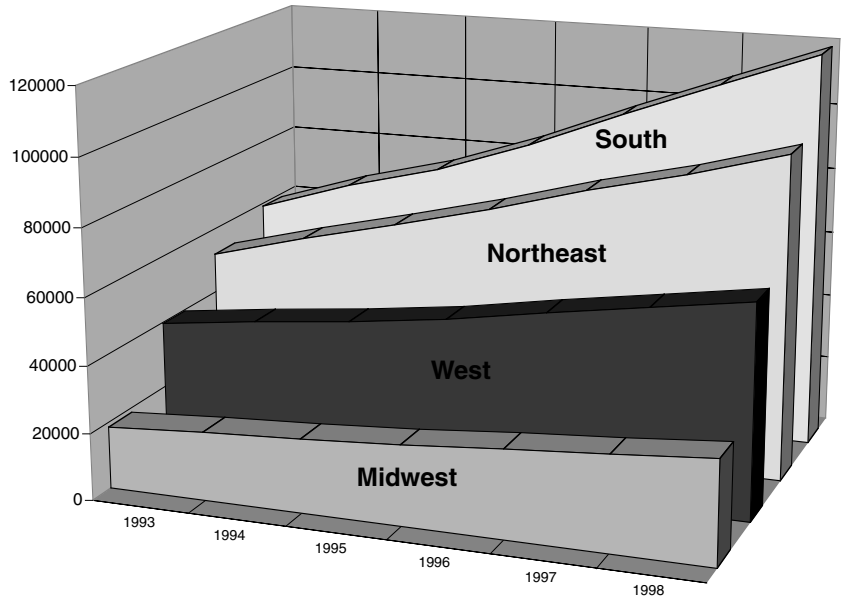

FIGURE 1.6 Estimated persons living with AIDS by U.S. region, 1993–99. (Adapted from CDC, *HIV/AIDS Surveillance Report*, 12, 2000.)

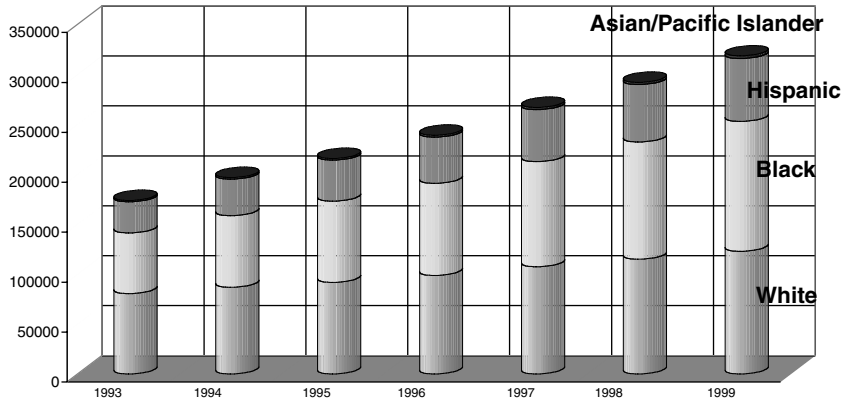

FIGURE 1.7 Estimated persons in U.S. living with AIDS by race/ethnicity, 1993–99. (Adapted from CDC, *HIV/AIDS Surveillance Report*, 12, 2000.)

C. Regional HIV/AIDS Epidemics

1. Developing Countries

The impact of the HIV/AIDS epidemic in the developing world has been staggering. Because of the tremendous number of infected individuals in many countries and the lack of access to care for HIV infection, the repercussions of AIDS will be

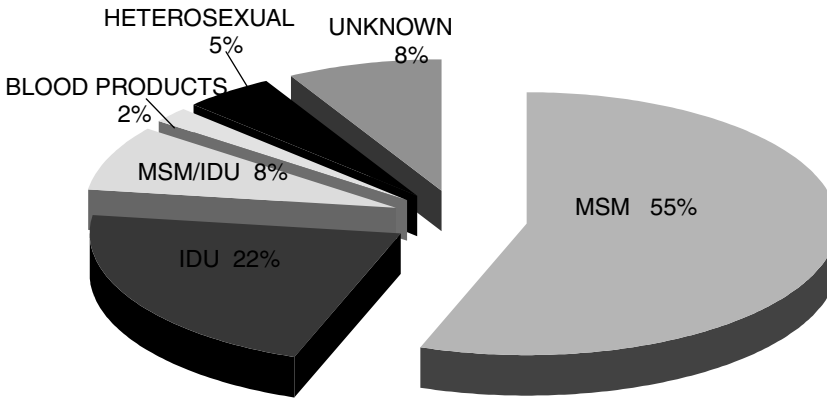

FIGURE 1.8 Distribution by transmission category of U.S. adult male AIDS cases through mid-2000.

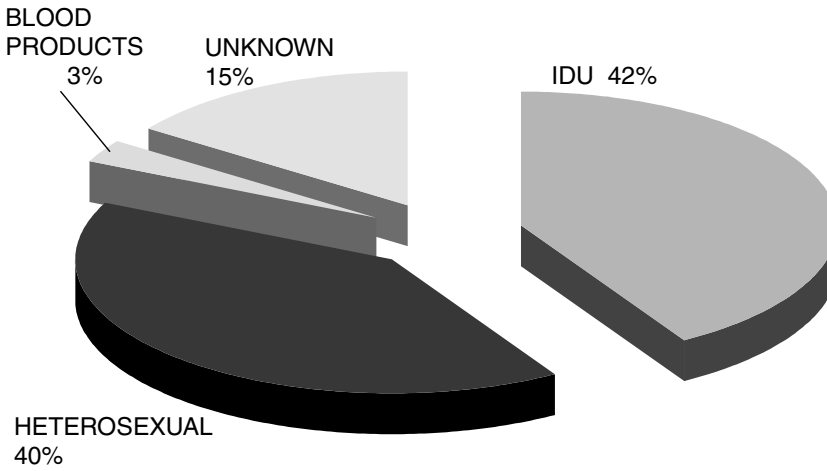

FIGURE 1.9 Distribution by transmission category of U.S. adult female AIDS cases through mid-2000.

felt for generations even if transmission were stopped immediately and a cure were discovered.

By the end of 1999, there were sixteen countries where the seroprevalence of HIV infection in the general population was estimated to be 10% or greater and seven countries where it was greater than 20%, all in sub-Saharan Africa. The hardest-hit country in the world was Botswana where prevalence was estimated to be over 35% and where it is anticipated that over two-thirds of 15-year-olds will eventually die of AIDS.[12]

a. Africa

The earliest documented case of HIV infection was identified retrospectively in a blood sample taken in 1959 from a man in Kinshasa, Democratic Republic of Congo.[13] Soon after AIDS was first seen in the United States in the early 1980s, it was recognized that an HIV/AIDS epidemic had been present, undetected, in Africa for years to decades. The impact of the epidemic in sub-Saharan Africa has been staggering. As of 1999, 24.5 million, or 71%, of the world's HIV/AIDS cases had occurred in Africa. In South Africa, which has the largest number of infected individuals, 4.2 million were living with HIV/AIDS. Overall prevalence in sub-Saharan Africa was 8.57% and 12 countries face a prevalence of at least 10%.[6]

b. Asia

The impact of the HIV/AIDS epidemic in Asia has varied substantially from region to region. Southeast Asia, especially Thailand, saw an explosive increase in cases in the early 1990s.[14,15] The introduction of infection in this region was initially through needle-sharing by injection drug users[12] with the commercial sex industry accelerating the spread. Thailand currently has the highest reported estimated seroprevalence of HIV infection, 2% in the region. The HIV/AIDS epidemic is expanding rapidly in other East Asian countries inlcuding Cambodia, Myanmar, Malaysia, Vietnam, and China.[6] In recent years, India has witnessed a sharp rise and currently has the largest number of known cases, 4 million despite an estimated seroprevalence of only 1%.[6] Korea and Japan have reported relatively few cases and data from China are incomplete.

c. Latin America

The epidemic in South America followed a pattern similar to that in the United States. Homosexual men were the first group affected, followed by injection drug users, and, finally, heterosexual partners and children born to infected mothers.[6]

d. Caribbean

Early in the epidemic in the United States it was recognized that recent immigrants from the Caribbean countries, especially Haiti and the Dominican Republic, who often had no apparent risk behavior, were being diagnosed with HIV infection. Heterosexual transmission accounts for the vast majority of reported cases at present, with 14% attributed to homosexual transmission.[6] The estimated adult prevalence of HIV infection in Caribbean countries is over 2%, second only to that of sub-Saharan Africa. The lowest seroprevalence in the region is 0.02% in Cuba.[16]

2. General Population: Europe

The estimated adult seroprevalence in Europe is 1%, comparable to that in the United States. As in the United States, the commonest mode of spread of HIV varies by region, with incidence rates rising quickly in Eastern Europe as a result of increased prevalence of injection drug use,[6] although increased rates of heterosexual spread have also been seen. It is estimated that the total number of HIV-infected individuals doubled between 1997 and 1999 in states formerly of the Soviet Union. In Western Europe, a pattern similar to that in the United States has

been seen with homosexual men affected first, followed by injection drug users, heterosexual partners, and children born to infected women.

3. General Population: United States

Since HIV testing is not mandatory and universal and reporting of HIV infection is not required by all states, complete prevalence data for the U.S. population are not available. However, an indication of the number of HIV-infected individuals can be obtained from large-scale HIV screening programs, such as testing of military recruits and Job Corps applicants.

a. Military Recruits

Routine screening for HIV antibody has been conducted among applicants for military service (including ROTC and service academies) as part of their initial health assessment since 1985. Overall, HIV seroprevalence has declined among this population from 0.15% in 1986 to 0.035% in 1997 (197 men, 29 women).[6] The relative prevalence among women has increased compared with that among men and, as in other cohorts, individuals of color are more likely to be infected.

b. Job Corps Applicants

Individuals entering the Job Corps have been routinely screened for HIV infection since 1987. Data for the period 1990 to 1996 revealed declining rates of infection and an overall seroprevalence of 0.2% (0.28% among women, 0.2% among men). As in the military data, prevalence was highest among African-Americans and Hispanics.[17]

In interpreting data from the military and Job Corps it is important to recognize a potential bias because individuals who know that they are infected may be less likely to apply to organizations which require testing.

III. TRANSMISSION CATEGORIES: UNITED STATES

A. Mother-to-Child Transmission

HIV can be transmitted from mother to child before, during, and after delivery through breast-feeding[18] (see Chapter 9), especially when the maternal viral load is high.[19] An early triumph of antiretroviral therapy was the demonstration that zidovudine, and subsequently other drugs, could significantly reduce the rate of mother-to-child transmission. Because of the widespread practice of identifying infected mothers during pregnancy and administering appropriate therapy,[20] the rate of transmission has fallen dramatically, from approximately 25% to less than 3%, in recent years in the United States.[10] It has been suggested that the complete elimination of pediatric HIV infection is within reach in developed countries.[21] In the developing world, however, where antiretroviral drugs may be scarce and where breastfeeding is often the only adequate means of providing nutrition to the newborn,[22] this strategy has not had as significant an impact.[23]

B. Homosexual/Bisexual Men

In the early years of the HIV/AIDS epidemic in the United States, the seroprevalence of HIV infection among men who have sex with men (MSM) was astonishingly high in many areas. The San Francisco cohort study in the early 1980s indicated a baseline prevalence of 48.5%.[24] The prevalence of infection was found to be highest (70.8%) among men who reported more than 50 sexual partners during the preceding 2 years and lowest (17.6%) among those who had abstained from sexual contact for that period. The vast majority of men (95.7%) in this series had practiced anal or orogenital sex or both, within the preceding 2 years. Receptive anal intercourse and the use of dildos or douches were the practices associated with the highest risk of infection. As the epidemic progressed and routes of transmission were better defined, changes in sexual practices resulted in a dramatic reduction in the number of new infections in this cohort—18.4% per year from 1982 to 1984 to 4.2% in early 1986. New York City data reflected a significant decline in other sexually transmitted disease (STD) among MSM during this period.[25] This encouraging data must be balanced, however, by other observations indicating most of the decline in transmission of HIV infection has occurred among older homosexual/bisexual men.[10] A steadily increasing proportion of reported AIDS cases has occurred among African-American and Hispanic MSM. Fifty-two percent of cases in MSM occurred in these ethnic groups in 1998 compared with 31% in 1989.[9] Evidence of a continued high rate of transmission among young MSM has been reported. In 1996, a survey of urban STD clinics in several states indicated an average HIV prevalence of 7% among this group.[6]

C. Heterosexual Transmission

HIV may be isolated from semen[26] as well as from cervicovaginal secretions. Transmission of infection from males to females appears to be more efficient than it is from females to males. This is most likely related to the higher concentration of virus present in semen compared with that in cervicovaginal secretions. The larger volume of semen involved as well as more prolonged exposure of vaginal mucosa to infectious material may also play a role. Overall, the likelihood of transmission from male to female has been estimated to be 0.05 to 0.15% per sexual contact, while the likelihood of transmission from female to male is 0.3 to 0.9%. Other factors that appear to influence heterosexual transmission rates are discussed in Chapter 2.

D. Injection Drug Users

The prevalence of HIV infection among injection drug users in the United States has varied greatly from region to region and among various populations. In the 1980s, it was estimated that more than 60% of injection drug users in the New York metropolitan area were HIV-infected. The prevalence of HIV infection remained stable at 50% in separate cohorts of intravenous drug users in New York City studied in 1984 and again from 1990 through 1992,[27] a finding which suggests a decline in

transmission rates after 1984. Changes in drug use behavior, particularly a decrease in reported needle sharing, appear to have been largely responsible for this decline.[27] Nonetheless, as the proportion of reported AIDS cases among MSM has declined, the proportion among injection drug users has risen from 17% in 1983 to 22% in 1999.[10]

The prevalence of HIV infection in injection drug users is closely linked to heterosexual spread in the United States.[28] As heterosexual transmission has accounted for an ever-increasing proportion of reported AIDS cases (4% in 1985 compared with 16% in 1999), over 50% of these individuals report sexual contact with an injection drug user.

E. Blood Product Recipients

Patients with hemophila who had received therapy with factor VIII concentrate preparations were among the first individuals recognized to be at high risk for AIDS. By 1984, as many as 78% of such patients in the United States may have had HIV infection.[29] Patients treated with cryoprecipitate or fresh frozen plasma and those with hemophilia B had much lower rates of infection. Overall, the likelihood of infection correlated with the quantity of exposure to clotting factor concentrates derived from large donor pools.[30] Transmission of HIV infection by transfusion of other blood products was soon recognized.

The risk of HIV transmission via transfused blood products declined rapidly after universal screening of donated blood came into effect in the mid-1980s. After this screening began, it was estimated that the risk of infection fell to 1 in 40,000 units of blood. Further refinements of the screening process subsequently have likely reduced the rate even further. It should be recognized, however, that individuals who receive transfusions in areas of the world with significant HIV prevalence but lacking in effective HIV screening programs remain at risk.

IV. SELECTED PATIENT GROUPS: UNITED STATES

A. Patients Attending Sexually Transmitted Disease Clinics

Individuals diagnosed with sexually transmitted diseases are three to five times more likely to contract HIV infection.[31] A median seroprevalence of almost 20% was found among gay men attending STD clinics in 16 U.S. cities. Heterosexual patients who injected drugs had a median prevalence of 4.8%. Patients diagnosed with sexually transmitted diseases should be strongly encouraged to undergo testing for HIV infection.[32]

B. Female Commercial Sex Workers

The prevalence of HIV infection among women who trade sex for money or drugs is influenced by several variables. These include drug use, geograhic location, race, and the setting in which the sex trade is carried out. Studies of women working in two distinct facets of the sex industry in New York City in the late 1980s indicated seroprevalences of 55% among street prostitutes[33] and 1% for women working for

escort services or in massage parlors.[34] In a more recent study,[35] also from New York, nearly 35% of more than 1500 street prostitutes were infected. This proportion rose to 61% among those using injection drugs. Older age and Hispanic ethnicity were also associated with a greater likelihood of HIV infection in this study. In a study involving more than 2000 young women in New York, Miami, and San Francisco, over 30% of women who exchanged sex for money or drugs were found to be HIV-infected.[28]

In the developing world published prevalence rates of HIV infection among female sex workers have reached remarkably high levels, especially in urban areas in Thailand (65%),[36] India (29%),[37] Peru (4 to 16%),[38] and East Africa (15 to 36%).

C. Emergency Department Patients

The prevalence of HIV infection among patients visiting an inner-city hospital emergency room was examined by Kelen and colleagues.[39] Overall, 5.2% of more than 2000 patients tested positive for HIV antibody. Black men between 30 and 34 years age were found to have the highest seroprevalence (11.4%). A statistically significant association between HIV infection and penetrating trauma was observed. Of patients denying HIV risk factors, 3.1% were seropositive. The prevalence of unrecognized HIV infection was 4%. Significantly, in a large multicenter study, Marcus and colleagues found that 69% of HIV-seropositive emergency patients were not known by hospital staff to be infected.[40] Despite these facts and the large numbers of patients with sexually transmitted diseases who are seen in emergency rooms, most emergency departments reported that they did not routinely test these patients for HIV infection in a recently published survey.[41]

V. OTHER GROUPS OF CONCERN: UNITED STATES

A. Women Who Have Sex with Women

Approximately 2% of adult and adolescent females reported with HIV/AIDS have a history of sexual contact with other women.[42] The vast majority of these individuals report other potential risk factors for HIV transmission, especially injection drug use and sexual contact with high-risk men. Although the exact risk of female-to-female sexual transmission of HIV infection is unknown, it appears to be extremely low. No evidence for such transmission was found in an evaluation of over 90,000 female blood donors.[43] Several apparent cases of such transmission have been described, however.[44–46]

B. Household Contacts of Infected Persons

Early in the history of the HIV/AIDS epidemic, particularly before the causative agent was discovered, there was great concern that infection could be spread by casual nonsexual contact, specifically the forms of routine contact that might occur between members of the same household or between schoolchildren and their classmates.

Friedland and colleagues[47] screened household nonsexual contacts, both adults and children, of HIV-infected patients and found no evidence of such horizontal transmission. One of 101 such household members was found to be infected: a 5-year-old child who was thought to have acquired the virus before birth. Despite sharing of such household items as toilets, towels, and in some cases razors, nail clippers, and toothbrushes with the infected individual for a median of 22 months, no household member acquired infection. Physical contact, including kissing, hugging, and helping to bathe and dress the HIV-infected family member, also was found to pose no risk of contagion in this study.

Although initial fears of widespread transmission of HIV infection within households have not been realized, rare instances of such horizontal, nonsexual transmission have been reported.[48,49] In each case extensive exposure to blood or bloody fluids or both, of the index patient preceded transmission to the household contact.

C. Healthcare Workers

From the beginning of the HIV/AIDS epidemic through the end of 1999, 56 instances of documented occupational transmission of HIV infection to healthcare workers had been reported in the United States,[8] 39 (70%) of whom were nurses or laboratory technicians. An additional 138 cases of possible occupational transmission had been reported, 110 (68%) in the following occupations: nurse (35), clinical laboratory technician (17), health aide/attendant (15), emergency medical technician/paramedic (12), housekeeper/maintenance worker (13), non-surgical physician (12), and surgeon (6). In these cases, although no specific occupational exposure could be identified, no non-occupational route of transmission was apparent. The majority (86%) of documented occupational transmission came after needlestick exposures and overall, 88% of exposures leading to transmission were to blood.

VI. ADVANCES IN MANAGEMENT OF HIV DISEASE

A. Newer Antiviral Agents

The impact of modern antiretroviral therapy on the HIV/AIDS epidemic in the United States and other developed countries has been profound. Among patients receiving effective therapy, survival and quality of life often improve greatly and the risk of opportunistic infection declines. Despite side effects and the inconvenience of taking the necessary numbers of drugs and pills, the development of these therapies has been the most important accomplishment of the past decade (see Chapter 10 and 11).

1. Failure to Improve Care for Certain Populations

As in other areas of medical progress, large segments of the population have been left behind by the advances in therapy of HIV/AIDS. Individuals of color and those confronting poverty, unstable living conditions, homelessness, substance abuse, or mental illness more often come to diagnosis and care late, encounter difficulty complying with treatment and follow-up and, as a result, manifest viral

resistance to even the most potent of current therapies. An increasing emphasis is being placed on improving access to and maintenance in care for such individuals. More comprehensive systems of care emphasizing convenience and flexibility as well as improvements in the tolerability of therapy will be critical in this effort.

VII. THE IMPACT OF AIDS

A. Developed Countries

Although the devastation wreaked by the AIDS epidemic has been most massive in the developing world, particularly sub-Saharan Africa, its impact in the United States and other developed countries has been remarkable. As just one illustration of this: it is estimated that 28% of HIV-infected adults living in the United States are the parents of minor children.[11] The approximately 120,000 children so affected are often growing up in an environment where they are witnessing the deterioration of their parent's health and, as a result, attempting to assist the parent in running the household, caring for siblings, and obtaining medical care.

1. Hospitalization

Since the advent of effective antiretroviral therapy and, with it, the decreased incidence of opportunistic infections, hospitalization rates and inpatient lengths of stay have, in general, declined substantially. At our institution, a municipal hospital in New York City, the average number of inpatients with AIDS-related diagnoses has fallen from a high of 35 in the early 1990s to fewer than 10, despite a growing outpatient population.

2. Systems of Care

Increasingly, it has been recognized that effective care of HIV-infected individuals often requires an extensive multidisciplinary approach. Medical and mental health providers as well as medical subspecialists (particularly in gastroenterology, oncology, and pulmonology) along with nonmedical specialists in dermatology, gynecology, neurology, and oral health are needed to provide appropriate screening and care. In addition, nurses, social workers, health educators, administrators, and a variety of other types of professionals are needed. Nonphysician practitioners including physician's assistants and nurse practitioners are, for many programs, critically important. Because of the increasingly specialized knowledge needed to care for HIV-infected individuals, criteria for specialist certification have been developed in some locales.

B. Developing Countries

Access to care and appropriate medications remain enormous obstacles in the developing world, where the HIV/AIDS epidemic is most concentrated. With few exceptions, prevention campaigns have met with little or no success. The costs of antiviral medications and of the laboratory facilities required to monitor their use put modern

therapy far out of reach of most of the world's HIV/AIDS population. The impact of the disease in the countries most affected will continue to grow far worse even if all HIV transmission were to stop.

FREQUENTLY ASKED QUESTIONS

1. When did the first documented HIV infection occur?

   Although AIDS was first recognized in 1980 and 1981 among male homosexuals in the United States, the earliest documented case of HIV infection dates to 1959 and was acquired in Africa.

2. What region has the largest number of current HIV/AIDS cases?

   Sub-Saharan Africa

3. What region has the fastest growing prevalence of HIV infection?

   The Indian subcontinent

4. In what areas of the world is the incidence of HIV infection declining?

   Thailand has seen a reduction in new cases since a sudden increase in the early 1990s. The number of newly reported AIDS cases in the United States has declined every year since 1993. Between 1993 and 2000, new adult cases fell from 78,834 to 25,341. The annual incidence of new HIV infections can only be estimated, since not all states require reporting of HIV infection without AIDS. It is possible that the prevalence of HIV infection is actually rising despite falling numbers of reported AIDS cases, since current antiretroviral therapy forestalls the development of AIDS and overall disease progression.

5. In the United States, when did routine screening of blood for HIV begin?

   1985

6. What is the estimated seroprevalence of HIV infection in the United States population?

   0.3%

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2 Pathogenesis and Natural History of HIV Infection

CONTENTS

I. INTRODUCTION

The natural history of HIV/AIDS spans a considerable period of time (see Table 2.1). On average, 10 years, much of it asymptomatic, transpire between the time of initial infection and the appearance of clinical AIDS among people not receiving antiretroviral therapy. This slow clinical progression, which typically includes a long asymptomatic period, corresponds to a changing balance between viral replication and host response. The clinical manifestations are intertwined with this pathogenetic progression. In many individuals, host factors influence the course of disease greatly. It is hoped that an increasing understanding of the subtleties of host response will lead to more effective preventive and therapeutic strategies.

In this chapter the typical patterns of viral replication and immune response are first reviewed from the perspective of clinical events experienced by the patient. Following this, factors that affect host susceptibility to HIV infection and to clinical progression of disease and aspects of host immune response, both cellular and humoral (including mucosal), are reviewed. Finally, several important clinical implications of the pathogenetic processes of HIV infection are underscored.

TABLE 2.1
Events in the Natural History of Untreated HIV-1 Infection

Incubation Period	1–6 weeks
Earliest Detectable Viremia	2 weeks
Acute Retroviral Syndrome	2–6 weeks
Earliest Detectable Antibody	6–24 weeks
Asymptomatic Period	1–10+ years
Progression to AIDS	7–11 years

II. CLINICAL STAGES OF HIV INFECTION

A. Primary Infection

The reported incubation periods of primary HIV infection vary from 1 to 6 weeks.

1. Clinical Features

The illness associated with acute infection may range from a heterophile-negative mononucleosis pattern to aseptic meningitis. Fever, sore throat, oral ulcers, and a generalized scarletiniform are common features[1,2] (see Table 2.2). Generalized lymphadenopathy typically occurs in the second week of illness and symptoms frequently last a month or longer. Some patients describe such features as weight loss, nausea, diarrhea, cough, oral candidiasis, photophobia, lightheadedness, and depression. It has been pointed out that 10% of patients do not have any of the commonest features: fever, pharyngitis, or cervical lymphadenopathy.[3]

2. Incidence

Retrospective studies suggest that an acute illness occurs in 53 to 93% of HIV infections,[1,3] although its severity is quite variable. This high incidence of a characteristic illness associated with acute HIV infection provides an opportunity for early diagnosis. Of concern to primary care providers and specialists alike, however, is the fact that the syndrome is rarely diagnosed. It is a certainty that many cases of heterophile-negative mononucleosis and aseptic meningitis seen in areas with a high prevalence of HIV infection actually represent acute infection with HIV but go undiagnosed.

TABLE 2.2
Clinical Features of Primary HIV-1 Infection

Common
Fever
Sore throat
Oral ulcers
Scarletiniform rash
Lymphadenopathy (second week)
Occasional
Weight loss
Diarrhea
Cough
Photophobia
Depression

3. Diagnosis

The clinical features of primary HIV infection are nonspecific and are most likely to be misinterpreted as a respiratory viral syndrome or infectious mononucleosis. This is particularly true if the potential route of HIV infection is not recognized. In areas of high HIV seroprevalence, especially prolonged nonspecific febrile illnesses, aseptic meningitis, unexplained lymphadenopathy, or mouth ulcerations should be considered possible or likely manifestations of acute HIV infection.

4. Viral Events

A major difficulty in establishing the diagnosis of the acute HIV syndrome is that the standard diagnostic tests for HIV infection, the ELISA/Western blot antibody tests (see Chapter 3) are typically negative during the first two weeks of illness. Only by measuring plasma HIV RNA can the diagnosis be confirmed early in the disease. The plasma viral load rises quickly after infection and typically reaches very high levels, as high as 10 million particles per mL of blood,[4] after which it begins to decline shortly after acute infection, even before the appearance of neutralizing antibodies. In a series of 74 adults, most of whom were homosexual men with acute infection, viral load peaked in a range from 27,000 to 1.6 million copies per mL and then decreased by an average of 6.5% per week for the first four months.[5] Although the peak viral levels were not predictive of prognosis within the first 120 days in this study, the rate of disease progression was greatest among individuals with high viral loads after that point. The early decline in plasma viremia may be the result of antibody-dependent cellular cytotoxity (ADCC) and specific cytotoxic T lymphocytes.[6,7] Although detectable virus disappears from the plasma, viral replication continues at a high level within lymphoid tissues, even during the asymptomatic period of disease.[8,9] Most HIV is thus produced in lymphoid tissue and rapidly released into the circulation. It has been estimated that 10 billion viral particles are produced and cleared each day.[10] This rapid viral turnover is related to the production and destruction of approximately 2 billion CD4+ lymphocytes daily. Massive viral turnover coupled with a high rate of mutation leads to an increasingly diverse population of virus in infected individuals.

As discussed in Chapter 10, this phenomenon results in rapid emergence of resistance to antiviral drugs when viral replication is not well suppressed. For example, resistance may appear within a few weeks in patients receiving monotherapy with antiretroviral agents.[11] As a further result of rapid viral turnover, infecting strains tend to mutate from relatively low-virulence to high-virulence characteristics. During the course of HIV infection, in many patients, so-called syncytium-inducing varieties[12,13] appear, which replicate more rapidly and infect T lymphocytes more efficiently and preferentially over monocytic cells, leading to more rapid CD4+ cell decline[14] and clinical progression.[15]

5. Immunological Events

As mentioned above antibody to HIV is normally not detectable during the acute symptomatic phase of infection but may be detected as early as two weeks after infection in some individuals. Diagnostic confusion can result from this delay.

Unfortunately, the "window" period, that is the period between infection and the appearance of detectable antibody, may be much longer, 3 to 6 months, in others. Rare instances of delayed seroconversion with a window period of more than 12 months have been reported.[16] If, however, viral RNA is detected in the absence of detectable antibody, the diagnosis of acute HIV infection is confirmed.

It is noteworthy that most of the clinical and immunological features associated with acute HIV infection have come from studies of homosexual men. Insufficient information is currently available on the syndrome in women and in injection drug users of both genders, although the features are assumed to be comparable.

CD4 lymphocyte counts decrease steadily after acute infection. In the series cited previously, counts fell by an average of 5.2 cells/mm^3 per week for the first 160 days.[5]

B. Asymptomatic Period

Following the disappearance of symptoms of acute retroviral illness after 4 to 6 weeks, HIV infection enters an asymptomatic phase which typically lasts for years.

Individuals with asymptomatic HIV infection may come to medical attention in a wide variety of ways. Those who are aware that they are HIV-infected may have sought testing because of a history of risk behavior or other perceived risk. Others are diagnosed after being offered testing by a primary care provider on the basis of risk assessment. Still others may have undergone required testing for life insurance application, for immigration, or during the course of donating blood.

1. Viral Events

Viral replication continues throughout the asymptomatic phase of infection, primarily in the lymph nodes.[9] Mononuclear cells in extranodal sites, such as the central nervous system, may also become infected. Syncytium-inducing viral strains, which often appear coincident with clinical progression, are rarely detected during this period.

C. Symptomatic Infection after the Acute Period

This asymptomatic phase of HIV infection, which lasts several years in most individuals, may be rarely as short as a few months or as long as fifteen years or more. The average time of progression from acute infection to clinical AIDS is approximately 8 to 11 years and is within 15 years in 78 to 100% of individuals.[17] As noted previously, this phase in marked by ongoing viral replication within lymphoid tissues.

1. Clinical Events

Symptomatic HIV infection typically appears insidiously. Nonspecific complaints such as persistent fever, significant (more than 10%) unintentional weight loss, chronic (more than one month) diarrhea, or enlarged lymph nodes may predominate. In many HIV-individuals early infectious complications such as seborrheic dermatitis, oral candidiasis, localized herpes zoster, bacterial pneumonia, or reactivation of tuberculosis appear years before an "AIDS-defining" condition is diagnosed.

2. Coming to Medical Attention

Individuals in the early symptomatic phase may thus come to medical attention in a variety of ways. For the primary care provider it is imperative that signs, symptoms, and disorders such as those described above be recognized as potential harbingers of AIDS and that such individuals are offered and strongly encouraged to undergo HIV antibody testing.

3. Viral Events

Syncytium-forming strains of the virus appear in many patients coincident with the onset of the symptomatic phase of infection. Viral resistance becomes more prevalent among patients exposed to antiretroviral drugs. Plasma viremia increases and infected lymph nodes may begin to involute. As symptomatic infection progresses, the proportion of CD4+ lymphocytes containing actively replicating virus increases.

4. Immunologic Events

Typically, the decline in the CD4+ lymphocyte population accelerates more rapidly during the symptomatic phase of HIV infection.

D. AIDS

1. Case Definition

The case definition of AIDS was developed for surveillance purposes. This definition, which involves both clinical and immunological parameters (see Box 2.1), is still used by all states for reporting of infected individuals to public health authorities, although an increasing number of localities are now reporting all HIV infections, including those representing earlier stages of disease and not meeting the AIDS case definition. With the advent of modern antiretroviral therapy in the mid-1990, two things occurred that rendered the case definition less usable for clinical decision making:

- Many patients formerly meeting the case definition experienced significant immune reconstitution and no longer met the immunological criteria.
- Individuals at all stages of disease have, in many instances, sustained complete suppression of viral replication. In such individuals, as well as in many other partial responders, the prognostic importance of a diagnosis of AIDS changed and survival and clinical progression rates improved.

2. Viral Events

Syncytium-forming isolates predominate in an increasing number of patients and plasma viremia continues to rise. Multiple strains of the virus are often detectable.

3. Immunological Events

Absolute CD4+ lymphocyte counts fall below 200 cells/mm^3 and CD8+ cells counts fall as well. Cutaneous anergy becomes common and opportunistic infections appear.

BOX 2.1
Surveillance Case Definition of AIDS (Adults)

Indicator diseases diagnostic of AIDS if HIV antibody status is unknown

Opportunistic Infections

- Candida infection of the esophagus, trachea, bronchi, or lungs
- Extrapulmonary cryptococcal infection
- Cryptosporidiosis with more than 1 month of diarrhea
- Cytomegaloviral retinitis
- Cytomegaloviral infection involving sites other than the spleen, liver, or lymph nodes
- Mucocutaneous herpes simplex infection with ulcer of more than 1 month's duration
- Herpes simplex infection of the esophagus, lungs, or bronchi
- Disseminated infection with Mycobacterium avium complex (MAC) or Mycobacterium kansasii involving sites other than the lungs, skin, or cervical or hilar lymph nodes
- Pneumocystis carinii pneumonia
- Progressive multifocal leukoencephalopathy
- Cerebral toxoplasmosis

Malignancies

- Kaposi's sarcoma in a person less than 60 years of age
- Primary cerebral lymphoma

Indicators diagnostic of AIDS only if laboratory evidence of HIV-1 infection is present

- HIV encephalopathy
- HIV wasting syndrome
- CD4+ lymphocyte count < 200 cells/mm^3 or <14% of total lymphocytes

Opportunistic infections

- Disseminated histoplasmosis at site other than the lungs or cervical or hilar lymph nodes
- Disseminated coccidioidomycosis at site other than the lungs or cervical or hilar lymph nodes
- Isosporiasis with diarrhea of more than 1 month's duration
- Any atypical mycobacterial infection at site other than the lungs, skin, or cervical or hilar lymph nodes
- Recurrent nontyphoidal salmonella bacteremia
- Pulmonary tuberculosis
- Nocardiosis
- Recurrent bacterial pneumonia

Malignancies

- Kaposi's sarcoma at any age
- Primary lymphoma of the brain at any age
- Small noncleaved lymphoma
- Immunoblastic sarcoma
- Invasive cervical cancer

E. Long-Term Nonprogressors

In some individuals, the natural history of untreated HIV infection pursues a different path. Approximately 5% of infected individuals remain asymptomatic with normal CD4+ lymphocyte counts for longer than normal. These individuals are termed *long-term nonprogressors*.[18,19] A variety of factors appears to be involved in nonprogression of HIV infection, including a brisk antibody[20,21] or CD8+ cell[19,22] response and a lower rate of mutation of the virus.[23,24] Sustained or rising levels of neutralizing antibody also characterize long-term nonprogressors.[25] Alterations in cell surface receptors necessary for HIV to enter cells also appear to be important in some individuals (see below).

III. FACTORS INFLUENCING DISEASE PROGRESSION

A. Immune Activation

It has been suggested that immune activation caused by other infections, such as sexually transmitted diseases or those caused by helminths or other parasites, may result in more rapid clinical progression of HIV infection.[26] This has been suggested as a possible explanation for what appears to be more rapid progression of disease among African populations. The observation that immune activation is more common among persons living in Africa than among those in Europe, regardless of ethnicity,[27] lends support to this theory.

B. Viral Dynamics

As noted above, HIV becomes detectable in the plasma shortly after infection has occurred, and viral load reaches high levels prior to the appearance of specific antibody. Virus then typically becomes undetectable in plasma. Previously, it was assumed that viral replication slowed or stopped at this point, corresponding to a period of clinical latency. However, it is now clear that viral replication continues at a high rate within lymphoid tissues. Virus may also become latent, however, within resting CD4 lymphocytes and memory cells, because it cannot complete its cycle of replication until cellular activation takes place.

C. Viral Subtypes

HIV-1 exists in several genetically distinct forms or clades (see Figure 2.1). Three major phylogenetic groups, designated M, O, and N, have been identified. Most viral strains are in the M, or major, group. These subtypes are designated A through H and J. The vast majority of isolates from the United States and Western Europe have been subtype B. A, C, and D are common in Africa; E and C are the predominant strains in Southeast Asia and India, respectively.[28–30] Increasingly, non-B subtypes are appearing in the United States as a result of the greater mobility of the world's population. In one recent study in New York City, nearly 5% of newly diagnosed patients were infected with non-B subtypes.[31] The types and subtypes of HIV-1 cannot be distinguished with standard antibody testing kits.

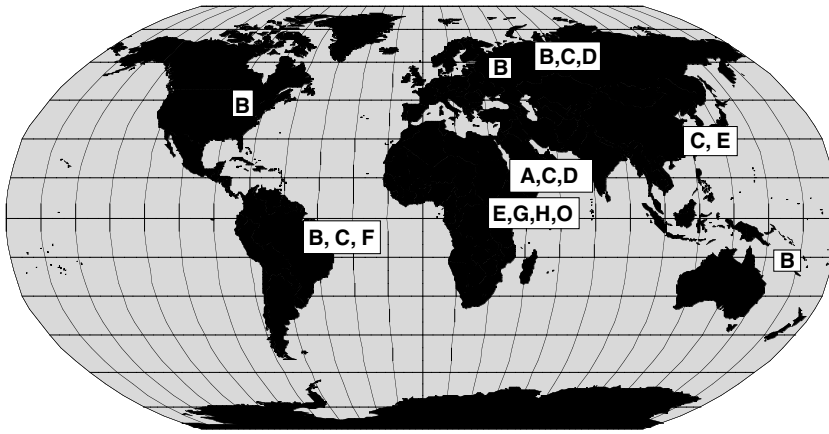

FIGURE 2.1 Global distribution of HIV-1 groups and subtypes. (Adapted from Hu, D. et al., *JAMA,* 275*,* 210*,* 1996.)

HIV-1 genetic diversity has implications for measuring plasma viremia. Tests to measure plasma viral RNA may underestimate the viral load in patients infected with non-B strains of the virus.[32] The test most commonly used in clinical practice at this time and the only one approved by the Food and Drug Administration at the time of this writing, the Amplicor HIV-1 Monitor Test, version 1.0, has this disadvantage. Underestimates of plasma viral load may lead to delays in initiating antiretroviral therapy (see indications in Chapter 10)[33] or even raise doubts about the diagnosis of HIV infection. Newer techniques, such as the Amplicor 1.5[34] and others, which have a greater sensitivity for non-B subtypes, are based on branched-chain DNA signal amplification[35,36] and are becoming available.

Little is known about the relative host immune response to various viral clades and subtypes.[37] If cellular or humoral immune responses are significantly different to different subtypes, vaccine development could be hampered substantially.

IV. HOST SUSCEPTIBILITY

A. Risk Factors for Transmission

Most exposures to HIV do not result in infection. Factors that dictate the likelihood that clinical infection will take place have received increasing attention in recent years.[38,39] Some HIV-exposed but seronegative individuals have been shown to have specific immune activation to HIV,[40] suggesting the possibility that low-level infection which remains subclinical can occur. Although the full significance of this phenomenon is not yet known, a variety of factors have been demonstrated to increase the likelihood of transmssion of HIV and the development of clinical infection.

1. Importance of Viral Load

Plasma viral load correlates closely with the risk of heterosexual transmission. In a large study from Africa, individuals with viral loads greater than 50,000 copies/ml were approximately 12 times as likely to transmit HIV through heterosexual contact as those with viral load between 1500 and 3000 copies/ml. Transmission did not occur when the viral load was below 1500 copies/ml in this study.[41] The risk of transmission is not eliminated in all patients with low viral loads, however, because the virus may be present in genital secretions as well.

2. Genital Ulcers

The presence of genital ulcers caused by syphilis, chancroid, herpes simplex infection, or other disorders appears to significantly increase the likelihood of HIV transmission during sexual contact.

3. Circumcision

Circumcision appears to significantly reduce the likelihood of heterosexual transmission of HIV infection. In a study from Africa no transmission was documented among 50 circumcised males in discordant couples followed for a period of 30 months. In this study it was concluded that much of the difference in relative rates of female-to-male and male-to-female transmission that are seen between Africa and North America could be attributed to the protective effect of circumcision.[41]

B. Resistance to HIV Infection

It has long been recognized that some individuals do not develop clinical HIV infection despite repeated exposures. Although all of the factors which dictate relative resistance or susceptibility to infection have not yet been elucidated, several have been identified.

1. Chemokine Receptor Status

In addition to the CD4 receptor, a number of coreceptors on the cell membrane are necessary for HIV to enter and infect cells. CXCR4, one such receptor, is a coreceptor on T lymphocytes;[42] CCR5, another receptor, is the major coreceptor on macrophages.[43] The two moieties, both of which normally serve as chemokine receptors, are the predominant, though not the only, coreceptors identified thus far. Several mutations in the gene coding for CCR5 have been identified. Individuals with these mutations have reduced expression of the coreceptor.[44] Less than 1% of the population is homozygous for this mutation. These individuals are largely protected against HIV infection[45] and those heterozygous for the mutations may experience slower disease progression once infected.[46,47] For reasons that are not yet clear, these mutations may not be as protective among injection drug users as they are among homosexual men.[48]

2. Major Histocompatibility Complex

Certain human leukocyte antigen (HLA) types, which are genetically determined, are associated with a lower rate of susceptibility to HIV infection.[49,50]

3. Age

Rates of disease progression are faster and survival is shorter among HIV-infected individuals over the age of 50.[51–53] This phenomenon is due, at least in part, to the higher rate of such comorbid conditions as cardiovascular disease, cancer, diabetes, and chronic lung disease.[54] However, because more than 25% of HIV-infected elderly patients are unaware of their HIV risk,[55] there is often a delay in seeking care. This, possibly coupled with intrinsic waning of the immune response with aging and the misdiagnosis of HIV-related disorders as diseases of aging (e.g., AIDS dementia vs. Alzheimer's disease), may account for much of the apparent alteration of the natural history of HIV infection in the aged.[56]

V. THE IMMUNE RESPONSE TO HIV INFECTION

A. Mucosal

It is estimated that more than 90% of HIV cases in the world have resulted from mucosal transmission, that is, through heterosexual or homosexual contact. Such mucosal surfaces as the oropharynx, rectum, and genital mucosa provide the initial defense against infection. For this reason, the mucosal immune response to HIV infection has been the subject of increasing research attention.[57] In addition to the anatomical barrier represented by an intact mucosal surface, adjacent lymphoid tissue (e.g., tonsils, Peyer's patches) and specialized cells with the mucosal surface (M cells) contribute to mucosal defenses. Langerhans cells are dendritic cells that trap antigens at the mucosal surface and are the first cells in the body where HIV can be detected after infection has occurred.[58]

HIV-specific antibody, particularly of the IgG class, is detected in the mucosal fluids of HIV-infected individuals, although synthesis of mucosal antibody in response to new antigenic challenge is impaired.[59] Mucosal antibody to HIV is derived locally and from the serum.[60,61] The local immune response may account for the fact that rates of HIV transmission per sexual contact are low—one in several hundred. Vaccines stimulating mucosal immunity may eventually take advantage of this extensive component of the immune system.

IgA is the dominant immunoglobulin present in saliva, tears, milk, and gastrointestinal secretions, while IgG dominates in the genital tract.[62] IgA is present in two subclasses, IgA1 and IgA2. Antibody to HIV is typically IgA1, which dominates in the respiratory and upper gastrointestinal tract. Both subclasses are present in roughly equal amounts in the lower intestinal tract and the female genital tract.[63]

B. Cellular

HIV-specific helper (CD4+) T lymphocytes are typically absent throughout the course of HIV infection. Because of this, aspects of the immune response which are dependent on CD4+ cell function are blunted. These include: B cell activation and antibody production, natural killer cell activity, cytokine production, and cytotoxic T lymphocyte (CTL) function. CD8+ cytotoxic cells represent the major defense against HIV early in the disease[7] through lysis of infected cells.[64] These cells,

however, decline in number as the disease progresses, in part because of the absence of CD4+ cells to stimulate their action.

C. The Impact of Therapy on the Immune Response

As noted previously, virus-specific CD4+ lymphocytes are normally not detected during HIV infection. It is thought by some that these cells are produced rapidly early in the course of primary HIV infection but are quickly infected and destroyed.[8,65] For this reason, early antiretroviral therapy may help to maintain CD4+ helper cell function by reducing the number of cells infected.[66,67]

VI. IMPLICATIONS FOR MANAGEMENT

The pathogenesis and natural history of HIV infection have several important practical implications for management.

A. Diagnosis

As noted above, the acute retroviral illness is both common and relatively unique but is seldom recognized clinically. Protracted illnesses (i.e., more than 2 weeks) consistent with acute HIV infection should be considered suspicious, especially in areas with high HIV prevalence. The long period of clinical latency, during which the patient may have substantial immunological decline and may transmit infection to others, may confound diagnosis of HIV infection as well. Providers must be vigilant to perform a risk assessment for HIV infection on all patients regardless of perceived risk (see Chapter 3) and not be misled by an absence of symptoms and the appearance of good health in these individuals. HIV testing should be offered and encouraged liberally, especially in high prevalence areas.

B. Therapy

The treatment of HIV infection has gone through several major evolutionary steps in recent years, reflecting the natural history of disease. Early in the epidemic, only symptomatic patients were felt to benefit from antiretroviral therapy. With advances in treatment and with the widespread availability of assays of plasma viral load, the goal of therapy is now to suppress viremia (greater than 20,000 copies/ml; see Chapters 10 and 11) in order to prevent or forestall immunologic decline and the appearance of symptoms.

C. Risk of Opportunistic Infection

It has long been known that the risk of opportunistic infection correlates best with the CD4 lymphocyte count. This may reach critical levels (<200 cells/mm^3) necessitating preventive therapy long before the appearance of symptoms.

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3 Testing for HIV Infection

CONTENTS

I. INTRODUCTION

Rapid and reliable testing of blood for antibody to HIV was developed and made widely available by the mid-1980s, not long after the discovery of the virus. Since that time, several important factors have affected strategies for HIV testing. First, and perhaps most important, it was soon obvious that the majority of HIV-infected individuals were asymptomatic and that clinical criteria were inadequate to diagnose early infection. The public health implications of this fact have been far-reaching, since HIV can be transmitted throughout the course of infection. Second, advances in antiretroviral therapy have made it imperative to detect HIV infection as early in the asymptomatic phase as possible when therapy is most effective. Third, antiretroviral therapy can dramatically reduce the risk of mother-to-child transmission during pregnancy, childbirth, and breastfeeding if HIV infection can be diagnosed in the mother by the second or third trimester. Fourth, it has become increasingly clear that only by an understanding of the distribution of HIV infection in the population through seroprevalence studies can allocation of resources for prevention and medical care be focused. Fifth, prevention of transmission of HIV infection to healthcare workers by means of needlestick injuries and other potential exposures is facilitated by the rapid testing of the source patient. For all of these reasons, HIV testing efforts have been expanded and, to some extent, targeted. Several states have established mandatory testing programs for pregnant women and neonates. Partner notification and contact tracing efforts have been enhanced in some areas. Public education campaigns intended to increase testing among high risk populations have been expanded and legal protections have been developed to reduce discrimination against HIV-infected individuals.

Most HIV testing continues to be conducted following administrative and laboratory procedures developed in the 1980s. In recent years, home test kits have been marketed with only partial success and very rapid tests for antibody detection have been developed. Since the mid-1990s, detection of viral antigen, especially RNA, has become a tool in the management of antiretroviral therapy.

II. METHODS OF TESTING

A. Antibody Tests

Infection with human immunodeficiency virus, type 1 (HIV) is diagnosed by detection of specific antibody to the virus in blood (see Figure 3.1) or, in rare instances, other body fluids. The sensitivity and specificity of current blood tests for antibody exceed 99%.[1] An important limitation of the most widely used assays, however, is that antibody is not detectable for weeks to months after infection has occurred. Although most infected individuals test positive after three months, seroconversions as late as six months after primary infection have been reported.[2]

1. Enzyme-Linked Immunosorbent Assay (ELISA)

The standard screening blood test for HIV antibody is the enzyme-linked immunosorbent assay (ELISA). The test employs HIV antigens on a solid phase, either beads or microtiter wells. Specimens of the patient's serum or plasma are incubated

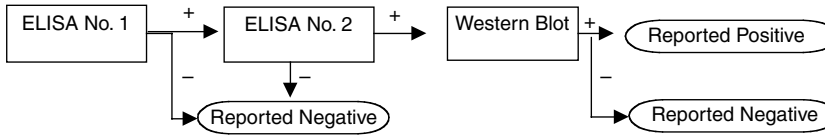

FIGURE 3.1 Standard procedure for HIV-1 serum antibody testing.

with the antigen preparation. If antibody to HIV is present in the specimen, it binds to the antigen. Antibody bound in this fashion is then detected by the addition of an antiglobulin-enzyme conjugate followed by a reagent, which reacts with the enzyme to produce a color change. When measured spectrophotometrically, the degree of color change is proportional to the amount of anti-HIV antibody present.

2. Western Blot

In the standard procedure, confirmatory testing is performed on specimens testing positive for ELISA on two determinations. The confirmatory test in widest use is the Western blot, a more specific, though more labor-intensive technique. The procedure is as follows:

1. Disrupted virus is electophoretically fractionated on gel.
2. Antigenic bands are transferred to nitrocellulose, which is then cut into strips and incubated with the patient's serum.
3. An anti-immunoglobulin reaction detects antibody bound to the nitrocellulose strip.

Several different antibodies to HIV typically are identified by Western blot, and interpretation of results may occasionally be difficult.

The Western blot may be reported as positive if bands are detected that include one of the following[3,4]:

Any two proteins (p) or glycoproteins (gp) of p24, gp41, or gp120/160
Protein p24 or p31 plus gp41 or gp120/160
One or more bands from each gene product group (gag, pol, env)

When antibody is detected in a pattern not regarded as positive, the result may be reported as inconclusive or indeterminate. Such indeterminate patterns, particularly isolated antibody to p24, may be seen early during seroconversion in patients who have recently become infected. However, some individuals with indeterminate Western blot results are found to be uninfected on further testing.[5]

3. Rapid Antibody Tests

A significant disadvantage of conventional antibody testing as outlined above is that results are typically not available for several days, especially when Western blot confirmation of a positive test is performed. This delay causes a significant proportion of individuals to never receive their test results because they do not return.

a. Single-Use Diagnostic System (SUDS)

A more rapid antibody test, the Single-Use Diagnostic System (SUDS; Murex Corp., Norcross, GA) for HIV-1, has been licensed to address this and other problems associated with the delay in results by standard techniques. The sensitivity and specificity of SUDS, which is performed on blood and takes approximately 15 minutes, is comparable to that of ELISA, and Western blot confirmation of positive results is still required. However, as in the case of ELISA, a negative result does not require confirmation and can be reported to the individual being tested at the same encounter.[6]

b. OraSure Test

The OraSure test (Epitope Co., Beaverton, OR) is the only oral test currently approved by the Food and Drug Administration. Oral fluid is obtained on a test strip and tested for IgG to HIV-1 by enzyme immunoassay.[7] Positive tests must be confirmed by Western blot. Sensitivity and specificity are comparable to ELISA. Although final results are typically not available for 3 days, OraSure provides a convenient means of testing individuals in community settings where drawing and storing blood specimens is not feasible.

4. Testing for Variant Viral Strains

Current antibody tests were developed primarily in the United States and Europe and diagnostic accuracy data were based on their sensitivity and specificity in detecting the clade B subtype of HIV-1 which is seen most commonly in those areas. Although current ELISA techniques can detect all subtypes of HIV-1, the accuracy of current tests in detecting distinguishing antibody to HIV-1 from antibody to HIV-2, which is endemic in Africa, has been challenged.[8]

B. Antigen Tests

Antigens of HIV-1 may be detected by several techniques.

1. Polymerase Chain Reaction for Viral RNA

At present, quantitative measures of viral RNA by polymerase chain reaction (PCR) have replaced older techniques such as p24 antigen detection, because of the clear relationship between RNA PCR, response to antiretroviral therapy, and prognosis (see Chapters 10 and 11). In this technique, levels of viral RNA in specimens of plasma or other body fluids can be amplified by the annealing of complementary binders to various segments of denatured viral RNA followed by successive cycles of denaturation and annealing which results in progressive amplification of the reaction ultimately enabling the detection minute amounts of viral RNA in the specimen. This assay is currently the only approved test for use in individuals testing positive for HIV-1 antibody for evaluation and monitoring of antiretroviral therapy.

Unlike antibody tests, however, HIV RNA PCR tests are not able to detect all subtypes of the virus. Newer techniques under development are capable of detecting strains such as group O.[9–11] At present, patients from areas of the world where non-B

subtypes are prevalent, who have tested positive for HIV antibody but have an undetectable viral load by RNA PCR, should be re-evaluated using one of these techniques.

2. Branched-Chain DNA

Another quantitative method of testing for viral nucleic acid is the branched-chain DNA (bDNA) assay. This assay employs an ELISA-like system and does not involve PCR. An advantage of bDNA is that it is capable of detecting more viral subtypes than RNA PCR, although false negative results may also occur with this technique.[9]

III. TESTING STRATEGIES

A. Targeted Testing

Because the seroprevalence of HIV infection in the general U. S. population is less than 1%, most practitioners and organized programs direct testing and counseling efforts to persons who are known to be at high risk of HIV infection.

B. Routine Testing

Routine testing is more broad-based than targeted testing. It may be directed toward a segment of the population, for example, pregnant women, regardless of perceived risk of HIV infection, or can be directed even more broadly to become part of routine health screening activities for all adult patients. The relative merit of these strategies is not completely clear. It will be dictated by several factors including:

The effectiveness of risk assessment
The prevalence of HIV infection in the population which would dictate the overall yield of testing as well as the sensitivity and specificity of results
The cost of large-scale testing

In a San Francisco study comparing routine testing to targeted testing based on a questionnaire completed by the patients, Phillips and Fernyak concluded that routine testing was the most cost-effective approach.[12] It is likely that this conclusion is not applicable to areas with low HIV seroprevalence, however.

IV. RISK ASSESSMENT

In view of the high level of accuracy of current tests to detect HIV infection, one could ask why an assessment of an individual's risk of HIV infection before testing is important. There are several reasons why a careful risk assessment should be performed and documented before testing. Among these are the following:

If an individual at low pretest risk of infection tests positive, the likelihood of a false-positive result must be considered and ruled out with repeated testing or testing by an alternative technique, such as an antigen assay.
Conversely, if an individual at high risk tests negative, the possibility of a false-negative should be entertained.

A careful assessment of risk may discourage unnecessary testing and help the provider focus efforts on those most likely to be infected.
Counseling regarding risk of transmission may be facilitated by a detailed understanding of the individual's specific risk behavior.

Among adults HIV is transmitted almost exclusively by needle sharing during injection drug use or by sexual contact. Because HIV-infected individuals may remain asymptomatic for years after infection has occurred, the goal of risk assessment should be to identify past and present high risk behavior. Despite the diversity of opinion on testing strategies, obtaining an accurate history of risk behavior and assessing the risk of HIV infection in patients who may be unable to provide a complete history have become increasingly vital skills for the primary care physician and are likely to remain the most important components of HIV testing procedures.

A. Sexual History

Although the sexual history is regarded as an essential element of the general medical evaluation, surveys have indicated that a large proportion of physicians do not obtain a complete history of sexual behavior from their patients.[13] The reasons given for this omission vary, although embarrassment and lack of specific training in obtaining the sexual behavior were blamed by many physicians in one large survey.[14] Unfamiliarity with the diversity of sexual practices and HIV transmission patterns may lead to improper counseling[15] and needless testing of patients at minimal risk of HIV infection.[16]

Discussing current and past sexual behavior at the time of initial assessment of adult and adolescent patients serves several important purposes: it allows the clinician to assess the risk of HIV infection and to make specific suggestions to the patient about necessary changes in sexual practices; it may lead to identification of sexual partners at risk for infection, should the patient prove to be HIV-infected, so that testing of these individuals may be explored with the patient; and it may establish an atmosphere in which the patient more freely discusses sexual behavior at subsequent visits. In addition, it should be recognized that national and international efforts to fully characterize the AIDS epidemic depend on accurate assessments of routes of transmission.

All adult patients should be asked appropriate questions about past and current heterosexual and homosexual behavior, including (1) number of partners, (2) frequency of anonymous sexual contact, (3) prostitute contact, (4) history of sexually transmitted diseases, (5) condom use, (6) risk behavior of current and previous sexual partners, and (7) specific sexual practices. Avoiding labels by asking "Have you ever had sex with another man?" may be more effective at eliciting accurate information than asking "Are you homosexual?" Despite a history of same-sex encounters, the individual may not consider him/herself to be homosexual, bisexual, or lesbian.

Men giving a history of sexual contact with other men should be asked about specific sexual practices, including anal intercourse, oral-anal, or oral-genital contact and douching. Because receptive anal intercourse and douching are associated with a

particularly high risk of HIV infection (see Chapter 1), such information may allow the practitioner to estimate the pretest probability of HIV infection more precisely. More important, however, detailed knowledge of the patient's sexual practices may allow the provider to make specific recommendations about altering behavior.

B. Substance Abuse History

Patients should be questioned thoroughly about previous and current drug use and needle sharing. Although HIV transmission occurs through needle sharing among injection drug users, the use of drugs by other routes, such as inhalation or smoking of cocaine, may also be associated with increased risk, perhaps through an increase in high-risk sexual activity.

V. PRETEST COUNSELING

Counseling regarding HIV testing is best conducted by individuals with specific training in techniques and procedures and with a working knowledge of current HIV/AIDS medical care. Mechanisms of referral into medical care should be established prior to testing and a program of follow-up of test results, whether positive or negative, should be in place. When the decision is made to offer HIV testing to an individual, counseling addressing the specific reasons for testing, as well as the test's limitations, should be provided. It is important that the patient understands the specific reasons that testing is indicated and how the test results will be used in his or her overall medical care. A judgmental attitude must be avoided, and patients should be strongly encouraged to discuss openly their feelings about the need for testing and their concerns about the testing procedure.

The practitioner should try to anticipate the reaction to a positive or negative test result and explore with the individual the likely impact that a positive test result would have on his or her life. Although pretest counseling cannot take the place of a thorough psychiatric evaluation, it can help identify patients who might benefit from psychiatric intervention. The reported increased risk of suicide among HIV-infected patients[17] underscores the need for a thorough exploration of the individual's feelings before testing. Asking the patient what he or she expects the test result to be may aid in anticipating the impact of a positive test result.

Local regulations governing confidentiality and notification of contacts should be discussed before the test is conducted.

A. Objectives

Pretest counseling has the following objectives:

To establish rapport
To explain the testing procedure, including confidentiality and partner notification procedures
To explain the meaning of a positive or a negative test result
To discuss potential medical benefits of testing
To provide information about HIV infection and treatment options

To review means of reducing the likelihood of transmission
To anticipate the individual's likely reaction to a positive or negative test result
To obtain and document informed consent according to local requirements

1. Establishing Rapport

People undergo HIV testing for a variety of reasons. Some may realistically suspect that they are infected because of high-risk behavior, exposure to a person known to be infected, or the occurrence of symptoms. Others, such as health care workers, may fear that they have contracted HIV infection after a single possible exposure. Occasionally, people with little or no apparent risk of infection undergo testing because it is required for immigration, life insurance, or other purposes. In some cases excessive fear of infection or misinformation regarding routes of transmission may lead an individual to seek testing, sometimes repeatedly, despite assurances that infection has been excluded. The means of establishing rapport differ according to the individuals seeking testing.

Individuals who have engaged in high-risk behavior should be supported and encouraged in their decision to undergo testing. The person should be questioned about past sexual behavior and drug use, to establish the likelihood of infection on clinical grounds and to begin the process of identifying potential contacts if he or she proves to be infected. The practitioner can offer support by acknowledging the courage the individual has shown in agreeing to be tested. It may be advisable to provide advice on safe sexual practices and other means of preventing transmission during pretest counseling.

2. Explaining the Testing Procedure

It should be explained clearly that conventional HIV tests do not detect antibody for weeks to months after infection and that for this reason a single negative result cannot exclude HIV infection in a person who has recently engaged in high-risk behavior. It should be made clear during pretest counseling that repeated testing may be necessary to completely rule out the possibility of infection. Local regulations governing confidentiality of test results, specifically, whether the individual testing positive will be reported by name to public health authorities, and procedures and requirements regarding notification of sexual and needle-sharing partners of individuals testing positive should be explained. Depending on local regulations, HIV test results may be disclosed under certain circumstances; these should be clarified. If anonymous testing is available, the patient should be informed of this option.

3. Explaining the Medical Benefits of Early Diagnosis

The chronic nature of HIV infection should be explained and the term *AIDS* defined. With patients who are asymptomatic, it should be pointed out that (1) AIDS most often evolves slowly, (2) antiretroviral therapy usually leads to a delay in progression of disease, and (3) new forms of therapy are being studied extensively. Symptomatic patients can also be reassured that therapeutic options are available for them and that determining if HIV infection is present will allow for better, more appropriate medical care.

4. Reducing the Risk of Transmission

See discussion later in this chapter.

5. Anticipating the Individual's Reaction to the Test Result

Consideration should be given during pretest counseling to explore with patients their potential reaction to a positive or a negative test result. Asking patients what they expect the result to be and what they would do if they learn that they are infected may help identify those likely to have an extreme emotional crisis or to consider suicide or other serious acts. Such screening, however, does not take the place of formal psychiatric evaluation. Individuals undergoing HIV testing had a high incidence of mood disorders in one series[18] and may be at risk for depression. Psychiatric consultation before HIV testing and counseling should be strongly considered for patients with a history of mental illness.

6. Obtaining Consent

Local regulations regarding procedures for obtaining informed consent vary. The practitioner should be familiar with such regulations and should ensure that consent is obtained properly and in a noncoercive fashion. It is especially important that regulations regarding mandatory reporting of HIV test results and notification of sexual or needle-sharing partners are thoroughly explained.

VI. POSTTEST COUNSELING

Formal counseling after HIV testing should be conducted regardless of the test result. For the patient testing positive, a counseling session provides the opportunity to review information about transmission and plans for medical care and to assess the individual's reaction. The goals of counseling should be:

- To advise the patient on ways of avoiding transmission of infection to others
- To discuss notification of others who may have been infected and to assess the risk of domestic abuse and other potential ramifications of such partner notification
- To determine the need for emotional support or psychiatric referral
- For the patient testing negative, to reinforce changes in behavior to eliminate the risk of HIV infection, discussed before testing, and to determine the need for repeat testing
- For the patient testing positive, to make specific plans for entry into care

A. Reducing the Risk of Transmission

Individuals who remain actively engaged in risk behavior should be informed that they remain at high risk of acquiring and/or transmitting infection and, of course, urged to alter their behaviors. Drug treatment options should be explored with active

injection drug users. If high-risk behavior has continued, HIV testing should be repeated in 3 to 6 months.

All patients should be informed of the following facts about HIV transmission:

- Mutually monogamous sexual intercourse between uninfected individuals carries no risk of HIV infection.
- HIV-infected individuals can transmit the virus even when they appear to be completely healthy.
- No form of oral-genital, anal, or genital sexual contact with an infected person is known to be free of risk of HIV transmission.
- The use of condoms diminishes but does not eliminate the risk of sexual transmission of HIV infection.
- If condoms are used, latex brands with spermicidal compounds are preferable, and the condom should be left in place for the duration of sexual contact.
- Injection drug users should under no circumstances share needles and should observe risk reduction in sexual practices. Drug treatment should be urged and arranged as efficiently as possible.
- Spills of blood or other body fluids should be cleaned and disinfected by the infected individual if possible.
- Although donated blood is screened for HIV antibody, HIV-infected individuals, as well as those testing negative but at continued risk of infection, should be instructed to refrain from donating blood, semen, body organs, or any other tissue.
- Because of the small but definite risk of transmission of HIV infection in the health care setting, HIV-positive individuals should be instructed to inform physicians, dentists, or other healthcare providers of their status.

Nonsexual household contacts, including friends and family members of HIV-infected persons frequently express fear that they will become infected. To prevent physical and emotional isolation of the infected person, the practitioner should seek to allay these fears by explaining that simple precautions will eliminate any small risk. A face-to-face meeting with close friends or family members may be helpful.

For additional information regarding risk of transmission, please see Chapter 1.

B. Planning for Further Testing

Individuals testing negative who have engaged in high-risk behavior within 6 months before testing should be advised that recent infection has not been excluded. Repeated testing after an interval of at least 3 months should be scheduled, and the patient should be advised that he or she may be capable of transmitting HIV infection to others during this interval.

C. Partner Notification

Mandatory notification of sexual or needle-sharing partners of HIV-infected individuals went into effect in New York state during the year 2000. Historically, notification of partners has been strongly encouraged and providers could resort to

notification by public health authorities. Partner notification is complex and confronts a number of significant obstacles including:

The long period of time, spanning years in most cases, between initial HIV infection and the time most infected individuals are diagnosed necessitates the identification and notification of partners whom the individual may have overlooked or whose whereabouts are unknown.
With the exception of spouses, the identification of partners requires the individual to cooperate in a process which may expose him/her to embarassment, legal action, or violence.
Individuals testing positive, who do not return for their results, may have known partners who may escape notification.
Individuals at risk of HIV infection may avoid testing because of the requirement of partner notification, which although anonymous, may lead to the individual's HIV status being indirectly revealed.

Despite these concerns, all infected individuals should be urged to notify sexual partners and medical personnel involved in their care of their status. The practitioner should follow local regulations regarding partner notification if the patient appears unwilling or unable to participate.

The risk of domestic violence committed by a notified partner on the index patient has been specifically addressed in the New York legislation, which requires a domestic violence assessment to be performed prior to partner notification. Notification may be deferred in instances where the risk of violence is judged to be high.

VII. LEGAL AND ETHICAL ISSUES OF HIV TESTING

Since the beginning of the HIV/AIDS epidemic, great controversy has existed regarding confidentiality of test results. No final consensus has been reached regarding the balance between individual privacy and the need for epidemiologic information and the responsibility of public health authorities to inform individuals at risk from an infected sexual or needle-sharing partner. In general, confidentiality of test results has been given paramount importance. As the epidemic continues, however, and legal precedents and ethical insights accumulate, changes in current testing and reporting procedures may be anticipated.

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4 Overview of HIV-Related Disorders

CONTENTS

I. INTRODUCTION

Infection with the human immunodeficiency virus (HIV-1) leads to a complex multisystem disease. Opportunistic infections and malignancies resulting from the progressive immunologic impairment that is central to the disorder may involve any organ system. However, a more direct relationship between HIV infection and endorgan dysfunction also exists. Such clinical syndromes as dementia, cardiomyopathy, and nephropathy, which are commonly seen in HIV-infected patients, appear to be caused by the virus itself in many cases.

Many of the clinical manifestations of HIV infection occur early in the course of the disease, before the onset of opportunistic infections and malignancies. Some infections, including pneumococcal pneumonia, oral candidiasis, human papilloma virus (HPV) infection and other sexually transmitted diseases, viral hepatitis, and tuberculosis, although seen with greater frequency in HIV-infected individuals, are not considered AIDS-defining conditions because they occur frequently in the general population as well. Similarly, many idiopathic disorders, such as autoimmune thrombocytopenia and Reiter's syndrome, are also seen more commonly but not exclusively in patients with HIV infection and are therefore not considered diagnostic of AIDS.

Highly active antiretroviral therapy (HAART) has dramatically reduced the incidence of many of the complications of HIV infection, those due to immune deficiency as well as direct endorgan syndromes caused by the virus itself. Such progress, while vitally important for patients in care, does not impact a large proportion of HIV-infected individuals who present for care acutely after the onset of opportunistic infections or other HIV-related disorders. In recent years, in New York City, approximately one third of newly-diagnosed AIDS patients first came to medical attention with such complications. It is, therefore, important that providers caring for HIV-infected patients maintain their abilities in the diagnosis and management of these "traditional" AIDS-related disorders even in the era of HAART therapy.

The primary care provider must be prepared to recognize and evaluate the great diversity of clinical manifestations of HIV infection. Distinctions between AIDS-defining disorders and other clinical syndromes associated with HIV infection,

TABLE 4.1
Common Skin Manifestations of HIV-1 Infection

Disorder	Reported Frequency	Stage	Reference
Seborrheic dermatitis	50%	AIDS	1
Candidiasis	37%	All	1
Other fungal infections	30%	All	2
Xerosis	30%	All	2
Herpes simplex	22%	All	2
One or more	92%	All	1

although important for surveillance purposes, often become somewhat artificial in practical management.

This chapter provides an overview of major HIV-related disorders, whether AIDS-defining or not, arranged by organ system. Detailed discussions of the diagnosis and treatment of various disorders will be found in subsequent chapters.

A. Skin Disorders

Dermatologic manifestations of HIV infection are present in most patients and are common at all stages of disease[1,2] (see Table 4.1). Although not life-threatening, disorders such as seborrheic dermatitis, psoriasis, xerosis, and alopecia are often extremely disturbing to the patient. Other processes involving the skin represent serious, potentially fatal complications. These include Kaposi's sarcoma and cutaneous manifestations of opportunistic infections such as crytpococcosis, pneumocystosis, tuberculosis, histoplasmosis, and herpes simplex or varicella zoster infection. An increase in the severity of dermatologic symptoms may be associated with overall clinical progression.[3]

1. Seborrheic Dermatitis

Severe and refractory seborrheic dermatitis is a common sequela of HIV infection, especially among dark-haired men.

2. Ichthyosis

Dry skin is frequently seen in association with HIV infection. Flaking and pruritis, which may be extreme, are often very troubling to patients.

3. Herpes Virus Infections

Localized or disseminated infection with herpes simplex is common in HIV-infected individuals and may take a variety of forms.[2] Localized infection most typically occurs in the perianal or genital region and, unlike genital herpes in non-HIV-infected individuals, may cause chronic, destructive, ulcerating lesions that may erode into the rectum, scrotum, or other adjacent structures. Herpes simplex infection may also

be seen as nonhealing mouth or lip ulcers or as disseminated ulcerating lesions. Varicella zoster virus may cause severe primary infection (chickenpox) in nonimmune patients or may reactivate as localized (shingles) or generalized herpes zoster. Shingles in the setting of HIV infection is often quite severe with destructive lesions and severe postherpetic pain.[4]

4. *Bartonella* Infections

Infection with bacteria of the genus *Rochalimaea* (*R. henselae* and *R. quintana*) has been described in association with a generalized rash highly associated with HIV infection.[5] Typical lesions are red papules that may bleed when traumatized, although crusted, scaling plaques, subcutaneous nodules, and a variety of other lesions have been described.[6] The infection may involve a wide variety of visceral sites, especially bone and liver (hepatic peliosis).[7] Differentiation from Kaposi's sarcoma and other disseminated bacterial or fungal infections may be impossible without biopsy. In 1993, the genus *Rochalimaea* was reclassified and included in the genus *Bartonella*. The organisms associated with bacillary angiomatosis are now termed *B. henselae* and *B. quintana*.

5. *Rhodococcus Equi* Infections

Rhodococcus equi, a bacterium previously associated only with pulmonary infection in horses, has been described as a respiratory and soft-tissue pathogen in a small number of HIV-infected individuals.

6. Systemic Opportunistic Infections

a. Cryptococcosis

A variety of skin lesions has been associated with cryptococcal infection. Most often, papules resembling molluscum contagiosum have been described,[8] although cellulitis and nodular lesions may also be seen.

b. Mycobacterial Infections

Cutaneous manifestations of mycobacterial infection may include nonhealing ulcers, nodules, pustules, and papules.[9]

c. Histoplasmosis

Histoplasmosis may present as papular or ulcerative lesions, either localized or generalized, involving either the epidermis or mucosal areas. Similar lesions may be seen in association with other so-called geographically restricted fungal infections, including coccidioidomycosis and blastomycosis.

7. Malignancies

a. Kaposi's Sarcoma

Kaposi's sarcoma, a cutaneous, systemic neoplasm, was among the first disorders recognized to be associated with AIDS. Among patients with AIDS, Kaposi's sarcoma occurs most frequently in individuals who acquired HIV infection through sexual

contact, particularly male homosexuals.[10] It has been observed that the incidence in this group has declined steadily since the beginning of the AIDS epidemic, although the reasons for this decline are unclear. Recent data suggest that a herpes-like virus, human herpesvirus 8, may be the etiologic agent[11,12] and may lead to KS most rapidly among men who acquire HHV-8 infection after HIV infection.[13]

AIDS-related Kaposi's sarcoma differs from classic Kaposi's sarcoma in its tendency to produce multiple lesions and visceral involvement. In addition to the skin, frequent sites of involvement include mucous membranes, the gastrointestinal and respiratory tracts, lymph nodes, and the spleen.[14,15] Involvement of the liver,[16] heart,[17] and other unusual sites has also been described.

There has been a dramatic decline in the incidence of Kaposi's sarcoma since the advent of potent antiretroviral therapy in the mid-1990s and regression of Kaposi's lesions may be seen in individuals receiving such therapy.[18]

b. Melanoma

Malignant melanoma appears to occur more frequently in the setting of HIV infection.[19] The course may be particularly aggressive.[20]

B. Neurological Disorders

HIV has a marked predilection for the central nervous system (CNS), and involvement in the form of aseptic meningitis may be evident during primary infection. Evidence of so-called HIV encephalopathy was seen in the majority of AIDS patients at autopsy in an early study.[21] The CNS is also a frequent site of HIV-related opportunistic infections and malignancies (see Tables 4.2 and 4.3). The term AIDS dementia complex is used to characterize the direct clinical and pathologic results of HIV infection of neural tissue typically occurring at advanced stages of immunodeficiency. Peripheral neuropathy is also frequently seen in these patients and, like dementia and myelopathy, may become extremely debilitating as well as demoralizing. As in the case of other complications of advanced HIV infection, CNS disease, both HIV-related and opportunistic, has decreased in incidence since the advent of effective antiretroviral therapy.[22]

TABLE 4.2
Common Focal Neurologic Disorders

Disorder	Frequency	Diagnostic Evaluation	Reference
Toxoplasmosis	2% AIDS	CT or MRI, serum antibody therapeutic trial, PET or SPECT scanning, biopsy	28
Progressive multifocal leukoencephalopathy	2–5% AIDS	CT or MRI, biopsy	33
Lymphoma	1–9% AIDS	CT or MRI, PET, SPECT scanning, biopsy	

TABLE 4.3
AIDS-Related Nonfocal Neurologic Disorders

Disorder	Frequency	Diagnostic Studies	Reference
Cryptococcal meningitis	Initial AIDS Dx in 7%	CSF exam, serum CSF antigen, culture	37
Tuberculous meningitis	Not reported	CSF exam, culture	
CMV encephalitis	Histologic evidence in 24% of AIDS patients at autopsy in early study	CSF exam, tissue exam	41

1. Central Nervous System

Since the earliest days of the AIDS epidemic, it has been recognized that infection of the nervous system by HIV may be associated with aseptic meningitis,[23] myelopathy,[24] peripheral neuropathy,[25] and dementia.[26,27]

a. Focal Disorders

Toxoplasmosis Cerebral toxoplasmosis, caused by the protozoal parasite *Toxoplasma gondii*, was the initial manifestation of AIDS in approximately 2% of patients in early statistics,[28] although the widespread use of trimethoprim-sulfamethoxazole for prevention of *Pneumocystis carinii* appears to have reduced the incidence of symptomatic toxoplasmosis. Nonetheless it remains a frequent cause of focal neurological disease, particularly among individuals with previously undiagnosed advanced HIV infection. Focal abnormalities, including hemiparesis, aphasia, ataxia, visual field deficit, cranial nerve palsies, and movement disorders, are evident in most cases. However, such nonfocal findings as lethargy, confusion, psychosis, and coma are also encountered and may lead to diagnostic uncertainty. The incidence of seizures in cerebral toxoplasmosis has been reported to be approximately 16%,[27] comparable to that seen in AIDS dementia.

Although only tissue examination (biopsy or autopsy) can establish a diagnosis of cerebral toxoplasmosis with certainty, imaging studies of the brain, either CT or MRI, may be suggestive enough to allow for a presumptive diagnosis. Mass lesions are almost always demonstrated by these techniques. Lesions of toxoplasmosis are typically located in the basal ganglia and hemispheric corticomedullary junction[29] and are usually, but not always, bilateral. In contrast CT, lesions characteristically show a peripheral pattern of uptake, so-called ring enhancement. Single photon imaging CT (SPECT) and positron emission tomography (PET) can aid in the distinction between cerebral toxoplasmosis and a common mimicker, lymphoma.[30] Lymphoma typically produces isotope uptake in the mass lesion while toxoplasmosis does not. No imaging study has completely replaced brain biopsy for diagnosis in ambiguous cases.

Serologic studies also may aid in the distinction between toxoplasmosis and AIDS dementia or other CNS disorders. Immunoglobulin G (IgG) antibody to *T. gondii* is present in the serum of 97 to 99% of AIDS patients with cerebral toxoplasmosis.[28]

A finding of a higher titer of antibody in the cerebrospinal fluid (CSF) than in the serum is particularly suggestive of cerebral toxoplasmosis. Serologic testing is of limited utility, however, because most adults in the general population have *T. gondii* antibody and cerebral toxoplasmosis can occur in the absence of antibody.

A therapeutic trial with sulfadiazine and pyrimethamine is appropriate in cases with suggestive radiographic and clinical features. Clinical and radiographic responses often may be evident within several weeks. Such empirical therapy, if successful, provides indirect supporting evidence for the diagnosis of toxoplasmosis. The response rates of patients treated on the basis of clinical and radiographic findings are comparable with those of patients with biopsy confirmation.[31] Nonetheless, histologic examination of brain tissue remains the only definitive means of diagnosis and is occasionally necessary, particularly when the response to therapy is inadequate.

Lymphoma Primary CNS lymphoma is the initial manifestation of AIDS in less than 1% of cases overall but occurs with increasing frequency at advanced stages of HIV infection. Most patients have clinical and radiographic findings of one or more intracerebral mass lesions. Focal lesions with contrast enhancement, often indistinguishable from toxoplasmosis, are typically seen on CT. Multiple lesions are seen less commonly than in toxoplasmosis, but distinguishing between these two disorders on clinical and radiographic examination is often impossible. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) have been shown to aid in the distinction between CNS lymphoma and nonneoplastic disorders in AIDS.

Histologic examination of the brain provides conclusive evidence of lymphoma and should be strongly considered for patients with this characteristic not responding to therapy for toxoplasmosis.[32]

Progressive multifocal leukoencephalopathy Progressive multifocal leukoencephalopathy (PML), caused by the JC papovavirus, is a progressive demyelinating disease that may be present in association with a variety of immunodeficiency states or, in rare instances, in normal hosts. PML was reported in early series to occur in 2 to 5% of AIDS patients.[33] Typical symptoms include personality change, memory loss, and language disturbances. However, focal neurologic abnormalities also may occur,[34] facilitating the distinction between PML and AIDS dementia.

Definitive diagnosis of PML requires histologic confirmation by brain biopsy or autopsy. However, the diagnosis occasionally may be made presumptively on the basis of brain imaging studies. Lesions of PML typically appear as areas of lucency within the white matter, rarely exerting mass effect.[35] CT scans may be normal in PML, however, and double-dose contrast studies[36] or MRI may improve the diagnostic yield.

Tuberculosis Tuberculosis involving the central nervous system can present as a lymphocytic meningitis with or without cranial nerve involvement or as a mass lesion which may be difficult to distinguish from other, more common entities such as toxoplasmosis and lymphoma. Enhancement of the basilar meningitis and hydrocephalus may also be seen. The diagnosis of focal infection of the brain with *Mycobacterium tuberculosis* normally requires tissue examination. Tuberculous meningitis

should be suspected in cases, acute or subacute, of lymphocytic meningitis, especially among persons born in areas of the world where tuberculosis is highly endemic. Low CSF glucose and high protein in the absence of another cause are also suggestive.

Nocardiosis Nocardiosis is seen rarely in the setting of AIDS. Infection may involve the lungs, skin, brain, or a variety of other sites. Brain lesions are typically focal and demonstrate enhancement similar to that seen in toxoplasmosis and several other disorders (see above). Diagnosis can be confirmed by demonstration of the organism in tissue specimens or abscess fluid.

b. Nonfocal Disorders

Cryptococcal meningitis CNS infection with the yeast *Cryptococcus neoformans* has been the initial opportunistic infection in 7% of reported cases of AIDS.[37] It is unclear at present if improvements in antiretroviral therapy have had an effect on the relative incidence of this infection. Among patients with undiagnosed HIV infection, however, cryptococcosis remains a common presenting complication.

Fever and headache are the most common features of infection.[38] Although the neurological examination is typically nonfocal, a great variety of focal abnormalities may be seen in occasional patients. These include hemiparesis, blindness, deafness, and seizure, among others. Brain imaging studies are usually normal or demonstrate only widening of the sulci and ventricular enlargement.[39] The diagnosis is confirmed by examination of the CSF. India ink stain of the CSF is positive for yeast cells in more than 70% of cases,[38] and culture and cryptococcal antigen assays are positive in more than 90%.[38,40] The cellular response in the CSF is usually modest, with fewer than 20 mononuclear cells per cubic millimeter, although higher cell counts may be seen. The CSF protein level is elevated and the glucose level is depressed in the minority of cases.[38]

Cytomegalovirus encephalitis Histologic findings of cytomegalovirus (CMV) infection were present in the brains of 24% of patients in one early study.[41] A number of specific neurologic syndromes have been associated with CMV infection in AIDS. These include diffuse encephalitis;[42] a characteristic ventriculoencephalitis marked by cranial nerve palsies, gaze-directed nystagmus, and decreased CSF glucose concentration;[43] and a polyradiculomyelopathy.[44] CNS involvement by CMV is seen more among patients with CMV retinitis, which fortunately has become less common since the advent of effective antiretroviral therapy. The diagnosis of these syndromes, which tend to be rapidly progressive, is usually made on clinical grounds, although encephalitis may be associated with characteristic periventricular lesions seen on CT or MRI,[42] and CMV may be detected in the CSF by in situ hybridization.[45]

Herpes simplex encephalitis Herpes simplex virus is a common cause of encephalitis in normal hosts and has been described in association with HIV infection,[46] although it appears to be uncommon. Onset of symptoms is usually abrupt with fever and headache. Rapid progression to focal neurological abnormalities is the rule, and grand mal seizures are common. Occasionally these features are absent, however, and the presentation is one of a nonfocal, diffuse cerebritis. Computed tomography of the brain may demonstrate focal hemorrhagic areas, typically in the temporoparietal

regions, either unilaterally or bilaterally. Initial imaging studies may be normal on occasion, however, and should be repeated if the diagnosis is in doubt. Cutaneous lesions and other extraneural manifestations of herpes simplex infection are usually absent.

HIV encephalopathy Dementia caused by HIV infection may become evident before or after the onset of AIDS-defining opportunistic infections or malignancies but typically becomes evident in advanced, symptomatic stages of disease and immune system depression, particularly among patients not receiving effective antiretroviral therapy. In one early series, more than half of AIDS patients developed dementia within 2 months of their first symptom of HIV infection.[26] Symptoms of dementia may remain stable for long periods or suddenly worsen, particularly when the patient's condition deteriorates. The overall incidence of AIDS dementia was shown to be declining in one large series after the introduction of zidovudine.[22] Further reductions have been seen since the introduction of multidrug antiretroviral therapy.

Early symptoms of dementia may include forgetfulness, inability to concentrate, and confusion and may be accompanied by loss of balance, leg weakness, or difficulty with handwriting and pathologic reflexes.[47,48] Patients often display apathy and social withdrawal or changes in mood. When mild, findings of early AIDS dementia may be misinterpreted as or coexist with symptoms of depression or anxiety. Headaches or seizures occasionally occur.

AIDS dementia typically follows a course marked by steady deterioration over a relatively short period. In advanced cases psychomotor retardation, mutism, and incontinence may be prominent and the incidence of ataxia, motor weakness, and tremors increases.

The results of diagnostic studies are nonspecific. Approximately two thirds of patients are found to have a mildly elevated CSF protein level, and 20% have a mononuclear pleocytosis.[26] A substantial proportion of patients have immunoglobulin and oligoclonal bands in the CSF.[26] Viral cultures or tests for viral RNA or other antigen such as p24 may be positive. However, none of these findings, including detection of the virus, is diagnostic of AIDS dementia.

Computed tomography (CT) typically reveals findings of diffuse cerebral atrophy, including widened cortical sulci and, less commonly, enlargement of the ventricles. Atrophy, however, may also be present without clinical findings of dementia; it was reported in 33% of adult AIDS patients in several early series.[49] Diffuse white matter abnormalities with focal areas of demyelination may also be present.

Magnetic resonance imaging (MRI) has been demonstrated to be more sensitive than CT in evaluating patients with AIDS dementia.[50] In several series[49] MRI detected focal lesions that were missed on CT in 44% of cases.

Systemic disorders For many reasons HIV-infected patients are prone to systemic disorders that may cause nonfocal CNS abnormalities, particularly at advanced stages of immunodeficiency. Among these are the following:

1. Hypoxemia resulting from diffuse pulmonary infections or malignancies
2. Anemia resulting from bone marrow involvement by opportunistic infections as a side effect of therapy or as a direct result of HIV infection

3. Hyponatremia resulting from a variety of causes
4. Hypoglycemia complicating pentamidine therapy
5. Uremia complicating HIV nephropathy or caused by nephrotoxic agents such as pentamidine, foscarnet, or amphotericin B
6. Vitamin B12, folate, or thiamine deficiency
7. Hepatic encephalopathy complicating viral or alcoholic liver disease

Depression of serum sodium, if severe or sudden, can cause encephalopathy and seizures. Such hyponatremia may be associated with inappropriate secretion of antidiuretic hormone due to medications or pulmonary disorders. Congestive heart failure, which may be otherwise occult, and primary or secondary hypoadrenalism may also present as hyponatremia.

Medications commonly used in the treatment of HIV patients may cause alterations in mental status. Common examples include efavirenz and gabapentin. Efavirenz (Sustiva) has been associated with delusions, acute depression, inappropriate behavior, dizziness, abnormal dreams, and insomnia. Gabapentin (Neurontin), used in the treatment of peripheral neuropathy and seizure disorders, can cause somnolence, ataxia, nervousness, depression, and a variety of other central nervous symptoms. For more complete discussion of medication side effects, see Chapter 15.

c. Peripheral Nervous System

HIV-related neuropathy A variety of syndomes involving the peripheral nerves is commonly seen in association with HIV infection. An acute polyneuropathy or cranial nerve palsy may occur shortly after infection.[25] Peripheral neuropathy, often in the form of a demyelinating polyneuropathy or mononeuritis multiplex is seen in 20% of patients with symptomatic HIV infection.[25] In more advanced cases, particularly among patients with AIDS, the most common peripheral nervous system complication is a distal, predominantly sensory, neuropathy.

Medication-related neuropathy Several medications used to treat HIV infection, specifically didanosine (ddI), zalcitabine (ddC), and zidovudine (AZT), may cause peripheral neuropathy.

C. Ophthalmologic Disorders

The eye is a major site of involvement in HIV-related disorders. Opportunistic infections involving various structures within the eye as well as HIV-associated retinopathy and periocular disease such as Kaposi's sarcoma may all produce symptomatic disease. Fortunately ophthalmologic complications of HIV/AIDS have become significantly less common among patients receiving effective antiretroviral therapy. Nonetheless, periodic full ophthalmologic examinations should be performed routinely on all HIV-infected patients, and consultation should be sought promptly for any patient with visual complaints.

1. Opportunistic Infections

a. Cytomegalovirus (CMV) Retinitis

Historically, CMV retinitis has been the most commonly diagnosed opportunistic infection of the eye in AIDS. It was seen in 28% of patients in one large series prior to the advent of highly active antiretroviral therapy (HAART).[51] Without specific therapy, progression to blindness is common and vision may be threatened at the time the infection is first detected. Bilateral involvement was seen in 35 and 42% of patients in published series.[52,53] Retinal detachment is a common complication.[52] Progression of CMV retinitis, despite treatment, is most common with severe immunodeficiency and high HIV viral loads. Over the past four years, coincident with the use of HAART, the incidence of CMV retinitis has declined sharply and newly diagnosed cases have become a rarity in many centers.[54,55]

b. Miscellaneous Opportunistic Infections

A variety of other ocular infections has been reported association with HIV infection. Among these are syphilitic optic neuritis,[56,57] choroiditis and optic atrophy associated with cryptococcal meningitis[58–60] caused either by direct invasion of the optic nerve or by increased intracranial pressure, endophthalmitis caused by *Mycobacterium avium-intracellulare* complex (MAC), keratitis caused by varicella zoster virus,[61] and choroiditis caused by *P. carinii*.[62]

2. Kaposi's Sarcoma

Of 100 male homosexuals with Kaposi's sarcoma, 20 were found to have ocular involvement in one series.[63] Lesions were present on the eyelid in 16 patients and on the conjunctiva in 7. Subcutaneous lesions may become evident as spontaneous swelling around the eye or involving the eyelids in the absence of characteristic skin lesions.

3. Inflammation of the Eye Associated with Immune Recovery

As noted previously, the incidence of CMV retinitis has declined significantly since the advent of highly active antiretroviral therapy in the mid-1990s. However, intraocular inflammation, including anterior uveitis, vitritis, cataract formation, cystoid macular edema, and edema of the optic disk, has been described in patients with prior CMV retinitis who manifested immune recovery on antiretroviral therapy.[64]

D. Disorders of the Oral Cavity

The oral cavity may be involved by a variety of opportunistic infections, as well as by Kaposi's sarcoma and lymphoma (see Table 4.4). In addition, periodontal disease is more common in the setting of HIV infection. For this reason, it is recommended that HIV-infected patients have regular screens for intraoral and dental pathology.

TABLE 4.4
Major Oral Manifestations of HIV Infection

Disorder	Frequency	Reference
Gingivitis/Periodontitis	50%	67
Candidiasis	90% AIDS	65
Xerostomia	10% AIDS	65
Hairy leukoplakia	7% AIDS	
Aphthous ulcers	3%	68

1. Infections

a. Candidiasis

Oral candidiasis, which most often appears as white plaques on the buccal mucosa, pharynx, or tongue or as angular cheilitis may be seen at all stages of HIV infection but is most common and most severe among patients with advanced degrees of cellular immune dysfunction. In such individuals, infection is also most likely to extend into the esophagous and create swallowing and nutritional problems. Candidiasis resistant to oral azole antifungal agents has become increasingly common in recent years and remains a major source of morbidity among patients at advanced stages of disease.

b. Herpes Simplex Infection

In one early series, 10% of AIDS patients were found to have oral herpes simplex infection.[65] Lesions are typically painful, progressive ulcerations but may appear as fissures in some cases.

c. Hairy Leukoplakia

Hairy leukoplakia, white lesions usually found on the sides of the tongue, is commonly seen at all stages of HIV infection, particularly among homosexual men. The appearance of hairy leukoplakia may be predictive of clinical progression. Evidence of an association with Epstein-Barr virus has been reported.[66]

d. Gingivitis and Periodontal Disease

Necrotizing ulcerative periodontitis occurs in as many as half of patients with symptomatic HIV infection.[67] Severe gingivitis even in the absence of dental plaque is also frequently encountered.

e. Miscellaneous Infections

Oral lesions, usually in the form of ulcerations, may be seen in syphilis, tuberculosis, histoplasmosis, cryptococcosis, and anaerobic infection.

2. Malignancies

a. Kaposi's Sarcoma

Kaposi's sarcoma (KS) historically has been the most common oral malignancy in AIDS, although effective antiretroviral therapy has led to a decline in incidence of KS in recent years. Lesions, which may be mucosal or submucosal or both, typically

appear on the palate, gingiva, or buccal mucosa. Oral Kaposi's sarcoma may occur in isolation or with widespread skin or visceral involvement.

b. Lymphoma

AIDS-related lymphoma may become evident as nodular or ulcerating oral lesions.

3. Aphthous Stomatitis

Oral aphthous ulcers occurred in 3% of HIV-infected patients in one large series[68] and account for the majority of nonhealing mouth ulcers.[69]

4. Miscellaneous Disorders

Xerostomia, exfoliative cheilitis, and nonspecific ulcerations were seen in 10%, 9%, and 3%, respectively, in one series.[65]

E. Pulmonary Disorders

1. Opportunistic Infections

a. Pneumocystis Carinii Pneumonia (PCP)

PCP, one of the first infections described in association with AIDS, remains a common initial opportunistic infection in the United States and other developed countries, although its incidence has declined dramatically among HIV-infected individuals in medical care and receiving specific prophylaxis. PCP is ultimately diagnosed in 80% of patients who do not receive prophylaxis.[70] Almost all cases occur among patients with CD4+ lymphocyte counts below 200 cells/mm^3.[71]

The clinical manifestations of PCP are nonspecific. The onset of symptoms may be insidious over days to weeks or fulminant. Most patients complain of fever, cough, and dyspnea and have a subacute course. Chills, sputum production, and chest pain are less common. In rare cases, fever or exertional dyspnea may be the only manifestation of disease. The clinical features may be modified and rendered less severe and more slowly progressive in patients receiving prophylaxis. In particular, upper lobe infiltrates and cystic changes are seen more frequently in patients receiving aerosolized pentamidine.[72]

Bilateral infiltrates are seen on chest radiographs in almost all cases, although unilateral infiltrates, nodules, and cavities occasionally occur. Pleural involvement is extremely unusual (see Table 4.5). In some cases the chest radiograph may be completely normal.

PCP is often associated with diffuse, bilateral pulmonary uptake on gallium scanning, which may be apparent before the appearance of radiographic abnormalities. It should be recognized, however, that radiographic and gallium scan findings associated with PCP are nonspecific. Other AIDS-related processes, particularly Kaposi's sarcoma, tuberculosis, histoplasmosis, strongyloidosis, toxoplasmosis, cryptococcosis, cytomegaloviral infection, and lymphocytic interstitial pneumonitis, as well as bacterial pneumonia, may produce identical radiographic patterns. For this reason histologic or cytologic confirmation of the diagnosis of PCP is necessary in most cases and desirable in all. Examination of induced sputum or specimens obtained at bronchoscopy is almost always effective in confirming the diagnosis.

TABLE 4.5
Radiographic Patterns in Common HIV-Related Pulmonary Disorders

	Radiographic Patterns	
Disorder	**Typical**	**Unusual**
Pneumocystis carinii pneumonia	Diffuse, bilateral infiltrates, pleural involvement rare; bullae may be present	Nodules, focal infiltrate, X-ray may be normal in mild cases
Kaposi's sarcoma	Diffuse nodular infiltrates, pleural involvement common	
Tuberculosis	Apical, upper lobe infiltrates, cavities, pleural effusion	Lower lobe infiltrate (30%), diffuse infiltrates mimicking PCP
Bacterial pneumonia	Lobar infiltrate, pleural effusion common	Diffuse, bilaterail infiltrates mimicking PCP

Occasionally, pneumothorax may complicate PCP. Patients presenting with unexplained pneumothorax who are at risk for PCP should be considered strongly for empiric treatment.[73] Pneumothorax occurring during treatment for PCP confers a worse prognosis. Individuals with recurrent or bilateral pneumothoraces should be evaluated for thoracoscopy, pleurodesis, or surgical repair.

b. Cryptococcosis

The central nervous system (CNS) is the most common site of involvement by *Cryptococcus neoformans* in AIDS. However, respiratory infection may occur with or without concomitant CNS infection. A variety of radiographic patterns have been associated with pulmonary cryptococcosis. These include interstitial infiltrates and hilar lymphadenopathy, either alone or in combination.[74] Empyema[75] and the adult respiratory distress syndrome[76] have also been described.

Cryptococcal infection may coexist with PCP and other respiratory disorders. The diagnosis is made by lung biopsy or alveolar lavage. Blood cultures and serum cryptococcal antigen assay may also aid in the diagnosis.

c. Histoplasmosis

Disseminated infection with the fungus *Histoplasma capsulatum* is occasionally seen in AIDS patients from endemic areas such as the midwestern United States and Central and South America. Pulmonary involvement with diffuse, bilateral infiltrates was seen in approximately 40% of cases in one series.[77] Hilar lymph node enlargement and extrapulmonary involvement, particularly nodular skin lesions or hepatosplenomegaly, may be clues to the diagnosis of pulmonary histoplasmosis. The diagnosis is usually confirmed by lung biopsy or bronchoalveolar lavage.

d. Coccidioidomycosis

Progressive pulmonary infection caused by *Coccidioides immitis* occurs with increased frequency among HIV-infected patients living in endemic areas of the American Southwest.

e. Cytomegalovirus Infection

Cytomegalovirus (CMV) infection is frequently found at postmortem examination[78] in the lungs of patients who die with AIDS. In clinical series, however, isolated CMV pneumonia is rare, although evidence of CMV infection is often found in association with PCP or other opportunistic respiratory infections.

f. Toxoplasmosis

Pulmonary toxoplasmosis may mimic PCP on radiographic examination or produce focal infiltrates or nodular densities. Lactate dehydrogenase levels, often elevated in PCP, may be extremely high in pulmonary toxoplasmosis.

g. Bacterial Pneumonia

Patients with HIV infection are at high risk for infection with *Streptococcus pneumoniae*[79] and *Hemophilus influenzae*.[80] Community-acquired pneumonia caused by *Pseudomonas aeruginosa* has been described in patients who had recently been hospitalized.[81] Clinical signs and symptoms and radiographic findings may be atypical, particularly among patients at advanced stages of immune deficiency. Diffuse lung involvement and fulminant progression are more common than in non-HIV-infected patients.

h. Mycobacterial Infection

Tuberculosis Infection with *Mycobacterium tuberculosis* is very common among HIV-infected patients, at all stages of immune deficiency. The HIV/AIDS epidemic accounted for much of the sudden increase in tuberculosis cases seen in U.S. urban centers in the mid-1980s. The clinical and radiographic manifestations may be atypical in the setting of HIV infection. Lower lobe infiltrates and mediastinal lymph node involvement are common.[82]

Atypical mycobacterial infection Atypical mycobacteria, particularly *Mycobacterium avium* complex (MAC), are frequently isolated from respiratory secretions from HIV-infected patients, especially those at advanced stages of immune deficiency. Most often, no associated respiratory syndrome or radiographic abnormalities are seen in these patients. On occasion, however, MAC infection may cause lung nodules, focal infiltrates, or cavitary lesions similar to those seen in tuberculosis.

2. Malignancies

a. Kaposi's Sarcoma

Bronchopulmonary involvement with Kaposi's sarcoma typically becomes evident as a subacute illness characterized by dyspnea and dry cough occasionally accompanied by hemoptysis or pleuritic chest pain. Fever may be present. Airway involvement may result in wheezing.[83] Clinical progression may be gradual or fulminant, and respiratory failure may occur. Radiographic features are nonspecific and may mimic other disorders, but the presence of diffuse nodular infiltrates, hilar lymphadenopathy, and pleural disease may suggest the diagnosis. In some cases, however, findings may closely resemble those of PCP or other AIDS-related disorders. In contrast to PCP, however, the gallium scan is usually negative in pulmonary Kaposi's

sarcoma, and lactate dehydrogenase levels are usually normal or only slightly elevated. Cutaneous Kaposi's sarcoma lesions are usually present but may not be, making the etiology of the lung disease particularly obscure. The diagnosis may be confirmed by lung biopsy, although autopsy data indicate that the sensitivity of this procedure is limited.[83] Visualization of characteristic red-purple lesions in the large airways by bronchoscopy may allow a presumptive diagnosis and therapy, even without histologic confirmation.

b. Lymphoma

Lymphoma is the second most common AIDS-associated malignancy after Kaposi's sarcoma. Although extranodal involvement is seen frequently in AIDS-associated non-Hodgkin's lymphoma (occurring in 87% of cases in one large series),[84] the lungs are a relatively unusual site. The reported incidence of pulmonary involvement varies from 0 to 25%.[85] Clinical features are nonspecific, and respiratory symptoms are not always present. Chest radiographs may demonstrate abnormalities of the thoracic lymph nodes, lung parenchyma, or pleura. The diagnosis is confirmed by histologic examination.

F. Cardiovascular Disorders

Cardiovascular manifestations of HIV infection, resulting from both the disease and its treatment, have been increasingly recognized in recent years. Although these disorders have received relatively little attention, it has been estimated that 5000 patients per year have heart disease as a result of HIV infection itself or of related disorders. The incidence of significant coronary disease resulting from antiretroviral therapy is not yet fully clear. The aging of the HIV/AIDS population, however, has been accompanied by a growing incidence of symptomatic heart disease associated with traditional risk factors such as hypertension, diabetes, hypercholesterolemia, and tobacco use (see Chapter 13).

Opportunistic infections and malignancies may involve the heart, but in many (perhaps most) patients with symptomatic heart disease, the cause is obscure. Substantial evidence exists to indicate that HIV itself may infect heart tissue and cause clinically significant disease. In one large series 5% of AIDS patients had symptoms of heart disease, usually caused by opportunistic infection or malignancy.[86] Male homosexuals and intravenous drug users were equally affected. Myocarditis and pericardial effusion are the most commonly reported cardiac manifestations.[87] Echocardiographic abnormalities are commonly seen in advanced HIV infection. Pericardial effusions and ventricular dysfunction were each noted in 29% of hospitalized AIDS patients[88] and in 26% and 30% of AIDS patients overall[89] in two published series.

1. Myocardial Disease

Disorders of the myocardium may be related to opportunistic infections, malignancies, or coronary artery disease, or they may appear without definable cause.

A large number of opportunistic pathogens have been associated, in rare instances, with myocarditis in HIV-infected patients. Among these are *P. carinii, M. tuberculosis,*

M. avium-intracellulare complex, *Cryptococcus neoformans, Aspergillus fumigatus, Candida albicans, Histoplasma capsulatum, Coccioides immitis, Toxoplasma gondii*, herpes simplex, and cytomegalovirus.[90,91] However, myocarditis is not a common manifestation of infection with any of these organisms. With some, myocardial involvement has been reported only in the setting of widespread multisystem infection and has often been first recognized at postmortem examination. The clinical significance of myocardial infection in many such cases is unclear.

Idiopathic cardiomyopathy, possibly directly related to HIV infection, was detected in 44 (15%) of 296 patients in one prospective study.[92] Dilated cardiomyopathy was associated with advanced disease and low CD4+ cell counts and was predictive of poor survival, although spontaneous improvement in heart function has also been described.[93]

2. Pericardial Disease

Pericardial disease is common in patients with advanced HIV infection, sometimes coexisting with cardiomyopathy. Significant but clinically silent pericardial effusions were detected by echocardiography in 7 (26%) of 27 male homosexuals with AIDS.[89]

Pericardial involvement may complicate tuberculosis, atypical mycobacterial infection, cryptococcosis, nocardiosis, and infection with herpes simplex virus or cytomegalovirus.

Effusions may be large enough to result in hemodynamic compromise, and both pericarditis and cardiomyopathy should be considered in the evaluation of dyspnea in patients with HIV infection.

3. Endocarditis

Nonbacterial thrombotic endocarditis, a disorder of unknown origin that may be associated with a variety of wasting diseases, may be seen in association with HIV infection. The condition may be associated with systemic emboli.

HIV-infected injection drug users who continue to use drugs remain at risk for infective endocarditis, which is more likely to be caused by conventional bacteria, particularly *Staphylococcus aureus* that by opportunistic pathogens otherwise associated with AIDS.

G. Gastrointestinal and Hepatic Disorders

1. Diarrheal Illness

Diarrhea has been recognized as a common manifestation of HIV infection and AIDS since the earliest days of the epidemic. In developing countries, massive diarrhea with profound wasting and ultimate death in association with HIV infection has been seen in association with many infectious agents and as a nonspecific manifestation of immune deficiency. In the United States and other developed countries, a variety of infectious agents, most notably protozoal parasites, has caused great morbidity among patients, especially those at advanced stages of disease. Intestinal involvement by the AIDS-related malignancies, Kaposi's sarcoma, and

non-Hodgkin's lymphoma may also cause diarrhea and other gastrointestinal complaints. More recently diarrhea as a side effect of therapy, particularly with protease inhibitors (see Chapters 10, 11, 15), and colitis due to *Clostridium difficile* toxin in association with an array of antibiotics have achieved great importance. In many instances, however, a specific cause of diarrhea cannot be identified and the effect of HIV on the bowel mucosa (so-called AIDS enteropathy) or the immune deficiency itself is presumed to be causative. Overall, the incidence of diarrhea associated with identified pathogens has fallen dramatically among patients receiving antiretroviral therapy.[94] Specific agents associated with diarrhea are briefly reviewed here. Approaches to therapy are discussed in subsequent chapters.

a. Bacteria

Agents that frequently produce diarrheal illness in normal hosts, *Salmonella, Shigella*, and *Campylobacter*, are commonly encountered in the setting of HIV infection and may produce more refractory symptoms, prone to relapse with discontinuation of therapy. *Clostridium difficile* has become a common cause of diarrhea among patients with advanced degrees of immune deficiency who receive antibiotics, especially those who have been recently hospitalized. In a recent series, up to 6.4% of patients discharged from this hospital had *C. difficile*-related diarrhea. Clindamycin use, penicillin use, and CD4+ cell count less than 50 per mm^3 were found to be risk factors.[95]

b. Parasites

Several protozoal parasites which had not been recognized as human pathogens prior to the AIDS epidemic are frequently identified in the stools of patients with protracted diarrhea. *Cryptosporidium parvum*, the most common of these, is seen almost exclusively among patients with less than 150 CD4+ cells per mm^3 and frequently responds to antiretroviral therapy, particularly if there is significant immune reconstitution.[96] The diagnosis is made on examination of stool stained with the modified acid-fast technique. Other similar parasites that may be seen include *Isospora belli*, microsporidia, and cyclospora. Amebiasis and giardiasis may also cause diarrhea but are encountered less frequently than the novel parasites mentioned above.

c. Mycobacteria

Mycobacteria tuberculosis may cause infection of the small bowel which may manifest as persistent diarrhea without other evidence of tuberculosis. *Mycobacterium avium* complex (MAC) may be found in the bowel wall among patients with symptoms of chronic wasting and diarrhea.

d. Viruses

The enteric viruses that are frequently associated with diarrhea in normal hosts, including rotaviruses, caliciviruses, and others, may be seen in association with HIV infection, but do not appear to cause protracted illness.[97] For this reason and because no specific therapy is available for these agents, they are not usually identified outside of a research setting. Cytomegalovirus (CMV) appears to be the cause of diarrhea in as many as one quarter of AIDS patients, especially those with the most advanced degrees of immune deficiency. This usually represents infection of the colon and

typically presents with small-volume, frequent bowel movements, often containing blood or mucous, and is associated with fever and other systemic signs of infection. Specific antiviral therapy with agents active against CMV is often effective,[98] but antiretroviral therapy, when effective, often leads to resolution of symptoms.

e. Medications

Most, if not all, of the antiretroviral agents currently in use may cause diarrhea. The protease inhibitors, particularly ritonavir and nelfinavir and, less commonly, didanosine, zidovudine, and delavirdine are all associated with diarrhea, which may make them intolerable.

2. Esophagitis

Esophageal involvement with candidiasis, cytomegaloviral, or herpesvirus infection or by lymphoma or Kaposi's sarcoma has been described in varying frequency in relation to HIV infection. Candida esophagitis is a common initial opportunistic infection.

Diagnosis of esophagitis can often be made on clinical grounds when symptoms of dysphagia and/or odynophagia are present. Oropharyngeal thrush is suggestive of candida esophagitis in the presence of these symptoms. Definitive diagnosis is usually made by endoscopy with biopsy of the esophageal mucosa if necessary.

3. Pancreatic Disorders

Several medications commonly used in the treatment of HIV infection and its complications may cause pancreatitis. Most common among these are didanosine, pentamidine, zalcitabine, and ritonavir.[99] Autopsy data indicate that the pancreas may be involved by a number of opportunistic infections, including mycobacteriosis, toxoplasmosis, pneumocystosis, and a variety of fungi, as well as by HIV itself.[100] Pancreatitis resulting from alcohol use, biliary tract disease, trauma, and other medications may also be seen.

4. Biliary Tract Disease

Several AIDS-related disorders may be associated with biliary obstruction. Both cryptosporidiosis and cytomegaloviral (CMV) infection may be associated with stenosis of the common bile duct or sclerosing cholangitis[101] or both. CMV has also been reported in association with acalculous cholecystitis.[102] Biliary involvment in HIV infection produces typical symptoms of abdominal pain, nausea, and vomiting. Obstruction may predispose to secondary bacterial infection.

5. Viral Hepatitis

Because of common routes of transmission with HIV, both hepatitis B and hepatitis C are common among HIV-infected individuals. Although not opportunistic pathogens, both hepatitis B virus (HBV) and hepatitis C virus (HCV) can influence the clinical course of patients with HIV infection. As antiretroviral therapy has improved the prognosis of HIV infection, individuals co-infected with HBV and/or HCV may now survive to progress, in larger numbers, to chronic liver disease.[103] This is true

especially among individuals who acquired HIV infection by injection drug use, because of the high rates of both HBV and HCV infection in this population.[104]

a. Hepatitis B

More than half of HIV-infected individuals in the United States have serologic evidence of exposure to HBV. Co-infected individuals (HIV and HBV) are more likely to reactivate acute hepatitis and have a three-fold higher risk of progression to chronic hepatitis B.[105,106] This may represent a relative inability to clear HBV because of the immune deficiency caused by HIV. HBV levels are higher in co-infected individuals than in those who are HBV positive and HIV negative.[107]

b. Hepatitis C

Approximately 9% of HIV-infected individuals in the United States are co-infected with hepatitis C virus (HCV),[108] including as many as 90% of those with a history of injection drug use.[109] Clinical illness occurs in less than half of infected individuals and follows exposure to the virus with a mean incubation period of approximately 50 days. Symptoms are typically mild and nonspecific in many (anorexia, malaise, abdominal pain). Jaundice occurs on only 20 to 30%[110] and elevations of ALT are common. Antibody appears after an average of 8 or 9 weeks but may take many months in some individuals. Acute hepatic failure is extremely unusual.

Despite the generally mild or asymptomatic nature of acute HCV infection, the majority of patients (75 to 85%) develop chronic infection.[111] The majority of chronically infected patients manifest elevated ALT levels, often intermittently, but 30 to 40% have no abnormalities of liver function tests.[112] Thus, these tests cannot be used to exclude active infection. Clinical illness develops insidiously and occurs in approximately 10 to 25% of patients, with cirrhosis complicating 10 to 20% of cases and hepatocellular carcinoma 1 to 5%.[113,114]

Co-infection with HIV appears to accelerate the natural history of HCV infection in some patients.[115] It is recommended that all HIV-infected patients be tested for HCV antibody. Treatment guidelines for hepatitis C are discussed in Chapter 8.

6. Gastrointestinal Malignancies

a. Rectal Carcinoma

The risk of anal squamous cell cancer is four- to eight-fold higher among HIV-infected men, particularly those with a history of homosexuality.[116]

b. Lymphoma

The gastrointestinal tract was the most common (24%) extranodal site of involvement by non-Hodgkin's lymphoma in AIDS patients in one large series. Any segment of the bowel may be involved. Symptoms are typically nonspecific but may include bleeding, perforation, or intestinal obstruction.

7. Malabsorption

Malabsorption may be seen in association with HIV infection. Several infections, particularly cryptosporidiosis and isosporiasis, may cause protracted periods of malabsorption. Lymphoma involving the small bowel is a rare cause.

H. Renal Disorders

Individuals infected with HIV are prone to a variety of renal disorders. The most common of these is termed HIV-associated nephropathy (HIVAN). HIVAN is seen disproportionately in African-American males and injection drug users. It typically presents with proteinuria and progressive renal failure. Kidneys appear normal-sized or enlarged on imaging studies and progression to endstage disease is the rule.

Several reports have suggested that HIVAN can be reversed, partially at least, by antiretroviral therapy.[117,118] Corticosteroids[119] and angiotensin converting enzyme inhibitors may produce temporary improvement.

Opportunistic pathogens, particularly cytomegalovirus, mycobacteria,[78] *Cryptococcus neoformans*, and *Histoplasma capsulatum*[120] and a number of medications commonly used in the treatment of HIV-infected patients may be nephrotoxic in some individuals. These include pentamidine, amphotericin B, foscarnet, and trimethoprim/sulfamethoxazole. Heroin nephropathy may be difficult to distinguish from renal disorders of other etiologies in active users, and renal manifestations of intercurrent infections such as bacterial endocarditis or other disorders may be present.

I. Endocrinological Disorders

1. Gonadal Disorders

In one autopsy series,[121] 39% of male patients were found to have testicular involvement by opportunistic infections. The most common pathogens were CMV, mycobacteria, and toxoplasma. Functional hypogonadism was documented in 50% of male AIDS patients in one series,[122] and significant depression of circulating testosterone levels was seen with the degree of depression correlating with overall clinical status.

2. Adrenal Disorders

Adrenal cells can be infected with HIV *in vitro*,[123] and the adrenal gland may be a site of involvement of AIDS-related infections and malignancies, including cryptococcosis, mycobacterial infection, and Kaposi's sarcoma.[124] Although functional hypoadrenalism was found in 20% of patients in an early clinical study,[125] more recent data suggest that it is far less common.[126] Symptoms seen in patients with HIV infection are similar to those seen in other settings and may include fatigue, anorexia, weight loss, nausea, abdominal pain, diarrhea, and darkening of the skin.[127] A selective mineralocorticoid deficiency associated with weakness and orthostatic hypotension has been described.[128] Because the symptoms of adrenal insufficiency may be confused with those of advanced HIV infection, the clinician should be particularly aware of this reversible disorder. Persistent hyponatremia or hyperkalemia and pronounced orthostatic hypotension should be considered possible indications for adrenal function testing. It has been noted that hyperkalemia may not be present in some patients with adrenal insufficiency and diarrhea.[129]

TABLE 4.6
Musculoskeletal Manifestations of HIV-1 Infection

Disorder	Reported Frequency: All Stages of HIV Infection
Arthralgia	35%
Arthritis	12%
Reiter's syndrome	10%
Painful articular syndrome	10%
Psoriatic arthritis	2%
Polymyositis	2%

Adapted from Berman, A. et al., *Am J Med*, 85, 59, 1988.

J. Musculoskeletal Disorders

Muscoloskeletal complaints are common during the course of HIV infection and may arise at any stage of the disease (see Table 4.6). In some cases these symptoms are among the first experienced by the patient. It has been pointed out that the initial manifestations of disease in some cases are reminiscent of those of systemic lupus erythematosis[130] and may include arthralgias, cytopenias, butterfly rash, proteinuria, and abnormal urinary sediment.

In one early survey of HIV-positive patients, 72% were found to have rheumatologic manifestations,[131] including arthralgias (34.7%), arthritis (11.9%), Reiter's syndrome (9.9%), painful articular syndrome (9.9%), psoriatic arthritis (1.9%), and polymyositis (1.9%). Arthralgias, which may be mild or severe, most typically involve the knees, shoulders, elbows, or ankles, although the spine or small joints of the hands may also be involved. Features suggestive of sicca complex[132] or Sjogren's syndrome[133] may also occur. The causes of these various conditions are unknown. HIV may play a direct role in the pathogenesis of some of these disorders; others, such as Reiter's syndrome, may sometimes represent reactive states reflecting infection with other organisms commonly seen in HIV-infected individuals.

Myalgias and arthralgias are often a feature of the acute syndrome associated with HIV infection at the time of seroconversion (see Chapter 2). Polymyositis has also been associated with HIV infection, as has a variety of autoimmune disorders including thrombocytopenia, circulating rheumatoid factor, and anticardiolipin antibodies,[134] as well as autoantibodies such as antinuclear, antilymphocyte, and antigranulocyte autoantibodies.[135]

1. Reiter's Syndrome

Reiter's syndrome typically affects young men and appears to be more common in HIV-infected individuals than in the general population. Nearly 10% of patients in various stages of HIV infection had findings consistent with Reiter's syndrome in one prospective series,[131] although other series have indicated a prevalence of less in 1%.[136] In contrast, the annual incidence of Reiter's syndrome was only 0.0035% among a general population of men under 50 years of age.[137]

Several possible reasons for the apparent association between Reiter's syndrome and HIV infection have been proposed.[135] Co-infection with organisms such as *Chlamydia* species, known to precipitate Reiter's syndrome, may account for some cases, particularly among patients who test positive for the human lymphocyte antigen B27 (HLA-B27). Bowel infections caused by organisms commonly seen in HIV-infected patients but not previously linked to Reiter's syndrome, such as *Cryptosporidium* organisms or other pathogens not yet characterized, may prove to be important. The stimulation of the immune response that occurs with the onset of Reiter's syndrome may trigger the progression of a preexisting HIV infection. Conversely, the immunodeficiency produced by HIV infection may lead to the development of Reiter's syndrome by an unknown mechanism.

Winchester and colleagues[138] described 13 HIV-infected patients with complete or incomplete Reiter's syndrome that became evident as arthritis in all cases and as urethritis and conjunctivitis in the majority. Several patients in this series, as well as ones in a comparable series by Berman and colleagues,[131] had such typical features as keratosis blennorrhagia, stomatitis, or balanitis. Of 12 patients, 9 tested positive for HLA-B27.

The arthritis in three patients tended to be severe, most often involving the knees and shoulders. Bone erosions were documented in seven cases. Three patients in one series[138] were found to be infected with organisms known to precipitate Reiter's syndrome (*Shigella flexneri* in two patients; *Campylobacter fetus* in one), and several other patients had concomitant culture-negative diarrhea or urethritis.

Treatment of HIV-related Reiter's syndrome with nonsteroidal anti-inflammatory agents or corticosteroids is often unsuccessful. Progressive Kaposi's sarcoma and overall clinical deterioration occurred in two patients following treatment of Reiter's syndrome with methotrexate.[138]

2. Psoriatic Arthritis

Papulosquamous skin rashes such as seborrheic dermatitis and psoriasis appear to occur more often in HIV-infected patients. In one series,[131] 5% of patients had psoriasis and 2% had findings compatible with psoriatic arthritis. Duvic and colleagues[139] described 13 HIV-infected patients with psoriasis, including 9 in whom skin lesions developed after the onset of HIV-related symptoms. Three of these patients had coexistent Reiter's-like symptoms with arthritis, urethritis, and conjunctivitis. Psoriasis-associated arthritis may be severe and deforming.

As with Reiter's syndrome, the apparent relationship between HIV and psoriasis and its associated arthritis in some individuals is not well understood. No definite association has been established in these patients between HLA-B27 expression and psoriasis-associated arthritis. In fact, in one series,[131] two patients with severe arthritis were HLA-B27 negative. Nonsteroidal anti-inflammatory drugs, sulfasalazine, or gold therapy[140] may be effective in treating psoriatic arthritis. For refractory cases, methotrexate may be considered, although, as noted above, such therapy may result in clinical progression of HIV infection.

3. HIV-Associated Arthritis

A form of seronegative arthritis not associated with Reiter's syndrome or psoriasis has also been described in some HIV-infected patients.[135] Rynes and colleagues[141] described four patients with oligoarticular arthritis involving the lower extremities. Three of these patients met criteria for the diagnosis of AIDS. In all four cases the arthritis was severe and debilitating, although synovial fluid examinations demonstrated little or no inflammation. No infections known to precipitate reactive arthritis were documented in any of the patients. Three of the four were HLA-B27 positive.

4. Polymyositis

Polymyositis is the most frequent muscle disorder seen in association with HIV infection. In one large prospective study,[131] 2% of patients were found to have polymyositis on initial evaluation. As with other HIV-related musculoskeletal syndromes, polymyositis may become evident at various stages of HIV infection and may in fact be the initial manifestation.[137]

Polymyositis typically becomes evident with proximal muscle weakness, muscle wasting, and elevated creatine kinase levels, often to more than five times normal.[135] Electromyographic studies demonstrate abnormalities characteristic of myopathy. In reported cases in which histologic information is available, inflammatory infiltrates of the involved muscles have usually been demonstrated.[135]

5. Sjogren's Syndrome and Sicca Complex

Sicca complex (xerostomia or xerophthalmia) may be seen in association with HIV infection with and without typical features of Sjogren's syndrome. Couderc and colleagues[132] described five HIV-positive patients with progressive generalized lymphadenopathy and sicca complex with lymphocytic infiltration of salivary glands. Lymphocytic infiltration of one or more extrasalivary sites, including the lungs, liver, kidneys, or bone marrow, was also demonstrated in each of these patients, all of whom had serologic evidence of infection with Epstein-Barr virus. In contrast to most cases of classic Sjogren's syndrome, none of the patients was found to have antinuclear antibodies, rheumatoid factor, or other autoantibodies. The relationship among sicca complex, Sjogren's syndrome, and HIV infection remains uncertain, however.

6. Osteoporosis

Osteoporosis may be seen in association with protease inhibitor therapy. Individuals with this condition may develop pathologic fractures.

K. Hematological Disorders

A remarkable array of hematological disorders may be seen in HIV-infected individuals. These include anemia, leukopenia, thrombocytopenia, coagulopathy, myelofibrosis, hemophagocytosis, plasma cell hyperplasia, and lymphoma.

Some disorders appear to result from the direct effects of HIV on hematopoietic precursor cells; others reflect the production of autoantibodies and perhaps other

autoimmune mechanisms. Depletion of CD4+ lymphocytes is, of course, characteristic of HIV infection and at the heart of the immunologic disorders associated with AIDS. Other cell lines, including erythrocytes, granulocytes, and monocytes, may also be directly or indirectly affected by HIV. Refractory anemia, leukopenia, and thrombocytopenia are common in advanced disease. Abnormalities of the peripheral blood smear may include anisocytosis, poikilocytosis, and rouleaux formation. Bone marrow examination, particularly in advanced disease, may reveal dyserythropoiesis, erythroid hypoplasia, megaloblastosis, reticuloendothelial iron block, and a variety of other abnormalities.

Several opportunistic infections associated with AIDS, most notably mycobacteriosis, may involve the bone marrow and lymphoid. Chronic parvovirus infection involving marrow erythroid precursors may occur. A number of therapeutic agents commonly used in HIV infection, especially zidovudine, ganciclovir, acyclovir, and antifolate compounds often cause significant cytopenias due to bone marrow depression.

In rare cases hematological manifestations, particularly autoimmune thrombocytopenia, dominate the clinical picture. In patients at advanced stages of immunodeficiency, several disorders, particularly drug toxic effects and involvement of the marrow by opportunistic infections, may coexist.

1. Autoimmune Thrombocytopenia

Thrombocytopenia is common in HIV-infected individuals. It may be present at any stage of the disease[142] and does not have clear prognostic significance.[143] Mechanisms include both elaboration of antiplatelet antibodies[144] and deposition of immune complexes on the platelet surface.

If possible, the diagnosis of autoimmune thrombocytopenia should be made only after bone marrow examination confirms that platelet production is not depressed. Involvement of the marrow by opportunistic infections or malignancies, or side effects of several commonly used medications, especially ganciclovir, AZT, and antifolate agents such as trimethoprim-sulfamethoxazole or sulfadiazine, may result in thrombocytopenia. Other causes of peripheral consumption of platelets, including hypersplenism, disseminated intravascular coagulation, and drug-induced autoimmune thrombocytopenia should be excluded.

2. Other Coagulation Disorders

Patients with HIV infection frequently have anticardiolipin antibodies.[134] Clinically significant thrombosis and thromboembolism occur in some of these individuals.[145] Lupus-like and heparin-like anticoagulants have also been demonstrated in association with HIV infection[146] as have abnormalities of fibrin polymerization possibly related to high levels of gamma globulins characteristic of HIV infection.

3. Lymphoproliferative Disorders

a. Lymphoma

The association between HIV infection and lymphoma was recognized in the early days of the HIV/AIDS epidemic, and non-Hodgkins lymphoma (NHL) was considered an AIDS-defining condition by the mid-1980s. It was recognized that most

AIDS-related lymphomas were of B cell origin and frequently presented in extranodal sites, especially the central nervous system and gastrointestinal tract.[147,148] It was also clear that lymphoma in the setting of HIV infection carried a particularly poor prognosis and pursued an aggressive course, especially in the setting of advanced immune deficiency.

Over the past 15 years, knowledge of AIDS-related lymphomas has increased greatly.[149] It is now recognized that they represent a heterogeneous group of disorders. The most common histological patterns are non-cleaved cell lymphoma, including Burkitt's lymphoma, and diffuse large cell lymphoma.[150] Often, several types of histological features are seen within the same lymphoma.[151] Further, it appears that Hodgkin's disease is also seen with increased frequency in the setting of HIV infection.[152] Thirty percent of AIDS-related B cell lymphomas have evidence of Epstein-Barr virus (EBV) infection[153] and prior EBV may be a risk factor for the development of lymphoma,[154] although the exact link between EBV infection and HIV-related lymphoma remains controversial. Human herpesvirus 8 (HHV-8) has been associated with both Kaposi's sarcoma and a peculiar type of NHL affecting serous body cavities such as the pleural, peritoneal, and pericardial spaces.[155]

The clinical presentation of NHL in the setting of HIV infection is remarkably variable, but widespread extranodal disease is common. Cerebral involvement typically presents with a focal neurological deficit and a mass lesion on cerebral imaging. As discussed above, differentiation between CNS lymphoma and other focal neurological disorders, particularly toxoplasmosis, may be difficult because the radiographic appearance of lesions may be identical. If the clinical situation permits, empiric therapy for toxoplasmosis is generally warranted in patients manifesting cerebral mass lesions with ring-enhancement on computed tomography. Patients failing such therapy should be regarded as possibly having lymphoma. Although histological examination is generally required for diagnosis of lymphoma, PET and SPECT, as discussed above, may aid in the distinction between lymphoma and toxoplasmosis.

Gastrointestinal lymphoma typically presents with nonspecifc abdominal pain, unexplained fever, occult or clinical bleeding, ascites, or bowel perforation with peritonitis. The diagnosis is generally suspected on the basis of abdominal imaging, but tissue confirmation is required. Lymphoma at other extranodal sites similarly presents with nonspecific features. Pulmonary involvement may feature nodules, focal or diffuse infiltrates, or pleural effusions which may mimic pneumonia or tuberculosis. As a rule, the challenge in diagnosing extranodal lymphoma is distinguishing from more common entities that typically involve the endorgan in question.

Similar to NHL, Hodgkin's disease (HD) associated with HIV infection tends to present as a multicentric disorder with a high incidence of "B" symptoms at presentation. Extranodal involvement, especially of the liver, spleen, and marrow, is also more common than in non-HIV-related HD, and the disease appears to pursue a more aggressive course.[149]

Non-Hodgkin's lymphoma (NHL) has been reported as the initial AIDS-defining condition in approximately 4% of AIDS cases in the United States and an additional 5% of AIDS patients subsequently develop NHL.[156–158] Unlike Kaposi's sarcoma and many HIV-related opportunistic infections, the incidence of NHL does not

appear to be decreasing since the advent of highly active antiretroviral therapy in the mid-1990s.[18]

b. Castleman's Disease

Castleman's disease (angiofollicular lymphoid hyperplasia) is a lymphoproliferative disorder which shares some features with lymphoma, including nonspecific respiratory and consitutional symptoms, hepatosplenomegaly, and lymphadenopathy, which may be massive in some cases. Multicentric Castleman's disease has been associated with HIV infection.[159] In some instances, particularly in HIV-infected homosexual men, it may precede the development of Kaposi's sarcoma,[160] and it appears to be associated with human herpesvirus 8 or Epstein-Barr virus infection.[161]

L. Genital Tract Disorders

1. Cervical Neoplasia

It has long been recognized that HIV-infected women have a higher incidence of genital human papilloma virus (HPV) infection, cervical intraepithelial neoplasia and, very likely, cervical cancer (see Chapters 9 and 13). This association appears to be true when risk factors for HPV infection other than HIV infection are controlled for and seems to increase with worsening immune deficiency.[162]

2. Sexually Transmitted Diseases

Sexually active HIV-infected patients may be at high risk for sexually transmitted diseases, both inflammatory (gonorrhea, chlamydia) and ulcerative (syphilis, herpes simplex, chancroid). Vaginal candidiasis, particularly if recurrent and severe, is a common, often overlooked, initial manitestation of HIV infection in women. The approach to diagnosis of these disorders is similar to that taken for non-HIV-infected patients and is outside the scope of this discussion. In the ambulatory setting, particular attention must be paid to screening for syphilis with periodic serum tests and for human papilloma virus infection with periodic pelvic examination.

M. Psychiatric Disorders

Psychiatric disturbances, particularly depression and anxiety, are common among HIV-infected patients. Patients with a history of risk behavior may display denial by avoiding testing. Social isolation, guilt, and uncertainty are common after a diagnosis of AIDS.[163] Stress associated with learning of a positive test result for HIV or being informed that an AIDS-related illness has been diagnosed may precipitate psychiatric crises and feelings of anger, fear, and confusion. It has been shown that AIDS may be associated with a greatly increased risk of suicide.[164]

It may be difficult to distinguish between psychiatric symptoms and those reflecting organic disease, particularly AIDS dementia complex. Opportunistic infections and malignancies as well as medications affecting the CNS may initially cause symptoms suggesting psychiatric disorders. Cerebral toxoplasmosis, lymphoma, cryptococcosis, tuberculosis, listeriosis, and neurosyphilis may all present with a clinical picture of toxic psychosis. It is especially important that these conditions

be excluded with appropriate diagnostic studies in patients presenting with the new onset of psychotic symptoms. Reactions to medications may also be confused with psychiatric disorders. For example, hypoglycemia resulting from pentamidine therapy may manifest as delerium. Efavirenz may cause confusion and vivid nightmares (see Chapters 10 and 15).

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5 General Approach to HIV Infection

CONTENTS

I. INTRODUCTION

Beginning in the late 1980s, testing for human immunodeficiency virus (HIV) infection became commonplace. As a result of greater public awareness of acquired immunodeficiency syndrome (AIDS) and increasingly easy access to counseling and testing services, many individuals perceiving themselves to be at risk of infection underwent voluntary testing. Widespread prenatal testing programs as well as mandatory testing of military recruits, applicants for immigration, and many persons

applying for life or health insurance have identified individuals who were unaware of their risk. Simultaneously, advances in therapy and preventive strategies for certain AIDS-related opportunistic infections have provided a strong medical indication for identifying HIV infection in its earliest stages.

These trends have resulted in large numbers of HIV-positive patients seeking medical care before the onset of AIDS. However, many primary care physicians, including some practicing in areas where HIV infection is common, lack familiarity with HIV-related disorders[1] and with relevant laboratory diagnostic tests. Sexual counseling and or substance abuse treatment of patients at risk of HIV infection may vary greatly among practitioners. Nonetheless, as testing efforts intensify, increasing numbers of individuals will present for care.

General guidelines for the care of all HIV-infected patients are provided in this chapter. Although the information included is oriented toward the asymptomatic patient, much of the overall approach to initial assessment and follow-up care is equally applicable to patients in symptomatic phases of the disease. General health maintenance for the HIV-infected adult is discussed in detail in Chapter 13. Issues of special importance in the care of women are presented in Chapter 9. Evaluation of specific symptoms and signs is reviewed in the next chapter. Therapy of specific HIV-related disorders is discussed in Chapters 7 and 8.

II. OVERALL MANAGEMENT STRATEGY

A. Issues in Medical Management

Medical management of HIV-infected individuals involves several strategies:

- Clinical and immunologic staging
- Appropriate antiretroviral therapy if indicated
- Prevention of opportunistic infections
- Screening for conditions highly associated with HIV infection, such as tuberculosis, viral hepatitis, and sexually-transmitted diseases
- General health maintenance, including screening for hypertension and hypercholesterolemia in all patients and age-appropriate cancer screening for men (prostate) and women (cervical, breast) (see Chapter 13)

In addition, referral for substance abuse treatment, nutritional and dental assessment, psychiatric evaluation, and subspecialty services are frequently necessary and a specific focus on adherence to therapy is essential.

These services should be integrated as much as possible to maximize convenience and to reduce the risk of medication interactions. The provider coordinating care should be trained, experienced, and knowledgable in the care of HIV-infected individuals at all stages of disease.

1. Clinical Staging

The distinction between AIDS and HIV-infection without AIDS has become somewhat less important because laboratory markers including CD4 lymphocyte count and viral load are more reliable indicators of disease stage, response to therapy, and prognosis.

Nonetheless, the distinction between symptomatic and asymptomatic HIV infection continues to have relevance. For example, symptomatic infection, other than the acute retroviral syndrome, is universally considered an indication for antiretroviral therapy regardless of laboratory parameters. For this reason, each patient should be carefully screened for HIV-related symptomatic disorders as discussed below.

2. Immunologic Staging

Immunologic staging by means of lymphocyte subset analysis is essential for adequate evaluation and management of HIV infection. As discussed in Chapter 2, the CD4+ lymphocyte count provides invaluable guidance to the clinician and, to a large extent, dictates the approach to therapy and monitoring.

Lymphocyte analysis should be performed as part of the initial assessment of all patients. The analysis should be repeated as dictated by immunologic stage and clinical events. For patients whose initial CD4+ cell count is above 500 cells/mm^3, the count should be repeated every 6 months; for those with initial counts between 200 and 500 cells/mm^3, every 3 to 6 months. When the count is below 200 cells/mm^3, or if such symptoms as nonspecific fever, oral candidiasis, weight loss, diarrhea, or neurologic manifestations of HIV infection develop at any immunologic stage, the lymphocyte subset analysis may be especially helpful in determining when to initiate or alter antiretroviral therapy. Although the CD4+ cell count is an important parameter in the decision to initiate antiretroviral therapy (see Chapter 10), the CD4+ cell response of patients receiving therapy is somewhat unpredictable and, for this reason, is less useful in gauging response to therapy and overall prognosis.

3. Screening for HIV-Related Complications

The patient should be questioned thoroughly about current and prior medical conditions. Disorders that are particularly suggestive of HIV infection include tuberculosis, bacterial pneumonia, severe or disseminated herpes zoster infection, oral candidiasis, severe seborrheic dermatitis, or unexplained, persistent, generalized lymphadenopathy. Persistent, unexplained fever or significant (>10%), unintentional weight loss should be considered symptoms of HIV infection.

4. Mental Illness

History of diagnosed mental illness should be ascertained. Symptoms of depression (insomnia, anorexia, psychomotor retardation, frequent crying, etc.) and anxiety should be sought. The routine use of an abbreviated standardized depression scale should be considered.

5. Assessing Likelihood of Treatment Adherence

Adherence to therapy for HIV infection is very difficult for many and requires not only a commitment on the part of the patient but an understanding of potential obstacles in the patient's life which, unless addressed, may make compliance with a complex regimen of medications all but impossible (see Chapters 10 and 11).

6. Living Conditions

Stable living conditions greatly enhance the likelihood that an individual will be able to comply with therapy. Homelessness, with limited access to water and no ability to store medications properly, is particularly devastating and must be addressed before there can be any reasonable hope of maintaining an individual on antiretroviral therapy. Persons living in marginal housing may find it difficult to tolerate even minor side effects of the medications because of lack of heat, air conditioning, or ventilation or the need to walk up many stairs. Institutionalized patients, whether in temporary shelters or in more long-term facilities, may have medications confiscated or lost or may be forced to reveal their HIV status in order to obtain appropriate care.

7. Substance Abuse

Active substance abuse, including alcoholism, is generally incompatible with effective HIV therapy. Each patient must be screened for this and, once substance abuse is identified, it must remain an issue of active discussion for the primary care provider at each encounter with the patient. Appropriate referrals should be made and care should be monitored closely. Individuals who live within a network of other substance abusers cope less well with the impact of HIV infection,[2] even if they have stopped drug use. Structured HIV treatment programs may seek to provide peer counselors as well as group and individual therapy sessions to provide a more supportive social structure for such individuals.

8. Comprehension

Many patients are not prepared for the complexity of HIV therapy and the need to maintain a strict timetable for taking medications. It is often helpful to provide labeled containers for medications separated by individual doses (pillboxes) as a reminder. It should be recognized that individuals who are employed and out of the house during the day may have as much or more difficulty in maintaining complex medication schedules as those who are homebound.

9. Dietary Patterns

Because some antiretroviral agents must be taken on an empty stomach and others must be taken with meals in order to maximize drug levels, many patients need assistance in creating a schedule for their medications. This issue is magnified among people who are homeless or who lead disordered or chaotic lives for any reason. The importance of the proper timing of meals should be discussed clearly whenever antiretroviral therapy is initiated or changed.

10. Commitment

Each patient must feel committed to beginning and maintaining antiretroviral therapy. Since the advent of multidrug therapy, concern about the potential side effects of medications, particularly the protease inhibitors, has been expressed in many quarters.

It is not unusual that patients have been exposed to these concerns in an unbalanced manner and do not fully appreciate the potential benefits of effective therapy. Reservations about therapy may not be voiced by the patient for fear of insulting or angering the provider. For this reason and since nearly perfect compliance with treatment is necessary to achieve durable suppression of viral replication, it is essential that the patient be given the opportunity to express any reservations felt about beginning treatment. An accepting atmosphere must be provided for this discussion so that the provider is better able to understand and respond to concerns about the safety or effectiveness of treatment. If an individual decides against beginning therapy, it is usually best to accept the decision with the plan of revisiting it at a later time. Antiretroviral therapy is rarely if ever indicated on an urgent basis and incomplete compliance due to patient reservations or confusion can rapidly lead to the emergence of drug resistance and a limitation of future treatment options.

11. Assessing the Impact of the Diagnosis

Patients who have received appropriate counseling should be questioned about their understanding of the disease, routes of transmission, and recommended changes in their sexual practices and lifestyle. If counseling has not yet taken place, it should be approached as outlined in Chapter 3.

When informed of a positive HIV test result, patients may react with a range of feelings, including denial, anger, guilt, depression, or apparent indifference. Although individual practitioner styles differ, questions designed to explore such reactions should be asked in an understanding, accepting manner and patients should be encouraged to discuss their feelings.

Many asymptomatic patients do not initially believe that they are infected and question the validity of positive test results. In such cases the meaning of the test result should be reviewed and discussed (see Chapter 3) and, if doubt remains, repeat testing should be considered.

Most asymptomatic patients presenting themselves for medical treatment are young adults with little or no history of significant health problems. It is important for the primary care practitioner to determine the impact of HIV infection on the patient's daily life. Disruption of family support mechanisms and, in some cases, worsening of existing alienation from family and friends are common. Employment, housing, and financial concerns may become paramount for some individuals. Appropriate questioning about these areas may lead the physician to arrange family counseling or social service intervention and demonstrate to the patient that there is an interest in providing assistance and support.

Patients presenting themselves for initial assessment may be confused about the distinction between HIV infection and AIDS. The relatively long natural history that HIV-related disease usually pursues should be explained and emphasized. Questions about prognosis are often asked by the patient at the first encounter. Although specific predictions are unwise and likely to be inaccurate, an atmosphere of both realism and hope should be established. After immunologic staging has been completed, the short-term risk of AIDS-related complications should be more easily assessed.

12. Assessing Family Structure

The provider should understand the patient's family structure in order to anticipate problems in appointment and medication compliance as well as to assist the individual in coping with the diagnosis of HIV infection. In a large-scale assessment of factors influencing access to healthcare among HIV-infected women in New York,[3] it was found that home responsibilities, particularly childcare, may have a significantly negative impact on a woman's ability to comply with medications and appointments. Some women were found to be essentially neglecting their own care in favor of their children, HIV-infected or not. In addition, patients with children may be extremely concerned about the possibility that their children are also HIV-infected or about planning for the children's care if they themselves should require hospitalization, be incapacitated, or die. It is also important to have an awareness of the adult support system available to the patient so that coping strategies involving close friends or relatives can be explored. Important issues such as the patient's wishes regarding confidentiality within the family and household must be clarified.

13. Permanency Planning

Patients differ in their understanding of and concern for long-range planning. Some are concerned almost immediately after learning that they are HIV-infected about the impact on their loved ones if they were to die. Others may wish to defer a discussion of such issues until they themselves understand more about the disease and their own prognosis. The provider should guide this discussion in a manner that takes into account the clinical and immunological stage of the patient, comorbidities, and the likelihood of response to antiretroviral therapy. In general, the prognosis of most patients has improved substantially since the advent of combination antiretroviral therapy (see Chapter 10). For this reason, the provider discussing long-term issues should be very knowledgable in the natural history of HIV infection and the impact of therapeutic advances. Certain areas should be discussed with virtually all HIV-patients as well as patients with other serious chronic medical conditions. These include advance directives, designation of a health proxy, and creation of a will, especially if the patient has dependents.

14. Family Planning

HIV-infected women or the female sexual partners of HIV-infected men may inquire about the safety and advisability of childbearing. Counseling should be provided regarding the potential risk of vertical transmission and measures which must be taken to reduce this risk (see Chapter 9). The possible risk of premature delivery, intrauterine growth retardation, and death *in utero* should also be discussed in an objective manner. The potential risks, both known and unknown, to the fetus of antiretroviral therapy or other medications that the mother needs to take during pregnancy or breast feeding should be explained. The possible implications of raising a child while under treatment for HIV infection should be pointed out and the potential impact on the child of early loss of one or both parents must be faced objectively.

Although the risk of vertical transmission has been reduced considerably by perinatal antiretroviral therapy, it is not possible to completely reassure an individual woman that she would not transmit HIV infection to her child even if her viral load is undetectable and her CD4+ lymphocyte count is normal.

III. MEDICAL HISTORY

A carefully obtained medical history of a patient with HIV infection can provide the clinician with many important insights (see Box 5.1). Because HIV infection is largely a disease of young adults, patients in an early, asymptomatic stage most commonly feel well and have no significant chronic illnesses. Many patients doubt that they are infected at all, particularly those referred for medical assessment simply because of a positive screening test result. This attitude stems in part from the popular misconception that HIV infection and AIDS are synonymous terms and represent a rapidly progressive, debilitating disease. In later stages of the disease some patients may be inclined either to deny or to exaggerate somatic complaints. Cognitive defects, perhaps reflection the AIDS dementia complex, may interfere with some patients' ability to accurately relate their medical history or their current complaints.

HIV-infected individuals are regarded as asymptomatic only if there is no history of AIDS-related opportunistic infections, malignancies, or symptoms compatible

BOX 5.1
Major Components of the Medical History

- Current symptoms
- General medical history
  - Chronic medical disorders
  - Chronic psychiatric disorders
  - Prior acute illnesses
  - Hospitalizations
  - Cardiac risk factors
  - Medication allergies
  - Current and prior medications
  - Sexually transmitted diseases
  - Current and prior substance abuse
  - Pregnancy history
  - Nutritional history
- History of complaints potentially related to HIV infection (see Chapter 6)
- Place of birth
- Recent travel
- Immunization history
- Current and past sexual practices
- Employment history
- Housing history

with the direct effects of HIV infection. What follows are several areas of information that should be covered when obtaining the medical history:

Evaluation of the patient's reaction to the diagnosis of HIV infection
Evaluation for symptoms of HIV infection
Evaluation for current or previous evidence of immunodeficiency
Assessment of the risk of specific HIV-related disorders
Assessment of immunization status
General medical history
Assessment of past and current behaviors and the likely impact of testing positive on future risk behavior
Country of birth, upbringing
Significant travel (including military)
Medications
Allergies

IV. PHYSICAL EXAMINATION

The physical examination should be thorough and appropriate for the patient's age and medical history. In addition, it should be specifically directed toward identifying HIV-related abnormalities (see Boxes 5.2 and 5.3). The differential diagnosis and recommended diagnostic workup of abnormal physical findings are discussed in the next chapter.

A. Vital Signs

Orthostatic changes in heart rate or blood pressure may indicate volume depletion, autonomic neuropathy, or adrenal insufficiency. An increase in respiratory rate or resting heart rate may suggest congestive heart failure resulting from HIV cardiomyopathy. Fever, even if low-grade, should prompt a thorough evaluation for infection (see Chapter 6).

B. Skin

HIV-infected individuals, especially those with significant immunodeficiency, frequently have abnormalities of the skin, hair, and nails. Common mucocutaneous disorders such as seborrheic dermatitis, xerosis, psoriasis, and folliculitis are generally easily recognized. Herpes simplex oral or genital infections are often present as ulcerating lesions on the lips, anterior oral cavity, perineum, penis, or perirectal region. Occasionally herpes simplex may produce more disseminated infection with ulcerating lesions on the trunk, face, and extremities.

Varicella zoster virus may produce any of its typical manifestations, including primary varicella (chickenpox), dermatomal zoster (shingles), or disseminated zoster. Dermatomal zoster may manifest as a severe infection, sometimes leaving permanent scarring, years before the onset of AIDS.

Several opportunistic infections may become evident as papular or pustular skin lesions. These include cryptococcosis, tuberculosis, histoplasmosis, bacillary angiomatosis, and pneumocysosis. Molluscum contagiosum is seen frequently in HIV-infected

BOX 5.2
Common Nonspecific Signs and Symptoms of HIV-1 Infection (All Stages)

General
- Fever
- Weight loss
- Lymphadenopathy (generalized)

Dermatologic
- Seborrheic dermatitis
- Xerosis, ichthyosis
- Fungal infection
- Molluscum contagiosum
- Herpes zoster
- Herpes simplex

Ocular
- Retinal hemorrhages, exudates
- Dry eyes

Oral
- Gingivitis
- Ulcerations
- Angular cheilitis
- Thrush
- Xerostomia
- Hairy leukoplakia
- Parotid gland enlargement

Cardiovascular
- Pericardial rub

Third heart sound

Gastrointestinal
- Hepatomegaly
- Splenomegaly
- Diarrhea

Musculoskeletal
- Arthralgia
- Reiter's syndrome

Neurologic
- Peripheral neuropathy
- Memory loss
- Difficulty concentrating

patients at all stages of immunodeficiency and may appear on the face, neck, trunk, or extremities. The lesions are smooth, dome-shaped papules which often have an umbilicated center containing a waxy plug.

The lesions of Kaposi's sarcoma may be evident on any part of the body but most commonly occur on the face (particularly the tip of the nose), the ears, the trunk, and the extremities. Subcutaneous lesions may resemble cellulitis. Mucous membrane involvement is particularly common and lesions are often seen on the gingival surfaces, palate, and peritonsillar areas.

C. Lymphoid System

A careful assessment for lymphadenopathy should be made by examining all lymph node beds systematically at each visit. Although generalized lymph node enlargement is a common finding, particularly in patients who have not yet become profoundly immunosuppressed, asymmetric lymphadenopathy or rapidly enlarging nodes in one or more areas may be a clue to the presence of a lymphadenopathic infection or malignancy. The cervical (anterior and posterior), jugular, supraclavicular, axillary, epitrochlear, inguinal, and femoral areas should be palpated and the size and character of any palpable nodes carefully documented.

BOX 5.3
Selected Signs and Symptoms of AIDS-Related Disorders

General
- Fever, weight loss
- Lymphadenopathy (localized or generalized)

Dermatologic
- Ulcerations (herpes simplex)
- Pustules (herpes simplex, mycobacterial, or fungal infection)
- Nodules (Kaposi's sarcoma, lymphoma, mycobacterial, or fungal infection)

Ocular
- Painful ulcerations (herpes simplex)
- Nodules (Kaposi's sarcoma, lymphoma)

Respiratory
- Persistent cough (*Pneumocystis carinii* pneumonia, TB)
- Dyspnea (*Pneumocystis carinii* pneumonia, pulmonary Kaposi's sarcoma, TB)

Gastrointestinal
- Odynophagia (esophagitis)
- Diarrhea (nonspecific, protozoal infection, medication-related, bacterial)
- Hepatomegaly (mycobacterial or other opportunistic infection, lymphoma, Kaposi's sarcoma)
- Jaundice (biliary involvement with cytomegalovirus, cryptosporidiosis, or isosporiasis; viral hepatitis, medication-induced)

Neurologic
- Cognitive dysfunction (AIDS dementia)
- Focal cerebral deficit (toxoplasmosis, lymphoma, progressive multifocal leukoencephalopathy)
- Persistent headache (cryptococcal meningitis, tuberculous meningitis, toxoplasmosis, lymphoma, medication-induced, sinusitis)

D. Eyes

The eyes should be examined at each visit. Annual thorough examination by an ophthalmologist is advisable. The conjunctival sacs should be carefully examined. Petechiae detected here may be a clue to the presence of systemic emboli, as may be seen in infective or thrombotic endocarditis. The fundoscopic examination should be emphasized and performed at each visit. Detecting fundal hemorrhages or exudates may provide evidence of retinitis caused by cytomegalovirus, *Toxoplasma gondii,* or other pathogens and should prompt a thorough examination by an ophthalmologist. Visual field defects suggest focal neurologic disorders such as toxoplasmosis of lymphoma and justify neurologic referral and appropriate brain imaging studies. The periorbital area is a common location for cutaneous and subcutaneous Kaposi's sarcoma lesions.

E. Oropharynx

The examination of the oropharynx in HIV-infected patients must be especially thorough because abnormalities are often found. Common lesions include thrush (appearing as a cheesy exudate that typically occurs on the dorsum of the tongue, buccal mucosa, or palate), hairy leukoplakia (white streaks and patches on the sides of the tongue), herpes simplex (painful ulcers, vesicles, or generalized erythema),

aphthous stomatitis (painful ulcers), or Kaposi's sarcoma. Rarely, lymphoma, histoplasmosis, cryptococcosis, and tuberculosis may present with oral ulcers or mass lesions. Dental caries should be noted and the patient should be referred at least annually for thorough dental examination.

F. Sinuses

The examiner should palpate for tenderness over the paranasal sinuses and mastoids. Both symptomatic and asymptomatic sinusitis are encountered commonly at all stages of HIV infection.

G. Chest

Breathlessness, tachypnea, and a dry cough exacerbated by deep inspiration often signal the presence of HIV-related pulmonary disorders or congestive heart failure. However, the chest examination may be normal in a patient with early respiratory infection or malignancy.

Bronchial breath sounds, dullness to percussion, or other signs of consolidation suggest bacterial pneumonia. Localized wheezing may indicate airway compression by tumor or an obstructing endobronchial lesion due to Kaposi's sarcoma.

Findings compatible with pleural effusion may suggest tuberculosis, pulmonary Kaposi's sarcoma, congestive heart failure, or bacterial or fungal pneumonia.

H. Heart

Because of the high incidence of HIV-related myocardial and pericardial disease, evidence of left ventricular dysfuncton (e.g., third heart sound) or pericardial effusion should be carefully sought.

Valvular disease is particularly common among patients with a history of intravenous drug use and previous endocarditis, but noninfectious thrombotic endocarditis may also occur in patients in other high-risk groups.

I. Abdomen

Enlargement of the liver or spleen may be encountered early in the course of HIV infection or may reflect late involvement with opportunistic infection or malignancy. Isolated splenomegaly may be an indication of portal hypertension and advanced cirrhosis. Localized upper abdominal tenderness may indicate biliary or pancreatic disease. Lower abdominal tenderness may suggest colitis (e.g., cytomegaloviral or antibiotic-associated), appendicitis, or ileitis (related to tuberculosis, histoplasmosis, or other localized intestinal infection). Intra-abdominal lymphoma often causes nonspecific, diffuse abdominal pain with or without mass lesions. The diagnostic approach is dictated by the stage of HIV infection and associated findings.

J. Genitourinary System

A careful examination of the genital area should be conducted in order to identify lesions associated with sexually transmitted diseases (ulcers, vesicles, urethral discharge, genital warts). Bimanual and speculum vaginal examination should be performed

in women and Pap smear obtained. Palpation of the testicles and prostate should be performed in men.

K. Rectal Examination

Anorectal carcinoma is seen with increased frequency among HIV-infected homosexual men. For this reason, a careful rectal examination should be performed periodically (e.g., as part of the annual assessment). Fecal occult blood testing and/or sigmoidoscopy should be conducted as a routine screening test for all patients age 50 or greater as well as for those at particularly high risk of colon cancer (see Chapter 13).

L. Extremities

The extremities should be examined for edema and cyanosis as well as for muscle atrophy and joint inflammation or deformity. Venous thrombosis may be seen in association with HIV infection because of immobility and, perhaps, hypercoagulable states such as the antiphospholipid syndrome.

M. Nervous System

A thorough neurologic assessment directed toward detecting evidence of peripheral neuropathy (motor and sensory examination and deep tendon reflexes), focal neurologic deficits, and myelopathy, as well as a careful evaluation of mental status, is important at any stage of HIV infection. Subtle cognitive deficits can be detected in a large proportion of patients. An effort should be made to identify and characterize problems such as memory loss and difficulty concentrating.

V. INITIAL DIAGNOSTIC STUDIES

Diagnostic studies at intake are conducted in order to screen for undiagnosed medical disorders and to assess for potential side effects of therapy. Follow-up studies to be obtained when antiretroviral therapy is commenced and thereafter are discussed in Chapters 10 and 11.

A. Complete Blood Count

Because of the high incidence of anemia, thrombocytopenia, and white blood cell abnormalities, a complete blood cell count should be part of the initial evaluation and routine follow-up screening in all patients.

B. Biochemical Profile

A number of abnormalities may be detected in asymptomatic patients at various stages of HIV infection on routine biochemical tests. Common among these disorders are hyponatremia, liver function abnormalities, elevation of bilirubin, and abnormalities of creatinine and urea nitrogen.

C. Liver Function Tests

Liver enzymes and indicators of hepatic synthetic function, such as albumin, may provide the first indication of acute or chronic liver disease. Establishing the presence of disorders such as chronic viral hepatitis, cirrhosis, and biliary inflammation or obstruction is critical in the selection of medications and the targeting of screening efforts for hepatitis B and C.

D. Toxoplasma Antibody

The presence of antibody to *Toxoplasma gondii* identifies the patient at risk for reactivation of toxoplasmosis during the latter stages of immune deficiency. Determining whether antibody is present is important for two reasons:

1. The selection of prophylactic regimen to prevent *Pneumocystis carinii* pneumonia (PCP) may or may not include an agent active against *T. gondii*. Trimethoprim-sulfamethoxazole, the most effect agent for PCP prevention, also is an effective agent in preventing toxoplasmosis.
2. Pentamidine, however, which is often used in the sulfa-intolerant patient for PCP prophylaxis is not effective against *T. gondii* and, in such patients, alternative agents must be prescribed.

E. Hepatitis Serology

The natural history of both hepatitis B and C appears to be accelerated by co-infection with HIV. Identification of individuals infected with hepatitis B virus (HBV) allows further evaluation for disease activity and potential therapy. Individuals with negative HBV serologies should be immunized. In the case of hepatitis C virus (HCV), individuals with antibody should be further evaluated for disease activity with viral load studies and serial liver enzyme measurements. Although there is currently no vaccine to prevent HCV, patients who have evidence of chronic infection should receive hepatitis A vaccine (if not immune) because of the potential for fulminant hepatitis A.

F. Syphilis Serology

Syphilis is more common among HIV-infected individuals than in the general population. Manifestations of disease may be more severe in co-infected individuals and the natural history of syphilis in its progression through primary, secondary, latent, and tertiary stages may be accelerated dramatically in some individuals. Active screening and appropriate therapy are especially important for these reasons.

G. Chest X-Ray

In HIV-infected patients with respiratory symptoms, the value of the chest radiograph is clear. The yield of screening radiographs performed in cases of asymptomatic HIV infection, however, may be low. Nonetheless, evidence of healed or

active tuberculosis, enlargement of thoracic lymph nodes, pleural disease, and interstitial infiltrates may be detected on radiographic examination in the absence of symptoms.

H. Pap Test

The relatively high incidence of cervical neoplasia (see Chapter 10) in women infected with HIV necessitates an organized approach to screening with pelvic examinations, Pap tests and, in some high risk individuals, colposcopy (see Chapters 9 and 13).

I. Tuberculin Skin Test

Because of the high rate of co-infection with *Mycobacterium tuberculosis* in HIV-infected individuals, tuberculin skin tests should be performed at intake and, in individuals with negative tests, annually thereafter. Because active tuberculosis may be remarkably occult in some individuals and preventive therapy appears to be quite effective in tuberculin positive patients whether co-infected or not, the approach to testing should be organized and diligent. Induration of 5 mm or greater is considered positive in HIV-infected individuals. Anergy testing is not recommended.

J. Measurement of Viral Load

Plasma viral load, measured by RNA-PCR, should be conducted as early in the initial assessment process as feasible (see Chapters 2 and 11). Such information permits early identification of patients with immediate indication for antiretroviral therapy (see Chapter 10) and appropriate triage for frequency of follow-up visits.

VI. PREVENTION OF OPPORTUNISTIC AND OTHER INFECTIONS

Since the mid-1980s it has been recognized that prevention of certain opportunistic infections prolongs overall survival in HIV/AIDS.[4] As a result this strategy has been a cornerstone in the care of HIV-infected patients. Prophylaxis directed at *Pneumocystis carinii* pneumonia, toxoplasmosis, and *Mycobacterium avium* complex infection has been considered the standard of care for selected patients, based on CD4 cell counts, for years.[5] These guidelines were developed on the basis of data from before the widespread use of current antiretroviral multidrug regimens. Patients responding to this therapy often have significant return of cellular immune function.[6,7] Because of this, since the advent of highly active antiretroviral therapy (HAART), abundant evidence has accumulated that the incidence of most AIDS-related opportunistic infections has decreased, especially among patients with significant restoration of cellular immune function and control of viral replication.[8]

A. *Pneumocystis Carinii* Pneumonia (PCP)

Patients with a history of AIDS-related opportunistic infection or malignancy and those with a CD4+ lymphocyte count below 200 cells/mm^3 are at extraordinarily high risk for the development of PCP. At particularly high risk are those with a prior episode of PCP. In one prospective study prior to the advent of modern antiretroviral therapy, 16 of 30 patients with Kaposi's sarcoma who received no prophylaxis developed PCP within approximately 2 years.[9] One third of early patients with an initial CD4+ lymphocyte count of 200 cells/mm^3 or less developed PCP by 36 months in the Multicenter AIDS Cohort Study. Approximately 80% of patients receiving zidovudine but no specific PCP prophylaxis had recurrences within 24 months.[10] On the basis of these and other data, routine administration of therapy to prevent PCP has been an accepted standard of care since the early days of the AIDS epidemic and is considered a mandatory component of care.

Four agents, trimethoprim-sulfamethoxazole, pentamidine, dapsone, and atovaquone have been shown to provide protection against the development of PCP and are in wide use.

1. Trimethoprim-Sulfamethoxazole (TMP-SMX)

A large number of studies have demonstrated that TMP-SMX confers excellent primary and secondary protection against PCP. It is currently regarded as the agent of choice. None of 142 patients with CD4+ lymphocyte counts below 200 cells/mm^3 developed PCP while receiving daily TMP-SMX (80 mg TMP/400 mg SMX or 160 mg TMP/800 mg SMX) as primary prophylaxis over a mean follow-up period of 264 days.[11] In secondary prophylaxis, Hardy and colleagues[12] found an 11.4% rate of recurrence over a median period of follow-up of 17.4 months among patients receiving TMP-SMX (160 mg/800mg daily). Lower-dose regimens with intermittent dosing (twice or three times weekly) appear to be approximately as effective as daily therapy.

TMP-SMX also confers protection against cerebral toxoplasmosis[13] and certain bacterial infections.[12]

2. Pentamidine

In a large, prospective study aerosolized pentamidine administered monthly was shown to reduce the relapse rate of PCP by 50% in patients receiving treatment after an initial episode.[14] On the basis of such efficacy data, inhaled pentamidine came into widespread use for prevention of PCP beginning in the late 1980s and was approved for this use by the U.S. Food and Drug Administration for patients with a history of PCP or a CD4+ lymphocyte count below 200 cells/mm^3. The recommended dose is 300 mg once monthly diluted in 6 ml sterile water and adminstered at 6 L per minute from a 50-psi compressed-air source by Respirgard II (Marquest, Englewood, CO) nebulizer.[10]

Although clearly effective for most patients, pentamidine administered in this fashion has been associated with several problems including pneumothorax[15] and

extrapulmonary pneumocystosis.[16] Patients in whom PCP does develop while they are receiving aerosolized pentamidine may have unusual radiographic patterns with predominant upper lobe disease,[17] potentially delaying diagnosis.

Recently several studies have indicated a high failure rate of pentamidine prophylaxis in patients with CD4+ lymphocyte counts below 60 to 75 cells/mm^3.[18,19] The relatively high cost and complicated logistics of aerosolized pentamidine therapy also represent disadvantages.

3. Dapsone

Dapsone is a sulfone antibiotic long used in the treatment of leprosy. In several dosing regimens, both alone and in combination with pyrimethamine, it has been shown to confer varying degrees of protection against the development of PCP in high-risk, HIV-infected patients. In a large, prospective study, dapsone (100 mg by mouth twice weekly) was found to be effective in prophylaxis with an overall failure rate of 18% over a mean period of follow-up of 42 weeks.[20] In a retrospective chart review of patients intolerant of TMP-SMX, Jorde and colleagues[21] found a 14% prophylaxis failure rate among patients receiving dapsone (100 mg by mouth three times weekly) over a mean follow-up period of 9 months. In a prospective study of patients initially receiving treatment with dapsone (100 mg weekly) plus pyrimethamine (25 mg weekly), PCP developed in 8.3% of patients over a mean follow-up period of 313 days.[22]

a. Comparative Studies

On the basis of large prospective trials, TMP-SMX appears to be more effective than inhaled pentamidine in preventing both initial (primary prophylaxis) and recurrent (secondary prophylaxis) episodes of PCP. Comparing monthly pentamidine regimens to daily regimens or oral single-strength (80mg/400mg) or double-strength (160mg/800mg) TMP as primary prophylaxis, Van der Graaf and colleagues[23] reported that 11% of patients receiving pentamidine and none of the patients receiving either of the TMP-SMX regimens developed PCP during a mean period of follow-up of 264 days. In a study of secondary prophylaxis comparing regimens of TMP-SMX (double-strength, once daily) and monthly inhaled pentamidine, Hardy and colleagues[12] found recurrence rates of 11.4% and 27.6% respectively, after 18 months of follow-up.

4. Atovaquone

Atovaquone (1500 mg daily) represents another alternative for patients intolerant of TMX-SMP. Its effectiveness in preventing PCP is approximately equivalent to that of dapsone,[24] although it is considerably more expensive and has variable absorption.

5. Discontinuation of Prophylaxis for PCP

In most cases, primary prophylaxis can be safely discontinued in patients whose CD+ cell count has risen above 200/mm^3 for at least 3 months.[25]

B. *Mycobacterium Avium* Complex (MAC)

Preventive therapy with either clarithromycin (500 mg twice daily) or azithromycin (1200 mg weekly) is recommended for individuals with CD4 cell counts of less than 50/mm^3.

1. Discontinuation of Prophylaxis for MAC

Prophylaxis may be safely discontinued in patients whose CD+ cell count has risen above 100/mm^3 for at least 3 months and who have had sustained viral suppression.[25]

C. Toxoplasmosis

Patients with positive serologic test for toxoplasmosis and CD4 cell count less than 100/mm^3 should receive preventive therapy with trimethoprim-sulfamethoxazole (TMP-SMX; one double-strength tablet daily). For individuals intolerant to TMP-SMX, a variety of other regimens may be considered. These include:

Dapsone (50 mg once daily) + pyrimethamine (50 mg weekly) + leucovorin (25 mg weekly)
Dapsone (200 mg weekly) + pyrimethamine (75 mg weekly) + leucovorin
Atovaquone (1500 mg daily) +/– pyrimethamine (25 mg daily) + leucovorin (10 mg daily)

1. Discontinuation of Prophylaxis for Toxoplasmosis

No criteria have yet been established for discontinuation of prophylaxis.

D. Secondary Prophylaxis: Special Considerations

Relatively little data are available addressing the need for continuing lifelong suppression (so-called secondary prophylaxis) of established opportunistic infections, with the exception of CMV retinitis, after viral suppression and immune reconstitution has been accomplished with HAART therapy. Several studies have demonstrated that secondary prophylaxis of CMV retinitis may be suspended, at least for a while, among patients who have had a good virologic and immunologic response to HAART therapy.[26–28] Current guidelines reflect this observation and allow for the discontinuation of CMV antiviral therapy for patients who do not have sight-threatening disease and maintain increases of CD4 cell counts of 100 to 150 cells/mm^3 for 3 to 6 months.[25]

Limited data suggest that secondary prophylaxis for *Pneumocystis carinii* pneumonia,[29] *Mycobacterium avium* complex,[30] toxoplasmosis, and cryptococcal infection[30] might be safely discontinued under certain circumstances. However, current recommendations are to continue secondary prophylaxis indefinitely for these conditions.

E. Vaccines

1. Pneumococcal Vaccine

Pneumococcal infection, particularly pneumonia, is seen with increased frequency in HIV-infected individuals, even prior to the onset of severe immune deficiency (see Chapter 4). Vaccination is recommended for all symptomatic and asymptomatic HIV-infected patients, although response to the vaccine may be suboptimal. Revaccination every 5 years is probably appropriate.[25]

2. Influenza Vaccine

Influenza may be especially severe in the setting of HIV infection.[31] Secondary bacterial pneumonia may also be life-threatening. For this reason, annual immunization during influenza season is recommended for all HIV-infected patients.

3. Hepatitis A Vaccine

Individuals with antibody to hepatitis C virus (HCV) who lack antibody to hepatitis A virus (HAV) should be immunized against hepatitis A because of the increased risk of fulminant hepatitis in HCV-positive patients who contract hepatitis A.[25]

4. Hepatitis B Vaccine

Individuals lacking surface antibody to hepatitis B virus (HBV) should be vaccinated against HBV.

F. Other Measures to Avoid Infectious Complications

Patients should be instructed in effective handwashing and encouraged to maintain personal hygiene. Specific risks of contagion should be considered, these include occupational exposure, pet-related infections, travel, and foods.[25]

1. Occupational Exposure

Patients should be counseled about potential risk of occupational exposure to opportunistic pathogens.[25] The risk of uncontrolled exposure to *Mycobacterium tuberculosis* should be eliminated for individuals working in healthcare facilities, homeless shelters, and diagnostic laboratories. Patients living in areas endemic for histoplasmosis should avoid heavy exposure to soil, bird or bat droppings, and construction sites. Contact with farm animals may increase the risk of cryptosporidiosis, salmonellosis, and toxoplasmosis. The risk of infection with cytomegalovirus, hepatitis A virus, and cryptosporidium may be increased in child daycare facilities.

2. Pet-Related Infections

Contact with cats increases the risk of toxoplasmosis, bartonellosis, and cryptosporidiosis. Cats obtained should be more than a one year old and in good health. Litter boxes should be cleaned frequently and, if possible, by an HIV-negative, nonpregnant individual. Strict handwashing should be observed after any contact with cat

droppings or litter and after any handling of the cat. Cat scratches should be avoided, if possible, and, if they occur, washed thoroughly to reduce the risk of bartonellosis. If illness, particularly diarrhea, develops in the cat, a veterinarian should be consulted promptly.

Reptiles should be avoided to reduce the risk of salmonellosis. Gloves should be worn when cleaning fish tanks to avoid infection with atypical mycobacteria. Exotic pets should be avoided.

3. Travel

Several issues should be considered by the HIV-infected traveler:

- Travel to developing countries increases the risk of exposure to enteric pathogens, tuberculosis and, depending on the itinerary and anticipated activities, other potentially dangerous infections such as histoplasmosis, leishmaniasis, and strongyloidiasis.
- Access to medical care may be limited.
- HIV infection is a contraindication to most live-virus vaccines, such as those to prevent yellow fever or measles. Some of these vaccines are recommended for travel to certain areas.

4. Foods

To reduce the risk of salmonellosis, poultry should be cooked until no longer pink in the middle and foods containing raw eggs should be avoided. Water from rivers, lakes, streams, etc. may transmit cryptosporidiosis. As with all travelers, HIV-infected persons should avoid drinking tap water or eating fresh vegetables or fruits that may have been washed in tap water, in order to avoid enteric pathogens associated with traveler's diarrhea, such as *E. coli*.

G. Antiretroviral Therapy

Guidelines for the initiation and management of antiretroviral therapy are discussed in Chapters 10 and 11.

H. Follow-Up Care

1. Routine Care

A plan of care should be formulated for each patient, taking into account clinical and immunologic stage and viral load. Because of the high frequency of both minor medical complaints (see Chapter 7) and medication side effects (see Chapter 11), provision should be made for walk-in visits if feasible.

2. Urgent and Emergency Care

Patients should be provided with a means of rapidly contacting a provider with access to their medical records in the event of a sudden change in their condition. No universally accepted guidelines for triage and emergency management of HIV-

infected patients have been created. However, certain common symptoms should prompt urgent evaluation and care. These include:

Acute shortness of breath
High fever
Severe headache
Focal neurological findings or change in mental status
Focal or generalized seizure
Severe diarrhea, vomiting, or abdominal pain
Severe skin rash

Patients should be routinely instructed that they should go to the emergency room or seek immediate care from their provider if any of these symptoms develop.

Other symptoms should be evaluated within a few days but do not necessarily require emergency care. Among these are:

Mild-to-moderate vomiting or diarrhea
Persistent cough without high fever or shortness of breath
Mild skin rash
Low-grade fever (less than 102 degrees) without rigors

Patients should receive clear instructions on accessing care under any circumstances. A telephone triage system with a provider (e.g., a nurse) knowledgeable in HIV care should be considered in any practice or clinic caring for a large number of patients. A medication list should be provided to each patient so that treatment decisions can be made when the full medical record is not available.

3. Treatment Adherence

Adherence to treatment is critically important for patients taking antiretroviral therapy and medications to prevent or suppress opportunistic infections. Methods to evaluate and improve adherence to treatment are discussed in Chapters 10 and 11.

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6 Symptom-Oriented Evaluation and Management

CONTENTS

I. INTRODUCTION

A variety of medical complaints may be associated with HIV infection, especially at advanced stages of immune deficiency. A challenge for the clinician is to recognize how the presence of HIV infection may change the significance and implications of a specific complaint or physical finding. Among patients with advanced HIV infection, relatively minor complaints such as a headache, fever, or cough may signify life-threatening opportunistic infections or malignancies, which would not be considerations in the normal host. Even at earlier stages in the natural history of HIV infection, such common problems as diarrhea, chest pain, or fatigue must be viewed from the unique perspective of the complex, multisystem disorder that the virus causes. Furthermore, combination antiretroviral therapy has brought with it new disorders, most dramatically the lipodystophy syndrome producing novel clinical syndromes previously not seen in association with HIV infection. Finally, of course, the presence of HIV infection does not preclude other unrelated disorders.

This chapter presents an approach to the differential diagnosis and diagnostic evaluation of symptoms commonly encountered with HIV infection. Although minor complaints are common among HIV-infected patients (see Chapter 7), this chapter emphasizes the presenting manifestations of serious, debilitating, and life-threatening complications of HIV infection.

II. RECOGNIZING HIV INFECTION

A. The Acute Retroviral Syndrome

As discussed in Chapter 2, acute HIV infection is accompanied by a symptomatic illness in the majority of individuals. After an incubation period between 1 and 6 weeks, this illness is characterized by sore throat, skin rash, and, later, lymphadenopathy. Aseptic meningitis and other neurological abnormalities may also manifest in association with acute HIV infection. Despite its apparently high incidence, the acute retroviral syndrome is seldom diagnosed largely because it shares features with many other disorders and because the risk of HIV infection in an individual may not be recognized either by the individual or providers evaluating the complaints. What often marks the syndrome and may permit its recognition is its chronicity, often weeks to a month or more, while other similar illnesses, largely viral respiratory or enteroviral infections, typically last a week or less. Generalized lymphadenopathy and the diffuse rash which accompanies the syndrome are also rare in other viral infections among adult patients. Despite these potential clues, however, the provider evaluating unexplained aseptic meningitis or other "viral syndromes" should carefully question the patient about potential HIV exposure, particularly within the preceding month or two.

After a subsequent asymptomatic phase that typically lasts for several years, HIV-infected individuals may come to medical attention with signs of disease long before the appearance of the more dramatic, recognizable manifestations of acquired immunodeficiency syndrome (AIDS).

B. Symptomatic Infection

Because of the multisystem nature of HIV infection and the remarkable variety of associated clinical disorders (see Chapter 4), recognizing the nonspecific signs and symptoms of chronic HIV infection may be difficult, even among patients known to be at risk. When there is no clinical suspicion of HIV infection, this task may be impossible. The true significance of such nonspecific HIV-related symptoms as lymph node enlargement, diarrhea, and weight loss may not be initially recognized. Diagnostic confusion is particularly likely when the patient is not known to be at high risk for HIV infection and in geographic areas where prevalence rates are low. Even disorders associated with advanced stages of immune deficiency, such as invasive herpes simplex infection or lymphoma, may not initially be appreciated as being related to HIV infection. Therefore, evaluating disorders that result from HIV infection requires familiarity with the commonly seen syndromes, an ability to assess the likelihood of HIV infection, and a high level of awareness.

The likelihood that HIV-related signs or symptoms will be recognized as such can be increased by routinely and systematically questioning all patients about risk behavior during the course of the initial medical evaluation. Nonetheless, systematic risk factor assessment and directed testing may fail to identify a substantial proportion of HIV-infected patients because they are unaware of potential exposure or are reluctant to discuss risk behaviors.

Although some disorders, such as disseminated Kaposi's sarcoma, may be virtually diagnostic of HIV infection, all the symptoms and many of the specific disorders discussed in this chapter are encountered frequently in patients not infected with HIV. The new appearance of certain signs or symptoms, such as unexplained weight loss, fever, or persistent diarrhea, in a patient not known to be HIV-infected should prompt careful assessment or reassessment of potential risk factors. It should be kept in mind that many patients first come to medical attention with manifestations of advanced HIV infection, including AIDS, without any history of earlier HIV-related complaints.

What follows is an overview of the differential diagnosis and suggested diagnostic evaluation of several of the most common symptoms and signs seen in HIV-infected individuals. As with all patients, the evaluation of symptoms and signs of disease in HIV-infected patients must be individualized. The morbidity and cost of diagnostic studies must be taken into account and the extent of the diagnostic workup should reflect the likelihood that a treatable cause of the disorder can be identified.

The recent availability of a large number of new medications for the treatment of HIV infection and its complications has complicated the interpretation of symptoms. Side effects affecting the central nervous system, skin, or gastrointestinal tracts may cause diagnostic confusion with some of the entities discussed here. The reader is referred to Chapters 10, 11, and 15 for discussions of interpretation and management of medication side effects.

III. FEVER OF UNKNOWN ORIGIN

A. Incidence

Unexplained persistent fever, that is, fever of several weeks' duration for which no cause can be identified after a routine diagnostic evaluation, is a common phenomenon in HIV infection and may be encountered at any stage of disease.[1,2]

B. Differential Diagnosis

The differential diagnosis of persistent fever varies, depending on the stage of disease and degree of immunodeficiency. Self-limited fever is a common feature of acute HIV infection, but it is typically accompanied by other signs, including rash, headache, or oral ulcerations. Persistent fever may be seen in early symptomatic patients, especially in association with generalized lymphadenopathy; along with other constitutional signs, it was formerly termed lymphadenopathy syndrome or AIDS-related complex (ARC). This picture was associated with earlier progression to AIDS in early series.[3]

In patients with more advanced HIV infection, particularly those with CD4+ lymphocyte counts below 200 cells/mm^3 or with a previous diagnosis of AIDS, opportunistic infections may give rise to fever before the onset of more specific symptoms. A number of studies have demonstrated that mycobacterial infection is the most common cause of fever of unknown origin in this setting (see Figure 6.1).[2,4] A variety of other pathogens, including *Mycobacterium tuberculosis*, *Pneumocystis carinii* pneumonia (PCP), cytomegalovirus (CMV),[5] and, in endemic areas, histoplasmosis and leishmaniasis also may become apparent in this fashion. Visceral Kaposi's sarcoma

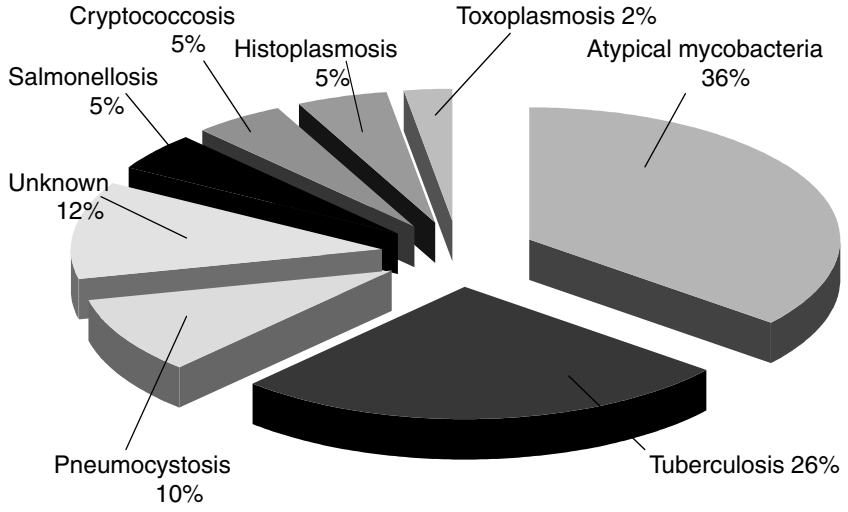

FIGURE 6.1 Causes of persistent fever in 42 AIDS patients. (Adapted from Pierone, G. et al., *International Conference on AIDS,* 1990.)

and lymphoma may cause nonspecific fever. Bacterial and fungal superinfections are particualry common among patients with indwelling intravenous catheters. Sinusitis, as well as periodontal and perirectal infections, all common in HIV-infected patients, occasionally become evident as undifferentiated fever. Endocarditis should be considered a potential cause of fever of unknown origin, especially among active injection drug users. Drug hypersensitivity is strikingly common in HIV-infected patients and may manifest as fever without any specific signs of allergy. This entity, common in HIV-infected patients, should also be considered when appropriate. For the purposes of this discussion, patients with specific endorgan syndromes, e.g., headache, cough, diarrhea, and rash, are excluded, and the approach to diagnosis presumes that fever is persistent (>2 weeks) and origin is obscure. Overall, the individual, most common cause of this clinical syndrome in advanced HIV disease is disseminated infection with *Mycobacterium avium* complex (MAC).[6]

C. Diagnostic Evaluation

The approach to a patient with persistent fever of unknown origin should be individualized, taking into account prior history, travel, exposure to other individuals who may have infection, animal exposure, and food history. Most important, the nature of prophylactic therapy the patient is receiving and the degree of immune impairment as indicated by the CD4+ lymphocyte count provide invaluable information to aid the clinician in determining the range of possible disorders to which the patient is susceptible (see Figure 6.2). If routine x-rays and laboratory studies, including cultures of blood, urine, and stool, repeatedly fail to provide a clue to the source of the fever, radionuclide scans or biopsy of the liver or bone marrow or both may reveal the diagnosis.

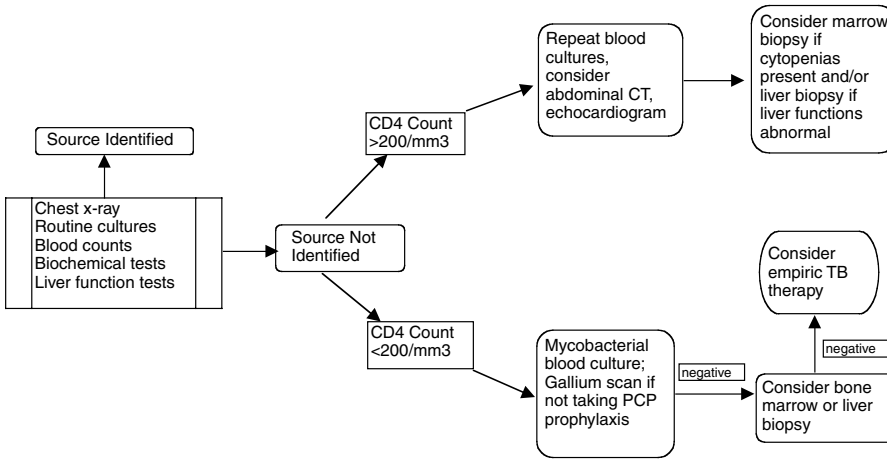

FIGURE 6.2 Suggested evaluation of persistent, unexplained fever.

D. Differential Diagnosis by CD4+ Cell Count

The opportunistic infections classically associated with AIDS [*Pneumocystis carinii* pneumonia (PCP), cerebral toxoplasmosis, cryptococcal meningitis, disseminated MAC infection, and locally invasive herpes simplex] occur exclusively in the setting of profound cellular immune dysfunction. In general, these disorders can be excluded in patients with stable CD4+ cell counts above 200/mm^3. Patients receiving and complying with trimethoprim-sulfamethoxazole prophylaxis are almost completely protected from both PCP and toxoplasmosis, and those receiving prophylaxis directed at MAC are at considerably lower of risk of developing symptomatic infection with this organism. Much of the published data on evaluation of fever has come from studies of patients with advanced immune deficiency. Fever at earlier stages of HIV infection, particularly among patients with CD4+ cell counts above 500/mm^3 should generally be evaluated as it would in non-HIV-infected hosts. It should be noted, however, that tuberculosis, infections due to *Streptococcus pneumoniae*, and herpes zoster occur at increased frequency even at early stages of HIV infection before the onset of significant, measurable cellular immune dysfunction.

1. Radionuclide Studies

Gallium-67 and indium-111 scanning may identify localized infections in some patients. In a study by Fineman and colleagues[7] of 36 AIDS patients with unexplained fever, 21 (78%) and 12 (44%) of 27 documented localized infections were identified by indium and gallium scanning, respectively. Atlhough less sensitive overall, gallium studies were particularly effective in detecting early PCP and infections involving the lymph nodes in this series. More recent reports have also found that gallium scanning leads to a diagnosis in a substantial proportion of AIDS patients with fever

of unknown origin.[8] However, the role of radionuclide scanning has not been established for patients at earlier stages of HIV infection.

2. Liver Biopsy

Because of the high incidence of liver involvement by opportunistic infections in AIDS, the value of liver biopsy in evaluating unexplained fever in HIV-infected patients (particularly those with a history of AIDS-related infections) appears to be substantially higher than in non-HIV-infected patients. In one series liver biopsy provided a specific diagnosis in most patients at various stages of HIV infection referred for evaluation of fever, but the diagnostic yield was more than twice as high in patients with a history of AIDS-defining infections than in those with no history of AIDS.[9] In this series liver biopsy was substantially more effective than bone marrow biopsy in detecting mycobacterial infection. The sensitivity of liver biopsy is particularly high in the presence of abnormalities of serum alkaline phosphastase[9] and liver function tests.[10] The yield of liver biopsy in the diagnosis of MAC infection was greater than that of bone marrow biopsy or blood culture in one comparative study.[11] The practical role of liver biopsy, however, has been controversial. Advocates point to the high diagnostic accuracy for mycobacterial infection, whereas others believe that most treatable infections diagnosed by liver biopsy may be identified by less invasive means.

3. Bone Marrow Aspirate/Biopsy

Examination and culture of bone marrow may identify the cause of unexplained fever in approximately one quarter of cases of patients with AIDS.[12] Disseminated infection with mycobacteria and *Histoplasma capsulatum* is commonly identified in this manner, particularly among patients at advanced stages of immune deficiency.

Bone marrow and culture in the evaluation of unexplained fever is probably most valuable when the CD+ lymphocyte count is below 200 cells/mm^3. Hematologic indications for bone marrow examination, such as thrombocytopenia or anemia, may arise at earlier stages of HIV infection.

4. Special Culture Techniques

Blood and tissue specimens, particularly of bone marrow and liver, should be stained specifically for the presence of mycobacteria and fungi. Because mycobacteria do not grow on routine culture media, pathology and microbiology laboratories should be informed when these organisms are suspected so that the specimen can be preserved properly and specific culture media can be used.

Disseminated histoplasmosis may be diagnosed by appropriate culture of blood or tissue specimens, although results of these tests are often negative or require several weeks of incubation. Serologic studies for histoplasmosis are relatively insensitive in immunocompromised patients.

Infection with CMV may be diagnosed by specific viral culture of blood or urine.

IV. LYMPHADENOPATHY

A. Incidence

Nonspecific lymph node enlargement was recognized as a common finding in HIV-infected patients early in the history of the HIV/AIDS epidemic. In one large study, 71% of HIV-infected homosexual men at various stages of disease were found to have significant lymphadenopathy.[13] The syndrome of persistent generalized lymphadenopathy, defined as unexplained palpable lymph node enlargement of more than 1 cm in two or more extrainguinal sites for at least 3 months, appears to represent a nonspecific reaction to HIV infection in most cases.

Such lymphadenopathy in early HIV infection often regresses with time, although the incidence of lymph node enlargement in AIDS and other advanced stage of HIV infection is less clear. Perhaps because hyperplastic lymph nodes tend to regress with progression to AIDS, autopsy series have shown low rates of significant lymphadenopathy.[14] However, involvement of the lymph nodes by opportunistic infections or malignancies becomes increasingly common as HIV infection progresses. Since the era of highly active antiretroviral therapy (HAART) began in the mid-1990s, a syndrome associated with immune reconstitution in which latent opportunistic infections are activated has been described,[15] often in association with significant lymphadenopathy.

Intra-abdominal lymphadenopathy was found in 48% of HIV-infected patients, primarily intravenous drug users, in one series[16] and correlated poorly with the presence of peripheral lymph node enlargement. Such lymphadenopathy has implications similar to those of generalized node enlargement and may represent nonspecific hyperplasia, infection, or malignancy.

B. Differential Diagnosis

The diagnostic significance of lymph node enlargement varies with the stage of HIV infection. As noted previously, a nonspecific generalized lymphadenopathy may be present at any point in the disease but is most common before the onset of profound immune deficiency and AIDS-related infections or malignancies. Histologic examination of lymph nodes from patients with persistent generaized lymphadenopathy typically reveals nonspecific hyperplasia. The challenge to the clinician is to distinguish persistent generalized lymphadenopathy, which requires no specific therapy, from opportunistic infection or neoplasm. Among the HIV-related infections that cause lymph node enlargement, mycobacterial infection, particularly tuberculosis, has been the most common in a number of published clinical series. In a retrospective chart review of lymph node biopsies in injection drug users in New York, 65% of biopsies from HIV-infected individuals revealed significant histologic findings, compared with 30% of specimens from non-HIV-infected patients.[17] Tuberculosis was the most common diagnosis in both groups in this study. Infection with *Mycobacterium tuberculosis* was also found on lymph node biopsy in 12 of 21 injection drug users undergoing evaluation of generalized lymphadenopathy in one series from New York City.[18]

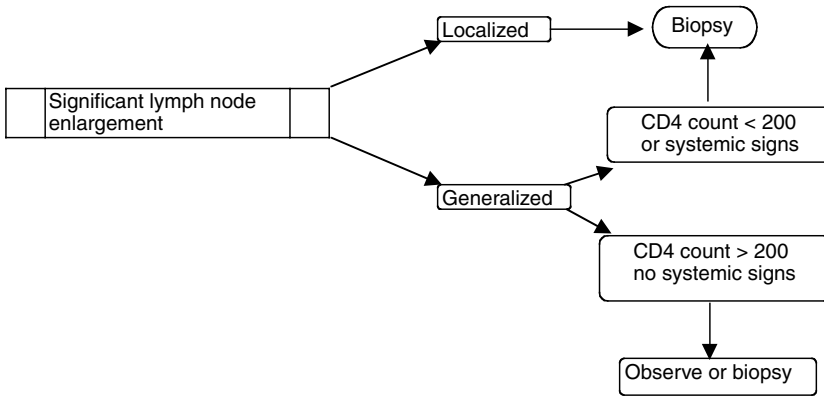

FIGURE 6.3 Suggested approach if lymph node biopsy is considered.

Bacillary angiomatosis, as well as infection with *Cryptococcus neoformans, H. capsulatum, Toxoplasma gondii*, and a variety of other organisms, may also involve the lymph nodes. Lymphoma may cause generalized or localized lymph node enlargement. Metastatic involvment of the lymph nodes was found in 44% of patients with cutaneous Kaposi's sarcoma in one autopsy series.

C. Diagnostic Evaluation

Lymph node biopsy should be performed in all cases in which a reasonable working diagnosis cannot be established on other grounds. Nonetheless, the decision to perform a biopsy must be individualized (see Figure 6.3). Patients with CD4 lymphocyte counts above 500/mm^3 who have symmetric, generalized lymph node enlargement may not require immediate biopsy because of the relatively small chance of opportunistic infection or malignancy. It should be noted, however, that lymphoma or lymphadenopathic Kaposi's sarcoma (KS) may occasionally occur before the onset of severe immune deficiency. While the incidence of KS has declined since the advent of current antiretroviral therapy, the incidence of lymphoma has not and, in fact, may be rising (see Chapter 4).

Patients at all stages with new, asymmetrical lymph node enlargement of uncertain etiology, particularly if it is rapidly enlarging, generally should undergo prompt biopsy. Those with lymphadenopathy confined to the inguinal region should be evaluated for syphilis and other sexually transmitted diseases (e.g., chancroid and lymphogranuloma venereum) before being considered for biopsy.

In skilled hands, fine-needle lymph node aspiration and cytologic examination may provide as much information as excisional biopsy and represents a less invasive alternative.

If lymph node tissue is obtained, specific stains and cultures for mycobacteria and fungi should be performed on all specimens because histopathologic studies alone may be misleading (e.g., granulomata may be absent in some cases of disseminated mycobacterial infection). With possible cryptococcal or *Toxoplasma gondii*

infection of the lymph nodes, serologic studies may be helpful in confirming the diagnosis.

Evaluation of deep intra-abdominal or intrathoracic node, where biopsy may be difficult, is especially challenging. If percutaneous biopsy is not feasible, bone marrow examination should be considered as a safe, intermediate diagnostic step. Open biopsy of lymph nodes in such cases is occasionally necessary, however, especially in the setting of unexplained fever or other systemic signs or when the lymph nodes are enlarging.

If the decision is made to defer biopsy, the patient should have frequent (monthly) reassessments. If additional lymphadenopathy develops or the nodes under observation undergo significant further enlargement or systemic signs such as fever, weight loss, or respiratory, gastrointestinal, or neurologic symptoms occur, biopsy should be reconsidered.

It should be remembered that the cause of lymph node enlargement can be definitively established only by tissue examination and culture.

V. HEADACHE

A. Incidence

Headache is a common complaint among HIV-infected patients in all stages of disease. Nearly 3% of patients who were admitted to an AIDS unit, as compared with 0.2% of those who were admitted to a neurology service, complained of headache in one series.[19] As the presence and severity of pain are subjective, it is important to recognize that pain at any site may be easily underestimated and HIV care providers often have an inadequate appreciation of pain and other complaints.[20]

B. Differential Diagnosis

The central nervous system is a common site of involvement by HIV and AIDS-related infections and malignancies. Cryptococcal meningitis and toxoplasmosis, the most common infections, and lymphoma are life-threatening disorders that are often accompanied by headache. Because headaches in HIV-infected patients often have such organic causes but are more often caused by non-life-threatening conditions, evaluation of this symptom may pose a difficult challenge to the primary care physician.

As with other clinical syndromes associated with HIV infection, the differential diagnosis is extensive and varies with the degree of immune deficiency. In general, headache is most likely due to a benign, non-infectious cause (migraine, tension headache, depression) early in the course of HIV infection, prior to the onset of significant immunologic impairment.[21]

HIV itself may cause meningitis at the time of acute infection or later in the course of disease. HIV meningitis may become evident as a self-limited process marked by fever, headache, and neck stiffness or as a chronic headache not associated with meningeal signs. This syndrome is seldom associated with signs of encephalopathy or focal neurologic deficits, which often accompany opportunistic infections involving the CNS.

When the CD4+ lymphocyte count falls below 200 cells/mm^3, opportunistic infections and CNS lymphoma become increasingly important causes of headache. Cryptococcal meningitis typically becomes evident as a subacute illness marked by fever and headache and, occasionally, focal neurologic signs. In a significant minority of cases the course may be more fulminant with rapid progression to coma and death. Cerebral toxoplasmosis is typically associated with headache, a depressed level of consciousness, focal neurologic abnormalities of recent onset, or a combination of these.

Sinusitis has been increasingly recognized as a complication of HIV infection at all stages of disease and may become evident as acute or chronic headache with or without clear evidence of sinus tenderness or nasal congestion. Periodontal disease, also common regardless of degree of immune deficiency, may also become evident as referred pain and headache. Localized varicella zoster infection frequently involves the head in HIV-infected patients and may present as obscure, unilateral headache prior to the eruption of characteristic vesicles.

Several medications commonly prescribed for HIV-infected also may cause headaches. A syndrome of fever, malaise, nausea, and headache may be encountered in patients receiving trimethoprim-sulfamethoxazole, and headache is a common side effect of several antiretroviral agents: the nucleoside reverse transcriptase inhibitors zidovudine (AZT) and zalcitabine (ddC) and the non-nucleoside reverse transcriptase inhibitors delavardine and efavirenz.

C. Diagnostic Evaluation

Because of the potentially life-threatening nature of the opportunistic infections and malignancies that may cause headache in HIV-infected patients, this symptom must always be regarded with concern and evaluated carefully and promptly, particularly in patients with CD4+ lymphocyte counts below 200 cells/mm^3 (see Figure 6.4).

In the patient with advanced immune deficiency, the evaluation of headache that lasts longer than several days, progressively worsens, or is accompanied by fever, neurologic abnormalities, or evidence of increased intracranial pressure should include CT or MRI and, if necessary, neurologic consultation. Serum cryptococcal antigen is almost always positive in cryptococcal meningitis. A lumbar puncture should be performed unless there is reason to suspect an intracranial mass lesion. Sinus radiographs or CT and dental evaluation should be considered for more subacute syndromes or if the workup is unrevealing.

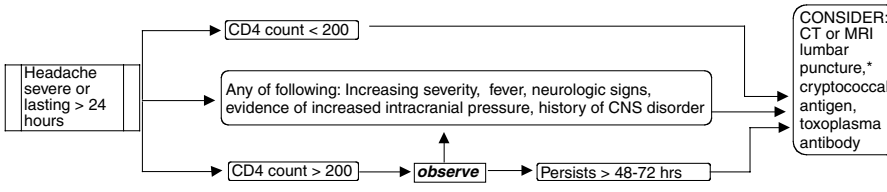

FIGURE 6.4 Suggested evaluation of persistent headache.

VI. SEIZURE

A. Incidence

Because CNS involvement by opportunistic infections, malignancies, and HIV itself is common, seizures are a relatively common manifestation of HIV infection (see Figure 6.5). In a retrospective review of more than 600 hospitalized patients at all stages of immune deficiency, 12% were noted to have new-onset seizures.[22] Of these patients, 46% had single and 54% had recurrent seizures. Seizures were generalized in 94%.

B. Differential Diagnosis

Approximately one third of HIV-infected patients with new-onset seizures are found to have an intracerebral mass lesion; 10 to 16% have meningitis and 3 to 11% have metabolic causes.[22,23]

Seizures have been reported to complicate 4 to 8% of cases of cryptococcal meningitis,[24,25] 14 to 23% of cerebral toxoplasmosis,[26,27] and 17% of cases of primary CNS lymphoma.[28] Less common HIV-related disorders such as CNS tuberculosis, PML, and herpes simplex encephalitis may also become evident as seizures, as may metabolic disturbances such as hyponatremia, uremia, and hypoglycemia complicating therapy with pentamidine.

The role of direct infection of the CNS by HIV is suggested by the observation that 7 to 44% of patients with AIDS dementia complex have seizures.[29] Recent studies have indicated that 24 to 46% of new-onset seizures may be attributed to HIV encephalopathy.[22,23]

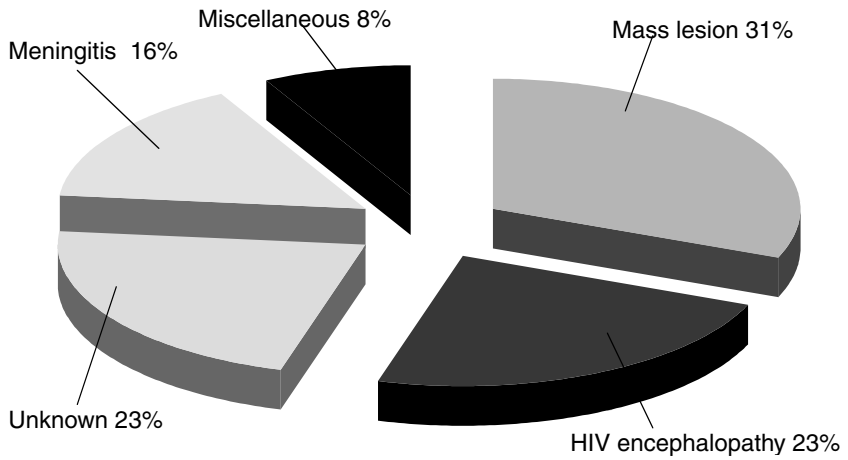

FIGURE 6.5 Etiologies of new-onset seizures. (Adapted from Holtzman, D.M. et al., *Am J Med,* 87, 173, 1989.)

C. Diagnostic Evaluation

HIV-infected patients with new-onset seizures, focal neurologic deficits, or both should undergo a thorough evaluation for CNS infection, malignancy, and metabolic derangements. Intracerebral mass lesions should be promptly excluded by CT or MRI. Serologic studies for toxoplasmosis and cryptococcosis may also provide helpful information.

VII. PERSISTENT COUGH OR DYSPNEA

A. Incidence

The lung is a target organ for many HIV-related disorders. Bacterial pneumonia and tuberculosis are seen more commonly among HIV-infected individuals than in the general population, even prior to or during the early stages of immune deficiency. True opportunistic respiratory infections, particularly *Pneumocystis carinii* pneumonia, are among the commonest complications of advanced immune deficiency. In addition, sinusitis, bronchitis, and other viral respiratory infections, including influenza, may be seen more frequently and cause more severe illness. Pulmonary hypertension may be seen, especially among patients with a history of injection drug use. Extrapulmonary disorders such as cardiomyopathy and hypercoagulable states with thromboembolic disease are also more likely in the presence of HIV infection. For all of these reasons, cough and dyspnea are frequent complaints among patients at all stages of immune deficiency.

B. Differential Diagnosis

The differential diagnosis of persistent cough or dyspnea in HIV-infected patients varies greatly with the stage of disease (see Table 6.1). In patients with CD4+ lymphocyte counts below 200 cells/mm^3 or with a history of AIDS, opportunistic respiratory infections such as PCP are of primary concern, particularly, but not exclusively, when fever or other systemic signs of infection are present. In contrast, bacterial pneumonia and pulmonary tuberculosis are common at all stages of HIV infection.

TABLE 6.1
Causes of Respiratory Complaints

CD4 cell count (per mm^3)	Likely Disorders
>200	Bacterial pneumonia, TB, bronchitis, sinusitis
<200	*Pneumocystis carinii* pneumonia, TB, bacterial pneumonia, KS, congestive heart failure

C. Diagnostic Evaluation

The evaluation of HIV-infected patients with a new or persistent cough should be guided, if time and the clinical situation permit, by the results of immunologic staging. New respiratory complaints in patients with CD4+ lymphocyte counts below 200 cells/mm^3 should be promptly evaluated with a chest radiograph and sputum analysis, including stain for acid-fast bacilli as well as routine fungal and mycobacterial culture. It should be recalled that PCP may present with a completely normal chest x-ray (see Chapter 4). If expectorated sputum is unrevealing or if PCP is suspected, sputum induction with immunofluorescent stain for *Pneumocystis* is appropriate. Properly performed, this procedure has a sensitivity in excess of 90%.[30] In cases where sputum cannot be obtained by induction, bronchoscopy with bronchoalveolar lavage (BAL) may be required to exclude the diagnosis of PCP.[31] Blood cultures should be performed in febrile patients. The patient should be quickly assessed for evidence of opportunistic malignancy or infection, particularly Kaposi's sarcoma and tuberculosis. Measurement of arterial blood gas levels and immediate hospitalization may be necessary, particularly for patients with progressive dyspnea accompanying a cough. If the chest radiograph is normal and there is no evidence of systemic bacterial infection, pulmonary gallium scanning may be useful in detecting early PCP.

If radiographic examination and gallium scanning provide no insight into the cause of cough, echocardiogram may identify patients with occult cardiomyopathy or pericardial disease causing congestive heart failure. The possiblity of bacterial endocarditis should be considered carefully, especially in patients who are active injection drug users.

Evaluation of cough in patients with CD4+ lymphocyte counts above 200 cells/mm^3 should include an early chest radiograph and assessment for systemic infection, in particular, infection caused by *Streptococcus pneumoniae, Hemophilus influenzae,* Legionnella species, or *M. tuberculosis*. In these patients, particularly those with CD4+ lymphocyte counts above 500 cells/mm^3, the diagnostic workup should also be directed at respiratory disorders unrelated to AIDS, such as asthma, chronic bronchitis, lung cancer, emphysema, and chronic interstitial disease.

VIII. CHEST PAIN

A. Incidence

Chest pain is an uncommon symptom in HIV-infected patients, although the exact incidence is unknown. As survival is prolonged by advances in therapy and the population of HIV-infected individuals ages, cardovascular disease is likely to become an increasingly common cause of chest pain. Perhaps accelerating this trend is the hyperlipidemia syndrome associated with antiretroviral therapy, which has been associated with progression of coronary artery disease in some individuals (see Chapters 10–13).

B. Differential Diagnosis

All HIV-infected patients with chest pain should be evaluated promptly with chest radiograph and electrocardiogram. If the pain is substernal, esophageal and cardiac causes are most likely. Patients with esophagitis usually note exacerbation of pain

with swallowing. The evaluation of such patients is outlined in the following section, which discusses dysphagia.

The evaluating of chest pain in the setting of HIV-infection should generally proceed along the same lines as indicated for other patients. Individuals with traditional risk factors for coronary artery disease (e.g., diabetes, smoking, hypertension, hyperlipidemia, family history) should be evaluated for acute ischemia, especially if they are taking antiretroviral therapy. Cocaine use, which is disproportionately common among HIV-infected individuals, also has been associated with acceleration of coronary artery disease as well as with acute coronary spasm.

Pulmonary causes of chest pain to be considered, especially if pain is accompanied by dyspnea at rest or with exertion, include pneumothorax resulting from active or past PCP, pulmonary embolism associated with hypercoagulability or immobility, or pulmonary hypertension related to prior injection drug use.

Substernal pain related to esophageal disorders (see below) is typically made worse by eating, but may, in some individuals, mimic acute myocardial ischemia.

IX. DYSPHAGIA AND ODYNOPHAGIA

A. Incidence

Difficulty swallowing (dysphagia) and pain on swallowing (odynophagia) are common complaints in HIV-infected patients, particularly among those at advanced stages of immune deficiency.

B. Differential Diagnosis

Esophageal candidiasis is the most common cause of dysphagia and odynophagia in patients with AIDS.[32] Other common esophageal disorders that may produce these symptoms include infection with herpes simplex virus, CMV or, in rare instances, other opportunistic pathogens. Esophageal ulcers directly related to HIV infection may also present in this fashion.

Other HIV-related disorders that may result in pain or discomfort on swallowing include painful oral lesions and noninfectious disorders involving the pharynx or esophagus, including apththous ulcers, Kaposi's sarcoma, squamous cell carcinoma, and lymphoma. Disruption of esophageal motility may complicate HIV-related esophageal disorders and contribute to the severity of symptoms.

The presence of oral candidiasis in patients with symptoms of esophagitis indicates a high likelihood of candida esophagitis. In one series esophageal candidiasis was demonstrated by upper gastrointestinal tract endoscopy in 88% of AIDS patients with oral candidiasis, regardless of symptoms.[33] However, either oral or esophageal candidiasis may occur alone. Pain on swallowing may be a clue to the presence of invasive infection.

C. Diagnostic Evaluation

Controversy exists regarding the optimum diagnostic workup for an HIV-infected patient with symptoms of dysphagia or odynophagia, specifically on the need for and timing of upper gastrointestinal tract endoscopy. Potential strategies include

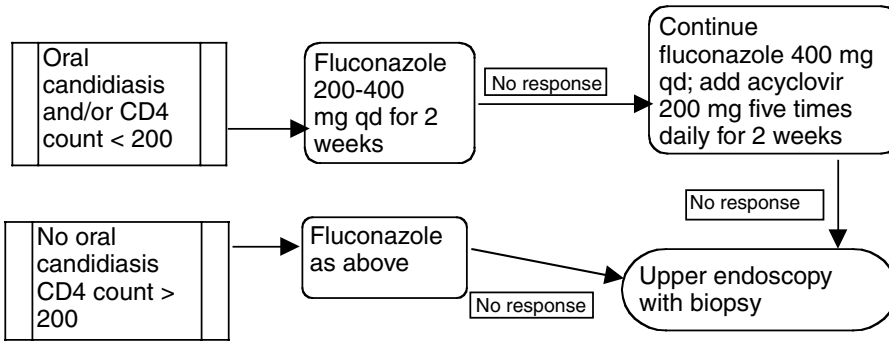

FIGURE 6.6 Therapeutic trial for patients with odynophagia.

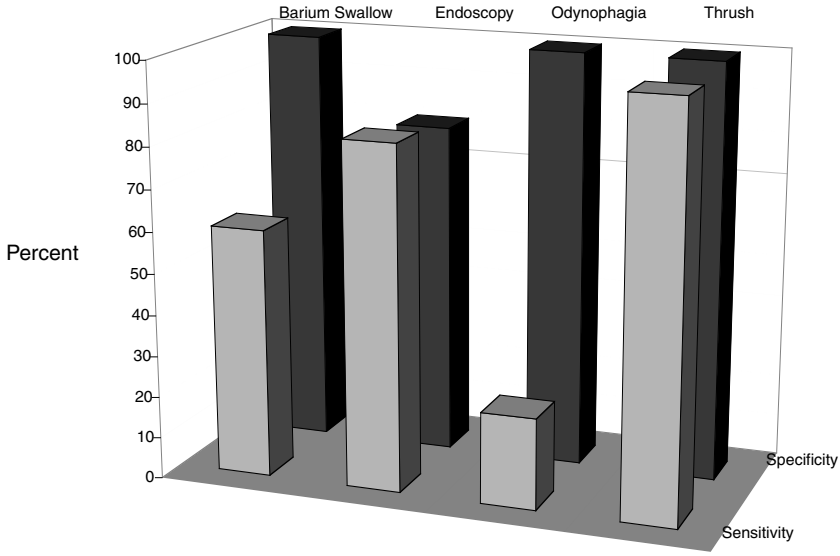

FIGURE 6.7 Diagnosis of Candida esophagitis. (Adapted from Porro, G. M. et al., *Am J Gastroenterol,* 84, 143, 1989 and Connolly, G. M. et al., *AIDS* 3, 453, 1989.)

endoscopy with biopsy as the initial diagnostic study, blind brushing of the esophagus through a nasogastric tube, barium radiography followed by endoscopy if the diagnosis is uncertain, and therapeutic trial of an antifungal agent such as fluconazole with radiographic or endoscopic investigation, or both for patients who do not respond to empiric therapy (see Figures 6.6 and 6.7).

In one large series in which double-contrast barium radiography was compared prospectively with endoscopy in HIV-infected patients who had a variety of upper gastrointestinal tract complaints, radiography had an overall sensitivity of only 31.1% and was particularly ineffective in detecting esophageal candidiasis.[34] In contrast, endoscopy was found to have a sensitivity of 97.5% in cases in which a diagnosis

was confirmed by histopathologic examination. These data indicate that negative results of barium radiography cannot always exclude active esophagitis. In another prospective study blind brushing of the esophagus through a nasogastric tube was found to have a sensitivity similar to endoscopy in the diagnosis of esophageal candidiasis in patients complaining of dysphagia or odynophagia.[35]

Despite the excellent diagnostic results that endoscopy provides, it may not be necessary that all patients be subjected to the discomfort, inconvenience, cost, and potential morbidity of this procedure. Because of the high degree of correlation between oral and esophageal candidiasis, a therapeutic trial of fluconazole can be considered in patients with oral candidiasis and esophageal symptoms, reserving endoscopy for those whose symptoms do not respond. Blind esophageal brushing, which could potentially be performed by the primary health care provider, might provide a relatively safe, inexpensive alternative to endoscopy in selected cases,[35] although the diagnostic sensitivity of the procedure compared with endoscopy has not been thoroughly evaluated.

When therapy for candidal esophagitis is initiated without histological confirmation of the diagnosis, it should be recalled that other HIV-related disorders may produce identical symptoms.

X. NAUSEA/VOMITING

A. Incidence

Nausea and vomiting are common complaints among patients with advanced disease as well as patients taking a variety of commonly used medications.

B. Differential Diagnosis

Disorders such as viral hepatitis, pancreatitis, biliary disease, or intestinal obstruction due to lymphoma, Kaposi's, or other mass lesions may present in this fashion. Many commonly used medications, including trimethoprim/sulfamethoxazole, protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors (especially nevirapine), hydroxyurea and macrolide antibiotics, isoniazid, and pyrazinamide may cause nausea and vomiting on the basis of hepatic or pancreatic inflammation or as idiopathic side effects. Persistent vomiting should also be considered a possible manifestation of increased intracranial pressure caused by cerebral mass lesions associated with toxoplasmosis, lymphoma, or other disorders.

C. Diagnostic Evaluation

Intestinal obstruction should be excluded with appropriate radiographic studies in any patient with persistent vomiting. Liver function tests, as well as amylase and lipase determinations, should be obtained. Abdominal imaging studies may be necessary to excluded cholelithiasis or mass lesions resulting in partial bowel obstruction. A careful neurological examination should be performed. If papilledema, focal neurological deficits, or headache is present or if no other etiology of persistent vomiting can be established, computed tomography or magnetic resonance imaging of the brain should be performed.

XI. ABDOMINAL PAIN

A. Incidence

Abdominal pain is a frequent complaint among patients at advanced stages of HIV infection and may reflect disease of the bowel, spleen, pancreas, peritoneum, liver, or biliary system as well as medication side effects. Bowel perforation and other surgical emergencies occur in HIV-patients, perhaps more frequently than in the general patient population. The challenge to the clinician is distinguishing among the large number of causes or origins of abdominal pain that do not require immediate intervention and the occasional intra-abdominal catastrophe or life-threatening medication effect.

Published studies of patients who seek medical attention with abdominal pain or intra-abdominal disease have focused on those with advanced HIV infection. Less is known about the incidence of abdominal pain in earlier stages of disease. In one series of more than 200 hospitalized AIDS patients, 12.3% reported abdominal pain for 2 or more days during their hospitalization.[36] In another study, 4.2% of more than 900 consecutive hospitalized AIDS patients required abdominal surgical procedures, including cholecystectomy, appendectomy, and exploratory.[37]

B. Differential Diagnosis

Pain associated with diarrhea or vomiting suggests infectious enteritis such as that caused by cryptosporidiosis, microsporidiosis, isosporiasis, or salmonellosis or infection with *Clostridium difficile* and other pathogens. Cryptosporidiosis was the most common intestinal infection in one large series of AIDS patients with abdominal pain, being seen in 31% of cases.[36] Infections with *Campylobacter* species and *Giardia lamblia* were also seen. The pain associated with intestinal infections in these patients was most often diffuse. Diarrhea and hypoalbuminemia were evident in the majority of cases, and more than 40% of patients complained of nausea and vomiting.

Pain localized to the right upper quadrant or more generalized throughout the abdomen may indicate biliary tract disease or hepatitis.

Generalized intra-abdominal infection with cytomegalovirus (CMV), cryptococcus or MAC is often associated with abdominal pain.[38] Diffuse pain with peritoneal signs should raise the possibility of peritonitis resulting from (1) bowel perforation caused by invasive infections or malignancies, including tuberculosis, histoplasmosis, CMV, aspergillosis, lymphoma, or Kaposi's sarcoma; or (2) direct involvement of the peritoneum by HIV-related infections such as tuberculosis, toxoplasmosis, histoplasmosis, or cryptococcosis. HIV-infected patients undergoing chronic ambulatory peritoneal dialysis appear to be at higher risk for bacterial and fungal peritonitis than other such patients.[39]

Midepigastric or left upper-quadrant pain may signify pancreatitis related to biliary tract disease or to drug therapy, particularly with pentamidine, didanosine, zalcitabine, lopinavir, or foscarnet. Appendicitis with typical right-sided abdominal pain may occur in association with CMV infection and aspergillosis.

An important and potentially life-threatening cause of abdominal pain is the syndrome of lactic acidosis, hepatomegaly, and hepatic steatosis associated with nucleoside therapy (see Chapters 10 and 11).

XII. GASTROINTESTINAL BLEEDING

A. Incidence

Although incidence data are sparse, significant bleeding appears to be an uncommon manifestation of HIV-related gastrointestinal tract disorders but is included in this discussion because it has a broad differential diagnosis and may rapidly become life-threatening.

B. Differential Diagnosis

Causes of bleeding not related to HIV infection should be sought in HIV-infected individuals with significant gastrointestinal blood loss. Potential HIV-associated causes include esophagitis, invasive infection of the small or large bowel (e.g., with CMV, salmonella, or aspergillus species), and Kaposi's sarcoma or lymphoma involving any region of the intestinal tract.

C. Diagnostic Evaluation

Evaluation should proceed as in non-HIV-infected patients. Confirmed or suspected bleeding should be investigated with barium studies and endoscopic procedures when indicated.

XIII. SPLENOMEGALY

A. Incidence

Splenomegaly is a common nonspecific manifestation of HIV infection at advanced stages of disease. More than 70% of AIDS patients were found at autopsy to have enlarged spleens in one early series.[40] A comparably high incidence of splenomegaly has been detected by computed tomography (CT).[41] The incidence of splenomegaly in earlier stages of HIV infection is less clear.

B. Differential Diagnosis

The cause of splenomegaly in HIV-infected patients is often obscure. The diagnostic evaluation should serve to exclude treatable diseases.

1. Opportunistic Infections

Opportunistic infections directly involving the spleen are most likely to occur in patients who are at advanced stages of immune deficiency. Infection with MAC, salmonella, and CMV, as well as involvement with Kaposi's sarcoma, was seen in one series of patients undergoing splenectomy.[42] Cryptococcosis and histoplasmosis with splenic involvement[14] and tuberculosis also have been described, as has a variety of less common infections. In tropical areas of South America, Asia, and Africa, visceral leishmaniasis and schistosomiasis should be considered.

2. Malignancies

The spleen is a common site of involvement by metastatic Kaposi's sarcoma[42] and lymphoma.[43]

C. Diagnostic Evaluation

The best diagnostic approach to splenomegaly in the setting of HIV infection is unknown. Large clinical series focusing on the causes of splenomegaly at various stages of HIV infection and the yield of various diagnostic tests are not available to guide the clinician. Because of this lack of clear data, it is probably prudent to attempt to identify a specific cause in all patients when feasible. The wide variety of disorders that may involve the spleen and the frequency with which splenomegaly is seen in HIV-infected patients may present obstacles to designing an efficient workup. Patients with splenomegaly and unexplained fever, weight loss, or other signs or symptoms that may represent a disseminated infection or malignancy should probably be evaluated more extensively than those without these.

Even in other asymptomatic patients, a careful effort should be made by means of the history, physical examination, routine laboratory data, and other diagnostic studies to establish a working diagnosis (e.g., nonspecific splenic enlargement caused by HIV infection itself or by a specific disorder unrelated to HIV infection, such as cirrhosis with portal hypertension).

Diagnostic studies of potential value include abdominal imaging studies to evaluate for mass lesions or abscesses within the spleen and to identify other organ involvement, such as hepatomegaly or lymphadenopathy, that might provide a clue to the cause of the splenic enlargement. A thorough evaluation of other common sites of involvement by opportunistic infections and malignancies is important, including the respiratory and gastrointestinal tracts, the skin, the lymphatics, and the central nervous system. Blood cultures for pathogens known to disseminate to the spleen, particularly MAC, cryptococcus, histoplasma, and CMV, as well as routine bacteria, may be necessary. Biopsy of the liver or bone marrow, if feasible, may aid in excluding disseminated infection (mycobacterial or fungal) or malignancy involving the spleen. Exploratory laparotomy may be necessary in rare instances of symptomatic patients in whom a definitive or reasonable working diagnosis cannot be made.

XIV. DIARRHEA

See Chapter 7.

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7 Diagnosis and Management of Minor Medical Problems

CONTENTS

I. INTRODUCTION

The number of medical disorders associated with immunodeficiency virus (HIV) infection continues to grow. Although life-threatening infections and malignancies have justifiably received the most attention, less devastating problems, often chronic and uncomfortable, may have an enormous impact on quality of life. The physician caring for HIV-infected patients is constantly confronted with a variety of these seemingly disparate disorders demanding effective management. Control of problems such as molluscum contagiosum, peripheral neuropathy, anorexia, and diarrhea may be difficult or impossible. This frustrating dilemma may exhaust both the patient and the provider. Distinguishing side effects of medications from HIV-related pathology is a constant challenge, particularly among patients with diarrhea, neuropathy, or skin rash.

With a combination of persistence and ingenuity, however, most of the conditions discussed in this chapter can be adequately controlled in the majority of patients.

What follows is a discussion of common HIV-related disorders that do not normally constitute a direct threat to life. Those included are at least partially amenable to medical therapy and can often be managed with little or no diagnostic evaluation. Other common problems such as headache, cough, fever, visual disturbance, and memory loss often represent serious complications of AIDS. The approach to these symptoms is covered in Chapter 6.

In some instances, complaints that initially appear minor may progress to devastating morbidity. This is especially true of neuropathy, diarrhea, and anorexia or wasting. Skin disorders such as molluscum contagiosum or seborrheic dermatitis may have severe cosmetic effects. Any of the disorders discussed may have a significant psychological impact on the patient leading to discouragement and poor adherence to antiretroviral therapy.

A. Mucocutaneous Disorders

1. Oropharyngeal Candidiasis (Thrush)

Oral candidiasis occurs in more than 90% of AIDS patients.[1,2] Asymptomatic colonization of the oropharynx by *Candida albicans*, even among patients without thrush,[3] is frequently present in homosexuals who are not HIV-infected. The onset of oral candidiasis was predictive of progression to AIDS in longitudinal studies prior to modern antiretroviral therapy.[4] The diagnosis of oral candidiasis is usually made on clinical grounds on the basis of characteristic white plaques on the palate, buccal mucosa, or tongue. Microscopic examination and culture of biopsy specimens or scrapings may be required to confirm the diagnosis in atypical cases. Symptoms are usually minimal in mild cases but extensive thrush can cause pain and alteration in taste and can lead to anorexia and difficulty in complying with medication regimens.

Several topical and systemic forms of therapy are effective for oral candidiasis. The most commonly used agents are oral fluconazole and clotrimazole given as a troche. Comparative data indicate that each is highly effective—response rates are greater than 90%[5]—although cure rates are higher with fluconazole[6] leading to a longer time to relapse. Ketoconazole, itraconazole, or topical nystatin may also be effective. Widespread use of these agents has, unfortunately, led to increasing rates of resistance of *Candida albicans* to these azole compounds[7–9] as well as emergence of *Candida krusei*, a species which is inherently resistant to these agents.

Clotrimazole troches should be taken five times daily and allowed to dissolve in the mouth over 15 to 30 minutes.[10]

Therapy with fluconazole is usually initiated at a dose of 200 mg daily and then continued at 100 mg daily until resolution occurs, typically within several days. Suppressive therapy should be considered in patients with frequent recurrences and may be given daily[11] or weekly.[12] *Candida* strains resistant to fluconazole may emerge during prolonged suppressive therapy,[5] leading to treatment failure. Itraconazole may remain effective in some cases of fluconazole resistance,[13] but, in severe cases, intravenous amphotericin B must occasionally be used to maintain symptomatic control. Results using an oral amphotericin suspension have been disappointing.[14]

Recently, evidence has emerged that lactoferrin and lysozyme, two proteins normally present in the saliva, may exert an inhibitory or fungicidal effect on various *Candida* species[15,16] and that mouthwash containing these compounds may be effective in some cases of refractory thrush.[17]

2. Apthous Stomatitis

Oral aphthous ulcers are a common complication of HIV infection. Because these lesions can be severe, they may interfere with eating to the point of causing malnutrition in extreme cases. Although data on the incidence are unavailable, the prevalence of major aphthous ulcers was 3% in one series that included more than 750 individuals.[18] Friedman and others[19] diagnosed aphthous stomatitis in 60% of HIV-infected patients with mouth ulcers not healing spontantiously within 2 weeks. Recurrent aphthous ulcers are usually seen in association with symptomatic HIV disease and significant immunodeficiency.[20,21]

The diagnosis is confirmed by excluding infectious causes by means of appropriate cultures and, if necessary, biopsy. Other common causes of mouth ulcers include infection with herpes simplex virus, cytomegalovirus (CMV), mycobacteria, and fungi.

Therapy with topical oral or intralesional corticosteroid preparations is generally highly effective.[22] Systemic therapy with prednisone is also effective[23] and may be administered briefly for severe recurrent attacks not responding to topical therapy. Pentoxifylline in a dose of 400 mg three times daily was found to be effective in a small number of patients in one study.[24] Thalidomide has also been reported to be effective,[25] but must be used under carefully supervised conditions because of the risk of teratogenicity.

3. Seborrheic Dermatitis

Seborrheic dermatitis is a chronic, inflammatory skin disorder commonly encountered in HIV-infected patients. Although the condition is diagnosed in less than 3% of the general population,[26] it was seen in more than 80% of patients with acquired immunodeficiency syndrome (AIDS) and in more than 40% of patients with symptomatic HIV infection in one series.[27] The cause of seborrheic dermatitis is unknown, although some data suggest a role for the fungus *Pityrosporum orbiculare*;[28] the significance of this organism in HIV-related seborrheic dermatitis has been challenged.[29]

Seborrheic dermatitis typically appears as patches of erythema and scaling involving the scalp, eyebrows, nasal folds, and cheeks. The skin behind the ears, over the sternum, and in the genital region may also be involved. Although the condition poses no significant threat to health, patients are often distressed because of its cosmetic impact.

Combined therapy with topical corticosteroids (e.g., 1% hydrocortisone cream applied twice daily) and topical antifungal therapy (particularly clotrimazole) is at least partially effective in most cases, although relapse rates are high.

4. Dry Skin

Generalized dryness of the skin (xerosis and ichthyosis) was seen in 30% of patients with AIDS or symptomatic HIV infection in one series[30] and can be a persistent source of discomfort. Typical manifestations are flaking, pain, and pruritis, which

may be intense. All skin areas may be involved. Patients should be instructed to use only soaps containing emollients. Liberal use of moisturing lotions may provide substantial relief.

5. Molluscum Contagiosum

Molluscum contagiosum is a skin infection caused by the Molluscum contagiosum virus, a member of the poxvirus family. It is thought to be transmitted by close, including sexual, contact. Typical lesions consist of umbilicated papules. Lesions are most commonly seen in the genital region and may regress spontaneously in normal hosts. Disseminated infection may be seen with HIV infection and other immunodeficiency states.

In one series[30] 9% of patients with AIDS or symptomatic HIV infection were found to have molluscum contagiosum lesions. Extragenital lesions are common in HIV-infected patients. The face is most frequently involved, although widespread dissemination may also be present. The diagnosis should be confirmed by biopsy because other HIV-related skin disorders, particularly cryptococcosis, may cause identical lesions.

Although molluscum contagiosum involves only the skin and does not pose a threat to survival, patients are often disturbed about the cosmetic effect, especially of facial lesions. Curettage, cryotherapy, or topical cantharidin may be effective for individual lesions, although attempts at treatment are often frustrated by continued dissemination. Dermatologic consultation, especially for management of facial lesions, should be considered.

6. Fungal Skin Infections

Cutaneous candidiasis and dermatophytosis were seen in 47% and 30%, respectively, of patients with AIDS and symptomatic HIV infection in an early series.[30]

Candidiasis is typically characterized by erythema and pustules in the intertriginous areas. Infections with dermatophytes (*Trichophyton mentagrophytes, T. rubrum*, and *T. tonsurans; Microsporum canis* and *M. audouinii*; and *Epidermophyton floccosus*)[31] may become evident as tinea cruris, tinea capitis, or tinea corporis or as psoriaform plaques. Fungal infection of the webs of the hands or feet occurs alone or may accompany onychomycosis. Tinea versicolor caused by the nondermatophyte yeast *P. orbiculare* is also commonly encountered in HIV-infected patients.

The diagnosis of fungal skin infections can usually be confirmed by culture and by microscopic examiation of scrapings after adding 10% potassium hydroxide.

Localized dermatophyte infections are best treated with topical agents. However, patients with nail, hair, or widespread cutaneous involvement usually require oral antifungal therapy. Topical imidazole compounds such as clotrimazole, miconazole, and ketoconazole generally are effective against dermatophyte and candidal infections as well as tinea versicolor. Medication should be applied twice daily, and therapy should be continued for several weeks.

In extensive dermatophyte infections or when topical therapy fails, systemic therapy with oral griseofulvin 250 to 1000 mg daily, depending on the preparation,

may be effective. Therapy should be continued for several months. Published experience with griseofulvin therapy in the setting of HIV infection, however, is limited. Infections caused by dermatophyte species unresponsive to griseofulvin or by *Candida* or *Pityrosporum* species may respond to therapy with oral ketoconazole or itraconazole. Dermatologic consultation should be considered in cases of widespread infection or when topical therapy is ineffective.

7. Pruritic Papular Eruption

This condition, the cause of which is unknown, may cause generalized pruritis. The rash, which typically waxes and wanes, consists of papules and nodules and often covers a large area of the body. Histologic findings include perivascular and perifollicular infiltrates by mononuclears and eosinophils. Therapy with antihistamines and topical corticosteroids has limited effectiveness. Ultraviolet phototherapy may be helpful in some cases.[32]

8. Fungal Nail Infections

Fungal infection of the nails (onychomycosis) is common in HIV-infected patients. The involved nails typically become white and opaque and may subsequently become deformed and fragmented. The condition may be caused by *C. albicans* or by dermatophytes, especially *T. rubrum*.

Therapy of onychomycosis in HIV infection has not been thoroughly studied. In general, oral rather than topical agents are needed. Griseofulvin (10 mg/kg daily) traditionally has been the drug of choice in non-HIV-infected patients. Data regarding toxic effects in HIV-infected patients are limited, however, and therapy must be continued for at least 6 months.

Both ketoconazole and itraconazole represent effective alternatives to griseofulvin. Infections in 13 of 16 patients were cured by 3 months of therapy with ketoconazole (200 mg orally per day) after nail avulsion in one series.[33] Infections improved in more than 50% of cases and were cured in 20% (toenail) and 43% (fingernail) in an open study of patients intolerant of griseofulvin.[34] Itraconazole has been shown to be highly effective in nail infections caused by *C. albicans*[35] and to be superior to griseofulvin in onychomycosis caused by dermatophytes.[36]

B. Sinusitis

Sinusitis, both allergic and infectious, occurs with increased incidence in HIV-infected patients and should be considered in the differential diagnosis of persistent headache, fever, and nasal or postnasal discharge. Symptoms may be acute or chronic and may, in some patients, persist in continuous or relapsing form for years. Conversely, a significant proportion of patients with radiographic evidence of sinusitis may be asymptomatic.

Small and colleagues[37] diagnosed atopic sinusitis associated with high circulating immunoglobulin (IgE) levels in 59% of 37 HIV-positive patients. In a review of magnetic resonance imaging (MRI) studies performed on 75 homosexual men without sinus-related complaints, Armstrong and colleagues[38] found moderate sinus mucosal

thickening in 7 of 52 HIV-infected men as compared with none in 23 HIV-negative controls. In a large, retrospective series, 72 (10.7%) of 667 inpatients admitted to an HIV ward were found to have sinusitis, 58% of whom were refractory to therapy.[39]

Although the precise pathogenesis of sinusitis in HIV-infected patients is unclear, a surprisingly wide variety of microorganisms has been implicated in some cases. Both typical sinus pathogens such as *Streptococcus pneumonia, Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pyogenes*, and *Staphylococcus aureus*[40,41] and unusual organisms have been reported, particularly among patients with severe immunosuppression. Among the less conventional organisms, *Pseudomonas aeruginosa*[42] appears to be particularly common. *Listeria* monocytogenes, *Aspergillus* organisms, zygomycetes, and CMV are rare causes.

As previously mentioned, the diagnosis of sinusitis may be obvious or obscure. It should be suspected in any patient with persistent, unexplained headache or prolonged fever in the setting of sinus complaints. Sinusitis should also be considered in patients with unexplained fever in the absence of specific complaints. Physical findings may be minimal, although nasal endoscopy has increased diagnostic accuracy.[43] Routine sinus x-rays are generally unhelpful. Computed tomography (CT) is the technique that best displays the anatomy of the sinuses, but it cannot distinguish viral from bacterial causes. Sonography and magnetic resonance imaging give less precise information.

Therapy of acute sinusitis should include both a decongestant, such as pseudoephedrine, and an antimicrobial agent dictated by severity of the symptoms. If the patient can be treated on an ambulatory basis, therapy with an antibiotic directed against the common pathogens listed earlier (e.g., amoxicillin, amoxicillin and clavulanate, trimethoprim-sulfamethoxazole, ofloxacin, or cefuroxime) may be effective. In more severe cases, particularly when the CD4+ lymphocyte count is below 200 cells/mm^3, broader antibacterial agents specifically active against *P. aeruginosa* should be considered. Parenteral therapy and drainage may be indicated in particularly severe cases. The choice of antimicrobial therapy should be tailored to the results of cultures. In any case, treatment should be continued for several weeks.

C. Peripheral Neuropathy

Symmetrical, distal sensory neuropathy is a common manifestation of HIV infection, particularly among patients with severe immune deficiency, with an annual incidence of approximately 8% when the CD4 cell count is below 100/mm^3.[44] The syndrome often presents initially with paresthesias but becomes progressively more painful in many individuals. A similar picture may be seen as a side effect of several nucleoside antiretroviral agents, zalcitabine, stavudine and, to a much lesser degree, didanosine. Approximately one quarter of individuals taking zalcitabine or stavudine will develop peripheral neuropathy[44,45] within several months. Unfortunately, discontinuation of these agents often leads to worsening of neuropathic pain for several weeks before, in most individuals, sensory abnormalities resolve.

The diagnosis of peripheral sensory neuropathy is usually made clinically, although myelopathy must be excluded if the diagnosis is in doubt. Other potential etiologies, particularly diabetes mellitus, neurosyphilis, and vitamin deficiencies should also be ruled out.

Therapy with analgesics is often inadequate. Other agents which may be effective in some cases include amitriptyline, gabapentin, carbamazepine, dilantin, or valproate. Unpublished data apparently have suggested that L-acetyl carnitine may also be effective, although no controlled data have been published at this time. In patients receiving any of the nucleoside agents associated with neuropathy, consideration should be given to changing the antiretroviral regimen. Alternatives among the nucleoside class—zidovudine, abacavir, and lamivudine—do not appear to cause peripheral neuropathy often.

D. Nonspecific Diarrhea

Diarrhea, defined as at least two watery bowel movements per day, is a common complaint among HIV-infected patients at all stages of disease. In Chapter 4, specific etiologic agents are reviewed, and in Chapter 8, the diagnosis and management of intestinal pathogens, including those which cause diarrhea, are discussed. Frequently, however, no specific etiology is identified and diarrhea persists for weeks or months, especially among patients at advanced stages of immune deficiency. In addition a number of antiretroviral agents, particularly protease inhibitors and other medications taken on a long- or short-term basis, may cause diarrhea. In many individuals only symptomatic therapy may be appropriate.

Specific features of the medical history may be helpful in identifying those patients whose diarrhea represents systemic or locally invasive infection. For example, *Mycobacterium avium* complex (MAC) or cytomegalovirus (CMV) infection are often associated with diarrhea in patients with advanced immune deficiency and typically cause systemic symptoms such as fever, weight loss, and anorexia. Findings of malabsorption suggest small bowel agents such as *Cryptosporidium*, while blood or mucus in the stool are often indicative of large bowel inflammation with invasive bacteria (e.g., *Salmonella, Shigella, E. coli, Clostridium difficile*, or amebiasis). Patients should be questioned about recent travel and past history of diarrheal illness.

Routine stool cultures and examination of the stool for parasites, including the coccidial organisms (*Cryptosporidium*, *Isospora*, etc.), should be performed on all patients presenting with chronic diarrhea (>30 days) or acute diarrhea in association with signs of invasion. In cases of persistent diarrhea where no etiology can be determined by stool analysis, endoscopy may be diagnostic.

Therapy of specific infections is addressed in other chapters (see above). Symptomatic therapy of diarrhea of unknown etiology is often frustrating. Antiperistaltic agents such as loperamide or diphenoxylate hydrochloride with atropine and opioids may lead to problems of hypomotility and even dependency. Kaolin and pectin mixtures, which act as absorbents, and bismuth preparations, which are antisecretory agents, may be tried but are seldom effective. The somatostatin analog octreotide, once used commonly for refractory diarrhea, has not been shown to be more effective than other therapies.

Many patients who achieve viral suppression with antiretroviral therapy experience resolution or improvement in chronic diarrhea. Diarrhea related to this therapy is discussed in Chapters 10 and 11.

E. Wasting

Involuntary weight loss (wasting) was recognized early in the epidemic as a common feature of HIV infection, even before the appearance of opportunistic infections and malignancies. Although modern antiretroviral therapy has dramatically improved prognosis and quality of life, wasting remains a common problem for many patients. In a recent report, over one third of individuals, half of whom were receiving antiretroviral therapy, met at least one criterion for the HIV/AIDS wasting syndrome.[46] This syndrome is discussed in Chapter 8.

F. Pain Management

Musculoskeletal, neuropathic, and gastrointestinal pain syndromes are common among HIV-infected individuals, especially those at advanced stages of immune dysfunction.[47] As in other conditions associated with pain, providers often underestimate the severity of pain in HIV-infected patients and frequently fail to treat pain adequately, often out of concern that dependency will result, especially in patients with a history of substance abuse, or because of lack of familiarity with available analgesics. The evaluation of pain should be performed in a systematic manner with a careful assessment of the impact on daily activities.

Patients reporting pain should be questioned thoroughly about location, pattern, and severity. Specific triggers and patterns of radiation of pain should be delineated. Symptoms associated with pain may give an indication of etiology (vomiting, diarrhea, visual disturbances, difficulty concentrating, joint stiffness, etc.) or of severity (diaphoresis, loss of mobility). The impact of pain on critical functions, including sleeping, eating, walking, sitting, and standing, should be discussed. A thorough history of prior pain therapy should be obtained.

Specific treatment strategies must depend on the presumed etiology of pain. Bone and joint pain may be more amenable to non-opioid medications such as acetominophen or nonsteroidal anti-inflammatory drugs. Anticonvulsants or tricyclic antidepressant agents are particularly helpful in the management of neuropathic pain. Opioids are available in a wide variety of systemic forms, both oral and topical application. The goal of pain management should be to maximize performance by balancing comfort with medication side effects. This often requires a graded approach, in which non-opiate drugs are used initially in increasing doses, if necessary. Opiate agents are typically reserved for cases in which no alternative has been effective. Little data suggest that the use of opiates in appropriate medical settings creates a significant risk of dependency.

G. Periodontal Disease

Periodontal disease is common in HIV-infected individuals and occurs in a spectrum ranging from linear gingival erythema (LGE) to necrotizing ulcerative periodontitis (NUP) and, occasionally, to necrotizing stomatitis (NS). These conditions are distinct from conventional periodontal disease in their severity and poor response to dental hygiene and professional care.

LGE presents as a band of erythema at the gingival margin, without the associated plaque seen in conventional periodontal disease.[48] In some patients this progresses to NUP, which features ulcerations, bleeding, and bone and tooth loss.[49] Progression to NS may occur with the appearance of larger, often necrotic, ulcers and localized lymphadenopathy as well as systemic signs of infection. A variety of aerobic and anaerobic bacteria, as well as *Candida* species have been proposed as etiologic agents in HIV-related periodontal disease. As in many of the conditions discussed in this chapter, periodontitis tends to be more severe and to progress more rapidly among patients with advanced immune deficiency.[50]

Asymptomatic patients should undergo routine dental screens once or twice annually. Although HIV-related periodontitis responds poorly to routine dental care, all patients with this condition should be referred to a dentist for management. Topical application of chlorhexidine,[51] systemic antibiotic therapy, and debridement of devitalized soft tissue and bone[52] may be necessary to prevent progression.

H. Sexual Dysfunction

Testosterone levels are depressed, in the absence of pituitary abnormalities, in one third to one half of HIV-infected men, with the lowest levels associated with advanced immune deficiency.[53] The majority of men report decreased libido, and impotence may occur in one third. Testosterone deficiency may also play a part in the loss of muscle mass associated with AIDS wasting. Indications for testosterone replacement therapy have not been fully established, although it often improves sexual function.[54]

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8 Therapy of Serious HIV-Related Disorders

CONTENTS

I. INTRODUCTION

Modern antiretroviral therapy has resulted in a dramatic reduction in the incidence of severe and life-threatening opportunistic infections associated with HIV infection. Such disorders as *Pneumocystis carinii* pneumonia (PCP), toxoplasma encephalitis and cryptococcal meningitis, which cost many lives, and CMV retinitis, a frequent cause of blindness during the first 15 years of the AIDS epidemic, have become unusual among patients receiving effective antiretroviral therapy. In fact many such patients have experienced such significant increases in CD4+ lymphocyte counts that preventive therapy for such previously common disorders as CMV retinitis, PCP, and toxoplasmosis infection has been withdrawn. Nonetheless, many patients continue to suffer and die from HIV-related opportunistic infections. There are several reasons for this. Many individuals enter care late and present with opportunistic infections as their initial manifestation of AIDS before antiretroviral therapy is instituted. In New York City in 1999, over 30% of patients with newly diagnosed AIDS presented with one of these "traditional" opportunistic infections. In addition, many have failed multiple antiretroviral regimens and have not seen significant immune reconstitution. Finally, prophylaxis directed against some opportunistic pathogens is not universally prescribed and taken.

For this reason, it remains important for the practitioner to have a thorough understanding of the diagnosis, treatment, and prevention of the major opportunistic infections associated with AIDS. This chapter focuses on treatment with abbreviated discussions of diagnosis and prevention where appropriate. Additional, more detailed information on these disorders can be found in Chapter 4 where each entity is reviewed in detail and the approach to diagnosis is reviewed and in Chapter 5 where preventive strategies are discussed. Information about the medications mentioned, including dosing regimens, side effects, and interactions, can be found in the drug compendium in the final chapter of this book.

II. *PNEUMOCYSTIS CARINII* PNEUMONIA (PCP)

A. Incidence

Pneumocystis carinii pneumonia has been the most common life-threatening opportunistic infection associated with AIDS and the most common AIDS indicator disease since the beginning of the epidemic. Although the incidence of PCP has fallen

dramatically since the advent of highly active antiretroviral therapy (HAART), it remained the estimated most common AIDS-defining infection in the United States through 1998.

B. Clinical Manifestations

A diagnosis of PCP should be considered in HIV-infected patients reporting new fever, nonproductive cough, dyspnea, or a combination of these. Symptoms may progress rapidly over a few days or gradually over weeks. In rare cases, the earliest clues to the diagnosis may be unexplained fever, spontaneous pneumothorax,[1] or rising level of serum lactate dehydrogenase.[2] Although preventive therapy with trimethoprim and sulfamethoxazole (TMP-SMX), dapsone, or inhaled pentamidine may be highly effective PCP, cases may occur despite compliance with such prophylaxis. Clinical and radiographic features, however, may be altered in these patients, particularly those receiving aerosolized pentamidine in whom upper lobe localization and cavity formation appear to be more common.

C. Diagnosis

1. Radiographic Studies

A radiographic pattern of diffuse interstitial and alveolar infiltrates is suggestive but not diagnostic of PCP. Thoracic lymphadenopathy and pleural involvement are unusual. Atypical patterns, including localized infiltrates and cavity formation, may also be evident.

2. Gallium Scanning

Diffuse uptake on gallium scanning of the lungs is suggestive but not diagnostic of PCP. A similar pattern of uptake may be seen in miliary tuberculosis. Gallium scanning should not be regarded as a means of confirming a diagnosis of PCP. This technique is best reserved for patients with mild respiratory complaints and normal chest x-rays.

3. Sputum Examination

Examination of induced sputum including immunofluorescent stain for *Pneumocystis*, if properly performed, has a diagnostic yield of over 90%.[3]

4. Bronchoscopy

Cysts of *P. carinii* usually can be demonstrated in bronchoalveolar fluid or transbronchial biopsy specimens stained by the Giemsa or methenamine silver techniques or direct fluorescent antibody stain.[4]

D. Therapy

Confirmed or suspected PCP may be treated with either TMP-SMX (20 mg/kg daily TMP and 100 mg/kg daily SMX in a fixed combination given in four divided doses) or pentamidine (4 mg/kg in a single daily doses). Reported response rates have been

in the range of 70 to 95%, depending on the severity of disease.[5] Prospective studies have failed to demonstrate a clear advantage of either pentamidine or TMP-SMX in safety or efficacy.

Side effects are common with both drugs. Rash and anemia were each encountered in approximately 40% of patients receiving TMP-SMX , whereas more than 60% of patients receiving pentamidine had nephrotoxic effects and approximately one fourth had hypotension or hypoglycemia in one controlled study.[6] TMP-SMX is generally favored by clinicians, with pentamidine held in reserve for patients failing or intolerant of this therapy.

1. Alternative Therapies

a. Clindamycin and Primaquine

Combination therapy with clindamycin (600 mg four times daily or 900 mg three times daily intravenously or 300 to 450 mg four times daily by mouth) and primaquine (15 mg base once daily by mouth) may be effective in some patients unresponsive to or intolerant of conventional therapy[7] and represents a third parenteral option in patients unable to take oral medications.

b. Atovaquone

The oral agent atovaquone is approved for the therapy of mild-to-moderate PCP for patients intolerant of TMP-SMX. In a dose of 750 mg three times daily, atovaqone is somewhat less effective than conventional therapy with TMP-SMX.[8] In a trial comparing atovaquone with pentamidine, atovaquone was similarly less effective but caused significantly fewer treatment-limiting serious side effects than pentamidine.[9]

c. Dapsone and Trimethoprim

Combined therapy with oral dapsone (100 mg/day) and TMP (20 mg/kg daily) has been shown to be as effective as conventional therapy for mild-to-moderate PCP.[10] As noted previously, oral therapy is appropriate only in selected cases.

d. Trimetrexate and Leucovorin

The antifolate drug trimetrexate, administered with leucovorin to avoid bone marrow toxic effects, has been shown to be effective in approximately two thirds of cases as either initial or salvage therapy for patients failing therapy with TMP-SMX or pentamidine.[11] Survival is greater with TMP-SMX, however, when compared with trimetrexate as initial therapy.[12]

2. Prognostic Indicators

Several factors have prognostic significance in HIV-related PCP, including the overall condition of the patient as indicated by degree of wasting and serum albumen level and the degree of gas exchange abnormality as indicated by arterial blood gas determination.[13]

Therapy for PCP is usually continued for 21 days, although longer courses may be necessary in severe infections. Oral therapy with TMP-SMX was effective in 90% of patients with initial episodes of mild-to-moderate PCP (partial pressure of oxygen > 60 mm Hg)[14] and can be considered for compliant patients without gastrointestinal tract disease who can be closely monitored for respiratory symptoms.

a. Adjunctive Therapy with Corticosteroids

Corticosteroids have improved the survival of patients with respiratory failure caused by PCP. In one series[15] the survival was 75% among patients with severe infection receiving a regimen of methylprednisolone (40 mg intravenously four times daily) and TMP-SMX in standard doses; in contrast, the survival rate was 18% among patients receiving TMP-SMX and placebo. In another controlled study, patients with moderate-to-severe PCP receiving prednisone (40 mg by mouth twice daily) in addition to TMP-SMX, TMP-dapsone, or pentamidine had a substantially lower risk of respiratory failure than those receiving standard therapy alone.[16]

In 1990, a consensus panel of the National Institute of Allergy and Infectious Disease recommended that patients with PCP whose oxygen pressure is below 70 mm Hg or whose arterial-alveolar oxygen pressure difference is greater than 35 mm Hg receive adjunctive corticosteroids within 72 hours of starting anti-PCP therapy. The panel recommended the following regimen: prednisone 40 mg twice daily, days 1 through 5; 20 mg twice daily, days 6 through 10; and 20 mg once daily, days 11 through 21. Concerns have been expressed that other undiagnosed opportunistic infections may accelerate because of further immunosuppression caused by corticosteroids. Although this risk must be considered, it appears to be small and the impact on survival of moderate-to-severe PCP of corticosteroid therapy has been substantial.

b. Management of Pneumothorax Complicating PCP

Pneumothorax complicates a small proportion of cases of PCP and confers a significantly worse prognosis. Spontaneous pneumothorax occurring in any patient at risk for PCP should prompt an investigation for this infection and, in general, empiric therapy for PCP should be considered.[1] Patients with recurrent pneumothorax should be considered for medical pleurodesis, thoracoscopy with resection of bullae, or surgical repair.

Primary and secondary prophylaxis of PCP represent cornerstones in HIV care. These topics are reviewed in Chapter 5.

III. TOXOPLASMOSIS

A. Clinical Manifestations

Toxoplasmosis is the commonest cause of cerebral mass lesions in patients with AIDS.[17] It typically presents as encephalitis associated with focal neurologic deficits. Onset may be sudden or gradual. Lethargy, confusion, headache, and hemiparesis are common symptoms.

B. Diagnosis

Although the presence of cerebral toxoplasmosis can be confirmed only by histologic examination of brain tissue, the diagnosis is most often made on clinical and radiographic grounds and response to specific therapy because of the potential morbidity of brain biopsy.[18]

Typical findings of cerebral toxoplasmosis include multiple, bilateral, ring-enhancing lesions demonstrated on computed tomography (CT) or magnetic resonance imaging (MRI). Solitary lesions also may be seen in some cases. Radiographic findings of cerebral lymphoma, cerebral tuberculosis, and, occasionally, other opportunistic infections may be indistinguishable from those of toxoplasmosis.

Blood tests for IgG antibody to *Toxoplasma gondii* may provide important information in patients with typical clinical and radiographic abnormalities because cerebral toxoplasmosis most often represents reactivation of remote infection. Infection is rarely present without such serologic evidence, although IgM antibodies are typically not detectable even in severe disease.

C. Conventional Therapy

The initial treatment of choice for cerebral toxoplasmosis is the combination of sulfadiazine (1 to 2 grams qid) and pyrimethamine (100 to 200 mg daily). This regimen is continued for 4 to 8 weeks after which sulfadiazine may be reduced to 2 to 4 grams in four divided doses daily and pyrimethamine to 25 to 50 mg daily. Leucovorin (5 to 50 mg daily) should be administered simultaneously. Clindamycin (600 mg qid) may be substituted for sulfadiazine and has been shown to be equally effective in initial therapy although not as effective in maintenance. Radiographic and clinical signs of improvement are usually apparent after 2 weeks of therapy. If no improvement occurs in this time period, other disorders, particularly lymphoma and tuberculosis, should be considered strongly.

In patients responding, suppressive therapy should be continued indefinitely, although consideration can be given to discontinuing this in cases where there is sustained immune reconstitution with CD4+ cell counts maintained over 200/mm^3 for 3 to 6 months.

1. Alternative Therapies

In recent years, evidence has accumulated that several alternative agents may be effective in some patients not responding to or unable to tolerate either sulfadiazine- or clindamycin-based regimens.

a. Azithromycin

Conflicting data regarding the potential role of azithromycin have been published. While progression of cerebral toxoplasmosis was seen in two patients treated with azithromycin alone in one study,[19] cases of apparent response to this azithromycin alone[20] and to combination therapy with azithromycin and pyrimethamine have been reported.[21]

b. *Atovaquone*

Following initial therapy with sulfadiazine/pyrimethamine, atovaquone was effective in long-term suppressive therapy in one study of 65 patients.[22] Although 26% of individuals in this study suffered relapses of cerebral toxoplasmosis, only the duration of initial therapy correlated with risk of relapse. Another study indicated that atovaquone may be effective in salvage therapy.[23] The dose of atovaquone used in both studies was 750 mg by mouth four times daily.

c. *Doxycycline*

In case reports, doxycycline has appeared to be effective[24] and ineffective.[25]

IV. CRYPTOCOCCAL INFECTION

A. Incidence

Cryptococcal meningitis is the most common type of culture-positive, CNS infection in patients with AIDS and has been the initial manifestation of AIDS in 2 to 7% of cases.

B. Clinical Manifestations

Cryptococcal meningitis may become evident with either subacute or acute manifestations. Fever and headache lasting from days to weeks are the most frequent symptoms. Seizures and focal neurologic abnormalities are rare. Nuchal rigidity is seen only in a minority of cases. Severe cases may be complicated by increased intracranial pressure,[26] obtundation, and focal neurological deficits including deafness and blindness, which may be sudden and irreversible.[27]

Cryptococcal infection may also involve sites outside the central nervous system, although most patients have concomitant meningitis. Other potential sites of involvement include the lungs, skin, heart, lymph nodes, adrenal glands, spleen, kidneys, prostate, eyes, placenta, and thyroid.

C. Diagnosis

The diagnosis of cryptococcal meningitis is confirmed by examination of the cerebrospinal fluid (CSF). India ink stain, cryptococcal antigen assay (serum and CSF), and culture are all positive in most cases. Extraneural infections may be diagnosed by biopsy; culture of tissue, blood, or other body fluid; or serum antigen assay.

D. Therapy

1. Extraneural Infection

Patients presenting with infection in the lungs or other extraneural sites should undergo lumbar puncture to evaluate for CNS involvement.[28] Little information is available on outcomes of various treatment strategies for extraneural infection in HIV-infected patients. There is a consensus that all such patients should receive systemic antifungal therapy and that surgical resection should be considered for

refractory pulmonary or skeletal lesions. Therapy with oral azole agents, particularly fluconazole with or without flucytosine, can be considered for patients with mild-to-moderately severe extraneural disease. Amphotericin B is most appropriate for individuals with severe disease.

2. Meningitis

Both amphotericin B and fluconazole are effective in the therapy of cryptococcal meningitis. However, mortality rates within the first 2 weeks of therapy are lower among patients receiving amphotericin B than among those receiving fluconazole (8% and 15%, respectively).[29] Combination therapy with amphotericin B (0.7 to 1.0 mg/kg intravenously daily) and flucytosine (100 mg/kg in four divided doses orally continued for at least 2 weeks) is considered the treatment of choice for HIV-associated cryptococcal meningitis. Patients intolerant of flucytosine may be treated with amphotericin B alone. Lipid-based amphotericin B preparations may offer a lower risk of nephrotoxicity, although dosing regimens are not as well established as they are for conventional amphotericin B. After successful induction therapy, fluconazole 400 mg/day or itraconazole should be administered for at least 10 weeks. Less desirable initial regimens include fluconazole (400 to 800 mg/day) and flucytosine (100 mg/kg/day for 6 weeks) or fluconazole or itraconazole alone.

Relapse rates after the completion of therapy may exceed 50%.[30] For this reason, following the completion of consolidation therapy, lifelong maintenance therapy with fluconazole (200 to 400 mg daily) should be instituted. Itraconazole, used for maintenance was associated with a significantly higher relapse rate than fluconazole in one series.[31] Amphotericin B (1mg/kg intravenously 1 to 3 times weekly) should be reserved for patients intolerant of or resistant to azole compounds.

a. Increased Intracranial Pressure

Neurological deficits, particularly hearing loss, can be more pronounced among patients with cryptococcal meningitis complicated by increased intracranial pressure. For this reason, it is recommended that patients with intracranial pressure greater than 250 mm H_2O undergo large volume CSF drainage.[28]

V. PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

A. Incidence

PML was reported in 2 to 5% of AIDS patients in the early years of the epidemic. The incidence has not been significantly reduced by widespread use of highly active antiretroviral therapy (HAART).

B. Clinical Manifestations

PML typically presents insidiously with personality change, memory loss, and language disturbances. The course is usually steadily progressive with successive focal neurologic deficits.

C. Diagnosis

Diagnosis is usually made on the basis of a characteristic clinical syndrome and brain imaging studies (either computed tomographic or magnetic resonance imaging) demonstrating multiple lucent areas within the white matter without mass effect or enhancement.

D. Therapy

Therapy of PML has been frustrating. No antiviral agent has demonstrated consistent efficacy. Potent antiretroviral therapy has resulted in clinical and radiographic improvement[32,33] in some individuals, as well as improved survival.[34] These drugs may reduce central nervous system replication of the JC virus, the causative agent of PML.[35] The addition of cidofovir to antiretroviral therapy may augment this effect and result in improved clinical outcome.[35]

VI. *Mycobacterium avium* Complex (MAC) Infection

A. Incidence

Mycobacterium avium complex (MAC) was isolated in 60% of cases in early autopsy series[36] and is a common cause of disseminated infection at advanced stages of HIV infection, generally occurring in individuals with CD4+ cell counts below 50/mm^3. As is the case of the other major opportunistic disorders associated with AIDS, the incidence of MAC infection has declined sharply since the advent of highly active antiretroviral therapy.

B. Clinical Manifestations

Unlike infection with *Mycobacterium tuberculosis* (*M. tb*), infection with MAC typically involves extrapulmonary sites. Symptoms are insidious and may include unexplained fever, weight loss, diarrhea, anemia, and liver or spleen enlargement. Occasionally, MAC can cause pulmonary syndromes indistinguishable from *M. tb* infection.

C. Diagnosis

The diagnosis of infection with MAC is usually confirmed by specific culture of blood or appropriate body fluid or on the basis of histologic examination of bone marrow or liver biopsy specimens. MAC is often isolated from respiratory secretions, although the significance of such a positive culture is unclear in the absence of progressive pulmonary disease.

D. Therapy

Significant progress has been made in the treatment and prevention of MAC infection in recent years. This progress reflects primarily the effectiveness of the macrolide antibiotics azithromycin and clarithromycin in both prevention and treatment. Mycobacteremia was eradicated or significantly reduced in 2 to 4 weeks among patients receiving clarithromycin in one large series.[37] Similar efficacy with azithromycin was demonstrated in a smaller study.[38] As in other mycobacterial infections, therapy of disseminated MAC infection with a single agent is associated with emergence of secondary resistance (46% to clarithromycin in the study just cited).

Standard treatment regimens for MAC include at least two agents, one of which should be either azithromycin (1200 mg weekly) or clarithromycin (500 mg twice daily). Ethambutol (15 mg/kg daily) is most often used as the second drug and is most effective when combined with clarithromycin. Second-line agents include rifabutin (300 to 450 mg daily), amikacin (7.5 to 15 mg/kg daily), and ciprofloxacin (500 to 750 mg bid).

Response to therapy is generally seen within 6 weeks, after which the regimen should be continued indefinitely. Treatment failure is often indicative of drug resistance. If this occurs, alternate regimens containing at least two additional agents may be necessary. It is likely, though not yet established, that treatment may be discontinued in patients receiving effective antiretroviral therapy when the CD4 lymphocyte count rises above 200/mm^3.

a. Primary Prevention

Current guidelines include the recommendation that all patients with no prior MAC infection receive prophylaxis with either clarithromycin (500 mg twice daily)[39] or azithromycin (1200 mg weekly)[40] to prevent disseminated MAC infection if the CD4 cell count is less than 50 cells/mm^3.[41]

VII. HERPES SIMPLEX VIRUS (HSV) INFECTIONS

A. Incidence

Herpes simplex virus infections were among the first disorders associated with HIV infection and AIDS[42] and occur in approximately 20% of patients not receiving antiretroviral therapy. Visceral dissemination occurs rarely. Encephalitis, pneumonitis, and hepatitis are the most common syndromes associated with such dissemination; however, virtually any organ may be involved.

B. Clinical Manifestations

Infection typically becomes evident with painful ulcerations on the lips, in the mouth, or in the genital region. Disseminated cutaneous infection and, in rare cases, visceral disease may also occur.

C. Diagnosis

The diagnosis of herpes simplex infection often can be confirmed by biopsy or scraping of a characteristic skin lesion with viral culture and/or immunofluorescent staining.

D. Therapy

Therapy with acyclovir (400 mg by mouth three times daily or 200 mg five times daily) is usually effective and reduces the duration of symptoms. The newer agents famciclovir and valacyclovir have not been superior to acyclovir in trials to date.

1. Alternative Therapy

Unfortunately, resistance to acyclovir frequently emerges in patients treated for several months with acyclovir and may become manifest as recurrent or expanding lesions occurring on therapy. Foscarnet (40 mg/kg intravenously three times daily) is almost always effective in such cases, although foscarnet resistance has also been described.

VIII. CYTOMEGALOVIRUS (CMV) INFECTIONS

A. Incidence

Cytomegalovirus (CMV) has been the most common opportunistic pathogen identified in autopsies of AIDS patients in some series and is the most frequent cause of sight-threatening retinitis. CMV infection accounted for 4% of AIDS-defining opportunistic infections in 1994[43] but has fallen dramatically in incidence since the advent of highly active antiretroviral therapy (HAART) in the mid-1990s (see Chapter 18).

B. Clinical Manifestations

Retinitis, esophagitis, and colitis are the most frequent specific clinical manifestations of CMV infection although virtually any organ may be involved.

C. Diagnosis

The diagnosis of CMV retinitis is strongly suggested by specific features of the fundoscopic examination. Ophthalmologic consultation is advisable for confirmtion. Endoscopic biopsy is usually required to confirm the diagnosis of esophageal or colonic infection.

D. Therapy

1. Retinitis

The therapy of CMV retinitis has improved significantly in recent years. Previously, after induction of therapy with either ganciclovir or foscarnet, intravenous therapy

with one of these agents was continued indefinitely. The observation that oral ganciclovir was nearly as effective in long-term maintenance as intravenous therapy [44] led to improvements in quality of life for many patients.

However, two major advances beginning in the mid-1990s have had a large impact on the management of this infection. The development of topical antiviral therapy of CMV retinitis,[45] both in the form of intraocular injection of ganciclovir, foscarnet, or cidofovir and as ganciclovir ocular implants, permitted high local concentrations in the eye while minimizing systemic side effects of these agents. In addition several studies have demonstrated that anti-CMV therapy can be discontinued in selected patients who have a virological and immunological response to HAART.[46]

Ganciclovir implants have the advantages of convenience. Although they need to be replaced every 6 to 8 months, intravenous therapy is not necessary and this form of therapy results in the longest delay in disease progression.

2. Colitis

Much less information is available on the management of CMV infections other than retinitis. Colitis and esophageal infection respond in the majority of patients to either ganciclovir or foscarnet in the induction regimens used for retinitis. The need for continued maintenance therapy is not clearly established and may vary among patients.

IX. INTESTINAL PARASITES

A. Incidence

Infections with the intestinal parasite *Cryptosporidium parvum* or *Isospora belli* were the initial opportunistic infections in approximately 1% of reported AIDS cases through the mid-1990s.[47] In contrast to most opportunistic pathogens associated with HIV infection, these organisms may produce illness in a significant number of individuals with CD4 cell counts above 200/mm^3. The environmental source of these organisms is usually unknown. Because *Cryptosporidium* is a common animal pathogen, concern has been expressed about the potential role of pet exposure in human infections, although this does not appear to be a significant risk factor.[48] Contaminated drinking water, however, has been associated with infection among HIV-infected individuals. A waterborne outbreak of *Cryptosporidium* in Milwaukee was followed by a sharp rise in human cases.[49]

B. Clinical Manifestations

Although *Cryptosporidium* may occasionally cause pulmonary infection,[50] both organisms are most associated with a syndrome of chronic and recurrent watery diarrhea. In addition, both may cause infection extending into the biliary or pancreatic duct system. Crampy abdominal pain, nausea, vomiting, malaise, and low-grade fever often accompany infection.[51] Uncontrolled intestinal infection can lead to malabsorption, wasting, and significant morbidity. Biliary involvement is most common in patients at advanced stages of immune deficiency.

C. Diagnosis

Infection with these organisms is determined by direct microscopic examination of the stool stained with the modified acid-fast technique. Both organisms appear as acid-fast oval structures which can be distinguished from each other by details of their morphology.

D. Therapy

Infection with *Isospora belli* typically responds to therapy with trimethoprim-sulfamethoxazole[52] and is effectively prevented by this medication when it is used to prevent PCP. In contrast, current therapeutic agents are not usually very effective in treating cryptosporidiosis. A variety of antiparasitic drugs has been shown to be ineffective. These include metronidazole, diiodohydroxyquin, tetracycline, chloroquine, primaquine, and quinacrine.[53] More recently, paromomycin alone or combined with azithromycin has been used with limited success. At present, antiretroviral therapy appears to be the most effective means of improving the symptoms of cryptosporidiosis.[54]

X. TUBERCULOSIS

A. Incidence

Beginning in 1986, after 30 years of steady decline, the incidence of tuberculosis in the United States began to rise.[55] This increase could be attributed in large part to increasing numbers of cases of active tuberculosis among HIV-infected individuals. Currently, it is estimated that approximately 6 million HIV-individuals worldwide, including 8% of those in North America, are also infected with *Mycobacterium tuberculosis*.[56]

The incidence of tuberculosis was 13.33 cases per 100 person-years among patients with CD4+ lymphocyte counts below 200 cells/mm^3 and positive tuberculin skin results in one series[57]—a risk nearly 40 times higher than in patients with CD4+ cell counts above 350 cells/mm^3 and negative tuberculin test results.

Complicating matters further, in the early 1990s outbreaks caused by organisms resistant to two or more conventional drugs, so-called multidrug-resistant tuberculosis (MDRTB), were seen in several urban areas of the United States.[58] Heightened surveillance for tuberculosis and more effective systems of care, including directly observed therapy, have begun to reduce the incidence of TB in HIV-infected patients in some areas, and a decline in cases of MDRTB has also been seen.

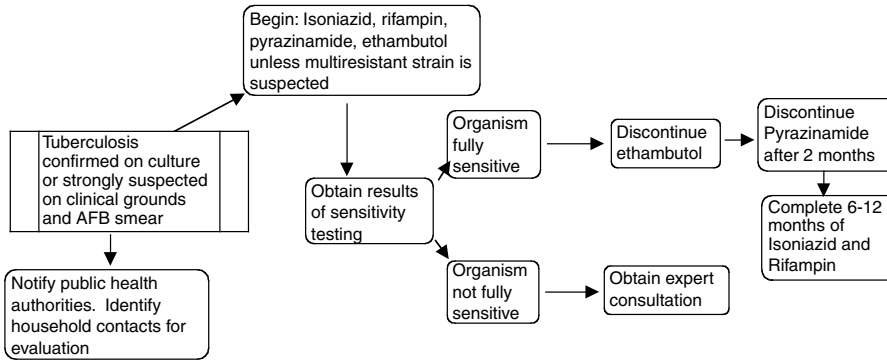
B. Clinical Manifestations

In most cases the clinical manifestations of tuberculosis in HIV-infected patients are comparable to those in other individuals. However, extrapulmonary infection (particularly lymphatic and miliary) is more common in HIV-related tuberculosis,[59] and distinctive pulmonary radiographic patterns, such as lower-lobe involvement, are seen more frequently.[60] Cavitary disease is less prevalent in HIV-related cases.[61]

C. Therapy

The response to therapy for tuberculosis is comparable with that seen in non-HIV-infected individuals,[62] although several factors associated with poor response to therapy have been identified.[63] These include low CD4+ cell count, MDRTB, and no use of directly observed therapy (DOT). As the incidence of multidrug-resistant tuberculosis has declined in recent years, the therapy of sensitive strains of *Mycobacterium tuberculosis* has received increased attention and novel approaches to therapy have been developed. Several important principles must be incorporated into the management of tuberculosis[64]:

1. Culture confirmation and susceptibility testing should be obtained in all cases of suspected tuberculosis.
2. Proven or suspected cases of pulmonary or laryngeal tuberculosis should be placed in respiratory isolation until they are no longer infectious.
3. All proven cases should be reported promptly to public health authorities.
4. HIV testing should be offered and strongly encouraged in all cases of confirmed tuberculosis.
5. Patients with sensitive organisms should be treated for 6 to 12 months (see Figure 8.1).
6. If treatment failure is suspected, two new drugs should be added to the regimen pending repeat susceptibility studies.
7. Individuals with latent TB (positive tuberculin test with no evidence of active infection) should also be treated (see Figure 8.2).



Notes: Pyridoxine should be administered with isoniazid. Rifabutin 150 mg po daily should be substituted for rifampin for patients taking saquinavir, nelfinavir, amprenavir, or nevirapine. Streptomycin should be substituted for rifampin for patients taking delavirdine or ritonavir. Rifampin dose should be increased to 450 mg in patients taking efavirenz.

FIGURE 8.1 Treatment of active tuberculosis in the setting of HIV infection. (Adapted from Horsburgh et al., *Clin Infect Dis, 31, 633, 2000.*)

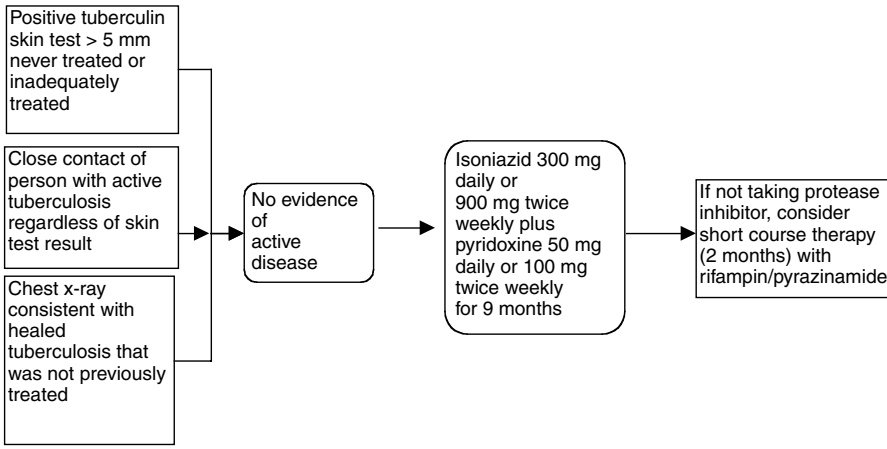


FIGURE 8.2 Treatment of latent tuberculosis in the setting of HIV infection.

In addition, directly observed therapy should be employed whenever noncompliance is likely and household contacts of persons with active tuberculosis, especially children under age 5 and immunosuppressed individuals, should be evaluated promptly.

XI. SYPHILIS

A. Incidence

During the last half of the 1980s, the incidence of primary and secondary syphilis, as well as congenital infection, began increasing dramatically, particularly in areas with high seroprevalence of HIV infection.[65] After a decline in cases, a resurgence has been seen in recent years, particularly among homosexual and bisexual men.[66]

B. Clinical Manifestations

Although the clinical and laboratory features of syphilis in HIV-infected patients are usually similar to those in uninfected patients, in some cases the presentation of syphilis appears to be altered by concomitant HIV infection. Progression of disease, despite standard therapy[67] and both false-positive (sometimes extremely high-titer) and false-negative serologic test results, has been reported.[68]

C. Diagnosis

It is recommended that serologic testing for syphilis be performed on all patients who acquired HIV infection through sexual contact or intravenous drug use.[69] Dark-field examination or direct fluorescent antibody staining of exudate from lesions should be performed when there is clinical suspicion of syphilis, despite negative results of serologic studies.

D. Therapy

Early syphilis (primary, secondary, and early latent) should be treated, as in non-HIV-infected patients, with benzathine penicillin (2.4 million units intramuscularly). Serologic testing should be performed at intervals of 1, 2, and 3 months after treatment. If titers of VDRL (RPR) do not decrease (twofold by 3 months in primary syphilis or by 6 months in secondary syphilis), a lumbar puncture should be performed to exclude neurosyphilis.[68]

In cases of late latent syphilis or infection of unknown duration, the CSF should be examined before therapy to exclude neurosyphilis. If there is no evidence of neurosyphilis, benzathine penicillin should be administered (2.4 million units intramuscularly weekly for 3 weeks). Patients with neurosyphilis, either symptomatic or asymptomatic, should receive intravenous therapy (aqueous penicillin G, 2 to 4 million units every 4 hours for 10 days).

Tetracycline (500 mg orally four times daily for 14 days) or doxycycline (100 mg orally two times daily for 14 days) should be used in the therapy for primary, secondary, or latent syphilis of less that 1 year's duration in cases of penicillin allergy. Tetracycline or doxycycline should be continued for 28 days in patients with late latent or tertiary syphilis who are unable to receive penicillin.

XII. HEPATITIS C

As prolonged survival has become commonplace among HIV-infected individuals, hepatitis C virus (HCV) has been recognized as a common infection, particularly among injection drug users, and a significant threat to both quality of life and survival. Recent data indicate that co-infection with HIV and HCV lead to an increase in the rate of hepatic complications and, perhaps, a shortened survival. Primary care providers are frequently unfamiliar with the diagnosis, assessment, and management of this infection.[70]

A. Incidence

The overall prevalence of hepatitis C in the general population is approximately 1.8%. Although the rate of new HCV infections has declined sharply over the past decade, largely due to screening of donated blood, the prevalence remains significantly higher than the prevalence of HIV infection. Most individuals with hepatitis C are chronically infected and asymptomatic but represent a reservoir of infection in the population and are at increased risk for cirrhosis and hepatocellular carcinoma.[71] Because of common routes of transmission, particularly needle sharing by injection drug users, co-infection with hepatitis C virus and HIV is seen commonly. It is estimated that between 50 and 98% of HIV-infected injection drug users are also infected with HCV.[72] Although HCV infection is seen much less commonly in individuals who contracted HIV through homosexual or heterosexual contact, sexual[73] as well as vertical[74,75] transmission of HCV may be somewhat more frequent in the presence of HIV infection.

The course of HCV infection also appears to be accelerated by co-infection with HIV, particularly in the presence of significant cellular immune deficiency. The HCV viral load and rate of viral replication are both typically increased in the presence of HIV infection[76,77] and progression of liver disease may also be hastened.[78–80] Six genotypes and almost 100 subtypes of HCV have been identified. Approximately 70% of HCV-positive individuals in the United States are infected with genotype 1, most commonly subtype 1a.[71]

B. Clinical Manifestations

The clinical manifestations of HCV infection have been well characterized in the general population. The majority of individuals with hepatitis remains asymptomatic and, unless tested for HCV antibody, unaware of the infection. During acute infection, jaundice and constitutional symptoms may be seen in 20 to 30% and 10 to 20%, respectively.[81] Among symptomatic patients during the acute phase, the clinical illness is indistinguishable from that caused by other hepatitis viruses.[81] Fulminant disease and hepatic failure are quite uncommon.[82]

Approximately 15 to 25% appears to resolve the infection completely after the acute phase of illness and have no detectable virus in the serum and normal liver function tests.[71] The remainder go on to chronic infection. About two thirds of chronically infected individuals manifest abnormalities of liver enzymes, particularly ALT, which may be constant or intermittent over years. HCV infection remains subclinical and insidious in the majority of those who are chronically infected for 10 or 20 years. Ultimately, the risk of cirrhosis and hepatocellular carcinoma in these individuals appears to be 10 to 20% and 1 to 5%, respectively.[83,84] It has been estimated that hepatocellular carcinoma occurs in 1 to 4% of cases of HCV-related cirrhosis annually.[71] A small study of non-HIV-infected individuals with 45 years of follow-up, however, found that 12% of patients ultimately developed liver disease and 6% died of it, suggesting a significantly better prognosis.[85]

As discussed above, these figures, which are derived from studies of the general population, may be overly optimistic for HCV infection occurring in the presence of HIV infection. Prognostic factors other than HIV co-infection are poorly understood, although it is clear that alcohol consumption is associated with more liver disease,[86] and superinfection with hepatitis A virus may precipitate fulminant hepatitis and hepatic failure.[87] As mentioned above, six genotypes and a host of subtypes of HCV have been distinguished. Although clinical features of all genotypes are comparable, response to therapy is variable, with genotype 1 typically responding more poorly to interferon therapy (see below).

C. Diagnosis

Assays for antibody to HCV (anti-HCV) are used to screen for HCV infection. Antibody is detected in more than 97% of infected individuals but a positive antibody test cannot distinguish between acute, chronic, and resolved infection. Positive tests by enzyme immunoassay (EIA) are confirmed by recombinant immunoblot assay (RIBA) to improve specificity.[71]

Detection of viral RNA, by polymerase chain reaction (PCR) or other amplification techniques, is possible 1 to 2 weeks after infection and may occasionally confirm the diagnosis of HCV infection in the absence of antibody. At the time of this writing, these techniques have not received final FDA approval, but are in common clinical use nonetheless. The sensitivity of these assays exceeds 95% in patients with active (acute or chronic) liver disease but is somewhat lower in HCV-infected individuals without liver disease.[71] Quantitative assays for viral RNA are commercially available, although it is not yet clear how treatment decisions should be made on the basis of these assays.

Six genotypes of HCV have been identified and may be distinguished by hybridization techniques. Genotyping, as will be discussed below, may have implications for therapy and prognosis.

D. Therapy

The therapy of hepatitis C is in a state of transition. Although effective treatments have been developed,[88,89] their applicability to individuals with HIV co-infection has been challenged by some. However, an expanding body of knowledge indicates that properly timed therapy for HCV infection can be beneficial in the presence of HIV infection, and reduction in hepatic disease achieved by control of hepatitis C may have significant benefits for co-infected patients.[72]

Interferon-alpha (IFN-alpha) is the antiviral agent that has been most thoroughly evaluated for the treatment of hepatitis C. Overall sustained (>1 year) response rates to monotherapy with IFN-alpha have been less than 20%[90,91] and even lower in the subset of patients infected with genotype 1. Combination therapy with ribavirin and IFN-alpha has yielded a durable response rate of approximately 50%, but is also less effective (< 30%)[88,89] in genotype 1 infections. Although it was initially widely assumed that the effectiveness of antiviral therapy for HCV infection in the setting of co-infection with HIV would be less effective, some recent data suggest efficacy of IFN-alpha monotherapy comparable to that seen in other patients,[92] although a sustained response may be significantly less likely in co-infected patients.[93] As in the case of HIV seronegative, combination therapy with ribavirin and IFN-alpha has yielded better results with initial response rates of 50% or higher.[94–96]

At present, antiviral therapy is recommended for individuals with HCV infection who have a high risk of progression to cirrhosis. Patients should meet the following criteria[71]:

- Persistent elevation of ALT
- Detectable HCV RNA
- Liver biopsy demonstrating either portal or bridging fibrosis or at least moderate inflammation and necrosis

It is recommended that patients with persistently elevated levels of ALT not receive interferon therapy outside of the setting of a clinical trial because of the risk of worsening liver function.[71] Patients with advanced cirrhosis should not be treated. Other contraindications to interferon therapy include active alcohol or other substance

abuse, major depression, cytopenias, hyperthyroidism, renal transplantation, or evidence of autoimmune disease.[71] Ribavirin may cause hemolytic anemia, bone marrow suppression, and renal failure. Because it is teratogenic, female patients must be cautioned not to become pregnant during therapy.[71]

Because of these restrictions on the use of current therapy, the need for liver biopsy, and the slow rate of progression of HCV-related liver disease in most patients, treatment decisions are challenging. In selected co-infected patients, however, control of HCV may improve quality of life and simplify the treatment of HIV infection considerably.

a. Screening for Hepatitis C

It is recommended that routine testing for HCV antibody should be performed for[71]:

Persons with a history of injection drug use
Persons who received clotting factor concentrates prior to 1987
Persons who have undergone chronic hemodialysis
Persons with persistent elevations of alanine aminotransferase (ALT)
Persons who received a blood transfusion or organ transplant prior to July 1992 or have been notified that they received blood from a donor who subsequently was found to be HCV-positive
Healthcare workers who have sustained sharps injuries or mucosal exposures to HCV-positive blood
Infants born to HCV-infected women

Many HIV programs and practitioners conduct HCV testing on all HIV-infected adults, regardless of transmission category.

b. Hepatitis A Vaccine

It is recommended that HCV-positive individuals who are not immune receive Hepatitis A vaccine to reduce the risk of fulminant hepatitis.

XIII. LYMPHOMA

A. Incidence

Non-Hodgkins lymphoma (NHL) represents the initial AIDS-defining disease in 4% of AIDS patients in the United States. Another 5% of patients subsequently develop lymphoma.[97–99] Although the vast majority of HIV-related lymphomas are NHL of B-cell origin, Hodgkin's disease (HD) also appears to occur with increased frequency among HIV-infected individuals,[100] even though it is not currently considered an AIDS-defining condition.

B. Clinical Manifestations

NHL is seen primarily among patients at advanced stages of HIV infection, and severe immune deficiency is associated with a more fulminant course. As discussed in Chapter 4, HIV-related NHL has several unique features. Extranodal involvement

with widespread disease at the time of diagnosis is common. The central nervous system, gastrointestinal tract, lungs, liver, spleen, and bone marrow are each commonly involved, and involvement of the oral cavity[101] or less common sites may be seen. The clinical course tends to be aggressive. Markers of Epstein-Barr virus (EBV) infection are present in approximately one third of cases. An unusual disorder termed primary effusion lymphoma (PEL), in which involvement is confined to serosal cavities such as the pleura, peritoneum, and pericardium, has been associated with human herpesvirus 8 (HHV-8) infection.[102]

C. Diagnosis

Confirming the diagnosis of NHL in the setting of HIV-infection may be challenging because of the unusual clinical presentations described above. Histologic confirmation is almost always needed. When nodal or extranodal tissue can be biopsied, this should be the primary approach to diagnosis. Cytological examination of pleural, peritoneal, or pericardial fluid may be diagnostic in cases of PEL. Bone marrow examination may provide the diagnosis in cases of widespread extranodal disease. Primary cerebral lymphoma represents a particular challenge since the clinical and radiographic manifestations may overlap with those of cerebral toxoplasmosis, a more common disorder. In general, HIV-infected patients with cerebral mass lesions exhibiting ring-enhancement by computed tomography should be treated empirically for toxoplasmosis if the clinical situation permits a potential delay in definitive diagnosis. Because toxoplasmosis generally responds rapidly, improvement after such a therapeutic trial can be used as presumptive evidence of toxoplasmosis. Lymphoma should be considered especially strongly in those patients not responding to several weeks of this therapy. Patients who have NHL who are receiving corticosteroid therapy for increased intracranial pressure may have a partial clinical and radiographic response during the therapeutic trial with antitoxoplasmosis therapy leading to a mistaken diagnosis of toxoplasmosis. PET and SPECT scanning may also be helpful in distinguishing cerebral lymphoma, which demonstrates increased uptake, from toxoplasmosis, which does not. Ultimately histological confirmation is generally necessary prior to treatment for cerebral lymphoma.

D. Therapy

Chemotherapy is typically used in the treatment of NHL outside of the central nervous system, because of the advanced stage of disease at presentation in most patients. In contrast, brain irradiation is the primary form of treatment of primary cerebral lymphoma. In the early years of the AIDS epidemic, chemotherapy for extraneural lymphoma was typically conservative, consisting of low-dose regimens to minimize side effects. This approach was considered appropriate, despite the high risk of relapse, because the ultimate survival of patients after the diagnosis of lymphoma was very limited and most often related to uncontrollable opportunistic infections. As the overall prognosis of HIV infection has improved with the advent of highly active antiretroviral therapy and the concomitant reduction in life-threatening opportunistic infections, this approach has been reevaluated and strategies designed to confer more significant long-term benefits are currently under study.

a. Castleman's Disease

Castleman's disease is a lymphoproliferative disorder that shares some features with lymphoma[103](see Chapter 4). Reported response to chemotherapy and to antiretroviral therapy have been disappointing. Interferon-alpha may represent an effective therapeutic option for this disorder.[104]

XIV. KAPOSI'S SARCOMA

A. Incidence

During the first 10 years of the AIDS epidemic, 94% of cases of Kaposi's sarcoma (KS) were reported among men, most of whom were white and had acquired HIV infection by sexual contact with other men. For reasons that are unclear, the incidence of KS began declining before the advent of highly active antiretroviral therapy.[105] The availability of effective antiretroviral therapy has coincided with a further reduction in incidence. Serologic and other evidence has strongly suggested that KS is caused by or associated with human herpesvirus 8 infection.[106]

B. Clinical Manifestations

KS typically becomes evident as macular or nodular lesions, often purple in color, on epidermal or mucosal surfaces or both. The mouth, face, trunk, and extremities are all frequently involved. There may be a single lesion or many. Visceral involvement is common, particularly of the lungs, lymph nodes, and gastrointestinal tract.

C. Diagnosis

Because several other AIDS-related skin disorders may resemble KS, the diagnosis requires histologic confirmation. Pulmonary involvement produces radiographic and clinical features comparable with those of *Pneumocystis carinii* pneumonia and other opportunistic infections. Gastrointestinal tract lesions may occur in any segment of the bowel; they may become evident with symptoms of bleeding or obstruction or may be clinically silent.

E. Therapy

Traditionally, AIDS-related Kaposi's sarcoma has been treated with local radiation, cryotherapy, surgical excision, or intralesional chemotherapy for limited disease, and systemic chemotherapy or alpha-interferon for widespread disease, all with mixed results. Recent data suggest that antiretroviral therapy alone may lead to regression of lesions in some cases.[107,108]

XV. AIDS WASTING SYNDROME

HIV infection has long been associated with significant weight loss. In the absence of active infection or other conditions specifically interfering with the ability to eat, an involuntary loss of at least 10% of body weight accompanied by diarrhea and fever for at least 30 days is termed the *AIDS wasting syndrome.*[109]

Until recently, therapeutic options had been very limited and largely ineffective. Predictably, however, this syndrome has become much less common since the advent of HAART.[110] In addition, newer therapies to either stimulate appetite or increase anabolism have been developed.

Megestrol acetate,[111] a synthetic progesterone, and Dronabinol,[112] a cannabinoid, can each stimulate appetite and promote weight gain in some individuals. Several anabolic steroid preparations and recombinant human growth hormones have been shown to promote weight gain and increase lean body mass in some studies.[113]

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9 HIV Infection in Women

CONTENTS

I. INTRODUCTION

HIV infection in women raises specific issues that are becoming increasingly critical in the societal response to the HIV/AIDS epidemic. In the developing world, approximately half of all HIV infections are seen among women. In the United States and other developed countries, women account for an increasing proportion of reported cases. The natural history and presenting features of HIV infection in women may differ somewhat from those in men, and exposure to the virus through heterosexual contact may go unrecognized by women unaware of the HIV risk of their partners. This represents an important obstacle to early detection and treatment of HIV infection in women. The possibility of transmission of HIV from mother to unborn child adds another dimension to the epidemic in women, and this route of transmission accounts for the vast majority of pediatric HIV/AIDS cases. Clinical trials of new treatments and clinical research in general have largely focused on men living in developed countries. The results of such research may not be directly applicable to women. Child care and other family responsibilities shouldered disproportionately by women have been shown to often stand in the way of medical care for women in families. Finally, the commercial sex industry remains a major source of transmission of HIV infection, particularly in developing countries. In this chapter the impact of these various factors on care of women and families will be discussed.

II. EPIDEMIOLOGY OF HIV INFECTION IN WOMEN

A. Current Trends: United States

Both the incidence of new HIV infections and the number of newly reported AIDS cases among women has risen steadily since the 1980s.

It is estimated that between 120,000 and 160,000 adult and adolescent women are currently living with HIV infection in the United States. In 1998, women accounted for 24% of newly reported AIDS cases and nearly 40% of newly reported HIV infections.[1] The route of transmission of HIV infection to women has shifted dramatically in the past decade. During the period 1991 to 1998, injection drug use accounted for 48% of HIV infections among women. However, by 1998, only 28% of reported women were infected by this route.[1] Another important trend has been the increasing shift of the burden of HIV infection into minority populations, both male and female. In 1998, for example, AIDS accounted for 13% of deaths among black women compared with 2% among Caucasian women.[1] As of 1999, 57% of women living with AIDS were African-American, 20% were Hispanic, and 23% were Caucasian. The epidemic has also increasingly affected women living in poverty or conditions of social upheaval. More than 80% of women with AIDS lived in

households with annual income less than $10,000,[1] 86% were unmarried, and 23% lived alone. Half had at least one child below the age of 15. The majority are unemployed and lack health insurance.

The geographical distribution of female AIDS cases has trended somewhat away from traditional high prevalence areas of the Northeast. In 1998 more new cases were reported from the South than from any other area of the country. Although the majority of female cases of HIV infection nationally now result from heterosexual transmission (see Figures 9.1 and 9.2), in some urban areas of the Northeast, injection drug use continues to account for more than half of reported cases.

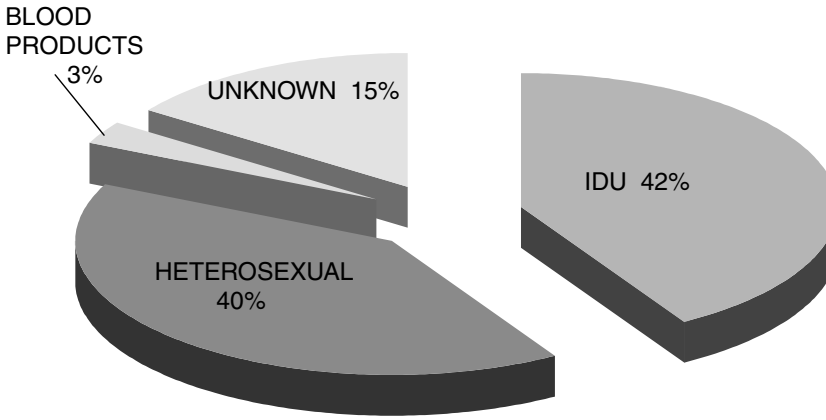

FIGURE 9.1 Distribution by transmission category of U.S. adult female AIDS cases through mid-2000.

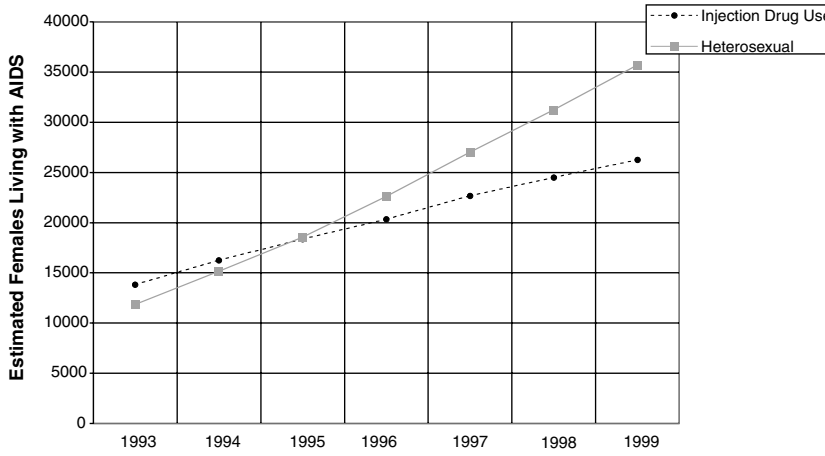

FIGURE 9.2 Trends in HIV transmission by injection drug use and heterosexual contact in U.S. females, 1993–99. (Adapted from CDC HIV/AIDS Surveillance Report, Vol. 12, 2000.)

B. Female Commercial Sex Workers

The prevalence of HIV infection among women who exchange sex for money or drugs is influenced by several important variables including drug use, geographic location, race, and the setting in which the sex trade is carried out. Studies of women working in two different facets of the sex industry in New York City in the late 1980s indicated seroprevalence rates of 5% among street prostitutes[2] and 1% among women working as call girls, for escort services, or in massage parlors.[3] In a later study, also in New York City, nearly 35%, including 61% of those using intravenous drugs, of more than 1500 street prostitutes were found to be HIV infected.[2] In this series infected women were significantly older and more likely to be Hispanic than African-American or Caucasian. Many other studies have confirmed the importance of injection drug use as a risk factor for HIV infection among female sex workers, particularly in the countries of North American and Europe.

C. HIV Infection in Segments of the U.S. Female Population

1. Military and Job Corps

The U. S. military and Job Corps perform routine HIV antibody testing on recruits and applicants. Such large-scale screening programs provide valuable insight into the extent of the epidemic. Of special importance is the prevalence of HIV infection among young adults. In 1997 the prevalence of HIV infection among female military recruits was approximately 0.006%, compared with a prevalence of 0.03% among men.[4] Both rates have declined over the past decade. In contrast, although overall seroprevalence among Job Corps applicants has also declined over this period, the relative proportion of infected women has risen. In 1996, 0.28% of women and 0.2% of men tested positive.[4] Prevalence of HIV infection is highest among African-Americans and Hispanics in both the military and Job Corps data.[5]

2. Women Undergoing Artificial Insemination

Few cases of apparent transmission of HIV infection by artificial insemination have been recognized. Although data are incomplete, it has been reported that the risk of transmission from an infected donor to a recipient is 0.5% per exposure.[6] Specific risk factors for such tranmission have not been defined.

D. HIV Infection in Women in the Developing World

At present, it is estimated that approximately 40% of AIDS cases worldwide are in women. Seroprevalence among the adult populations varies widely by region. It is highest in sub-Saharan African where 12 countries (Botswana, Central African Republic, Ivory Coast, Kenya, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Zambia, and Zimbabwe)[7] have a seroprevalence greater than 10%. In the highest prevalence countries, accounting for more than 95% of the world's HIV infections, women account for approximately half.

III. TRANSMISSION OF HIV INFECTION TO WOMEN

Sexual transmission of HIV infection from men to women accounts for the vast majority of reported AIDS cases among women worldwide and an increasing number of AIDS cases and new HIV infections in the United States. HIV can be isolated in semen, both in cell-free fluid and in mononuclear cells.[8] Overall, the likelihood of transmission from male-to-female appears to be in the range of 0.05% to 0.15% per sexual contact, and is significantly greater than the likelihood of female-to-male transmission. The reasons for this higher risk of transmission are not clear but one likely factor is the larger innoculum of virus contained in semen than in vaginal secretions (see Chapters 1 and 2).

A. Risk Factors for Sexual Transmission

Several risk factors for increased HIV replication in vaginal secretions have been identified. Bacterial vaginosis caused by *Gardnerella vaginalis* is associated with increased transmission of HIV[9] and increased vaginal HIV production.[10] It has also been noted that HIV levels in cervical and vaginal fluids rise shortly before and during menses, independent of plasma levels.[11]

A number of other risk factors that are thought or known to increase the likelihood of transmission of HIV infection from men to women have been identified. Among these are:

Active sexually transmitted disease
Lack of circumcision in the male partner
Use of spermicides
Cervical ectopy
Bleeding (including menstrual bleeding) during intercourse
Receptive anal intercourse
Advanced HIV infection in the male partner
Specific HIV subtypes

B. Reducing Heterosexual Transmission to Women

Proper use of male condoms is highly, although not completely, effective in preventing transmission of HIV through heterosexual intercourse. For example, no instances of transmission were identified between discordant couples using condoms consistently after 15,000 episodes of intercourse in a large European study.[12] The rate of transmission in couples not using condoms or using them intermittently was 13%.

It has been observed since the early days of the HIV/AIDS epidemic that heterosexual transmission between some discordant couples never occurred even when condoms were not used. More insight into this phenomenon has been gained in recent years. Strong cytotoxic T cell response was found in the majority of uninfected partners with frequent exposure to HIV in one small study.[13] Specific viral virulence factors and co-receptor (e.g., CCR5) status of the uninfected partner may also play a role in protection against heterosexual transmission.

Finally, antiretroviral therapy has been shown to reduce HIV shedding in semen.[14] It is assumed, probably correctly, that this ultimately reduces male-to-female transmission. However, the proportion of men actually rendered non-infectious

by therapy is unknown, and any HIV-infected man must, based on the present state of knowledge, be assumed to be capable of transmitting HIV even if he is receiving effective antiviral therapy with complete suppression of plasma viremia. Of course, viral resistance to antiretroviral drugs may result in high concentrations of virus in semen, even in some men receiving therapy.

IV. MOTHER-TO-CHILD TRANSMISSION

HIV infection may be transmitted from mother to child during pregnancy, at the time of delivery, or during the postnatal period through breast-feeding. Such vertical transmission has accounted for the majority of cases of AIDS in children. Specific risk factors for transmission have been identified in recent years and strategies of prevention have been refined. The most important predictor of transmission to the fetus is maternal plasma viral load.

Prospective studies have generally indicated that, in the absence of antiretroviral therapy, approximately one sixth to one third of children born to HIV-infected women will be infected.[15–19]

A. Risk Factors for Mother-to-Child Transmission

1. Maternal Viral Load

Maternal viral load has been shown to correlate with the likelihood of transmission,[20,21] although no lower limit of viral load has been established below which transmission cannot occur. High concentration of virus in maternal cervicovaginal secretions and, as a result, a relatively large viral load inoculated into the oropharynx of the infant may be even more important determinants of transmission.[22,23] In a United States study of nearly 500 women who received zidovudine during pregnancy, it was found that mother-to-child transmission did not occur among 107 women who had undetectable viral load (<500 copies/mL) at the time of delivery.[21] Similar results were seen in a comparable study from Zimbabwe[24] and in another United States study in which high maternal plasma viral load at any time during pregnancy was correlated with risk of transmission.[20] As might be expected from these findings, levels of HIV RNA in vaginal secretions correlate closely with plasma levels and fall with antiretroviral therapy.[25]

Maternal host factors may also facilitate or hinder transmission. In a study of 75 women, suppression of HIV by CD8 cells was shown to reduce the risk of transmission.[26] Other factors that appear to increase the risk of transmission include cigarette smoking and premature rupture of the membranes.[27]

2. Method of Delivery

Caesarian section has long been proposed as a means of reducing or eliminating the risk of transmission of HIV during delivery.[28,29] Because of the low risk of HIV intrapartum transmission when the viral load of the mother is less than 3000 copies/mL, the appropriateness of this method of delivery has been challenged when the maternal plasma viral load is low or undetectable.[30]

3. Breast-Feeding

HIV can be transmitted from mother to child during breast-feeding. In a study from Africa, 7% of infants born to HIV-infected mothers who had not received antiretroviral therapy to prevent vertical transmission acquired HIV infection through breast-feeding.[31] Transmission of HIV was likeliest during the first 5 months, but was documented throughout the 24 months of follow-up. Especially alarming is a study from Kenya indicating that 44% of cases of perinatal transmission result from breast-feeding.[32] Other data suggest, however, that rates of HIV infection may be roughly equal in breast-fed and bottle-fed infants.[33] These conflicting findings have made reaching a consensus about the advisability of breast-feeding difficult to achieve. Some feel that breast-feeding is advisable in developing countries where infant nutritional status may otherwise be in jeopardy, while others feel that HIV-infected women should be strongly counseled against breast-feeding, as they are in the United States. Pasteurization[34] or chemical sterilization of breast milk[35] has been proposed as an alternative strategy, although neither has been adequately evaluated.

B. Prevention of Mother-to-Child Transmission

In early 1994, an interim analysis of a double-blind prospective (AIDS Clinical Trials Group protocol 076) indicated that zidovudine given to pregnant women reduced the likelihood of mother-to-child transmission of HIV infection.[36] The treatment group in this study began zidovudine therapy (100 mg orally five times daily) between 14 and 34 weeks gestation and continued therapy intravenously (2 mg/kg loading dose followed by 1 mg/hr) through labor and delivery. Infants born to these mothers received zidovudine syrup (2mg/kg every 6 hours) for the first 6 weeks of life. The transmission rate in the treatment group was 8.3%, compared with 25.5% in the placebo group, a difference that was statistically highly significant. On the basis of this finding an independent safety monitoring board was formed. In 1994, it was demonstrated that zidovudine (AZT) given to the mother through the perinatal period reduces mother-to-child transmission by approximately 75%.[37] Subsequent studies have confirmed this[38] and established the efficacy of other antiretroviral regimens in this regard. Since this initial report, the administration of antiretroviral therapy in this manner has become a standard practice in the United States. The dramatic effectiveness of such preventive therapy (see Figure 9.3) has led to enhanced programs of prenatal testing of women and postnatal testing of their infants for HIV infection in many areas.

As newer antiretroviral agents have become available since 1994, including all of the protease inhibitors and non-nucleoside reverse transcriptase inhibitors, and as highly active antiretroviral therapy (HAART) has become more widespread, a number of issues have arisen regarding the optimal strategy for prevention of perinatal transmission. Because single-drug therapy with zidovudine or any other antiretroviral agent is not currently recommended in any other setting, the safety, efficacy, and long-term consequences of therapy with other agents have come under scrutiny. In addition, because resistant virus may be transmitted despite appropriately administered antiretroviral therapy,[39] treatment regimens for women who are suspected of having

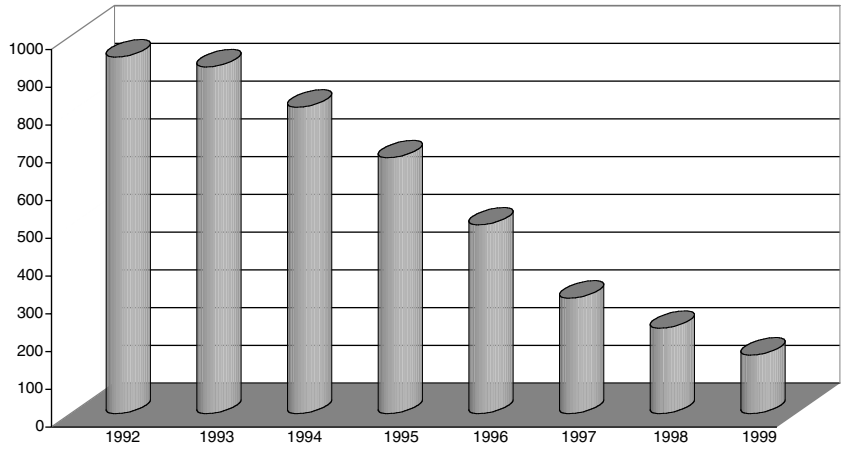

FIGURE 9.3 Estimated U.S. pediatric AIDS cases by year of diagnosis. (Adapted from CDC HIV/AIDS Surveillance Report, Vol. 12, 2000.)

or proven to have developed zidovudine-resistant viral strains have been developed. Finally, more cost-effective approaches have been sought which can be applied to large numbers of women living in developing countries. One strategy that has been explored is to use shorter courses of antiretroviral drugs in the hope of improving compliance and minimizing side effects. In a comparative study conducted in Africa, it was found that a single dose of nevirapine given at the onset of labor and a second postpartum dose with a single dose to the infant was as effective as the combination of zidovudine and lamivudine in preventing vertical transmission.[40] In another study, transmission was documented in 21.5% of the zidovudine group and 13.1% of the nevirapine group.[41] See Chapter 14, Case 3 for further discussion regarding antiretroviral therapy to prevent mother-to-child transmission.

The widespread use of antiretroviral therapy to prevent vertical transmission has occurred rapidly.[42] As a result, dramatic reductions in perinatal transmission and, thus, of pediatric AIDS in the United States have occurred in the last half of the 1990s.[43] Recent data indicate that 50% of HIV-infected pregnant women take antiretroviral therapy and that the overall rate of transmission is less than 3%. Such observations raise the prospect that vertical transmission could be completely eliminated in the United States[44,45] and other developed countries.

C. Diagnosis of HIV Infection in the Neonatal Period

Confirmation of HIV infection in the neonate requires direct evidence of circulating viral antigen, because passive transfer of maternal HIV antibody results in detectable antibody in the infant for the first 15 months of life, even in the absence of HIV infection. Adding to the diagnostic confusion is the phenomenon of late seroconversion, which results in some infected infants initially having antibody negative test results. In one reported case in a child who tested HIV negative after 6 months, detectable antibody developed at 22 months of age. Such problems of diagnostic ambiguity have been

largely overcome by the use of the polymerase chain reaction technique for measuring viral RNA or proviral DNA. Such studies performed in the first 48 hours of life can detect over 30% of infected infants. Sensitivity of these tests improves rapidly over the first 2 weeks such that virus can be detected in over 90% of infected children by 14 days. Infants initially testing negative should be retested at 3 to 6 months. HIV infection can be almost completely excluded in infants testing repeatedly negative at this point; however, antibody tests should be repeated periodically until negative.

Concern has been expressed that antiretroviral therapy given to the mother might reduce the sensitivity of tests to detect virus in the newborn. This appears not to be the case with current single-drug regimens.[46]

Because of the possibility of preventing transmission to the fetus, calls for routine prenatal screening of women have intensified and this practice has become more commonplace. In developing countries, however, particularly in Africa, transmission during pregnancy remains common and an increasing number of children are born HIV-infected. The HIV-infected woman caring for an infected child represents one of the most poignant images of the AIDS epidemic, particularly in the setting of extreme poverty where it usually occurs. As her own health may be failing, she must face the emotional trauma and logistic and financial burden of her child's sickness and death. Even in the United States, it is clear that the needs of an infected and ill child often prevent the mother from seeking adequate care for herself.

V. CLINICAL MANIFESTATIONS OF HIV INFECTION IN WOMEN

A. Primary Infection

The signs and symptoms of primary HIV infection have been elucidated primarily in studies using male cohorts[47] (see Chapter 2). In a recent series describing female sex workers in Kenya, several symptoms were found to be statistically associated with HIV seroconversion: fever, arthralgia, myalgia, diarrhea, vomiting, and non-inguinal lymph node enlargement.[47a]

B. Opportunistic Infections and Malignancies

The patterns and relative frequencies of AIDS-defining conditions are similar in men and in women with three exceptions:

- Cervical neoplasia[48] complicating human papillomavirus (HPV) infection is an AIDS-defining condition among women.
- Vaginal candidiasis is common as an early manifestation of HIV infection.
- Kaposi's sarcoma is more common among men.

1. Cervical Neoplasia

Cervical neoplasia, both cervical cancer and cervical intraepithelial neoplasia (CIN), is associated with HPV infection.[49,50] HPV infection is more common in the presence of HIV infection, especially with significant immunodeficiency[48] or high HIV viral load[51]

as are some HPV-related cervical neoplasms.[52,53] High-grade cervical lesions may be somewhat less associated with these parameters.[54] In a study of over 2000 HIV-infected women, it was found that 40% had abnormal Pap smears, including abnormal squamous cells of unknown significance (ASCUS) as well as squamous intraepithelial lesions (SIL) and CIN, compared with 17% among HIV-negative controls. Thirty percent of infected women had SIL compared with 7% of controls.[55] Vitamin A deficiency may represent an additional risk factor for the development of cervical neoplasia.[56]

2. Vaginal Candidiasis

In one large series from North America[57,58] vaginal candidiasis was the most common initial manifestation of HIV infection in women.

C. Disease Progression and Survival

Data regarding the relative rates of disease progression and overall prognosis of men and women have often been ambiguous. Although disease progression appears to be comparable, women tend to present later in the course of HIV infection. For example, death was the first reported clinical event in 27.5% of women and 12.2% of men without prior clinical HIV progression.[59]

In recent years, reports have appeared suggesting that women may have lower levels of viral RNA (often in the range of 35 to 50% lower) in the plasma than men at similar stages of disease.[60,61] Clinically, this may indicate a higher risk of disease progression among women with a given viral load than among their male counterparts.[62,63] The full clinical significance of these observations is not yet clear, and some series have failed to demonstrate a significant gender difference, particularly for women who acquired infection by the heterosexual route.[64]

D. Response to Therapy

Women have been underrepresented in clinical trials of new antiretroviral agents. For this reason, data from these trials must generally be extrapolated to women with some uncertainty. Several studies have indicated that the effectiveness of combination antiretroviral therapy in lowering the plasma viral load in women is approximately equal to that in men.[65,66] Nevertheless, pharmacokinetics of these agents may differ in men and women. For example, hormonal changes associated with the menstrual cycle may lead to variability in absorption and clearance.[67]

Adverse reactions secondary to therapy with nucleoside agents[68] or some protease inhibitors[69] appear to be more frequent in women.

VI. PRIMARY CARE OF HIV-INFECTED WOMEN

A. Disease Staging

Clinical and immunological staging of HIV infection in women permits, as it does in men, rational decisions regarding antiretroviral therapy and prophylaxis of opportunistic infection. Although some studies have suggested that women tend to have lower levels of viral load than men at similar CD4 cell counts (see above), the clinical

significance of this observation is unknown and staging (see Chapter 5) should be performed as it is in men.

B. Antiretroviral Therapy

Men have far outnumbered women in clinical trials of antiretroviral drugs. Because of this, concern has been raised that the pharmacokinetic properties and toxicity profile of these agents are largely unstudied. Gender differences in absorption and metabolism as well as body weight and fat distribution may have clinical significance. In addition, the hormonal changes associated with the menstrual cycle and with pregnancy may also affect the safety and efficacy of these agents in women.

C. Prevention of Opportunistic Infection

The patterns and incidence of AIDS-related opportunistic infections appear to be similar between the genders. Indications for preventive therapy directed at *Pneumocystis carinii* pneumonia, *Mycobacterium avium* complex, and tuberculosis are the same for men and women.

D. General Health Maintenance

As survival improves with current combination antiretroviral therapy, issues of general health maintenance are expected to become more important in the care of HIV-infected individuals. Both cardiovascular disease and cancer will most likely become more common in the coming years. Screening for hypertension and hypercholesterolemia should be carried out as it is for male patients (see Chapter 5).

E. Screening for Cervical Neoplasia

Careful gynecological screening of HIV-infected women is warranted because of the high incidence of cervical intraepithelial neoplasia (CIN) among HIV-infected women and concern about progression to cervical carcinoma.[50] Of note, both CIN and cervical cancer have been linked to infection with human papillomavirus (HPV), which is exceptionally prevalent and persistent in HIV-infected women. In one series, the prevalence of HPV infection was 58% and 26% in HIV-positive and HIV-negative women, respectively.[70] Furthermore, HPV infection is independently associated with high HIV plasma viral load and low CD4+ cell counts.[71]

For these reasons, it is recommended that HIV-infected women undergo a gynecological examination with Pap smear at baseline, 6 months, and annually thereafter.[72] It is advisable that women with a history of abnormal Pap smear be monitored every 6 months. If inflammation with reactive squamous cell changes is detected, the Pap smear should be repeated in 3 months. Women in whom atypical squamous cells of unknown significance (ASCUS) are found can be monitored annually. Patients with squamous intraepithelial lesions (SIL) should be considered for colposcopy and biopsy, particularly if the lesion is high grade. Women with invasive carcinoma should undergo colposcopy with biopsy or conization. Therapeutic options (radiation or surgery) should be considered.

It should be remembered that the sensitivity of Pap smears for SIL is in the range of 80 to 85%. For this reason, certain high-risk patients may require routine colposcopy.

F. Screening for Breast Cancer

The incidence of breast cancer is not known to be influenced by HIV infection. As the mean age of HIV-infected women increases because of improvements in therapy and longer survival, an increasing number will become candidates for routine screening mammography (see Chapter 13).

G. Obstacles to Care Faced by HIV-Infected Women

1. Access

It has been demonstrated that HIV-infected women tend to enter care later than their male counterparts and are less likely to receive medical care, including effective antiretroviral therapy.[73–75]

2. Treatment Adherence

Women often face more obstacles to care and to adherence with antiretroviral therapy than men do. Family responsibilities may lead to poor compliance with appointments, less tolerance of medication side effects, and a tendency to sacrifice one's own health for the health of a child or other loved one. A discussion of adherence issues and strategies to maximize compliance with therapy is included in Chapter 11.

VII. GENDER BIAS IN THE UNDERSTANDING OF HIV INFECTION

Most of the current understanding of the clinical manifestations and immunologic features of HIV infection has come from studies of men, particularly homosexual and bisexual men. In addition, almost all data regarding the effectiveness of antiretroviral therapy, as well as therapy of opportunistic infections and malignancies, have been accumulated through large clinical trials that have enrolled few women. This is true despite obvious differences in male and female heterosexual transmission and several important contrasts in the clinical features of HIV infection between men and women.

Possible sources of gender bias include:

- There is a higher incidence of AIDS in men in developed countries where most research has been conducted.
- There is a low level of recruitment of women into clinical trials of new therapies.
- Intravenous drug use among HIV-infected women in the early years of the epidemic was predominant. Women in this heterogeneous group have often been perceived as poor candidates for clinical trials and have lacked

the unified advocacy groups that represented male homosexuals in the planning of and recruitment for these trials.
- Access to health care for HIV-infected women is generally more limited than that of men.[74,75]

FREQUENTLY ASKED QUESTIONS

1. Is the prognosis of HIV infection the same in men and women?

   Most studies have indicated that survival and rates of disease progression are similar in men and women.

2. What is the significance of reported differences in viral load measurements between men and women at similar stages of disease?

   It has been demonstrated in a variety of studies that plasma viral load in women may be significantly lower than that in men at similar stages of disease. Although the full significance of this is not known, it may indicate that women with a given viral load will experience disease progression earlier than their male counterparts. Although indications for antiretroviral therapy are currently equivalent in men and women, this may change if the differences in viral load are demonstrated to have such clinical significance.

3. What is the most important risk factor for mother-to-child transmission?

   Maternal viral load. Circulating viral load has been shown to correlate with levels of virus in cervicovaginal secretions and in the oropharynx of the newborn.

4. How frequently should gynecological examinations with Pap smear be performed on HIV-infected women?

   It is recommended that all HIV-infected women have a baseline examination, follow-up examination at 6 months, and annually thereafter.

5. Are there circumstances in which they should be performed more frequently?

   Women with abnormal Pap smears should be evaluated every 6 months, or more frequently if inflammation is detected.

6. What are the significant epidemiological trends in the HIV/AIDS epidemic in women in the United States?

   In the 1990s heterosexual contact became the dominant mode of transmission of HIV infection to women, exceeding injection drug use. Increasingly, the epidemic has become concentrated in the African-American and Hispanic populations. The annual incidence of AIDS has fallen due to improvements in therapy, but AIDS accounted for 13% of deaths in young African-American women in 1998.

7. What are the risk factors for male-to-female transmission of HIV infection?

Lack of circumcision, cervical ectopy, active sexually transmitted disease, bleeding during intercourse, receptive anal intercourse, advanced HIV infection in the male partner, the use of spermicides and, perhaps, specific viral subtypes.

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10 Antiretroviral Therapy

CONTENTS

I. INTRODUCTION

Remarkable advances have been made in the therapy of HIV infection over the past decade. The development of several new classes of antiretroviral drugs and numerous large-scale clinical trials have led to a dramatic change in the management of HIV infection. Monotherapy with zidovudine (AZT) has given way to combinations of related nucleoside compounds and, finally, to the current standard of therapy, three-, four-, or five-drug regimens combining drugs from the three main therapeutic classes currently available, so-called highly active antiretroviral therapy (HAART). Such combination therapy has led to durable suppression of viral replication[1,2] for many individuals.

A sharp decrease in rates of clinical progression and hospitalization of HIV-infected patients has been observed since the advent of combination therapy.[3] The development of rapid quantitative measures of circulating HIV viral load and their widespread availability has brought a precision to antiviral therapy, and the emerging use of viral resistance testing is expected to lead to increasingly rational therapeutic decision making. Somewhat unexpectedly, it has become possible to discontinue prophylaxis against some opportunistic infections among some patients receiving HAART who have experienced significant restoration of immune function.

With the advances in therapy, however, have come a variety of new challenges. Viral resistance to each of the available drugs has been reported, and many individuals who have received various forms of HAART therapy for the past several years have manifested clinical and/or laboratory resistance to all available agents. It has been learned that resistance can develop remarkably rapidly. Raising the risk of resistance, complex antiviral regimens, which often called for patients to take many pills on confusing schedules, have heightened difficulties with compliance and subsequent secondary resistance.[4] Novel, unexpected side effects such as life-threatening lactic acidosis and the so-called lipodystrophy or fat-redistribution syndrome have become increasing problems among patients receiving antiretroviral therapy, and a host of drug interactions have also hampered the use of these agents. Finally, antiretroviral therapy does not always lead to significant restoration of immune function, especially in individuals at advanced stages of immune deficiency.

On the balance, though, improvements in therapy have been dramatic and undeniable and have triggered intense research into the development of newer antiretroviral agents and new classes of compounds as well as attempts to change pharmacokinetic parameters of older agents in order to improve the effectiveness and tolerability of therapy.

Therapeutic strategies in the management of HIV infection are in constant evolution. Indications for initiating therapy, for changing therapy as well as recommended dosing regimens, are subject to change as new data are accumulated. Nonetheless, at the time of this writing, a general consensus has emerged on each of these issues and will be presented in this chapter. In view of the rapid advances seen over a very few years, however, the reader is urged to consult updated treatment guidelines and the results of new clinical trials.

II. THE IMPACT OF ANTIRETROVIRAL THERAPY

A. Survival

Evidence abounds that HAART has dramatically improved the prognosis of HIV infection for many individuals since the introduction of protease inhibitors in 1996.

1. Opportunistic Infections, Malignancies

Effective antiretroviral therapy has had a major impact on the incidence of HIV-related opportunistic infections and malignancies. Although the relative frequency of such disorders as mucosal candidiasis, cytomegaloviral retinitis,[5] disseminated *Mycobacterium avium-intracellulare* complex (MAC), *Pneumocystis carinii* pneumonia (PCP), and Kaposi's sarcoma have remained constant, their overall incidence has dropped markedly.[6]

B. Transmission

The impact of effective antiretroviral therapy on transmission of HIV infection has been somewhat more difficult to assess. Although suppression of viremia reduces the risk of perinatal and, possibly, sexual transmission,[7] improvements in therapy have resulted in complacency leading some to resume or increase high-risk behavior.

III. GOALS OF ANTIRETROVIRAL THERAPY

Based on the correlation among viral load, immune function, and overall prognosis, the goals of antiretroviral therapy can be viewed as follows:

Durable suppression of viral replication
Stabilization or improvement in immune function as measured by CD4 cell count
Improvement in quality of life by reduction of HIV-related complications
Improvement in survival
Possible reduction in transmission of HIV

Specific antiviral regimens should be selected with the goal of maximizing viral suppression, minimizing side effects, and preventing or delaying the emergence of viral resistance in order to preserve future treatment options. It should be borne in mind that complete viral suppression may be unachievable, especially in the patient who has previously received combined antiretroviral therapy. However, even in such individuals, clinical improvement may be seen with partial suppression. Similarly, the CD4 lymphocyte count may not rise in some patients who achieve complete viral suppression and/or clinical improvement.

The risks of antiretroviral therapy, however, must also be taken into account. These include:

Medication side effects
Emergence of resistance with resultant reduction in future therapeutic options and potential transmission of resistant viral strains.

IV. INDICATIONS FOR INITIATING THERAPY

Current guidelines for therapy of HIV infection are based on the premise that early suppression of plasma viremia is critical in preserving immune function as long as possible.

In general, individuals meeting any of the following criteria should be considered for antiretroviral therapy:

Individuals within 6 months of primary HIV infection
HIV-infected individuals with CD4 lymphocyte count less than 500 cells/mm^3 or plasma HIV RNA levels exceeding 10,000 to 20,000 copies/mL
All others with symptomatic HIV infection

The strategy of early, aggressive antiretroviral therapy has been advocated on the basis of several hypotheses:

(1) that complete suppression of viral replication might permit cure of HIV infection within a period of several years,
(2) that immunological damage could be minimized and forestalled by early therapy, and
(3) that early therapy is more likely to lead to durable suppression of viral replication.

Although this approach has gained wide acceptance, data regarding these hypotheses have been somewhat ambiguous. As a result, the strategy of using intensive antiretroviral therapy early in the natural history of HIV infection has been challenged on the grounds that (1) patients may be exposed to drug toxicity and risk of viral resistance prematurely in many cases; (2) the long-term benefit of aggressive, early therapy on all patients has not yet been established with certainty; and (3) current strategies remain somewhat speculative.[8,9] Nevertheless, at the time of this writing, therapy in accordance with the above criteria has been recommended by a variety of expert panels and government agencies.[10] Many experienced practitioners go beyond these guidelines under various circumstances. For example, the CD4 cell cutoff of 500/mm^3 may be too high, particularly for patients who are clinically well and have low or undetectable viral load. In addition it may be appropriate to defer therapy among asymptomatic patients with low but detectable viral load as long as the CD4 cell count is reasonably preserved. Additional large-scale studies are now underway to address the timing of antiretroviral therapy in a more comprehensive way and to better define subsets of patients for whom therapy should be deferred or interrupted. For this reason, guidelines may well change repeatedly and the reader is advised to consult updated recommendations in this area.

Given the complexity of antiretroviral therapy and the high failure rate among patients who are not strictly adherent to their treatment regimens,[11] it is crucial that the decision to begin therapy be made jointly by the provider and patient only after extensive discussion of effectiveness, side effects, and adherence issues.

Several general issues need to be clarified by further study:

1. Can problems with medication adherence (pill burden, side effects, lack of patient motivation) and drug pharmacokinetics be reduced so that emergence of resistance can be delayed as long as possible?
2. What is the actual incidence of significant adverse reactions to antiretroviral therapy (e.g., the lipodystrophy syndrome associated with protease inhibitors), what are their long-term implications, and how can they be effectively managed?
3. Can immune reconstitution be predictably achieved in patients beginning antiretroviral therapy late in the course of HIV infection?
4. Will newer agents provide meaningful alternatives for patients who have exhausted treatment options with currently available drugs?

Until precise answers to these questions are available, it is probably wise for the provider to offer antiretroviral therapy to asymptomatic patients with CD4 cell counts between 350 and 500/mm^3 (as well as those with counts below 350/mm^3) according

to standard guidelines but to individualize treatment decisions based on an assessment of the patient's commitment to complying with therapy and ability to weather possible side effects.

V. ANTIRETROVIRAL DRUGS

At the time of this writing, three classes of drugs comprising a total of 15 compounds have been licensed for the treatment of HIV infection (see Boxes 10.1, 10.2, and 10.3) and several more are anticipated within the next few years (see below). Several other compounds in these classes as well as new classes of drugs are expected in the near future, and the reader is advised to consult recent guidelines and reviews for updated material. What follows is a general discussion of available agents, focused primarily on evidence of effectiveness and current clinical role for each agent. This discussion is most applicable to patients who have not received prior antiretroviral therapy (who are treatment naive). For more detailed information on dosing schedules, potential drug-drug interactions, and toxicity data, please see the drug compendium in the final chapter of this book.

BOX 10.1

Nucleoside Reverse Transcriptase Inhibitors (NRTI)

1. Abacavir (Ziagen)
2. Didanosine (ddI; Videx)
3. Lamivudine (3TC; Epivir)
4. Stavudine (d4T; Zerit)
5. Zalcitabine (ddC; Hivid)
6. Zidovudine (ZDV; Retrovir)
7. A fixed combination of zidovudine and lamivudine (Combivir)
8. A fixed combination of zidovudine, lamivudine, and abacavir (Trizivir)

BOX 10.2

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

1. Delavirdine (Rescriptor)
2. Efavirenz (Sustiva)
3. Nevirapine (Viramune)

BOX 10.3

Protease Inhibitors (PI)

1. Amprenavir (Agenerase)
2. Indinavir (Crixivan)
3. Nelfinavir (Viracept)
4. Ritonavir (Norvir)
5. Saquinavir (Invirase—hard gelatin capsule; Fortavase—soft gelatin capsule)
6. Lopinavir/ritonavir (Kaletra)

All drugs are available as pills, some also as liquids or powders. Zidovudine is available for intravenous infusion. Although clinical efficacy has been established for each drug individually, a one- or two-drug regimen with current agents is felt to be inadequate at this time.

A. Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

1. Mode of Action

NRTIs inhibit viral reverse transcriptase, thereby slowing or preventing replication within infected cells.

2. Evidence of Efficacy

Although antiretroviral agents should not be used in single-drug regimens outside of the setting of pregnancy (see Chapter 9), clinical evidence of efficacy will be briefly reviewed here in part to clarify the evolution of current therapy and to provide the reader with a basis for understanding the role of each drug in current and future therapeutic regimens.

a. Zidovudine (AZT, Retrovir)

Therapeutic benefit was established in early studies (ACTG 016, ACTG 019)[12,13] demonstrating a delay in disease progression for individuals with CD4+ lymphocyte counts between 200 and 500 cells/mm^3. Benefit was not established for asymptomatic patients in other studies.[14] The most compelling evidence of clinically significant antiviral effect came when zidovudine was shown to reduce the incidence of perinatal transmission of HIV (see Chapter 9).[15]

b. Didanosine (ddI, Videx)

As a single agent, no consistent differences in outcome were found between patients with little or no prior therapy receiving either zidovudine or didanosine.[16] For symptomatic patients with CD4+ lymphocyte counts below 300 cells/mm^3 or asymptomatic patients with counts below 200 cells/mm^3 who had received prolonged (4 months or more) prior therapy with zidovudine, didanosine (500 mg daily) was superior to zidovudine in delaying progression to AIDS, although it did not confer a survival advantage.[17]

c. Lamivudine (3TC, Epivir)

The clinical efficacy of lamivudine has been demonstrated primarily in combination therapy. Significant decreases in viral load have been demonstrated with zidovudine and lamivudine together when compared with either agent alone.[18]

d. Stavudine (D4T, Zerit)

Monotherapy with stavudine was superior to placebo in reduction of viral load at 12 weeks in one study.[19] In a large study of patients with CD4+ lymphocyte counts between 50 and 500 cells/mm^3 and at least 6 months of prior zidovudine therapy, individuals whose therapy was changed to stavudine had a significantly longer time to treatment failure than those maintained on zidovudine.[20]

e. Zalcitabine (ddC, Hivid)

Zalcitabine was initially approved for use only in combination with zidovudine. Although it was subsequently approved as monotherapy, it is not used in this fashion and is considered an adjunct to therapy with other nucleoside agents. Efficacy in combination with zidovudine was reported by Fischl and colleagues.[21]

f. Abacavir (Ziagen)

Abacavir is the newest of the nucleoside agents at the time of this writing. In a study of treatment-naive patients, combination therapy with abacavir, lamivudine, and zidovudine resulted in a significantly higher rate of complete viral suppression (75% vs. 37%) compared with lamivudine, zidovudine, and placebo.[22] In treatment-experienced patients, results have been mixed. Abacavir has also been shown to result in significantly greater viral suppression at 48 weeks when added to stable combination regimens after week 16, the so-called intensification therapy.[23] When substituted for protease inhibitors or used in regimens containing protease inhibitors (PI) or non-nucleoside reverse transcriptase inhibitors (NNRTI), abacavir has been comparable with other nucleoside agents.[24]

3. Patterns of Use

Two NRTIs are typically combined with either a PI or NNRTI in initial treatment regimens for retroviral-naive patients. Certain NRTI pairings are appropriate and others are not. For example, zidovudine and stavudine should not be combined because of clinically significant drug antagonism, while didanosine and zalcitabine may produce additive toxicities of pancreatitis or peripheral neuropathy. Appropriate combinations include zidovudine/lamivudine, zidovudine/didanosine, stavudine/lamivudine, stavudine/didanosine, and zidovudine and zalcitabine, although zalcitabine is less potent than the other agents and has fallen out of widespread use.[25]

Recent data indicate that regimens combining three NRTI agents (zidovudine, lamivudine, and abacavir) may be almost as effective as those employing two NRTIs (zidovudine and lamivudine) and a PI (indinavir).[26] However, at the time of this writing, further study is needed to establish the validity of these preliminary data and the full potential of regimens which do not employ either a PI or an NNRTI.

4. Resistance

Resistance to each NRTI has been documented and patterns of cross resistance established.

B. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

1. Mode of Action

NNRTIs inhibit viral reverse transcriptase by different mechanisms than the NRTI drugs.

2. Evidence of Efficacy

Several studies have demonstrated that NNRTIs have clinically significant antiretroviral activity and, when used in combination regimens, can provide additive activity to other agents to significantly lower viral load and raise CD4 counts. Regimens employing 2 NRTIs and either delavirdine or nevirapine appear to lead to less durable viral suppression than PI-containing regimens, especially in individuals with high pretreatment viral loads.[27] Side effects profiles and drug interactions as well as convenience of dosing (see Chapter 15) have led to preferences of some agents of this class over others.

However, a study comparing an efavirenz-containing regimen with a PI-containing regimen documented that the efavirenz regimen was more effective.[28] A recent study comparing two regimens, two NRTIs (zidovudine and lamivudine) and the PI nelfinavir vs. the same two NRTIs and nevirapine, found comparable response rates.[29] Another study comparing nevirapine and efavirenz in combination with two nucleosides indicate that they are approximately equal in effectiveness.[30] Based on these and other data, the use of NNRTIs has become increasingly common, especially in treatment-naive patients when there is a desire to avoid PIs or in patients intolerant of PI therapy.

3. Patterns of Use

In standard treatment guidelines, efavirenz is currently considered an acceptable alternative to a PI in combination with two NRTI agents[31] and, as indicated above, nevirapine may be equally effective in such combinations especially for individuals with pretreatment viral loads of fewer than 100,000 copies/mm^3. Because of their convenient dosing schedules (once daily and twice daily, respectively), efavirenz and nevirapine are generally favored, although delavirdine may significantly raise PI levels and may eventually have an important role in salvage regimens incorporating PIs.

4. Resistance

One important problem in the use of NNRTIs is that resistance to any of the three agents is indicative of resistance to all three.

C. Protease Inhibitors

1. Mode of Action

Protease inhibitors (PI) prevent cleavage of viral protein precursors required for HIV replication and entry into cells.

2. Evidence of Efficacy

Most agents in this class are potent inhibitors of HIV replication. Protease inhibitors, other than invirase, in combination regimens with nucleoside drugs have been shown to lead to significant clinical improvement and prolonged survival. The Invirase formulation of saquinavir, because of poor absorption, has been less effective. Dual protease inhibitor combinations are often used in instances of multidrug resistance.

The central role of PI-containing regimens has been reinforced by an international trial (the Atlantic study)[32] comparing the three most commonly used regimens for treatment-naive patients: didanosine and stavudine plus either indinavir (PI), nevirapine (NNRTI), or lamivudine (NRTI). The indinavir-containing regimen was found to lead to better rates of viral suppression in the most recent analysis of this study.

3. Patterns of Use

Protease inhibitors should be used as components of multidrug regimens. The soft-gel formulation of saquinavir (Fortovase), indinavir, nelfinavir, and amprenavir is typically administered in full dose while ritonavir, because of its relatively high incidence of side effects, is most often administered in a subtherapeutic dose in order to increase serum concentrations of the other protease inhibitors. Nelfinavir is particularly well tolerated and for this reason has become a common component of various HAART regimens.

4. Resistance

Resistance to one PI is often predictive of resistance to one or more other drugs in this class. Resistance testing may not fully reveal such cross resistance among PIs.

D. Regimens Containing PI and NNRTI or PI, NNRTI, and NRTI

Combining PI and NNRTI agents, although theoretically appealing, raises practical considerations because of interactions between drugs of these classes and difficult dosing schedules. Regimens which combine agents of all three classes may also be quite potent but may leave no proven options if resistance develops. For these reasons, such regimens are generally not advisable for initial therapy, unless primary viral resistance is documented. At present, the use of these combinations is typically reserved for salvage therapy in cases of virologic failure.

E. Hydroxyurea

1. Mode of Action

Hydroxyurea, a chemotherapeutic agent used in the treatment of a variety of neoplasms, has several effects that may be beneficial in HIV infection. Its primary mode of action is to inhibit DNA synthesis by blocking the ribonucleotide reductase. By reducing the intracellular pool of ribonucleotides (required for DNA synthesis) in this manner, hydroxyurea may raise levels of nucleoside drugs by enhancing their uptake. Hydroxyurea may also act by reducing activation of CD4+ cells and thus protecting them from the effects of HIV, while antiretroviral drugs suppress viral replication and reduce viral burden.

2. Evidence of Efficacy

Hydroxyurea combined with didanosine resulted in a significant reduction in viral load at 24 weeks compared with didanosine alone.[33] In a larger study, individuals, who had had complete viral suppression receiving indinavir, lamivudine, and either

zidovudine or stavudine, were randomized to continue their regimen or to change to indinavir, didanosine, and stavudine either with or without hydroxyurea. The study was ended early because of a high rate of side effects, including two cases of fatal pancreatitis, as well as virologic failure, in the hydroxyurea group.[34]

3. Patterns of Use

The use of hydroxyurea has been hampered by side effects in many patients. Since it can restore didanosine sensitivity to resistant viral strains, it may yet find an important role in reducing the spread of these resistant isolates.[34]

VI. CLINICAL SCENERIOS IN ANTIRETROVIRAL THERAPY

A. Treatment-Naive Patient

Many options are currently available for the patient beginning antiretroviral therapy for the first time. The relative advantage of PI-sparing, NNRTI-sparing, or three-drug class regimens has not been fully evaluated. At present, any of the regimens listed can be considered appropriate. Specific choices may be governed by considerations of convenience and side-effects profile.

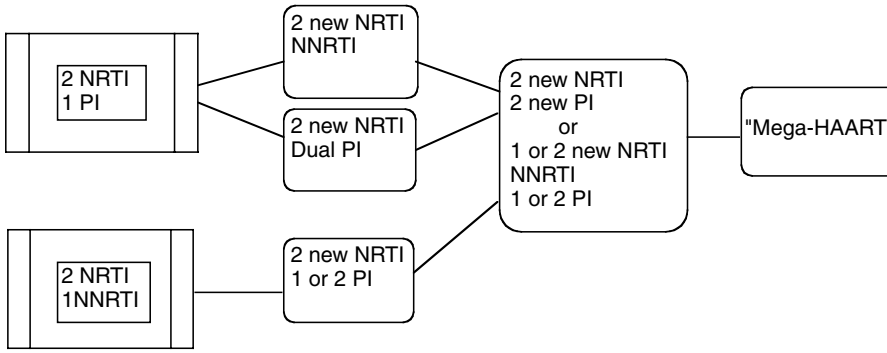
Several factors including patient acceptance and the likelihood of compliance, quality of life, and long-term therapeutic success should be considered before starting antiretroviral therapy.

B. Patient on Antiretroviral Therapy with Incomplete Viral Suppression

Although there is no uniform standard of virologic failure, a one-log reduction in viral load by 8 weeks of therapy is recommended as an indication of therapeutic success in published treatment guidelines. Failure to achieve this milestone or, ultimately, failure to achieve complete viral suppression is a common phenomenon in clinical practice. For patients achieving a partial response, several options exist. The simplest, and least studied, is so-called treatment intensification. In this strategy a single additional agent is added to a regimen that has produced partial, but not complete, improvement in viral load. It is prudent to reserve this option for patients with almost complete suppression (e.g., fewer than 1000 copies/mm^3) to avoid sequential drug resistance. The short- and long-term advisability of the strategy has not been evaluated.

C. Virologic Failure

Sequencing of antiretroviral therapy in patients who have not responded to their initial regimen is a complicated process (see Figures 10.1, 10.2). Little controlled data are currently available to guide the clinician in choosing subsequent regimens, but certain factors must be taken into account:



NRTI = nucleoside reverse transcriptase inhibitor
NNRTI = non-nucleoside reverse transcriptase inhibitor
PI = protease inhibitor
Mega-HAART = salvage regimens containing 6 or more agents

FIGURE 10.1 Empiric sequencing of antiretroviral therapy for patients failing initial regimen.

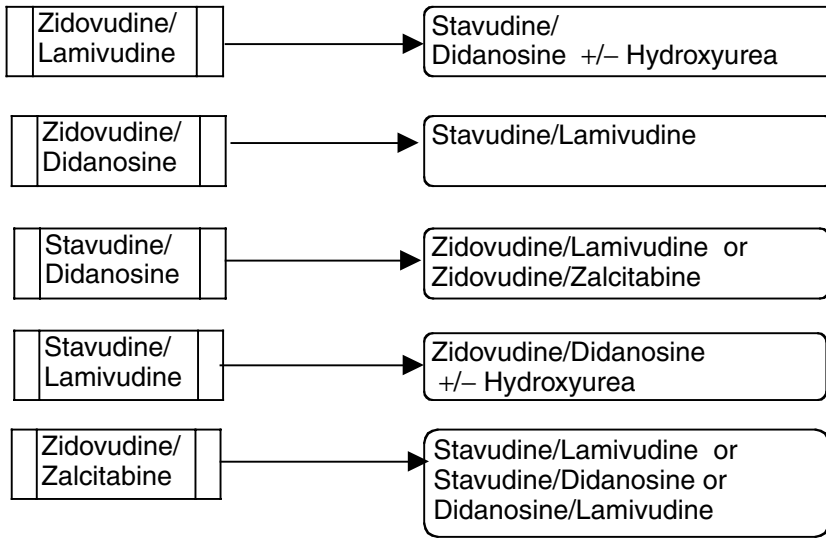


FIGURE 10.2 Appropriate combinations and sequencing of nucleoside reverse transcriptase inhibitors.

- Cross-resistance to other agents within a class (NRTI, PI, NNRTI) is likely and, in the case of NNRTI failure, should be assumed to be present.
- Resistance testing may fail to identify subpopulations of resistant virus.
- Structured treatment interuption (see below) may permit reappearance of sensitive viral strains and subsequent virologic response.

- Discordant responses to therapy (see below) in which a significant rise in CD4 cell count occurs despite failure to achieve complete viral suppression may be adequate under some circumstances when safe and effective options are very limited or nonexistent.

Possible strategies for sequencing of agents in patients who fail initial and subsequent regimens are illustrated in Figures 10.1 and 10.2.

D. Discordant Responses

Patients who remain on antiretroviral therapy often remain clinically stable with stable or, rarely, rising CD4+ lymphocyte counts despite virological failure.[35,36] This phenomenon, which likely reflects reduced fitness of viral strains with resistance mutations, provides a rationale for continuing a suboptimal, but well-tolerated, regimen when no alternatives exist. In a prospective comparative study from France, it was found that the likelihood of an AIDS-defining complication after 6 months of HAART was equal among patients manifesting a significant immunological response, regardless of virologic response,[37] although more long-term data are not yet available. Patients with a virologic, but not immunologic, response had significantly worse outcomes. Complete nonresponders had the worst prognosis. Observations such as this support the continued importance of CD4 cell-count monitoring[38] and serve as an indicator that immune reconstitution itself should be a primary goal of therapy.

Interestingly, and perhaps relevant to the phenomenon of discordant, multidrug-resistant viral strains often manifest diminished infectivity and rate of replication.[39]

VII. NEW ANTIRETROVIRAL AGENTS

A large number of other antiretroviral agents is currently in various stages of development (see Boxes 10.4 and 10.5). New compounds in each current class, i.e., NNRTI, NRTI, and PI, are in clinical trials

In addition, new classes of antiretroviral agents are currently in development:

1. Fusion inhibitors block viral entry into the cell by competitively binding to cellular receptors, either at the Gp41 transmembrane protein or at chemokine receptors (see Chapter 2).
2. Integrase inhibitors block the viral enzyme integrase, preventing integration of proviral DNA into host DNA.
3. Nucleoside zinc finger inhibitors can cause release of zinc from the viral nucleocapsid protein resulting in inhibition of replication.

It is unclear at this time from which, if any, of these novel drug classes will emerge clinically useful compounds. Most likely, the major advances in antiviral drug therapy will be derived from the existing classes of licensed drugs as these compounds are improved to enhance efficacy and compliance and limit the development of resistance.

BOX 10.4

Reverse transcriptase inhibitors
- Nucleoside
  - Lodenosine
  - FTC
  - DOTC
- Non-nucleoside
  - MK-442
  - AG1549
  - PNU-142721
  - DPC 961 and DPC 963
  - GW420867X
  - Calanolide A

Nucleotide analogs
- Adefovir
- Bis-POC PMPA (tenofovir DF)

BOX 10.5

Protease inhibitors
- BMS-232632
- Tipranavir
- L-756, 423
- DMP-450
- AG-1776

Immunologic therapy, either by means of administration of exogenous cytokines or compounds that block the effects of harmful endogenous inflammatory cytokines or by enhancement of the host immune response through vaccination, has also received much attention and may soon yield effective agents.

Among the immune system abnormalites associated with HIV infection is a deficiency of interleukin-2 (IL-2), a cytokine derived from T lymphocytes and natural killer cells. Administration of a recombinant preparation of IL-2 subcutaneously can augment the effects of antiviral drugs and raise CD4+ cell levels in individuals with early HIV-1 infection.[40]

A variety of other immunologically mediated therapeutic strategies are under study at present.

VIII. MONITORING ANTIRETROVIRAL THERAPY

The measurement of plasma viral RNA and of CD4+ lymphocyte counts, along with clinical assessment, can provide an accurate picture of disease activity and progression for most patients. It has been observed that blood levels of antiretroviral agents are variable among individuals, and treatment failure may indicate subtherapeutic

levels.[41] In the future, monitoring of drug levels may become a standard practice; however, at this time, access to such assays is limited.

A. Monitoring for Effectiveness

1. Viral Load

Plasma levels of viral RNA have been shown to correlate closely with clinical outcome. Over a dozen clinical trials, which included thousands of patients, have demonstrated this correlation in patients at various stages of disease and with a wide variety of prior treatment histories.[42–44] In addition, the level of viremia (so-called viral load) measured in this way provides the most precise means of establishing whether a response to antiviral therapy has occurred. In the untreated patient or in individuals on stable therapeutic regimens, viral load should generally be measured every 3 to 4 months.

In patients beginning therapy or those changing therapy for virological failure, viral load should be measured immediately prior to initiation and 2 to 8 weeks later, by which time it typically falls by at least 1 log in the presence of effective therapy. In most such patients, the viral load becomes undetectable (fewer than 50 copies/mL) by 4 to 5 months. An absent or incomplete response of the viral load to antiretroviral therapy should raise concerns about viral resistance or poor patient compliance with therapy.

At the time of this writing, only the polymerase chain reaction (PCR) measure of viral RNA has been approved by the U.S. Food and Drug Administration for clinical staging and assessment of therapy of HIV infection.

2. Lymphocyte Subsets

CD4+ lymphocyte count, expressed as cells/mm^3 of blood, is a somewhat less precise indicator of clinical stage and response than viral load, but is a valuable adjunctive study and can permit immunological staging and decisions regarding prophylaxis against opportunistic infections. CD4+ cell counts should be measured at the time of diagnosis of HIV infection and every 3 to 6 months thereafter. The CD4+ response to antiretroviral therapy can be unpredictable and, although a significant rise often occurs among patients treated with effective antiretroviral therapy, the absence of such a rise should not be taken to mean viral resistance or poor patient compliance if the viral load declines appropriately. This lack of correlation between viral load and CD4+ cell response is particularly common among patients with extremely low initial CD4 cell count (e.g., fewer than 50 cells/mm^3).

3. Clinical Signs and Symptoms

The appearance of signs and symptoms of HIV infection in a previously asymptomatic patient should be regarded as a poor prognostic indicator. As mentioned above, symptomatic HIV infection is considered an independent indication for the initiation of antiretroviral therapy regardless of viral load and immune parameters. The appearance of symptoms in a patient receiving antiretroviral therapy should prompt a reassessment of the treatment regimen and patient compliance.

B. Monitoring for Side Effects

1. Bone Marrow Depression

Bone marrow depression is most often associated with zidovudine or hydroxyurea therapy. Significant cytopenias become more common in the later stages of symptomatic HIV infection.

2. Lipodystrophy/Hyperlipidemia

In patients receiving protease inhibitors or efavirenz, serum triglyceride levels should be determined and routine biochemical tests, including liver function assays, should be run prior to beginning therapy and periodically thereafter.

3. Glucose Intolerance

Blood glucose levels should be monitored periodically among patients receiving protease inhibitors. Patients at high risk of glucose intolerance (e.g., obesity, hyperlipidemia, pancreatitis, family history of diabetes) may also be monitored with periodic determination of glycosylated hemoglobin (hemoglobin A1C) or glucose tolerance tests to identify intermittent periods of hyperglycemia.

4. Peripheral Neuropathy

Patients taking nucleoside drugs, particularly didanosine, zalcitabine, or stavudine, should be monitored for clinical signs and symptoms of peripheral neuropathy including numbness, tingling, or pain in the hands or feet. These symptoms are seen more commonly in patients with advanced HIV infection or prior history of neuropathy. Discontinuation of these agents usually results in gradual improvement.

5. Pancreatitis

Serum amylase levels should be monitored periodically among patients receiving zalcitabine who have a history of pancreatitis or ethanol abuse or who are at high risk for pancreatitis on the basis of hyperalimentation or underlying medical conditions. Didanosine should be avoided in patients at high risk of pancreatitis if possible. If such patients are receiving didanosine, amylase levels should be monitored periodically.

6. Lactic Acidosis/Hepatic Steatosis

The syndrome of lactic acidosis/hepatic steatosis (see above) has been most often been associated with nucleoside therapy. Manufacturers of individual nucleoside reverse transcriptase inhibitors recommend the following:

> Stavudine, abacavir, didanosine, lamivudine, and zalcitabine should be used with caution in patients at risk for liver toxicity, although cases of the syndrome have occurred in the absence of definite hepatotoxicity. These agents should be discontinued in any

patient developing signs consistent with lactic acidosis (including unexplained decrease in serum bicarbonate level) or liver toxicity.

7. Hepatotoxicity

Hepatotoxicity, which may be fulminant, has most often been associated with nevirapine therapy. The manufacturer strongly recommends monitoring of transaminases, particularly during the first 6 months of therapy, and discontinuing the drug if moderate or severe abnormalities occur. The drug should be avoided if liver function abnormalities recur upon rechallenge. The manufacturer of efavirenz recommends periodic monitoring of liver function tests in patients having a history of hepatitis B or C.

8. Miscellaneous Side Effects

Diarrhea is a frequent complication of protease inhibitor therapy. Both efavirenz and zidovudine can cause insomnia and mood alterations.

C. Drug Interactions

Numerous interactions between antiretroviral drugs, particularly protease inhibitors, and other medications have been described. Some interactions may cause serious morbidity or mortality (see Chapter 15).

D. Interpreting Virologic Failure

1. Confirmation

In general, virologic failure should not be based on the result of one viral load determination. Repeat testing is warranted, especially if a change in antiretroviral therapy is contemplated.

2. Measuring Drug Levels

Drug levels have been shown to correlate with clinical success for several agents. At the present time, however, these assays are not widely available.

3. Testing for Drug Resistance

It has become increasingly clear that testing for resistance to antiretroviral drugs is a useful and, in the opinion of many, essential means of directing therapy rationally. As issues regarding viral resistance are reviewed, however, it should be borne in mind that treatment failure has been documented in the absence of resistance and in many cases may be attributable to either poor patient compliance or inadequate drug levels.[45]

The role of resistance testing has been best established for treatment-experienced patients in whom patterns of resistance often correlate closely with subsequent response to antiviral therapy.[46]

TABLE 10.1
Mutations of the Reverse Transcriptase Gene of HIV-1 Associated with Viral Resistance to Nucleoside Reverse Transcriptase Inhibitors

Drug	Primary Mutations	Other Mutations
Zidovudine	K70R, T215Y/F	M41L, D67N, L210W, K219Q
Didanosine	L74V	K65R, V75T, M184V/I
Zalcitabine	K65R, T69D, L74V, M184V/I	
Stavudine	V75T	
Lamivudine	E44D, M184V/I	
Abacavir	K65R, L74V, M184V	M41L, D67N, Y115F, OW T215Y/F, K219Q, L210W1

TABLE 10.2
Mutations of the Reverse Transcriptase Gene of HIV-1 Associated with Viral Resistance to Non-Nucleoside Reverse Transcriptase Inhibitors

Drug	Primary Mutations	Other Mutations
Delavirdine	K103N, Y181C	P236L
Efavirenz	K103N, Y188L, G190S/A	L100I, V108I, P225H
Nevirapine	K103N, V106A, V108 Y181C/I Y188C/L/H, G190A	

Two types of assays can be performed to detect resistance to antiretroviral agents. Genotypic assays detect resistance mutations in viral genes, while phenotypic assays are more analogous to bacteriologic sensitivity testing and measure viral growth in various concentrations of antiviral drugs. Genotypic testing is generally more widely available, but both techniques have been shown to correlate with response to treatment in studies.

Neither method of resistance assay is currently available in routine clinical laboratories, although kits from a number of manufacturers were in development at the time of this writing. Genotypic resistance testing involves amplification of HIV-1 gene sequences by means of PCR from plasma containing a detectable amount of viral RNA for the purpose of identifying sequences known to confer resistance to specific antiretroviral agents[47,48] (see Tables 10.1, 10.2, 10.3). Genotypic testing as currently available lacks diagnostic sensitivity and results may be difficult or impossible to interpret by providers not conversant with genetic resistance patterns and their clinical significance. Drug-resistant mutant HIV strains may be detected at a level of 10 to 50%, depending on the laboratory and the specific mutation present.

TABLE 10.3
Mutations of the Protease Gene of HIV-1 Associated with Viral Resistance to Protease Inhibitors

Drug	Primary Mutations	Other Mutations
Saquinavir	G48V, L90M	L101/R/V, 154 V/L, A71V/T G73S, V77I, V82A, I84V
Ritonavir	V82A/F/T/S	K20M/R, V32l, L33F, M36I, M46I/L, I54V/L, A7IV/T, V77II84V, L90M
Indinavir	M46I, V82A/F/T/S	L101/R/V, K20M/R, L24I, V32I, M36I, I54V, A71V/T, G73S/A V77I, I84V, L90M
Nelfinavir	D30N, L90M	L10F/I, M36I, M46I/L, A71V/T V77I, V82A/F/T/S/184V, N88D
Amprenavir	150V, 184V	L10/F/I/R/V, V32I, M46I, 147V 154V

Phenotypic assays are commercially available and automated. As in genotypic assays, viral RNA is amplified from plasma, and recombinant viral strains to test for resistance to antiretroviral agents are created using laboratory strains of HIV. Concentrations of antiviral drugs required to inhibit 50% (IC50) and 90% (IC90) of recombinant viral strains are expressed relative to that of a standard laboratory strain. Unfortunately as in the case of genotypic resistance testing, a viral strain accounting for less than 10 to 50% of the viral population may fall below the level of detection.

a. Data Supporting the Use of Resistance Testing

Several studies have confirmed the utility of resistance testing in directing therapy of antiretroviral-experienced patients. D'Aquila and colleagues found that zidovudine resistance (phenotypic) was predictive of clinical progression and death among patients who had received at least 16 weeks of therapy.[49] A strong correlation between resistance by phenotypic assay and clinical outcome was also found by Deeks and colleagues in a study of salvage therapy among patients who had failed indinavir- or ritonavir-containing multidrug regimens. Subjects received four-drug combinations of nelfinavir, saquinavir, abacavir, and either another nucleoside agent or nevirapine. Sensitivity to more than one of the agents in the salvage regimen correlated with suppression of viral load.[50]

Several studies have similarly demonstrated the value of resistance testing using genotypic assays. Durant and colleagues randomly assigned patients who had failed combination therapy to standard alternative regimens or to therapy guided by genotypic assays for mutations in protease and reverse transcriptase genes. A significantly higher proportion of subjects in the latter group had significant reductions in viral load at 6 months.[51] Genotypic resistance patterns were also predictive of virologic response in a study by Zolopa and colleagues of patients who had failed therapy with saquinavir-ritonavir.[52]

b. Limitations of Resistance Testing

Despite its documented utility, viral resistance testing has limitations reflecting the current state of technology as well several unique features of the virus itself.

Viral diversity Viral genetic diversity is characteristic of HIV-1. HIV-infected individuals typically have several viral strains with potentially differing resistance patterns. Furthermore, clades of the virus differ in various parts of the world. Current resistance assays were developed primarily for clade B, the strain prevalent in Europe and North America.

Sensitivity As noted above, current assays, whether genotypic or phenotypic, are unable to reliably detect minority populations of resistant virus. For this reason, resistance demonstrated by either assay should be considered accurate, but absence of resistance should not be taken to mean all viral populations in an individual patient are sensitive or lack resistant mutations.

Availability The availability and standardization of resistance assays remain significant obstacles to their use at the time of this writing. With anticipated approval by the U.S. Food and Drug Administration, these issues should become less significant.

E. Issues in Compliance with Therapy

Compliance with antiretroviral therapy and adherence to complex treatment regimens is essential for achieving durable suppression of viral load. Even patients who only occasionally miss doses of their antiviral drugs run an increased risk of early emergence of resistance, viral breakthrough, and clinical progression.[11] The practical impact of treatment adherence is seen in the contrast between rates of viral suppression seen in clinical trials, often greater than 95%,[28,53] and those reported from clinical settings, often less than 50%.[4,54,55]

Many factors may represent obstacles to full compliance with therapy, however.

- Denial: Failure to accept the reality of HIV infection frequently leads patients, particularly those who are asymptomatic, to doubt the need for antiretroviral therapy or to be less than meticulous in taking their prescribed medications.
- Lack of acceptance of therapy: Side effects of therapy, concerns about safety, whether real or imagined, or skepticism about traditional medicine may lead some individuals to openly decline appropriate retroviral therapy or to adhere poorly.
- Number of pills: Such practical issues as the large number of pills, the fact that some antiretroviral medications must be taken either with meals or on an empty stomach, and lack of privacy in the home or workplace may lead even highly motivated patients to miss doses frequently.
- Depression: Depression, more frequent among HIV-infected patients at all stages of disease, may be accompanied by feelings of hopelessness so intense that therapy and visits to the provider seem pointless.

- Physical obstacles: A large proportion of HIV-infected individuals live in marginal housing or are homeless. Lack of a stable living situation has been shown to be a significant impediment to treatment adherence.[56]

For a more complete discussion of adherence issues and compliance with antiretroviral therapy, please see Chapter 11.

In most cases, interruption of HAART therapy is followed by rebound of viremia and decline in CD4 cell count. For this reason, such an interruption should occur only under controlled circumstances.

IX. STRUCTURED TREATMENT INTERRUPTION

Because of the limited number of antiretroviral agents available and the problem of cross resistance between agents, an increasing number of patients have exhausted all feasible drug combinations. It has been suggested that a planned, temporary discontinuation of antiretroviral therapy in such individuals may allow for an overgrowth of more fit, sensitive viral strains and subsequent improved response to therapy.[57] This strategy, termed *structured treatment interruption* (STI), has also been proposed as a means of enhancing the immune response to HIV following primary infection.[58]

Among patients with detectable viral load on therapy, STI has, in fact, been shown to result in reversion to more sensitive viral strains in several small studies,[59,60] although resistant subpopulations often persist in relatively small numbers.[61] Subsequent salvage therapy was successful in a significant number of such patients,[57] although CD4+ lymphocyte counts tended to fall significantly during the period off therapy. The long-term benefit of STI has not been established and persistence of resistant subpopulations of virus suggests that any benefit might be short-lived for many individuals. Until larger studies address this issue and better define the long-term impact on CD+ lymphocyte counts, STI should be considered an unproven strategy for salvage situtations.

In the setting of primary HIV infection, STI may lead to an enhanced immune response among patients treated after infection has occurred but before the appearance of antibody. Altfield and colleagues[58] studying seven such patients found an enhanced cytotoxic T lymphocyte (CTL) response after initial and subsequent STIs. In such patients, it is thought that viral rebound occurring during the STI serves as an autoinoculation leading to enhancement of the immune response, which was partially blunted by early therapy after primary infection. Although viral load may return to undetectable levels after the resumption of treatment in such patients,[62] the role of STI following treatment for primary infection is not yet clear.

X. ACHIEVING THE GOALS OF ANTIRETROVIRAL THERAPY

With current therapeutic strategies, durable suppression of viral replication as indicated by viral load is achieved in approximately 50% of individuals beginning therapy for the first time. Treatment failure appears to represent either viral resistance or poor patient compliance in most cases. As noted above, adherence to antiretroviral

therapy can be difficult, especially when treatment regimens are complex and confusing. It is the responsibility of the provider to specifically address adherence by fostering a close relationship with the patient. In this way, the patient will be more likely to be frank about compliance issues and the provider will be able to help formulate specific strategies for improvement. Treatment regimens should be as simple as possible and unnecessary medications should be eliminated. Reminders such as alarms, printed schedules and, when helpful, periodic telephone discussions should be considered even for apparently compliant patients. The support of family and friends should be enlisted when confidentiality permits. An intentional or unintentional interrupton of therapy with any of the agents in the regimen should be reported to and discussed with the provider. In general, if therapy must be stopped for reasons of logistics or lifestyle, all agents should be stopped, and ultimately resumed, simultaneously. Patients should be provided with an updated list of their medications and instructed to contact the provider promptly if they are hospitalized so that unnecessary interruption of therapy is avoided.

Among symptomatic patients with advanced immune deficiency, treatment regimens must be constantly reconsidered as the need for other, potentially interacting, drugs may arise. Interruption of antiretroviral therapy, although not desirable, may be inevitable in some of these patients.

Above all else, treatment adherence must be regarded as a likely constant struggle for all patients receiving antiretroviral therapy, and time should be set aside at each patient contact to discuss this vital issue.

XI. FURTHER DISCUSSION

A. Antiretroviral Therapy in Pregnancy

The use of antiretroviral therapy in pregnancy to prevent mother-to-child transmission is discussed in Chapters 9 and 14. The potential effects of antiretroviral agents on the developing fetus are listed in Chapter 15.

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11 Issues in the Care of the Patient Taking Antiretroviral Therapy

CONTENTS

I. INTRODUCTION

The ongoing care of individuals receiving highly active antiretroviral therapy presents many challenges. New agents have appeared frequently and treatment guidelines and strategies are continually being reevaluated and revised. Drug side effects, some peculiar and quite unexpected, are seen in many patients and often limit therapeutic options. The list of reported interactions, some potentially life-threatening, between antiretroviral agents and other medications continues to grow.

Further complicating matters is the fact that an extremely high level of adherence to therapy seems to be necessary to maintain suppresson of viral replication for as long as possible, although measures of adherence for individual patients are often inaccurate. Unfortunately the complex dosing requirements of combination antiretroviral therapy tend to make adherence very difficult. Strategies to improve adherence are receiving increasing research attention, but no universally effective measures have yet been reported. The relatively high incidence of mental illness and active substance abuse seen among many HIV-infected populations represents a nearly insurmountable obstacle to effective treatment for some.

Finally, because of the rapidly expanding understanding of the pathogenesis, clinical manifestations, and therapy of HIV infection, practitioners must make great efforts to remain current. It is not clear whether the emerging specialty of HIV care will attract sufficient physicians, nurses, social workers, and other professionals to provide state-of-the art treatment for the increasing number of individuals in need.

II. SIDE EFFECTS OF ANTIRETROVIRAL DRUGS

Despite the clear improvements in survival and quality of life associated with effective antiretroviral therapy, side effects of many of the commonly used agents produce a substantial amount of discomfort and morbidity for some individuals. Unfortunately, this problem is most often encountered with the most potent antiretroviral compounds, the protease inhibitors.

A. Managing Undesired Effects of Antiretroviral Therapy

1. Lipid Disorders

Elevation of cholesterol and triglyceride levels appears to occur in approximately 15 to 60% of individuals on therapy with protease inhibitor therapy.[1–3] The full clinical significance of these laboratory abnormalities is not yet clear, although they may be associated with premature coronary artery disease in some individuals.[2] It is likely that the implications of protease inhibitor–related hyperlipidemia is most significant for patients with other risk factors for coronary artery disease.

Treatment guidelines for hyperlipidemia related to protease inhibitor therapy have not been established. In other settings, the goal is generally to lower LDL cholesterol to below 100 mg/dL in patients with coronary artery disease, to 130 mg/dL in those without coronary artery disease but with coronary risk factors, and to below 160 mg/dL in patients without coronary artery disease or cardiac risk factors.[4]

2. Fat Redistribution

Changes in body fat distribution comparable with those seen in Cushing's syndrome have been described in association with protease inhibitor therapy and were present in 83% of patients in one series.[5] This disorder, referred to as the lipodystrophy or fat redistribution syndrome, presents as progressive central obesity and peripheral fat wasting. Lipomatosis, breast enlargement, cervical fat pad (buffalo hump), and visceral fat accumulation may also be seen. Dose reduction of antiretroviral therapy should not be considered because of the risk of viral resistance. Dietary fat restriction appears to offer no benefit.[6] Symptoms may resolve with discontinuation of protease inhibitors.

3. Hyperglycemia

Hyperglycemia with new-onset diabetes or exacerbation of existing diabetes has been reported in association with protease inhibitor therapy.[7,8]

4. Osteoporosis/Avascular Necrosis

Avascular necrosis may be seen in patients with hyperlipidemia while receiving protease inhibitors. Patients receiving these agents should be considered to be at high risk for spontaneous hip fracture. No treatment recommendations have yet been developed.

5. Diarrhea

Diarrhea is a common side effect of protease inhibitor therapy. Most patients respond to antiperistaltic agents or pancreatic enzyme preparations.

6. Peripheral Neuropathy

Peripheral neuropathy may complicate therapy with didanosine, stavudine, and zalcitabine and is particularly common in patients receiving combination therapy with didanosine, stavudine, and hydroxyurea. If symptoms are intolerable or progressive, it is usually necessary to discontinue therapy. In milder cases or when other treatment options are not available, painful neuropathy occasionally responds to tricyclic antidepressants, anticonvulsants, or gabapentin.

7. Hematological Abnormalities

Anemia and leukopenia may complicate therapy with zidovudine, although hematological side effects are considerably less common with current dosing regimens than they were with higher doses used in the past. In patients who must remain on zidovudine therapy, growth factors, including erythropoetin and granulocyte colony–stimulating factor, may maintain cell counts in an acceptable range.

8. Hepatic Steatosis/Lactic Acidosis

Hepatic steatosis and lactic acidosis have been seen in association with the nucleoside antiretroviral drugs (zidovudine, didanosine, zalcitabine, lamivudine, stavudine, and abacavir). The syndrome, which is felt to represent mitochondrial toxicity of these agents,

appears to be uncommon, occurring approximately every 1000 patient-years, but can be fatal. Early manifestations are nonspecific and include fatigue, abdominal pain, nausea, diarrhea, and shortness of breath. Progressive lowering of serum bicarbonate may be noted. Women and patients with obesity and/or underlying liver disease appear to be at greatest risk and stavudine may be more frequently associated with the syndrome than other agents. The only known treatment is supportive care and discontinuation of the antiretroviral agent, although a variety of other modalities, including therapy with riboflavin,[9] carnitine, and thiamine to improve oxidative phosphorylation have been used in a small number of patients. A mild form of the syndrome featuring moderately elevated lactate levels and abdominal discomfort may exist and may respond most readily to early discontinuation of nucleoside drugs.[10] The relationship between this entity and fulminant lactic acidosis with hepatic steatosis is not clear, however. Concomitant liver involvement may be necessary for the development of the life-threatening syndrome.[11] Considering the current level of uncertainty regarding the full clinical spectrum of this disorder, it is prudent to withdraw nucleoside therapy whenever unexplained hyperlactinemia is documented and to use these agents cautiously and under close observation in patients with known liver disease.

The long-term implications of the syndrome and the safety of reinstituting antiretroviral therapy have not been established.

B. Inflammatory Reactions to Successful Antiretroviral Therapy

Recrudescence or initial appearance of dormant infections may occur after initiation of antiretroviral therapy in some patients.[12] This peculiar and unanticipated phenomenon is typically seen shortly after therapy is begun and is associated with dramatic falls in circulating viral load and rises in CD4 lymphocyte counts. Opportunistic disorders reported to present in this manner include infections due to *Mycobacterium tuberculosis,*[13,14] *Mycobacterium avium* complex (MAC),[15,16] cytomegalovirus (CMV),[17,18] *Cryptococcus neoformans,*[19] *Histoplasma capsulatum*, and Herpes zoster[20] as well as progressive multifocal leukoencephalopathy.[21,22] Viral hepatitis (B and C),[23–25] not considered opportunistic infections, may also activate after the introduction of antiretroviral therapy.

The presentations of some of these infections may be atypical in the setting of immune reconsititution. For example, MAC infection, when symptomatic, usually causes systemic manifestations such as weight loss, malaise, and prominent GI complaints and, often, bacteremia and/or widespread bone marrow involvement in the setting of advanced AIDS. With immune reconstitution, focal infections such as lymphadenitis are typical and disseminated disease rare.[26] Vitritis,[27] often manifesting as ocular "floaters," and extraocular involvement,[17] particularly colitis and pancreatitis, appear to be more common in CMV infection during immune reconstitution than in advanced AIDS with severe immune deficiency.

Treatment guidelines for opportunistic infections occurring after immune reconstitution have not yet been developed. Several reports indicate that corticosteroids, in additional to antimycobacterial therapy, may be beneficial in patients with MAC or

tuberculosis complicating successful therapy.[28,29] In some situations, discontinuation of antiretroviral therapy may be necessary although this appears to be unusual and the immune reconstitution syndrome resolves despite continuation. No controlled data are available to support any of these strategies, however. Furthermore, it is not known how long therapy for opportunistic infections should be continued. Until more data are available, it is appropriate to manage infections occurring during immune reconstitution according to previous guidelines.

C. Retroviral Rebound Syndrome

A rebound of plasma viral RNA levels occurs after discontinuation of successful antiretroviral therapy.[30] In some instances, a clinical syndrome resembling that seen in acute primary retroviral infection may occur.[31,32]

D. The Emotional Impact of Survival

During the first 15 years of the AIDS epidemic, until the mid-1990s, long-term survival after the onset of symptoms was extremely unusual. Many individuals, however, have seen dramatic improvement in their medical condition and functional status since the advent of modern therapy. This phenomenon, though welcome, has brought with it new obstacles for patients responding to therapy. In many instances, HIV-infected individuals, assuming a short life expectancy, revealed previously secret risk behavior to loved ones, exhausted assets paying medical expenses, cashed life insurance policies, stopped working, and made many other drastic life changes. As their medical condition has stabilized, many such individuals have found themselves in the position of reconstructing their lives in a disorienting atmosphere of renewed hope and new challenges.

E. High Risk Behavior

Shortly after the effectiveness of HAART was established, alarming reports of increased high risk sexual behavior began to appear. In some areas of the country, significant numbers of homosexual and bisexual men and adolescents resumed or began unsafe sexual practices on the assumption that HIV infection could be prevented or cured with properly timed therapy (see Chapter 1).

III. MAINTAINING COMPLIANCE WITH TREATMENT

Adherence to antiretroviral treatment regimens is critically important. Even minor deviations from prescribed drug schedules can result in early emergence of resistant viral strains. Several studies have indicated that compliance in the range of 95% is required.[33,34] In other chronic illnesses, compliance with therapy is often poor.[35] One large study of HIV-infected patients indicated that only 60% were fully compliant with therapy,[36] despite the fact that most were receiving only single-drug therapy. As discussed in Chapter 10, antiretroviral schedules may be difficult for even the

most motivated patient to follow completely because of pill burden, timing of meals, and side effects. Compliance can be made even more difficult by the conditions in which many HIV-infected individuals live.[37] Homelessness or unstable housing, unemployment, substance abuse, mental illness, and family responsibilities all impact negatively on treatment compliance for large numbers of individuals.

The impact of poor compliance in HIV care is seen in the contrast between reported rates of viral suppression in research studies,[38,39] which often exceed 95% and those in studies in clinical settings, which often fall below 50%.[40–42]

This dilemma, that extraordinarily high rates of compliance with complex and difficult therapeutic regimens are essential for long-term success, is a critical problem faced by HIV-infected patients and their medical providers. For this reason, the approach to treatment adherence should be overt, organized, and continuous, and the success of any approach should be frequently reassessed.

A. Measures of Compliance

Compliance with antiretroviral therapy can be difficult to assess. Rates of virologic failure can give a general indication of the level of compliance within a clinic population. This information can be augmented by knowledge of viral resistance patterns so that virological failure due to resistance can be distinguished from that due to poor adherence to medication schedules. Although inadequate drug levels, even among some patients fully compliant with therapy, have been shown to lead to virologic failure, there is currently no widely available technique for measuring these.

Compliance is traditionally assessed in several ways[37]:

- Patient self-reporting: Although this data is simple to collect, it may be inaccurate if patients wish to deceive the provider or simply cannot recall medication schedules well enough. Patients who have difficulty keeping to treatment regimens because they lead chaotic or disorganized lives may be equally unable to recall how they have taken their medications. Patients often tend to overestimate compliance.[43] At times, however, patient self-reporting can be sufficiently accurate and has been shown to correlate with virologic response to antiretroviral therapy.[44]
- Pill counts: Whether by patient or provider, pill counts often provide more accurate information than patient self-reporting,[45] although overestimates of compliance are also possible by this measure.
- Drug level assays: Although the measuring of drug levels can provide important information about compliance,[46] these assays are expensive and not generally available.[47] The correlation between blood levels and therapeutic effect may not be as strong as it is for intracellular levels for some agents. Finally drug levels at best provide information only about recent compliance and may, therefore, overestimate overall compliance.
- Electronic monitoring systems: Sensors may be contained within medication bottle caps which can record each time the bottle is opened. Even

such systems may not provide a fully accurate indication of compliance, because they are not able to determine the number of pills removed.

B. Factors That Influence Compliance

1. Patient Factors

Most difficulties with compliance are based on patient factors.[48] Overt issues such as mental illness[49] and substance abuse[34] have been shown to be significant barriers to compliance with antiretroviral therapy. Somewhat more subtle barriers may exist for many individuals.[50–52] Among these are anxiety, lack of education, a perception that medications are not working, and a lack of conviction that they can successfully comply with therapy. Young age and male gender also correlate with poor treatment adherence.

2. System Factors

Adherence to antiretroviral therapy and compliance with appointments go hand in hand. Both can be enhanced by designing systems of care which are convenient for the patient. Flexible office or clinic hours with evening and weekend appointments may allow motivated working patients to remain in care more easily. A variety of services including primary care and subspecialty medical services, such as social, nutritional, and dental care, provided in a single site reduces the number of appointments. Recognition of the need for transportation, childcare, efficient visits, and short waiting times is essential. A great variety of community agencies offer services to HIV-infected individuals ranging from childcare to adult daycare to food and housing services to full case management. Such support services have been demonstrated to improve compliance.[53,54] These services should be identified and made available to eligible patients.

The use of a pharmacist to provide additional treatment education and strategies for medication compliance may be quite effective.[55] Peer educators and buddies as well as other professional staff should also be considered. A systematic means of identifying patients encountering problems with compliance can help ensure that resources will be directed to those who most need them.

C. Provider Qualifications

Provider experience in caring for HIV-infected patients has been shown to correlate positively with clinical outcome.[56–59] The rapidly evolving nature of our understanding of HIV infection pathogenesis and natural history and, most of all, the dramatic increase in knowledge about antiretroviral therapy necessitate a high level of provider sophistication and motivation to remain current with advances in the field. HIV providers must also be familiar with entitlements, especially drug assistance plans, available to their patients and with means of access to clinical trials. Recommended criteria for "HIV specialist" status vary but most include both training and experience-based qualifications.

D. Antiretroviral Regimens

1. Tailoring the Drug Regimen

A source of much confusion is the need to take certain medications once daily, some two, three, or four times daily, some at bedtime and some with meals. This complexity can be addressed by providing a daily schedule employing aids such as charts and pill boxes to patients linking the doses of each drug to an activity or meal that takes place at roughly the same time each day. Modifying medication regimens in accordance with lifestyle issues, if possible, can improve adherence.[60] This strategy may be especially necessary for patients who work full time in jobs where taking medications threatens their confidentiality, those with part-time or erratic work schedules, and those with extensive household and childcare responsibilities. All patients should be counseled to construct a weekly schedule of medications to help in anticipating day-to-day changes in their activities. Weekly pill sorting boxes may be helpful in this regard.

In cases of extreme difficulty with compliance, a system of directly observed therapy (DOT) with antiretroviral drugs could be considered if feasible. This approach has been highly effective in the treatment of tuberculosis. Obstacles to its use in HIV infection are substantial, however. These include the need for more than once-a-day dosing for most of the currently available antiretroviral drugs; inconvenience, especially for ambulatory patients with work or home responsibilities; and the fact that antiretroviral treament, unlike antituberculous treatment, must be continued indefinitely.

E. Addressing Side Effects

Patients should be instructed to anticipate possible side effects and given explicit procedures to follow (call, come to emergency room, etc.) in the event that side effects appear. Anticipation and effective management of side effects are important to maintaining compliance. If several treatment options exist, specific agents can be avoided if it is felt that the likely side effects would be especially intolerable or difficult to manage in an individual case. For example, patients suffering from moderate anemia may become profoundly symptomatic from bone marrow suppression with zidovudine. Didanosine and zalcitabine may be problematic in diabetic patients prone to peripheral neuropathy, and the diarrhea associated with protease inhibitors may be particulary difficult for a patient who is wasted or has preexisting diarrhea. Unfortunately, treatment options are often too limited to permit avoiding specific drugs. In this case, it is especially important that patients are made aware of the likelihood of side effects and treated as promptly and effectively as possible.

F. Education

The importance of adherence to prescribed treatment regimens should be emphasized at every appointment. Questions about adherence should be asked and patients should be encouraged to discuss any difficulties they are encountering with taking their

medications completely and at the proper time. The patients should be reassured that many side effects are self-limited or treatable.

Because of the large volume of information regarding therapy of HIV which is available to the general public in both written and electronic form, many patients have been exposed to conflicting opinions about antiretroviral drugs. Often the emphasis has been placed on unpleasant side effects or the possibility of treatment failure, and patients present for care highly skeptical about traditional therapy of any kind. It is helpful and important to discuss with patients their impressions of AIDS, HIV infection, and treatment options and to provide accurate information so that their decisions regarding antiretroviral therapy are soundly based. It is not unusual to find that patients, who expressed no concerns about therapy and appeared ready to comply, subsequently stopped or altered their treatment regimen without the provider's knowledge because of alarming, often distorted, information they had received. Trust in the provider and a working understanding of available, effective options help prevent this scenario.

FREQUENTLY ASKED QUESTIONS

1. What is the definition of virologic failure of antiretroviral therapy?

   Typically, the plasma viral load should fall by 1 log within the first 2 to 8 weeks after a new treatment regimen has been intitiated. In most patients, plasma viremia falls to undetectable levels by 4 to 5 months. Patients not achieving these milestones should be considered likely treatment failures.

2. What are the common side effects associated with therapy with each of the classes of antiretroviral drugs?

   Nucleoside agents: Anemia (zidovudine); peripheral neuropathy (didanosine, zalcitabine, stavudine); pancreatitis (didanosine, zalcitabine, stavudine); lactic acidosis/hepatic steatosis (all); life-threatening hypersensitivity reaction (abacavir).
   Protease inhibitors: Lipodystrophy syndrome (all); diarrhea (all); nephrolithiasis (indinavir).
   Non-nucleoside reverse transcriptase inhibitors: skin rash (all), anxiety/depression/insomnia/vivid dreams (efavirenz).

   See Chapter 15 for more complete discussion of side effects.

3. What are the indications for treatment of hyperlipidemia in patients receiving protease inhibitors?

   No clear indications for treatment have been developed at this time. National guidelines for treatment of hypercholesterolemia should be consulted (see text). Patients with other risk factors for coronary artery disease are most likely at highest risk.

4. What rate of treatment adherence is needed to avoid emergence of resistant viral strains?

Consistent adherence in the range of 95% appears to be necessary to maintain maximal viral suppression.

5. What is the rate of virologic failure of antiretroviral therapy reported in clinical series and how does it compare with that reported in research settings?

   Studies of patients taking antiretroviral therapy in clinic settings have indicated an adherence rate of approximately 50%. In contrast, 90% adherence or greater is common in clinical trials. This discrepancy raises questions about the applicability of clinical trial data to "real life" circumstances and also underscores the need for providers to concentrate on developing adherence strategies for their patients.

6. What factors contribute to poor treatment adherence?

   Mental illness and active substance abuse can create insurmountable obstacles to adherence with antiretroviral therapy. In addition, more subtle obstacles such as anxiety, lack of education, a lack of conviction that medications will help, concerns about privacy, memory deficits, inconvenience of the therapeutic regimen, and inconsistent access to water may all be major impediments to adherence. Male gender and young age also correlate with poor adherence.

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12 Managed Care and Quality Management Issues

CONTENTS

I. INTRODUCTION

In the United States and other developed countries, the cost of care for individual HIV-infected patients has fallen since the advent of modern antiretroviral therapy largely because of decreased rates of hospitalization and reduced hospital stays[1] as well as earlier diagnosis. The focus of care has moved increasingly into the outpatient setting. Almost simultaneously, managed care systems have proliferated in the United States. Quality management as a discipline in health care has also come to the fore in recent years. In this chapter, managed care issues, as they relate to HIV infection as well as quality management concerns, are reviewed.

II. MANAGED CARE

The creation of managed care plans for the care of HIV-infected patients has received much attention in recent years. It was estimated in 1998 that the direct cost of care of each HIV-infected individual was approximately $20,000 annually.[2] This accounts for less than 1% of total direct health expenses. More than three quarters of uninsured patients with HIV have received antiretroviral therapy, primarily through federal funding provided by the Ryan White CARE Act.

Medicaid currently provides reimbursement for the care of approximately half of the adults and 90% of children with HIV/AIDS in the United States.[3] Overall enrollment of Medicaid clients in managed care programs (all types) has risen from approximately 10% ten years ago to more than 50%.[4] However, Medicaid coverage has been criticized as unfair because of imposed limitations on utilization.[5]

The state of reimbursement for medical services for HIV-infected individuals in the United States varies by locale. Most states do not distinguish between HIV-infected individuals and other clients in calculating Medicaid benefits. Several states, however, have increased reimbursement for AIDS patients (Maryland, Massachusetts), and an increasing number of others have developed systems of enhanced reimbursement for high-risk patients in general (Colorado, Indiana, Maryland, Oregon).[6] Several states (e.g., New York, Tennessee) have sought to create specialized managed care plans for Medicaid patients with HIV/AIDS.[7–11] Such programs, referred to as Special Needs Plans (SNPs) in the New York model,[12] provide for capitated reimbursement for comprehensive care of patients with HIV/AIDS. Under capitated arrangements, insurers and providers negotiate annual per-patient fees. HIV/AIDS SNPs would provide enhanced services theoretically appropriate to the complicated care of HIV-infected individuals for enhanced levels of reimbursement. Provider and patient[13,14] attitudes toward such plans are often negative, however, because of a variety of concerns, such as potential loss of a trusted provider, bureaucratic issues, or poor access to subspecialty care.

Although it is hoped that capitated plans could be used to create centers of clinical excellence for HIV care,[15] health outcomes under managed care may not be equal to those in fee-for-service plans,[16] especially for patients with advanced disease.[17] It is recognized that provider experience has a favorable impact on survival among HIV-infected patients.[18] Some plans have been accused of providing inadequate provider expertise[19] or provider services.[20] Most states, with the current exception

of New York and Maryland, do not allow infectious disease specialists to serve as primary care providers.[6] Unfortunately, few published data on the overall medical and financial impact of managed care of HIV/AIDS exist.

It is clear that systems of care of individuals with HIV/AIDS and appropriate reimbursement of services must be designed to avoid the potential problems of provider incentives for ordering too many tests and plan financial incentives for denying care to the most needy patients.[21,22] It has been widely acknowledged that HIV/AIDS patients as well as providers must be closely involved with the development of managed care plans.[23]

A. The Potential Impact of Managed Care

1. Advantages

a. Less Fragmentation of Care

Managed care systems which include specific programmatic requirements and credentialling of providers have the potential to provide less fragmented care than traditional fee-for-service care.[10,24]

b. Cost Containment

The cost of care of patients with HIV infection can be considerable. Among the reasons for this are:

- An ongoing stream of expensive new antiretroviral agents, the cost of which can reach $12,000 to 18,000 annually[25] with the frequent use of 4- or 5-drug combinations
- The cost of viral load monitoring and viral resistance testing
- The frequent need for acute or chronic hospitalization or long-term care among patients with advanced symptomatic disease
- The need for ancillary staff to provide drug treatment and mental health treatment when necessary
- The frequent need for subspecialty care (e.g., gynecology, dermatology, gastroenterology)
- The need for frequent scheduled and unscheduled visits for symptomatic patients
- The need for periodic comprehensive reevaluations.
- The need for longer provider–patient sessions

Many of these factors are interrelated. For example, aggressive antiretroviral therapy and the availability of walk-in appointments can dramatically reduce hospital utilization. Rates of hospitalization have steadily declined in the United States in a number of reports since the advent of highly active antiretroviral therapy (HAART) in the mid-1990s. The overall cost of care has been reduced by the use of these new agents, despite their cost.

c. Standardization of Care

Standardization is appropriate and, in fact, critical for many aspects of HIV care. The most obvious example of this is seen in the prevention of opportunistic infections where uniform application of prevention strategies could have a profound

impact on the incidence of various life-threatening complications of HIV infection. Standardization is also important in the use of antiretroviral therapy. New therapeutic strategies developed in clinical trials and new therapeutic agents can be more rapidly effected across geographic and institutional boundaries if basic treatment algorithms are developed and periodically revised.

Clinical pathways are a form of treatment algorithm whereby a framework for systematic evaluation and treatment of medical disorders is applied consistently from patient to patient. Pathways have been developed for the management of several HIV-related conditions in the inpatient setting.[26] Although little information is yet available on the impact of clinical pathways on medical outcome in HIV/AIDS, at a minimum, the approach holds promise as a means of standardizing care of selected conditions.

2. Disadvantages

a. Overemphasis on Cost Containment

It has been demonstrated that maximum capitated reimbursement rates under Medicaid fall considerably short of the cost of HIV/AIDS care in many states.[27] An overemphasis on cost containment, perhaps the single greatest danger of managed care, can result in poor access to expensive but effective therapies, premature hospital discharge, inappropriate limitation of the use of diagnostic tests, cursory visits with providers, and other potentially dangerous deficiencies.

In addition, the monitoring of cost by staff unfamiliar with new developments and appropriate deviations from standard protocols can lead to incorrect denials of reimbursement and frustration on the part of providers. An overemphasis on cost provides an incentive for discrimination against individuals at advanced stages of disease who are considered likely to require more services.

b. Potential Delay in Incorporation of New Therapies and Diagnostic Modalities

Systems of HIV care must be flexible enough to rapidly incorporate new therapies and therapeutic strategies. Fixed formularies and rigid practice guidelines may rapidly lead to outdated treatment.

c. Alienation between Patient and Provider

The relationship between provider and patient is especially important in HIV/AIDS care for several specific reasons:

1. A high degree of compliance with antiretroviral therapy is essential to achieving maximal virological response and immune reconstitution. Individual counseling by the provider is the most effective means of monitoring and maintaining treatment adherence.
2. Many HIV-infected individuals lead disorganized lives because of active substance abuse,[28] poverty, or other obstacles. Time with the provider must be adequate to deal effectively with such obstacles to care.
3. Barriers of language, neurological function, culture, and fear are particularly common in the care of HIV-infected patients. Only a provider with sufficient time to bridge such barriers can adequately care for these patients.

B. Systems of Care

The current management of HIV infection and its complications lends itself, to some extent, to an algorithmic approach to diagnosis and therapy. Great effort has been expended by many authorities in the development of relatively rigid criteria for the timing of antiretroviral therapy and the monitoring of its therapeutic and adverse effects (see Chapter 10) as well as the prevention and therapy of opportunistic infections and the screening for important potential co-infections such as tuberculosis, syphilis, and viral hepatitis. Even counseling about reducing the risk of HIV transmission requires a systematic approach. These efforts have been undertaken to assure that HIV-infected individuals being cared for in a variety of clinical settings receive the benefits of a constantly improving therapeutic approach. In addition, a large number of clinical trials of new agents and new strategies is underway. These trials, of course, have systematic and rigid criteria for enrollment and follow-up. For these reasons, the ideal of managed care, that is, bringing consistent, effective, and efficient medical care to patients suffering from this complex disorder, may be especially relevant to HIV care.

III. QUALITY MANAGEMENT

Systems to evaluate the quality of care provided to HIV/AIDS patients have been developed by governmental bodies as well as managed care organizations. The impact of quality monitoring has not been extensively evaluated. What little information has been reported has been largely in the form of abstract presentations at conferences. Nonetheless, the complexity of the care of individuals with HIV/AIDS necessitates the development and monitoring of quality indicators within all systems of care provided to these patients. The specific quality indicators most associated with favorable outcome can be debated, but the need for monitoring is indisputable.

It is clear that the availability and quality of care offered to HIV/AIDS patients is variable, even in sophisticated healthcare systems. For example, access to new antiretroviral agents and other treatment advances has been shown to vary from region to region.[29] Less than half of HIV-infected adults in the United States are receiving regular medical care[30] and only approximately 85% of individuals with AIDS are receiving antiretroviral therapy.

Medical outcomes in HIV/AIDS care have been shown to be highly dependent on provider and institutional experience with AIDS-related disorders, especially for patients with advanced disease. Efficient access to subspecialty care is often unavailable.

High quality medical care of HIV-infected patients requires several basic components:

1. Ready access to a comprehensive program of primary care from the time an individual is initially diagnosed with HIV infection
2. Easy availability and appropriate use of markers of disease stage, i.e., viral load and T cell subset analysis

3. Access to new antiretroviral therapies
4. Access to entitlement information when appropriate and facilitation of the application process for entitlement services, including drug assistance plans
5. A system that permits a prompt, comprehensive medical assessment, thorough history, physical examination, and mental health assessment as well as screening diagnostic studies (complete blood count; renal function tests; electrolytes; liver function tests; and hepatitis A, B, and C tests as well as serological tests for syphilis and toxoplasmosis, chest x-ray, and tuberculin skin test)
6. Efficient referral to the care of a provider qualified and experienced in the care of individuals with HIV infection
7. Ready availability of specialty and subspecialty consultation in the following areas: ophthalmology, dentistry, neurology, dermatology, gastroenterology, gynecology, psychiatry, and general surgery

A. Selecting Quality Indicators

In establishing a program of quality assessment, it is important to set defined, measurable goals.[31]

1. Volume Indicators

Volume indicators, such as number of visits, newly enrolled patients, missed appointment rates, and demographic data, may provide insight into the effectiveness of a program in reaching the community it attempts to serve and of its success in retaining patients once enrolled. Such data is typically the simplest to obtain but gives only indirect information about medical outcomes.

2. Process Indicators

These indicators measure services offered, such as numbers of influenza vaccines, Pap smears, or patient education sessions. Although they provide insight into structural problems and staffing needs, they do not fully reflect outcomes.

3. Outcomes Indicators

Generally the most difficult data to extract, outcomes indicators provide the best measure of overall program effectiveness. Indicators such as hospitalization rates, opportunistic infection prevention, rates of viral suppression, provider competence, patient satisfaction, and treatment adherence, if measured accurately, provide a basis for redirecting, expanding, or modifying services. Because it is vitally important that adherence with antiretroviral therapy be kept at a very high level in order to avoid the emergence of drug resistance (see Chapter 10), appointment compliance and treatment adherence represent paramount quality outcomes indicators. See Chapters 10 and 11 for discussions regarding the measurement and improvement of treatment adherence.

a. Hospitalization Rates

Combination antiretroviral therapy has had the effect of dramatically reducing the need for hospitalization of patients with HIV/AIDS. In a large care system in Massachusetts, the hospital admission rate fell by 70% between 1995 and 1996.[32] Rates of and indications for hospitalization should be monitored concurrently. Such information can be used to evaluate the effectiveness of prevention of opportunistic infections and adherence to antiretroviral therapy. Hospital length-of-stay data can provide insight into efficiency of inpatient care systems. Patient satisfaction with inpatient care should be monitored systematically.

b. Provider Experience

Provider experience is related to outcome in the care of HIV-infected patients. In a New York state study, patients followed in clinics caring for at least 100 patients had a 50% decrease in relative hazard of death.[33]

If possible, patients should be under the direct care of providers with specific training and/or significant experience in treating HIV infection and its complications (e.g., 20 patient-years). Such qualifications have been developed to define the so-called HIV specialist by managed care organizations and governmental bodies.[34]

Because of the rapidly changing nature of HIV care, providers should be committed to continuous educational activities. Inexperienced providers should be supervised by HIV specialists for a period of at least several months. If any of these criteria cannot be met, indirect supervision should be arranged whereby an HIV specialist reviews care indicators at regular intervals and is readily available for consultation.

c. Prevention of Opportunistic Infections

The rates of most opportunistic infections have declined substantially among patients receiving effective antiretroviral therapy. Some of these infections, such as *Pneumocystis carinii* pneumonia (PCP) and toxoplasmosis, are almost entirely preventable in patients at risk by appropriate use of prophylaxis. For these reasons, adherence to guidelines for such prophylaxis represents a critical quality indicator for any program or provider caring for HIV-infected patients.

B. Testing and Counseling

Access to testing and counseling services as well as appointment waiting time represent important quality indicators. Uniformity of counseling, maintenance of confidentiality, partner notification, attrition rates between testing and post-test counseling appointments, and referral into care are each important indicators.

1. Access

Counseling and testing should be available on an appointment and a walk-in basis, if feasible. Hotline telephone numbers for counseling services facilitate community and provider access. Waiting time should be days rather than weeks to minimize attrition.

2. Uniformity of Counseling

Counselors should receive formal training. Counseling sessions should be periodically observed to assure that issues regarding partner notification, risk of transmission, and availability of services are being communicated in an understandable and compassionate fashion.

3. Attrition Rates

The rates of failure to return for test results, for post-test counseling, or for initial medical evaluation should be monitored concurrently. A mechanism should be developed for locating individuals who have not kept follow-up appointments while maintaining confidentiality. Locating of tested individuals is facilitated by obtaining accurate telephone numbers and addresses at the time of testing.

4. Change in Risk Behavior

The effectiveness of risk reduction activities should be periodically reevaluated through questionnaires and direct interviews.

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13 General Health Maintenance

CONTENTS

I. INTRODUCTION

During the first two decades of the HIV/AIDS epidemic, the individuals most affected have been young, previously healthy adults. Conditions more associated with an older population, such as cancer and coronary artery disease, could be largely ignored by physicians caring for these individuals in favor of the more immediate complications of HIV infection and immune deficiency. As the prognosis of HIV infection improves with effective antiretroviral therapy, other chronic disorders will become increasingly important among HIV-infected patients (see Table 13.1). Coincident with the epidemic, however, significant advances have come in the prevention and management of these other conditions, which, in some instances,

TABLE 13.1
Relationship Between HIV-1 Infection and Other Common Medical Disorders

Disorder	Relationship to HIV-1 Infection
Cancers	
Cervical	Likely increased incidence
Breast	None established
Colon	None established
Anal	Proven increased incidence
Prostate	None established
Melanoma	Likely increased incidence
Oral	None established
Testicular	None established
Lipid Disorders	
Hypertriglyceridemia	Increased incidence independent of therapy Associated with antiretroviral therapy, especially with protease inhibitors
Hypercholesterolemia	Associated with antiretroviral therapy, especially protease inhibitors
Decreased HDL cholesterol	Increased incidence independent of therapy
Atherosclerosis	Possible increase unrelated to therapy Probable increase secondary to therapy-related lipid disorders
Diabetes	Insulin resistance associated with antiretroviral therapy, especially with protease inhibitors

Adapted from multiple sources: see text

may become more immediately important to the middle-aged or older adult with HIV infection.

An additional consideration is the increasing susceptibility to infection that accompanies the normal aging process.[1] As the HIV/AIDS population ages, the impact of HIV infection on this so-called immunosenescence will become increasingly important.

In this chapter, strategies for routine health maintenance developed for the general population are examined and their application to the care of HIV-infected individuals is considered (see Table 13.2). The purpose of including this material in a book on the care of the HIV-infected patient is twofold. It is hoped that this inclusion will serve as an acknowledgement of the importance of routine health maintenance for these patients. In addition, because many practitioners caring for HIV-infected do not practice general internal medicine, this overview can serve as a quick reference to current preventive strategies.

Little data exist to direct the clinician in the general approach to health maintenance in the setting of HIV infection, but several conclusions can be drawn from recent findings. Furthermore, the possibility that HIV infection or antiretroviral therapy alters the natural history of cancer, atherosclerosis, dementia, or other high

TABLE 13.2
Suggested Screening Schedule for General Medical Disorders

Disorder	Screening Interval
Cervical neoplasia	Pap smear every 6 months Colposcopy if high risk (see text)
Breast cancer	Annual breast exam Mammography every 1 to 2 years for women 50 to 69
Colon cancer	Fecal occult blood test or sigmoidoscopy every 1 to 5 years beginning at age 50
Prostate cancer	Digital rectal exam annually after age 40 ?PSA in high-risk setting (see text)
Lipid disorders	Prior to initiation of antiretroviral therapy Annually in patients with cardiac risk factors, including prior hyperlipidemia
Hypertension	Every 2 years beginning at age 21 if diastolic >85, more frequently if >90 mmHg

Adapted from various sources: see text

prevalence conditions will be discussed. In addition to screening for occult disease, the primary provider should offer routine preventive counseling regarding smoking cessation, diet, and injury avoidance.

Because medical practitioners caring for HIV-infected patients often assume responsibility for general primary care, a brief discussion of screening and counseling strategies applicable to the general population is also provided. It should be borne in mind that general health maintenance services are not accessed by all those in the general population for whom they are recommended[2] for a variety of reasons. In a recent analysis of services in the United States, it was found that low educational level, lack of health insurance, and the cost of care all represented significant barriers.[3] Inadequate access to care is most dramatic among minority populations, especially African-Americans and Hispanics, the same groups disproportionately affected by the HIV/AIDS epidemic.

II. SCREENING STRATEGIES

A. Hypertension

It is recommended that blood pressure be measured in all individuals beginning at the age of 21.[4] Although the optimal screening interval has not been determined, a variety of experts have recommended every 2 years if the most recent blood pressure was 140/85 or less and annually if the last diastolic blood pressure was 90 mmHg or more. Blood pressure measurement is also recommended during routine visits for children and adolescents.

Although no direct association between hypertension and HIV infection has been defined, the incidence of both is disproportionately high among African-American men and women. For this reason, hypertension may be encountered more often by providers serving large groups of HIV-infected patients. The evaluation and management of hypertension in the setting of HIV infection should probably parallel that seen in other patients. Although no serious interactions have been reported to occur between antiretroviral drugs and common antihypertensive agents, the blood level of calcium channel blocking agents may be elevated by protease inhibitors and prescribing information should be consulted for combining specific agents.

The risk of cardiovascular disease among hypertensive patients who develop hyperlipidemia secondary to antiretroviral therapy has not been adequately defined.

B. Cancer

Although it has long been recognized that lymphoma (including Hodgkin's disease), Kaposi's sarcoma, and anorectal cancer are seen with increased frequency among HIV-infected individuals, some have suggested that a broader predilection to variety of solid tumors may also exist in these patients.[5,6] As expected in any medical condition as common as HIV/AIDS, a wide variety of malignancies may be encountered in HIV-infected individuals that may have no clear link to HIV infection. Among these are lung and breast cancer; cancers of the pancreas, bladder, and liver; multiple myeloma;[7] and squamous carcinomas of the head and neck.[8,9]

1. Breast Cancer

There is no data to suggest that the risk or natural history of breast cancer is different among HIV-infected women than in the general population. Breast cancer is the most common cancer diagnosed in women overall and the most frequent cause of cancer mortality of women between the ages of 15 and 54.[10] The lifetime risk of dying of breast cancer for women in the United States is estimated to be 3.6%.[11] Approximately one half of new breast cancer diagnoses occur in women under 65 years of age. Women with a first-degree female relative with breast cancer are at two- to threefold greater risk.[12] Late age at first pregnancy and nulliparity are also associated with increased risk, as are high socioeconomic status and exposure to high doses of radiation.

Interestingly, the incidence of breast cancer in Tanzania was found to decrease in retrospective analysis of cancer registry reports coincident with the AIDS epidemic.[13] The meaning of this observation is not clear, however, and little data are available to suggest that the natural history, clinical manifestations, and epidemiology of breast cancer are different in the setting of HIV infection.

Routine screening for breast cancer has received tremendous attention over the past 20 years and has been associated, in many studies, with earlier detection and greater overall survival. The timing of screening is controversial, however. In 1996, the United States Preventive Service Task Force Screening concluded that evidence supported routine screening by mammography every 1 to 2 years or annual breast examination and mammography on all women ages 50 to 69.[14]

2. Colon Cancer

In the general population, universal screening for colon cancer should begin at age 50, in the absence of specific risk factors, such as strong family history or inflammatory bowel disease,[15] according to the United States Preventive Services Task Force. It is currently recommended that screening be either by fecal occult blood test or sigmoidoscopy. The frequency of screening is controversial and recommendations ranging from every year to every 5 years have been put forth.[15] The American Cancer Society and several professional medical specialty societies have recommended that screening by fecal occult blood testing begin at age 40.

The applicability of these guidelines in the setting of HIV infection has not been established. Despite individual reports,[6] the incidence of colon cancer has not been shown to be higher among HIV-infected individuals than in the general population. However, the risk of anal squamous cell cancer is four- to eightfold higher among HIV-infected men, particularly those with a history of homosexual contact.[16]

Although screening strategies for this neoplasm have not been published, it is appropriate, pending additional guidance, to screen for colon cancer among HIV-infected patients in accordance with the general guidelines described above.

3. Cervical Cancer

As discussed in Chapter 9, HIV infection increases the risk of cervical neoplasia.[17] Screening by Pap smear can detect lesions that are precursors to cervical cancer. These lesions are cervical intraepithelial neoplasia (CIN) and squamous intraepithelial lesions (SIL), which may be detected years before cervical cancer. Several types of human papillomavirus (HPV),[18] especially types 16, 18, 31, 33, and 35, are strongly associated with CIN (grade II and III) and with invasive cancer.

In the general population, cervical cancer is associated with several risk factors, including early age at first intercourse, multiple male sexual partners, and cigarette smoking. Each of these risk factors is also associated with human papillomavirus (HPV) infection. Cervicovaginal HPV infection is significantly more prevalent among HIV-infected women than among HIV-negative controls (58% vs. 26%), even when other risk factors are controlled.[19] The prevalence of HPV infection rises with declined cellular immune status. It was 70% among women with CD4 cell counts of less than 200/mm^3 and is independently associated with high plasma HIV RNA levels. The likelihood of SIL and CIN also increases with declining CD4 cell count and rising HIV viral load.[20] HIV infection is also associated with significantly higher levels of HPV in vaginal secretions[21] as well as long-term persistence of HPV infection.[22]

Controversy exists over the best means of screening for cervical neoplasia in the setting of HIV infection. Although routine periodic Pap smears have been recommended by many,[23] and should be performed every 6 months, the false negative rate may be as high as 15 to 20%. In a population at such extremely high risk as HIV-infected women, especially those with CD4 cell counts below 200 cells/mm^3 or viral load greater than 100,000 copies per mL, Pap smears may not always be adequate for screening. Colposcopy may provide more diagnostic accuracy. At this time, because of the logistical difficulties of performing routine colposcopy, it is

most often performed at baseline and subsequently reserved for women with abnormalities on Pap smear, including abnormal cells of unknown significance (ASCUS), atypical glandular cells, SIL, or persistent, unexplained inflammation.

Women should be counseled about means of preventing HPV infection and cervical neoplasms, including safe sex practices and cessation of smoking.

Therapeutic options for cervical neoplasia are discussed in Chapter 9.

4. Prostate Cancer

Prostate cancer is exceeded only by lung cancer as the most common cause of cancer-related death among American men.[10] Although routine screening for prostate cancer has not been recommended by the U.S. Preventive Services Task Force,[24] various screening strategies are becoming increasingly prevalent. The American Cancer Society,[25,26] the American Urological Society,[27] and the American College of Radiology[28] all recommend routine screening with digital rectal examination (DRE) beginning at age 40 and with both DRE and measurement of serum prostate specific antigen (PSA) for African-American men and those with a family history of prostate cancer beginning at age 40 and for all men beginning at age 50.

No convincing association between HIV infection and prostate cancer has been demonstrated. Standard guidelines should be followed until further data regarding such issues as the incidence, natural history, and therapy of prostate cancer in the setting of HIV infection as well as the utility of screening in this population are available.

5. Skin Cancer

Some reports suggest that basal cell carcinoma[29] and malignant melanoma[30,31] are seen more frequently among HIV-infected individuals. Skin neoplasms may behave more aggressively in the setting of HIV infection.[32] Routine screening of the general population for skin cancer is not recommended[33] and even periodic self-examination is of uncertain effectiveness, although the American Cancer Society has recommended that all adults perform this monthly.[34] Because immunosuppression (as well as atypical moles, increased numbers of moles, family history, and white race) is considered a risk factor for melanoma[33] and a possible association between HIV infection and melanoma has been asserted, it may be prudent to consider HIV-infected patients, particularly those who are light skinned, a high-risk subpopulation. Patients identified to be at high risk of melanoma should be screened at regular intervals. Referral to a dermatologist for such surveillance may be appropriate if the primary care provider is not confident in performing skin examinations, especially for patients with multiple risk factors. Similarly, patients at high risk should be advised to limit sun exposure and use sun block,[35] although the effectiveness of such measures in preventing skin cancer has not yet been established with certainty.

6. Oral Cancer

Some reports suggest a higher incidence of oral mucosal cancers in patients with HIV infection.[36] In addition, the two neoplasms commonly associated with HIV infection, lymphoma and Kaposi's sarcoma, are frequently present in the mouth.[37] HIV-infected patients should undergo routine annual oral and dental examination.

7. Testicular Cancer

Seminoma may have an association with HIV infection.[29] Although the value of routine screening has not been established, the American Cancer Society recommends testicular examination every 3 years for men over the age of 20 and annually for men over 40.[25] Further data on the incidence and natural history of testicular cancer in the setting of HIV infection are needed to determine if this approach to screening is effective and adequate. Screening is most likely to be effective among men with conditions associated with a high risk of cancer, regardless of HIV status. These conditions include undescended testicles, testicular atrophy, and cryptorchidism. Tumor markers such as alpha-fetoprotein and human chorionic gonadotropin are not effective in screening.[38]

C. Lipid Disorders

Prior to the advent of highly active antiretroviral therapy, it was recognized that lipid disorders could be seen in association with HIV infection. Low cholesterol was associated with advanced immune deficiency, while high levels of triglycerides were seen at earlier stages of disease. HIV infection itself regardless of immune function was associated with low levels of HDL-C and apoA1 lipoprotein.[39] High levels of apolipoprotein E in association with hypertriglyceridemia have also been described.[40]

Screening strategies for hyperlipidemia may be complicated by the lipodystrophy syndrome seen among some patients receiving antiretroviral therapy, particularly with protease inhibitors (see Chapter 11). The long-term clinical implications of this syndrome are not yet clear and concern for risk of atherosclerosis must be balanced with the need for effective antiretroviral therapy. Patients with the lipodystrophy syndrome (see Chapters 10 and 11) typically have elevated levels of triglycerides, cholesterol, insulin resistance,[41] and, in some instances, clinical diabetes.[42] All of these disorders have been associated with acceleration of atherosclerosis among non-HIV-infected individuals.

D. Atherosclerosis and Coronary Artery Disease

Because of the association of antiretroviral therapy with hypertriglyceridemia and insulin resistance, the risk of premature atherosclerosis in patients taking HAART has received increasing attention in recent years. Reports of premature coronary artery disease associated with HIV infection appeared before the advent of modern antiretroviral therapy. Coronary endothelial abnormalities and frank atherosclerotic lesions were described in autopsy studies of young HIV-infected patients, including some children.[43,44] Serum markers of endothelial cell dysfunction, such as von Willebrand factor and tissue plasminogen activator, may be elevated in association with HIV infection,[45,46] and hypercoagulability may correlate with plasma HIV viral load.[47] High circulating levels of triglycerides, known to accelerate atherosclerosis in non-HIV-infected individuals, were seen in association with HIV infection prior to the advent of protease inhibitors or other, newer antiretroviral drugs.

Despite case-report evidence of accelerated atherosclerosis and the presence of physiologic markers of endothelial dysfunction, the full implications of hyperlipidemia and insulin resistance associated with antiretroviral therapy are currently unknown. Specifically, the impact of these factors on the natural history of coronary artery disease in the setting of HIV infection is not yet clear. An attempt was made to quantify the excess risk of coronary artery disease among patients developing hyperlipidemia in association with antiretroviral therapy. An excess of 1.4 cases of cardiovascular disease per 100,000 individuals every 10 years was based on predictive criteria from the Framingham study.[40]

As the full spectrum of atherosclerosis in HIV infection is elucidated, at present it is clear that coronary risk modification addressing smoking, obesity, hypertension, and exercise should be explored with HIV-infected patients[48] (see below).

1. Frequency of Screening for Hyperlipidemia

All patients should undergo lipid analysis before initiating antiretroviral therapy. Because hypertriglyceridemia and insulin resistance can appear within a few months of beginning therapy,[49] the analysis as well as fasting blood sugar determination should be repeated at 3 months, particularly in patients receiving protease inhibitors.[48] Lipid profile should be repeated no less frequently than annually for patients with elevated cholesterol and one or more cardiac risk factors.

2. Management of Hyperlipidemia

Diet and exercise have not generally been effective in lowering lipid levels among patients with the lipodystrophy syndrome.[50] Although lipid-lowering agents such as gemfibrozil and atorvastatin may be more effective,[51] treatment criteria have not been developed and the overall benefit of medical management of hyperlipidemia in the setting of HIV infection has not yet been established.

The hepatic metabolism of HMG-COA reductase inhibitors such as atorvastatin is reduced by protease inhibitors and blood levels may be significantly elevated. This phenomenon may cause symptoms of hypolipidemia, such as dizziness and headache.

Until specific treatment guidelines are developed, several considerations must be kept in mind when considering the management of hyperlipidemia in the setting of HIV infection:

1. Standard (non-HIV-specific) guidelines call for each patient to have a risk assessment for coronary artery disease. Risk factors include age (men >45 years, women: postmenopausal), hypertension, smoking, diabetes, history of cardiovascular disease in first degree relatives (<55 years for men and <65 years for women), and serum cholesterol less than 35 mg/dL. The threshold total cholesterol for dietary intervention in individuals with 0 to 2 risk factors is 240 mg/dL; in those with 2 or more risk factors, 200 mg/dL. In the presence of known cardiovascular disease, the threshold is 160 mg/dL. Drug therapy is recommended for patients with 2 or fewer risk factors,

more than 2 risk factors, and known cardiovascular risk factors at thresholds of 275 mg/dL, 240 mg/dL, and 200 mg/dL, respectively.
2. The applicability of such guidelines to patients developing hyperlipidemia while receiving protease inhibitors has not been established.
3. A method for calculating the long-term risk of cardiovascular disease in individual patients has not been developed, although the overall risk appears to be low (see above).
4. Significant interactions between cholesterol-lowering agents and antiretroviral drugs may yet be identified.

III. COUNSELING STRATEGIES

A. Smoking Cessation

The prevalence of smoking among HIV-infected individuals appears to be significantly higher than that (25%) in the general population.[52] A study from England found that more than 70% of HIV patients currently smoked and few desired to stop.[53]

Attempts have been made to study the impact of cigarette smoking on the natural history and clinical course of HIV infection, with conflicting results. Several studies have suggested that tobacco use accelerates the development of immune deficiency and clinical progression,[54,55] while other studies have failed to confirm this.[56,57] Specific manifestations and complications of HIV infection may be influenced by cigarette smoking. In a study comparing large groups of smokers and nonsmokers, community-acquired pneumonia, oral candidiasis, and oral hairy leukoplakia were more common in the smoking group, while progression to AIDS and the incidence of *Pneumocystis carinii* pneumonia and Kaposi's sarcoma were equal.[58] Others studies have demonstrated that smoking increases the risk of a variety of oral disorders[59] and probability of cryptoccal infection.[60] The risk of heterosexual transmission of HIV infection appeared to be increased among women smokers in a study conducted in Haiti.[61] Predictably, cigarette smoking is associated with accelerated deterioration of lung function among HIV-infected individuals.[62]

Patients should be questioned about current and past tobacco use, efforts to quit smoking, and symptoms of nicotine withdrawal. It is recommended that all patients who smoke receive smoking cessation counseling on a regular basis. The most effective form of individual counseling is a direct statement by the provider that smoking is harmful and that all tobacco use should stop. Specific information about health risk to the individual as well as children and pregnant women living in the household should be provided and emphasized.

Data from the general population indicates that stopping smoking at any age results in a reduction of smoking-related morbidity and mortality. Stopping before the age of 50 results in a 50% reduction of the risk of dying within the following 15 years.[63] The impact of smoking cessation on specific HIV-related disorders has not been evaluated.

Various means of individual and group counseling have been shown to be effective.[64] Self-help brochures and other materials are available from a variety of

sources, and smoking cessation programs are frequently available through community organizations. All such resources should be explored and made available.

All patients who smoke should be offered, as a minimum, a nicotine replacement and general advice on the value of quitting.[65] Nicotine gum may improve cessation rates[66,67] as well as appointment compliance rates. The nicotine transdermal patch, applied daily, may be more effective.[68] Clonidine, which can reduce symptoms of nicotine withdrawal, may also be a useful adjunct to counseling.[69] Unfortunately only a minority of patients have the motivation to stop smoking when the subject is first raised by the provider. The level of motivation may be even lower among HIV-infected individuals than it is in the general population.[53]

Patients who are pessimistic about their chances of long-term survival, realistically or not, may be especially difficult to motivate. Improving motivation often requires the involvement of several types of providers. The primary care physician can provide basic and repeated advice that should include the firm message to discontinue smoking. Follow-up by nurses and/or social workers can encourage and reinforce cessation. Specific motivational sessions may be offered through mental health professionals and antismoking organizations. The provider should maintain a focus on smoking cessation at each encounter, discuss obstacles, and inform the patient about available nicotine substitutes.

B. Promoting a Healthy Diet

Nutritional considerations in HIV infection are complex and vary according to the clinical and immunological status of the patient. A detailed dietary history should be obtained from each patient. Recommendations for the general population, such as limitation of dietary fat and cholesterol as well as consumption of fruits, vegetables, and grains, are most likely appropriate for otherwise healthy, immunologically normal HIV-infected adults.

C. Exercise

Regular moderate-to-intense physical activity can reduce the risk of coronary artery disease, hypertension, obesity, and diabetes. Aside from this general concept, however, specific counseling regarding exercise must be individualized. The high prevalence of disorders that impact an individual's ability to exercise (such as chronic interstitial lung disease, cardiomyopathy, malnutrition, and peripheral neuropathy) may represent obstacles to the application of standard recommendations.

FREQUENTLY ASKED QUESTIONS

1. How does HIV infection affect the incidence of common cancers other than Kaposi's sarcoma and lymphoma?

   None of the major causes of cancer morbidity and mortality, that is, breast, lung, pancreatic, colon, or prostate cancer, appears to be strongly associated with HIV infection. Squamous cell anal cancer is several times more common

among HIV-infected homosexual men. Cervical neoplasms in general and, most likely, cervical carcinoma are more common among HIV-infected women.

2. What is the prognostic significance of hyperlipidemia developing during therapy with antiretroviral drugs?

   The risk of cardiovascular disease among patients with this syndrome is currently unknown. Increasing risk may be seen as the population of HIV patients increases and ages and as more data are accumulated on the long-term effects of antiretroviral therapy.

3. What is the role of diet and/or lipid-lowering agents for this?

   General guidelines for the management of hypercholesterolemia are given above. The use of cholesterol-lowering agents for this syndrome has not been adequately studied.

4. How does the presence of HIV infection affect screening strategies for the following:

   a. Breast cancer

   Scant information has been reported on the incidence, clinical manifestations, or prognosis of breast cancer in the setting of HIV infection. For this reason, screening strategies developed for the general population (see text) should be used at the present time.

   b. Cervical cancer

   HIV infection, particularly when it is associated with significant immune deficiency, greatly increases the risk of HPV infection and cervical neoplasia. For this reason, more intense screening by means of Pap smears and colposcopy is recommended for HIV-infected women (see text).

   c. Prostate cancer

   As is the case with breast cancer, prostate cancer in the setting of HIV infection is largely unstudied. At present, screening should be carried out according to recommendations developed for the general population (see text).

   d. Colon cancer

   The incidence of anorectal cancer is increased among HIV-infected homosexual men. Such patients should be screened according to the guidelines for high-risk individuals (see text).

5. Does cigarette smoking affect the natural history or clinical manifestations of HIV infection?

Cigarette smoking has not had consistent impact on the natural history of HIV infection; however, oral complications, such as candidiasis and leukoplakia, are more common in smokers, and cigarette smoking accelerates the deterioration of lung function seen in many patients with advanced HIV infection.

6. How has antiretroviral therapy affected general primary care approaches?

Combination antiretroviral therapy has greatly increased the life expectancy of many HIV-infected individuals. For this reason, preventive strategies of screening for disease and counseling regarding tobacco use and diet are becoming more important.

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14 Case Studies

INTRODUCTION

This chapter consists of five hypothetical cases illustrating situations commonly encountered in relation to HIV infection in the ambulatory setting. Each case description is followed by a brief analysis that includes (where relevant) the following sections:

Differential Diagnosis

General diagnostic considerations in the evaluation of the presenting complaint or situation, as well as minor complaints and findings

Additional Information Needed

Specific questions that the patient or family should be asked as well as previous diagnostic information

Laboratory Studies

Initial laboratory tests to be performed

Other Diagnostic Studies

Additional tests to be considered if the initial laboratory evaluation does not result in a diagnosis

Therapeutic Considerations

Indications for therapy and prophylaxis

Indications for Hospitalization or Referral

Comments

Additional observations on specific issues illustrated by the case

Literature References

References not provided in other chapters of this book

Chapter References

Chapters in this book in which additional pertinent information and literature references can be found

The final case, The HIV-Infected Traveler, is presented in a different format, more appropriate to its subject.

CASE 1: ANTIRETROVIRAL THERAPY NAIVE PATIENT

A 28-year-old male with a history of sexual contact with men since the age of 15 presents 2 weeks after being informed by an anonymous testing site that his HIV test was positive. Past medical history is remarkable for two episodes of gonorrhea 2 and 7 years earlier and several periods of depression over the past year.

Social History

The patient works as a lawyer in a large firm and lives with a male partner. He does not use condoms because he is monogamous.

Physical Examination

Vital signs: normal
Skin: mild seborrheic dermatitis
Mental status: alert and oriented, affect flat

Differential Diagnosis

In view of the high-risk setting (unprotected sexual contact with another man) and the possible manifestation of HIV infection noted on physical exam (seborrheic dermatitis), the positive result on antibody testing is most likely accurate. Although this testing procedure has a sensitivity and specificity both in excess of 99%, some practitioners routinely repeat the antibody test on all newly diagnosed patients to reduce the small chance of a false-positive result.

The affect is concerning and warrants a systematic evaluation for depression and for organic mental disorder.

Additional Information Needed

Details of the medical history should be carefully obtained. Special emphasis should be placed on risk of chronic liver disease, pancreatitis, and coronary artery disease, as these may have significant implications for therapy.

Laboratory Studies

Complete blood count
Biochemistry profile
Liver function tests
Lipid profile
Serological studies for toxoplasmosis, syphilis, viral hepatitis
Lymphocyte subset analysis
Plasma viral load

Other Diagnostic Studies Indicated

Chest x-ray
Routine nutritional, dental, and ophthalmologic assessment to be considered

Therapeutic Considerations

Preventive therapy for *Pneumocystis carinii* pneumonia and *Mycobacterium avium-intracellulare* should be prescribed in accordance with updated guidelines (Chapter 5). In general, antiretroviral therapy should be initiated according to guidelines discussed in Chapter 10, if the patient's likely level of compliance is deemed to be high.

Pros and Cons of Starting Antiretroviral Therapy

As discussed in Chapter 10, exceptions to the routine application of guidelines should be considered on occasion. A patient who is unlikely to comply fully with antiretroviral regimens is at risk for the early emergence of viral resistance. Because little data are available on appropriate treatment of patients sustaining virologic failure, the initial regimen should be considered the most likely to be successful and, thus, initiation of therapy may be delayed until compliance is assured.

Indications for Hospitalization or Referral

If the patient meets indications for antiretroviral therapy, care should be provided or coordinated by a practitioner experienced and knowledgeable in the management of HIV infection, as provider expertise has been shown to correlate with medical outcome.

Comments

Other critical issues to be addressed in this case include:

1. Assessing the patient's reaction to the diagnosis of HIV infection
2. Frankly discussing how transmission to partners should be prevented
3. Notification of current and past sexual partners and arrangement of HIV testing for any such individuals

Chapter References

1. Initial assessment of patient: Chapter 5
2. Prophylaxis of opportunistic infections: Chapter 5
3. Antiretroviral therapy: Chapters 10 and 11
4. Provider expertise: Chapter 15
5. Assessing reaction to diagnosis, prevention of transmission: Chapter 3.

CASE 2: PATIENT FAILING ANTIRETROVIRAL THERAPY

A 35-year-old female diagnosed with HIV infection 5 years earlier presents for routine follow-up care. She has been taking zidovudine, epivir, and fortavase, her initial antiretroviral regimen, for the past 18 months. Her HIV viral load by RNA PCR was below 400 copies/mL 3 months earlier, CD+ cell count was 390/mm^3. Her viral load in blood drawn 3 days prior to her visit was 35,000 copies/mL and CD4+ cell count was 310/mm^3. She feels well, claims complete compliance with her regimen, is aware of the new laboratory results, and is quite concerned.

Differential Diagnosis

When a patient whose viral load was initially suppressed subsequently manifests virologic failure as this patient has, several possible explanations should be considered:

Noncompliance

Full compliance with antiretroviral therapy is critically important. Even occasional missed doses may lead to premature development of resistance. Compliance is difficult to measure and, ultimately, is usually gauged by the patient's own account. For this reason, a strong relationship between patient and provider is indispensible. Patients should be encouraged to be truthful and as accurate as possible in reporting on their level of compliance with medications. It should be borne in mind that patients who were initially compliant may have become less so for a variety of reasons, including side effects, change in lifestyle, a belief that medication is no longer necessary, or other personal reasons.

Viral Resistance

The emergence of viral resistance correlates with virologic failure in many cases.

Laboratory Artifact

The possibility of laboratory error should be excluded by repeating the plasma viral load after any significant rise which would lead to a change in therapy.

Vaccine Effect

Various vaccines, including influenza vaccine, can cause an elevation of plasma viral load.

Laboratory Studies: Viral Resistance Testing

Resistance may be inevitable in patients taking antiretroviral therapy for 18 months or longer as this patient has. It may also reflect incomplete compliance with therapy.

Resistance testing should be conducted when virologic failure is documented. These tests are valid only for drugs taken within 2 weeks of the time they are performed.

Therapeutic Considerations

Virologic failure occurring after 18 months as in this case should lead to consideration of a change in the entire regimen. The sequence of antiretroviral regimens is dictated by the strategy reflected in the choice of agents for the initial regimen. When changes are made because of virologic failure, it is prudent to change all drugs simultaneously. Resistance testing as currently performed cannot exclude resistant subpopulations and are most useful for documenting rather than ruling out resistance to any specific agent. Unfortunately, cross resistance among antiretroviral agents within a class is common and greatly complicates the therapeutic options for individuals failing more than one regimen. Cross resistance to all non-nucleoside agents (NNRTI) should be assumed. Resistance to ritonavir, indinavir, and saquinavir should be assumed after failure of a regimen containing any of the three. Partial cross resistance should be assumed between ritonavir and amprenavir after failure of a regimen containing either. In general, changing the nucleoside reverse transcriptase inhibitors (NRTI), zidovudine and lamivudine in this case, to didanosine and stavudine and substituting an NNRTI (a medication class to which the patient has not been exposed), a protease inhibitor (PI; e.g., nelfinavir), or a dual PI-containing regimen is required.

Structured Treatment Interruption

Structured treatment interruption (STI), in which all antiretroviral therapy is temporarily discontinued, may offer benefits in some patients experiencing virologic failure, especially those for whom no other appropriate drug combinations exist. In this setting, STI is typically followed by a fall in CD4+ cell count and a surge in viral load with wild-type, drug-sensitive viral strains predominating. Reinstitution of therapy often leads to a fall in viral load to levels below those seen prior to STI. Recovery of CD4+ cell counts is, however, often not seen. Because she failed her initial antiretroviral therapy, the patient described in this case would most likely benefit from a change in the antiretroviral regimen as discussed above. STI would be better reserved until multiple regimens have failed.

Indications for Hospitalization or Referral

It is imperative that all patients who have failed antiretroviral therapy be under the care of a provider experienced and knowledgeable in the management of HIV infection.

Chapter References

1. Virologic failure, drug sequencing, structured treatment interuption: Chapter 10
2. Viral resistance testing, assessing compliance: Chapter 11

CASE 3: HIV-INFECTED PREGNANT WOMAN

A 36-year-old female, 12 weeks pregnant, has been referred to you after an HIV antibody test, drawn at her first prenatal visit a week earlier, has been reported positive. The pregnancy is her first and she has had no significant medical problems in her life. She has been married for 4 years, has never undergone HIV testing previously, and denies injection drug use, blood transfusion, or known sexual contact with any HIV-infected individual. The physical examination is normal for her stage of pregnancy. Ultrasound has demonstrated that the fetus is viable.

Additional Information Needed

HIV risk behavior should be explored. If the patient is currently using injection drugs or engaging in high-risk sexual activity, the fetus and the pregnancy are at high risk. Screening and prior therapy for other sexually transmitted diseases (STD), as well as hepatitis B and C, should be reviewed. A complete STD screen should be repeated in the third trimester.

Laboratory Studies

Confirmatory antibody test should be performed if diagnosis is doubted.
Plasma viral load and CD4+ cell count should be determined monthly to confirm the effectiveness of antiretroviral therapy (see below).

Therapeutic Considerations

Antiretroviral Therapy

Antiretroviral therapy has been shown to dramatically reduce the risk of perinatal transmission of HIV infection. A variety of strategies has been proven to be effective. The first issue to be addressed is the staging of the mother's HIV infection with viral load and lymphocyte subset analysis. If the CD4 lymphocyte count is below 500/mm^3 and/or the viral load is above 10,000 to 20,000 copies/mL, combination antiretroviral therapy is indicated as in any other individual meeting these criteria (Chapter 10). If the patient has never received antiretroviral treatment, therapy should consist of a conventional regimen of 2 nucleoside agents and either a protease inhibitor or non-nucleoside reverse transcriptase inhibitor except efavirenz which is contraindicated during pregnancy. Unless there are specific contraindications, zidovudine should be included in the treatment regimen, because more data currently support the use of this agent to prevent vertical transmission than any other. If the woman meets neither of the above indications for antiretroviral therapy, as a minimum, zidovudine should be initiated at 14 weeks, continued through labor and delivery, and administered to the baby until 6 weeks of age. Some authors support the use of combination regimens even in women with CD4 lymphocyte counts above 500/mm^3 and viral load below 10,000 copies/mL to avoid the small risk of resistance resulting from single-agent therapy.

Caesarian Section

Caesarian section performed prior to the onset of labor and rupture of membranes can significantly reduce the risk of vertical transmission in women not receiving antiretroviral therapy or those receiving zidovudine alone. It is unknown if this approach can reduce the already low rate of vertical transmission in women receiving effective multidrug antiretroviral therapy, which stands at 2 to 3%. If viral load is significantly elevated (e.g., >10,000 copies/mm^3) in the third trimester, particularly in the presence of significant worsening of immunological function, consideration should be given to changing therapy. This is deemed likely to result in better viral suppression.

Medications During Pregnancy

Many drugs used in the treatment of HIV-infected individuals may be relatively contraindicated in pregnancy and are recommended only if necessary to reduce the risk of vertical transmission or to protect the life or health of the mother or infant. Prophylaxis of *Pneumocystis carinii* pneumonia and *Mycobacterium avium-intracellulare* infection (Chapter 5) with trimethoprim-sulfamethoxazole and azithromycin, respectively, should be used in accordance with standard indications. It is important, as in all pregnant women, that adequate folate intake is assured but especially in women taking trimethoprim-sulfamethoxazole. Efavirenz should be avoided and another NNRTI agent substituted, if indicated, because of animal data indicating a significant risk of neural tube defects associated with the use of this agent.

Partner Notification/Testing of Partners and Children

Partner notification should be discussed with the patient and planned as discussed in Chapter 3. Arrangements should be made for HIV testing of other children.

Comments

Maternal viral load correlates best with risk of transmission. Because of the effectiveness of antiretroviral therapy in preventing vertical transmission, HIV-infected women should not be counseled to routinely undergo termination of pregnancy. A woman already taking antiretroviral drugs when first seen should continue her regimen if she has achieved adequate viral suppression (Chapters 10 and 11). If the woman is taking efavirenz, another NNRTI compound should be substituted, if feasible. The long-term implications of HIV infection for the woman and for the possibly infected newborn should be reviewed.

Chapter References

1. HIV infection in pregnancy: Chapter 9
2. Antiretroviral therapy: Chapters 11 and 12
3. Routine care: Chapter 5

4. HIV testing and counseling: Chapter 3
5. Medications: Chapter 15

Literature References

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CASE 4: ACUTE HIV INFECTION

A 26-year-old female presented with recent onset of fever, sore throat, bilateral painful neck swelling, and skin rash. She was in her usual state of good health until 2 weeks earlier when she noted the onset of severe sore throat and fatigue.

She was seen by her private physician and given erythromycin for presumed streptococcal pharyngitis. Her symptoms did not improve and, on the third day of therapy, she noted a faint, erythematous rash on her face and upper trunk. Feeling that this might represent an allergic reaction to the antibiotic, she discontinued erythromycin. The rash persisted and, after ten days of continued symptoms, she noted bilateral neck swelling.

Her past medical history is notable for infectious mononucleosis at the age of 17. She was born and raised in the United States and received the usual childhood immunizations. Three weeks prior to the onset of her symptoms, she had returned from a 2-week vacation in Mexico.

Physical Examination

III-appearing female with erythematous macular rash on her face, upper trunk and arms

Vital signs: 103 degrees, BP 105/60, HR 112, RR 14
Throat: pharynx erythematous, bilateral tonsillar enlargement
Neck: supple; multiple, bilateral tender anterior and posterior cervical lymph nodes
Chest: clear
Heart: normal
Abdomen: normal
Extremities: normal
Neurological: normal

Laboratory

Complete blood count: normal
Electrolytes: normal
Liver function tests: normal
Chest x-ray: normal

Additional Information Needed

The patient should be questioned in detail about her vacation in Mexico. Information sought should include exposure to others with skin rash or fever, sexual encounters, insect bites, and medications as well as immunizations received prior to travel.

Differential Diagnosis

The duration of symptoms tends to exclude typical viral respiratory infections such as influenza, parainfluenza, or the common cold. Streptococcal infection is also unlikely to have persisted for 2 weeks, and the failure of erythromycin to improve

the symptoms also makes this unlikely. The prior history of infectious mononucleosis, if accurate, makes this diagnosis unlikely. Measles and rubella are also unlikely based on the duration of illness and the likelihood that she was immunized to both in childhood. Arboviral infection, particularly dengue, acquired in Mexico is possible. Secondary syphilis should be excluded. Acute HIV infection is compatible with the symptoms and apparent incubation period, especially if infection occurred during the time in Mexico.

Other Diagnostic Studies (to be considered)

Throat culture
Blood culture
Monospot
RPR
Antibody tests for cytomegalovirus, toxoplasmosis
HIV RNA PCR
HIV antibody test

The combination of detectable virus by HIV RNA PCR and the absence of HIV antibody would be compatible with acute HIV infection. Detectable antibody would indicate more longstanding infection, regardless of HIV RNA PCR results.

Therapeutic Considerations

There is no consensus at present regarding the role of antiretroviral therapy in acute HIV infection. If acute HIV infection is confirmed as above, however, consideration should be given to instituting therapy based on evidence that such early treatment may help preserve cellular immune response. Updated recommendations should be consulted.

Indications for Hospitalization or Referral

Acute HIV infection is rarely severe enough to warrant hospitalization and is ultimately self-limited. Initial diagnostic confusion is common, however, and patients may be hospitalized prior to confirmation of the diagnosis because of aseptic meningitis, extensive rash, evaluation of lymphadenopathy, or other indications.

Comments

Acute HIV infection is rarely diagnosed despite its high incidence in retrospective surveys of HIV-infected individuals. This most likely reflects the somewhat nonspecific nature of the syndrome. Clinicians evaluating adult patients with unexplained rash, persistent generalized lymphadenopathy, aseptic meningitis, or severe pharyngitis should carefully explore the risk of exposure to HIV.

Chapter Reference

1. Acute HIV infection: Chapter 2

CASE 5: HIV-INFECTED TRAVELER

A 30-year-old HIV-positive male businessman is planning a 3-week trip to Southeast Asia. He has been in care for five years, taking a regimen of zerit, epivir, and efavirenz as well as trimethoprim-sulfamethoxazole. His most recent viral load was undetectable and CD4+ cell count was 120/mm^3. He is asymptomatic.

Issues to Be Addressed

Legal Restrictions to Travel

Many countries deny entry to HIV-infected individuals, particularly those planning extended stays. Updated information regarding such restrictions should be obtained from the U. S. State Department.

Risk of HIV Transmission

The traveler should be cautioned to avoid sexual contact while traveling in order to eliminate the risks of transmission of HIV infection to others and of acquiring other sexually transmitted diseases, HIV-2, or, conceivably, variant strains of HIV-1.

Risk of Infection to the Traveler

The traveler should be advised to observe general precautions when traveling to tropical or subtropical countries. These include boiling of drinking water; use of bottled water; avoidance of fresh fruit and vegetables and undercooked meat, poultry, or fish to reduce the risk of intestinal parasitic or bacterial infections; and liberal use of insect repellent with multiple applications daily, if necessary.

Vaccinations against a host of infections are now available; some are appropriate for the HIV-infected traveler. Pneumococcal and influenza vaccine as indicated in Chapter 5 should be provided and kept up-to-date in all HIV-infected individuals. Similarly, nonimmune patients should receive vaccines against hepatitis B and, where appropriate (see Chapter 5), hepatitis A. In general, however, live-virus vaccines, including yellow fever vaccine, should be avoided in persons with CD4+ cell counts below 200/mm^3. Inactivated vaccines to polio, typhoid, and cholera can be safey administered if indicated. The value of diphtheria, tetanus, and pertussis vaccines is unclear.

Prevention of Malaria

Malaria prophylaxis should be prescribed in accordance with guidelines of the Centers for Disease Control and Prevention. Potential interactions between antimalarial compounds and antiretroviral drugs have not been well studied, however.

Prevention of Traveler's Diarrhea

Fluoroquinolone antibiotics are generally effective in the prevention and treatment of traveler's diarrhea. Patients taking trimethoprim-sulfamethoxazole for PCP

prevention, however, may not need additional chemoprophylaxis. This and other sulfonamide-containing compounds can result in severe photosensitization, especially in tropical or subtropical climates.

Maintaining Adherence to HIV-Related Medications

Because strict adherence to antiretroviral medications is critically important, the provider should discuss strategies to facilitate this. Access to sufficient drinking water several times each day must be assured. This is most easily accomplished when the traveler carries bottled water at all times. Medication schedules should be maintained as accurately as possible, even as time zones change. However, the patient should not be advised to decrease the dosing interval or "double up" on medications if he misses a dose. Prophylaxis against *Pneumocystis carinii* pneumonia and other opportunistic infections should be made as convenient as possible with alternate-day or, in the case of azithromycin, weekly doses if this fits the traveler's schedule.

What to Do in an Emergency

The traveler should carry a complete list of medications he is taking as well as a brief medical summary. Facilities for emergency care and access to providers knowledgeable in the treatment of HIV-related complications obviously vary greatly by locale. This fact must be taken into consideration by the traveler at high risk of HIV-related emergences, i.e., those with CD4+ positive cell counts less than 200/mm^3. The provider should seek to identify qualified practitioners or facilities from which the patient may seek care while traveling.

Commonsense Restrictions on Travel

Extended travel to developing countries carries many inherent risks to the severely immunocompromised individual. In instances where potentially dangerous live-virus vaccines are necessary, where access to clean drinking water is limited, or where the risk of multidrug-resistant falciparum malaria is present, travel is best avoided for such patients.

Chapter Reference

1. Routine immunization and infection prevention: Chapter 5

Literature References

Castelli, F. and Patroni, A., The human immunodeficiency-infected traveler, *Clin Infect Dis,* 31, 1403, 2000.
Centers for Disease Control and Prevention, Health Information for International Travel, 1999–2000.

15 Appendices

CONTENTS

I. INTRODUCTION

In this final chapter, a comprehensive drug compendium is provided in which clinical indications, dosing schedules, and side effects of medications commonly prescribed in the outpatient care of HIV-infected patients are presented. In addition, tables delineating common drug interactions and the potential for fetal risk of the antiretroviral agents are provided (see Tables 15.1, 15.2, 15.3).

II. DRUG COMPENDIUM

What follows is a compendium of medications commonly used in the treatment of HIV-infected patients. **Dosing guidelines given are for adults with normal renal function. Many drugs listed require dose adjustments for renal insufficiency and some for hepatic insufficiency and when used in combination with various other agents. The manufacturer's package insert should be reviewed for dose adjustment recommendations. Updated treatment guidelines, potential drug interactions, and the package insert information should be considered before prescribing these agents.**

TABLE 15.1
Interactions Between Antiretroviral Drugs

	Effect on Drug Level							
Drug	**Indinavir**	**Ritonavir**	**Saquinavir**	**Nelfinavir**	**Amprenavir**	**Nevirapine**	**Delavirdine**	**Efavirenz**
Indinavir	N/A	None	increase	increase	increase	none	none	none
Ritonavir	increase	N/A	increase	increase	?	none	none	none
Saquinavir	none	none	N/A	increase	decrease	none	?	decrease
Nelfinavir	increase	none	increase	N/A	none	none	decrease	none
Amprenavir	decrease	?	decrease	increase	N/A	?	?	increase
Nevirapine	decrease	none	?	increase	?	N/A	?	?
Delavirdine	increase	none	?	increase	?	?	N/A	?
Efavirenz	decrease	increase	decrease	increase	decrease	?	?	N/A

Note: On the basis of these interactions, it is recommended that efavirenz not be used with saquinavir or amprenavir unless another PI is included in the regimen.

Adapted from Carpenter, C. C. J. et al., *JAMA,* 283, 381, 2000.

TABLE 15.2
Antiretroviral Agents: Major Potential Drug Interactions with Non-Antiretroviral Agents

Antiretroviral Drug	Interaction
	Protease Inhibitors (all)
	Terfenadine, astemizole, cisapride: life-threatening cardiotoxicity Rifampin: marked decrease in levels of protease inhibitors, should not be combined
Indinavir	increases rifabutin levels increases benzodiazepine levels
Ritonavir	decreases theophylline levels increases opiate levels increases rifabutin levels increases benzodiazepine levels increases clarithromycin levels decreases levels of ethinyl estradiol (birth control pill)
Saquinavir	ketoconazole increases saquinavir levels
Nelfinavir	increases rifabutin levels increases benzodiazepine levels decreases levels of ethinyl estradiol (birth control pill)
Amprenavir	ketoconazole increases amprenavir levels
	Non-Nucleoside Reverse Transcriptase Inhibitors
Nevirapine	
Delavirdine	increases benzodiazepine levels
Efavirenz	
	Nucleoside Reverse Transcriptase Inhibitors
Zidovudine	may increase toxicity ganciclovir and other drugs that cause myelosuppression
Didanosine	additive toxicity with drugs that cause peripheral neuropathy, decreases quinolone levels, may decrease absorption of ketoconazole
Zalcitabine	additive toxicity with drugs that cause peripheral neuropathy
Lamivudine	
Stavudine	additive toxicity with drugs that cause peripheral neuropathy
Abacavir	

Note: Manufacturer's package insert should be consulted for additional information regarding potential drug interactions.

TABLE 15.3
Safety of Antiretroviral Agents in Pregnancy

Drug	Pregnancy Risk Category
Abacavir	C
Amprenavir	C
Delavirdine	C
Didanosine	B
Efavirenz	Contraindicated
Indinavir	C
Lamivudine	C
Nelfinavir	B
Nevirapine	C
Ritonavir	B
Saquinavir	B
Stavudine	C
Zalcitabine	C
Zidovudine	C

Category A: Adequate studies, no fetal risk
Category B: Either no fetal risk in animal studies but insufficient human data or fetal risk in animal studies not confirmed in adequate human studies
Category C: Either fetal risk documented in animal studies but insufficient human data or insufficient human and animal data (Category C drugs should be given only if the potential benefit outweighs potential harm to the fetus.)
Category D: Fetal risk documented in human studies; drug may be used in life-saving situation
Category X: Contraindicated

A. Antiretroviral Agents

Antiretroviral agents are used in combination regimens dictated by the clinical situation. For information regarding indications for antiretroviral therapy and the combination and sequencing of specific agents, see Chapters 10 and 11.

1. Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Class side effects: All NRTI agents may be associated with the hepatic steatosis/lactic acidosis syndrome, which may be severe and fatal. This syndrome is discussed in detail in Chapter 11.

a. Abacavir (Ziagen)

Route of administration: Oral
How supplied: 300 mg tablets; oral solution 20 mg/mL
Common side effects: Life-threatening hypersensitivity reactions have been seen in as many as 5% of patients receiving abacavir. For this reason,

patients developing a rash or any other signs of hypersensitivity while receiving this agent should not be rechallenged and the drug should be permanently discontinued. Bone marrow depression is occasionally seen.

Usual adult dosage: 300 mg bid

Instructions to patient: Patients should be instructed to discontinue use and contact the provider promptly if rash appears. Rechallenge with abacavir is contraindicated. Patient should be informed of this to avoid inappropriate use by other providers. This drug may be taken with or without food.

b. Didanosine (Videx, ddI)

Route of administration: Oral

How supplied: 25, 50, 100, 150 mg tablets; powder for oral solutions in various strengths

Common side effects: The most serious side effects associated with didanosine are pancreatitis and peripheral neuropathy, seen in 5% to 9% and 10% to 20% of patients, respectively. Both of these toxicities have precluded the use of didanosine in combination regimens with zalcitabine and, occasionally, with other nucleoside reverse transcriptase inhibitors.

Usual adult dosage: If body weight > 60 kg
200 mg q12h (tablets) or 400 mg qd*
250 mg q12h (powder)
If body weight < 60 kg
125 mg q12h (tablets) or 200 mg qd*
167 mg q12h (powder)

Instructions to patient: Didanosine should be taken on an empty stomach.

c. Lamivudine (Epivir, 3TC)

Route of administration: Oral

How supplied: 150 mg white, diamond-shaped tablets with 150 imprinted on the side; oral solution 10 mg/mL

Common side effects: None. Lamivudine is generally the best tolerated of the nucleoside drugs. What side effects occur (e.g., headache and diarrhea) are often self-limited. Bone marrow depression and peripheral neuropathy, two adverse reactions seen with other nucleoside agents, are encountered infrequently with lamivudine.

Usual adult dosage: 150 mg twice daily

d. Stavudine (Zerit, D4T)

Route of administration: Oral

How supplied: 15, 20, 30, 40 mg tablets; oral solution 1 mg/mL

Common side effects: Stavudine is chemically similar to zidovudine but differs in its side effects profile. While hematological toxicity is rarely seen, peripheral neuropathy, similar to that associated with didanosine and with zalcitabine is common, particularly among patients with CD4 cell counts below 100/mm^3, with prior neuropathy, and on other agents associated with peripheral

* not preferred.

neuropathy. Once established, neuropathy may be difficult to treat and may persist for several weeks after the drug is discontinued. Tricyclic antidepressants, anticonvulsants such as dilantin or gabapentin, or, if extreme, narcotic analgesics may relieve the pain of neuropathy.

Usual adult dosage: If body weight > 60 kg, 40 mg bid
If body weight < 60 kg, 30 mg bid

e. *Zalcitabine (Hivid, ddC)*

Route of administration: Oral

How supplied: 0.375 and 0.750 mg oval, beige tablets with HIVID 375 or HIVID 750 printed on the side

Common side effects: Peripheral neuropathy is the most significant side effect associated with zalcitabine therapy. This effect is dose-related and it usually, but not always, resolves with discontinuation of the drug. For this reason, it is recommended that zalcitabine not be combined with any other nucleoside agent except zidovudine. Pancreatitis and oral and esophageal ulcers are seen less commonly.

Usual adult dosage: 0.75 mg q8h

f. *Zidovudine*

Routes of administration: Oral, intravenous

How supplied: 300 mg white, oval tablets; 100 mg white capsules with blue band; syrup 50 mg/ 5 mL; IV infusion 10 mg/mL

Common side effects: The most important adverse effect of zidovudine therapy has been bone marrow depression manifesting as anemia and/or neutropenia. This is seen more frequently among patients at advanced stages of HIV infection, especially those with CD4 cell counts less than 100/mm^3, and typically begins between 2 and 4 months after therapy is instituted. In general, bone marrow depression has become less common as the recommended dose of zidovudine for adults has been reduced from 1500 mg to 600 mg daily. Exogenous erythropoetin is recommended for individuals with significant anemia and serum erythropoetin level less than 500 IU/mL. Granulocyte colony–stimulating factor may be used to maintain neutrophil counts. Other common side effects seen with zidovudine include headache, insomnia, and myalgia. Less common, although occasionally severe, side effects include myopathy and neuropathy. All zidovudine-related toxicities typically resolve with withdrawal of the drug.

Usual adult dosage: 200 mg tid or 300 mg bid

2. Non-Nucleoside Reverse Transcriptase Inhibitors

a. *Delavirdine (Rescriptor)*

Route of administration: Oral

How supplied: 100 mg tablets

Major side effect: The most frequent side effect associated with delavirdine is skin rash, which occurs in 18% of individuals. Prior sulfonamide-related

rash and Hispanic ethnicity may be risk factors for delavirdine-associated rash.

Usual adult dosage: 400 mg tablets tid

Instructions to patient: Tablets should be mixed with 3 ounces of water.

b. Efavirenz (Sustiva)

Route of administration: Oral

How supplied: 50, 100, 200 mg capsules

Common side effects: Over 50% of patients taking efavirenz experience one or more neurological side effects such as insomnia, nightmares, hallucinations, dizziness, or confusion. Preexisting depression or psychosis may also be exacerbated. As is the case with nevirapine and delavirdine, skin rash is also commonly seen with efavirenz. Less frequent side effects include elevated lipid levels, liver function abnormalities, elevated serum amylase, nausea, and diarrhea. It has been associated with fetal neural tube defects in animal studies and should not be used in pregnancy.

Usual adult dosage: Three 200 mg tablets daily

Instructions to patient: Efavirenz should be taken at bedtime to minimize the impact of CNS side effects.

c. Nevirapine (Viramune)

Route of administration: Oral

How supplied: 200 mg tablets; oral solution

Common side effects: Skin rashes, which can be severe in some cases, have been the most frequently reported side effect of nevirapine therapy. As is the case with delavirdine and efavirenz, skin rash appears to be more common among individuals of Hispanic heritage or with prior history of sulfa allergy. Liver function abnormalities as well as clinical hepatitis, which may be severe, and cholestasis have also been described.

Usual adult dosage: Days 1 to 14: one 200 mg tablet qd; day 15 forward: one 200 mg tablet bid

3. Protease Inhibitors

Class side effects/interactions: All protease inhibitors may cause gastrointestinal side effects such as nausea, vomiting and, especially, diarrhea. Hyperglycemia, insulin resistance, hyperlipidemia, and fat redistribution (the so-called lipodystrophy syndrome) have been associated with all of the drugs in this class and can limit their usefulness in some patients. Each drug is metabolized by the cytochrome P450 system and a wide variety of drug interactions, some significant, has been reported.

a. Amprenavir (Agenerase)

Route of administration: Oral

How supplied: 150 mg soft-gel capsules; oral solution

Common side effects: Perioral paresthesias, nausea, vomiting, skin rash (severe in rare cases)

Usual adult dosage: 1200 mg bid
Instructions to patient: Amprenavir may be taken with or without food; it should be stored at room temperature.

b. Indinavir

Route of administration: Oral
How supplied: 200, 333, 400 mg capsules
Common side effects: Kidney stones, elevation of indirect bilirubin, dry skin, brittle nails, nausea, vomiting, diarrhea.
Usual adult dosage: 800 mg tid
Instructions to patient: Indinavir should be taken with 12 ounces of fluid and without food. Good hydration should be maintained to help prevent the formation of kidney stones.

c. Nelfinavir (Viracept)

Route of administration: Oral
How supplied: 250 mg tablets; powder for oral solution (50 mg per level scoopful)
Common side effects: Diarrhea (typically resolves with continued use). Nelfinavir is generally the best tolerated of the protease inhibitors.
Usual adult dosage: 750 mg tid or 1250 mg bid
Instructions to patient: Nelfinavir should be taken with food.

d. Ritonavir (Norvir)

Route of administration: Oral
How supplied: 100 mg capsules, liquid (600 mg/7.5 mL)
Common side effects: Nausea, bitter aftertaste, circumoral paresthesias, diarrhea. Ritonavir is generally the most poorly tolerated protease inhibitor when used in full therapeutic doses.
Usual adult dosage: 600 mg bid. Because it is often poorly tolerated in full dose, ritonavir is most often used in a subtherapeutic dose (100 to 400 mg bid) to increase the serum concentration of other protease inhibitors. If used alone, a dose escalation schedule should be used (e.g., 300 mg bid with daily 100 mg bid incremental increase to a maximum total dose of 600 mg bid).
Instructions to patient: Ritonavir capsules must be refrigerated and kept away from light. Liquid should be used within 30 days or stored in a refrigerator.

e. Saquinavir (Fortovase)

Route of administration: Oral
How supplied: 200 mg soft-gel capsules. An older formulation of saquinavir, Invirase, has been largely replaced by Fortovase because of better bioavailability.
Common side effects: Diarrhea, nausea, headache (all generally mild).
Usual adult dosage: 1200 mg tid
Instructions to patient: Fortovase should be taken with meals but not with vitamin E supplements (each capsule contains 109 units of vitamin E). The capsules should be refrigerated.

f. Lopinavir/ritonavir (Kaletra)

Route of administration: Oral
How supplied: Soft-gel capsules (133.3 mg lopinavir, 33.3 mg ritonavir), oral solution (400/100).
Common side effects: Diarrhea, headache, fatigue, nausea. Pancreatitis, including severe with fatal outcome, has been reported.
Usual adult dosage: 3 capsules bid
Instructions to patient: Kaletra should be kept refrigerated.

4. Combination Antiretroviral Products

At the time of this writing, two products combining antiretroviral agents in fixed amounts are available:

Combivir (zidovudine/lamivudine)
Trizivir (abacavir/zidovudine/lamivudine)

B. Drugs Used to Prevent and/or Treat HIV-Related Infections

An ever-growing number of new and old agents have found roles in the therapy or prevention of HIV-related opportunistic infections. The medications discussed here are commonly used in the outpatient setting. This compendium is focused on the indications and use of these drugs in the setting of HIV infection, although many are used for a great variety of indications unrelated to HIV/AIDS.

1. Antiviral Agents

a. Acyclovir (Zovirax)

Routes of administration: Topical, oral, intravenous
Indications: Therapy of mucutaneous (oral, topical) or systemic (intravenous) herpes simplex infections; long-term suppression of mucocutaneous herpes simplex infections; therapy of localized or disseminated varicella zoster infection
Common side effects: Headache, rash, nausea, diarrhea, bone marrow depression; seizures, hepatic and renal toxic effects rarely
Usual adult dosage:
Herpes simplex, localized genital or oral: topical—every 4 hours while awake; oral—200 mg every 4 hours while awake; intravenous—15 mg/kg daily in three divided doses
Herpes simplex, generalized or visceral: intravenous as above
Varicella zoster, localized: oral—800 mg every 4 hours while awake
Varicella zoster, generalized or visceral: intravenous—10 to 12 mg/kg every 8 hours or 1 gram tid orally

b. *Cidofovir (Vistide)*

Route of administration: Intravenous
Indications: Cytomegaloviral infection, especially retinitis
Common side effects: Renal insufficiency, proteinuria, renal tubular acidosis
Usual adult dosage: 5 mg/kg IV weekly for 2 weeks followed by 5 mg/kg IV every 2 weeks

c. *Famciclovir (Famvir)*

Route of administration: Oral
Indications: Genital herpes simplex and localized herpes zoster infections
Common side effects: Headache, nausea, vomiting, diarrhea
Usual adult dosage: Herpes zoster: 500 mg every 8 hours for 7 days; herpes simplex: 125 mg bid for 5 days; 250 mg bid may be used for chronic suppression in patients with frequent episodes

d. *Fomivirsen (Vitravene)*

Route of administration: Intravitreal injection
Indications: Cytomegaloviral retinitis in patients not responding to or intolerant of other forms of therapy
Common side effects: Ocular inflammation, increased intraocular pressure
Usual adult dosage: 330 micrograms every 2 weeks for 2 doses, then once every 4 weeks

e. *Foscarnet (Foscavir)*

Route of administration: Intravenous
Indications: Cytomegaloviral infection not responding to other therapies, herpes simplex infection resistant to acyclovir
Common side effects: Renal insufficiency, proteinuria, seizures, hypokalemia, hypocalcemia, hypomagnesemia, neuropathy, gastrointestinal tract upset, liver function abnormalities, headache
Usual adult dosage: 60 mg/kg every 8 hours for 14 days followed by 90 to 120 mg/kg daily

f. *Ganciclovir (Cytovene)*

Routes of administration: Oral, intravenous, intraocular implant
Indications: Cytomegaloviral infection
Common side effects:
Systemic therapy: Bone marrow depression, fever, abdominal pain, confusion (all more common and severe with intravenous than with oral therapy)

Intraocular implant: Retinal detachment
Usual adult dosage:
Induction therapy: 5 mg/kg IV q12 h for 14 days
Maintenance therapy: 5mg/kg IV qd 5 times each week or 1000 mg po tid with meals

g. Valacyclovir (Valtrex)

Route of administration: Oral
Indications: Localized herpes zoster, genital herpes simplex
Common side effects: Similar to acyclovir; hemolytic-uremic syndrome.
Usual adult dosage:
Herpes zoster: 1 gram three times daily for 7 days
Genital herpes simplex (initial): 1 gram twice daily for 10 days
Genital herpes simplex (recurrent): 500 mg twice daily for 5 days
Genital herpes simplex (chronic suppressive therapy): 1 gram once daily

2. Antifungal Agents

a. Fluconazole (Diflucan)

Routes of administration: Oral, intravenous
Indications: Oral, esophageal candidiasis; chronic suppressive therapy of cryptococcal infection
Common side effects: None (GI upset rare)
Usual adult dosage: Oral or esophageal candidiasis: 200 mg by mouth initial dose followed by 100 mg daily; cryptococcosis or systemic candidiasis: 400 mg oral (or intravenous) followed by 200 to 400 mg daily

b. Itraconazole (Sporanox)

Routes of administration: Oral, intravenous
Indications: Histoplasmosis, blastomycosis, aspergillosis in patients intolerant of amphotericin B, oral candidiasis refractory to fluconazole
Common side effects: Nausea, abdominal discomfort
Usual adult dosage: 100 to 400 mg qd (oral)

3. Agents Used in the Prevention and Treatment of *Pneumocystis carinii* Infection and/or Toxoplasmosis

a. Atovaquone (Mepron)

Route of administration: Oral (liquid)
Indications: Mild to moderate *Pneumocystis carinii* pneumonia (PCP) (partial pressure of oxygen > 70 mmHG), prophylaxis of PCP in patients intolerant of trimethoprim-sulfamethoxazole; primary or secondary prophylaxis of toxoplasmosis

Common side effects: GI upset, headache, rash, fever
Usual adult dose:
PCP: 750 mg bid for 21 days.
Prophylaxis: 1500 mg once daily
Toxoplasmosis prophylaxis: 1500 mg qd (primary); 750 mg po q 6 to 12 h (secondary)
Instructions to patient: Take with meals

b. Clindamycin

Routes of administration: Oral, intravenous
Indications: Treatment of PCP (in combination with primaquine) or toxoplasmosis (in combination with pyrimethamine) in patients intolerant of sulfa drugs
Common side effects: Diarrhea (including antibiotic-associated colitis), skin rash
Usual adult dosage:
PCP (mild): Clindamycin 350 to 400 mg po q6h plus primaquine 15 mg base po qd for 21 days
PCP (moderate/severe): Clindamycin 600 mg IV q8h plus primaquine 15 mg base qd for 21 days
Toxoplasmosis: Clindamycin 600 mg po or IV q6h plus pyrimethamine 200 mg po once followed by 75 to 100 mg daily
Note: Clindamycin/pyrimethamine is effective in the secondary prevention of toxoplasmosis (clindamycin 300 to 450 mg po q6h to q8h plus pyrimethamine 25 to 75 po qd) but not PCP. Folinic acid (10 to 15 mg po qd) should always be given with pyrimethamine.

c. Dapsone

Route of administration: Oral
Indications: Therapy (with trimethoprim); primary or secondary prevention of *Pneumocystis carinii* infection; primary prevention or therapy of toxoplasmosis.
Common side effects: Hypersensitivity reactions, blood dyscrasias
Usual adult dosage:
PCP (mild): Dapsone 100 mg qd plus trimethoprim 5mg/kg po tid for 21 days
Prophylaxis: Dapsone 100 mg qd
Toxoplasmosis: Dapsone 100 mg qd plus pyrimethamine 200 mg po once followed by 75 to 100 mg po qd for 6 weeks
Prophylaxis: Dapsone 50 mg po qd plus pyrimethamine 50 mg po weekly

d. Pentamidine

Routes of administration: Aerosol, intramuscular, intravenous
Indications: Therapy (parenteral) or primary or secondary prophylaxis (parenteral or aerosolized) of *Pneumocystis carinii* infection

Common side effects: Systemic therapy: Hypotension, hyperglycemia, renal insufficiency, bone marrow depression (rare)
Aerosol therapy: bronchospasm
Usual adult dosage:
Pneumocystis carinii pneumonia (therapy): 4 mg/kg intravenously daily for 14 to 21 days
Pneumocystis carinii pneumonia (prophylaxis): 300 mg monthly by aerosol

e. Pyrimethamine

Route of administration: Oral
Indication: Toxoplasmosis, therapy or prevention (with sulfadiazine or clindamycin) or prevention (with dapsone)
Side effects: Folate deficiency, pancytopenia, hypersensitivity reactions
Usual adult dosage: varies with indication (see above)

f. Sulfadiazine

Route of administration: Oral
Indications: Therapy (initial and chronic suppressive) for toxoplasmosis (with pyrimethamine)
Common side effects: Hypersensitivity reactions, Stevens–Johnson syndrome, photosensitization, nephrolithiasis, bone marrow depression
Usual adult dosage: 2 to 6 grams in four divided doses

g. Trimethoprim/sulfamethoxazole (TMP-SMX)

Routes of administration: Oral, intravenous
Indications: Therapy, primary, or secondary prophylaxis of *Pneumocystis carinii* pneumonia; primary prophylaxis of toxoplasmosis
Common side effects: Hypersensitivity reactions, Stevens–Johnson syndrome, photosensitization, neutropenia, hepatitis.
Usual adult dosage:
Prophylaxis of *Pneumocystis carinii* pneumonia or toxoplasmosis: Double-strength tablet (160 mg trimethoprim, 800 mg sulfamethoxazole) every other day to twice daily.
Treatment of *Pneumocystis carinii* pneumonia: 15 to 20 mg/kg trimethoprim, 75 to 100 mg/kg sulfamethoxazole daily in four divided doses

4. Agents Used Primarily in the Treatment and/or Prevention of Mycobacterial Infection

a. Azithromycin (Zithromax)

Routes of administration: Oral, intravenous
Indications: Treatment and prevention of *Mycobacterium avium* complex (MAC) infection; treatment of toxoplasmosis in patients intolerant of standard therapy

Common side effects: Diarrhea, nausea, abdominal pain
Usual adult dosage:
MAC infection: 500 mg po qd (as part of multidrug regimen) (see Chapter 8)
MAC prevention: 1200 mg po weekly
Toxoplasmosis: 1200 to 1500 mg po for 6 weeks qd plus pyrimethamine 200 mg once, followed by 100 mg daily for 6 weeks

b. Ciprofloxacin/Ofloxacin

Routes of administration: Oral, intravenous
Indications: As components of combination regimens in the therapy of *Mycobacterium avium* complex (MAC) infection (see Chapter 8)
Common side effects: Nausea, vomiting, CNS effects
Usual adult dose: Ciprofloxacin 500 to 750 mg po bid; ofloxacin 200 to 400 mg po bid

c. Clarithromycin

Route of administration: Oral
Indication: Treatment (in combination regimens) and prevention of *Mycobacterium avium* complex (MAC) infection; treatment (with pyrimethamine) of toxoplasmosis in patients intolerant of standard therapy
Common side effects: Diarrhea, nausea, abdominal pain
Usual adult dosage: 500 mg bid

d. Ethambutol

Route of administration: Oral
Indications: In combination therapy of *Mycobacterium tuberculosis* (*M. Tb*) or MAC infection (see Chapter 8)
Common side effect: Optic neuritis
Usual adult dosage: 25 mg/kg/day for 2 months followed by 15 mg/kg/day

e. Isoniazid

Routes of administration: Oral, intramuscular, intravenous
Indications: Single drug therapy of latent tuberculosis; component of multidrug regimen in therapy of active tuberculosis
Common side effects: Hepatitis (may be severe), peripheral neuropathy, hypersensitivity reactions
Usual adult dosage: 300 mg per day orally

f. Pyrazinamide

Route of administration: Oral
Indication: Component of multidrug regimen in therapy of active tuberculosis or, with rifampin, short-course therapy of latent tuberculosis

Common side effects: Hepatitis, hyperuricemia
Usual adult dosage: 15 to 30 mg/kg daily orally (maximum daily dose: 2 g)

g. Rifabutin

Route of administration: Oral
Indications: Prevention or in combination regimens, treatment of MAC infection (see Chapter 8)
Common side effects: Myalgia, arthralgia, red urine, anterior uveitis when administered with clarithromycin
Usual adult dosage: 300 mg qd

h. Rifampin

Routes of administration: Oral, intravenous
Indication: Component of multidrug regimen in therapy of active tuberculosis or, with pyrazinamide, in short-course therapy of latent tuberculosis
Common side effects: Hepatitis, hypersensitivity reactions, orange discoloration of urine and tears; accelerates metabolism of methadone (may cause withdrawal symptoms), corticosteroids, oral hypoglycemic agents
Usual adult dosage: 600 mg daily

5. Selected Miscellaneous Therapeutic Agents

a. Dronabinol (Marinol)

Route of administration: Oral
Indication: Anorexia with weight loss
Common side effects: Drowsiness, personality change, hallucinations
Usual adult dosage: 2.5 mg bid

b. Erythropoetin (Epogen, Procrit)

Route of administration: Subcutaneous injection
Indications: Treatment of zidovudine-induced anemia if endogenous erythropoetin level is less than 500 mUnits/mL and other causes of anemia have been ruled out or treated
Common side effects: Fever, hypersensitivity reactions
Usual adult dosage: 100 units/kg three times weekly for first 8 weeks with increases of 50 to 100 mg three times weekly every 4 to 8 weeks to maximum of 300 mg three times weekly if necessary.

c. Megestrol (Megace)

Route of administration: Oral
Indications: Anorexia, unexplained weight loss

Common side effects: Abdominal discomfort, headache, breakthrough vaginal bleeding, decreased libido
Usual adult dosage: 800 mg once daily

d. Somatotropin (Serostim)

Route of administration: Subcutaneous injection
Indications: Weight loss, cachexia
Common side effects: Myalgia, fever, nausea, liver function test abnormality
Usual adult dosage: 55 kg body weight, 6 mg SC qd; 45 to 55 kg, 5 mg SC qd; 35 to 45 kg, 4 mg SC qd

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