1

Medical overview

Lori A. Panther, M.D., M.P.H.[1] and Howard Libman, M.D.[2]

[1] Assistant Professor of Medicine, Harvard Medical School, Beth Israel Deaconess Medical Center, Division of Infectious Diseases, Boston, MA
[2] Associate Professor of Medicine, Harvard Medical School, Director, HIV Services, Healthcare Associates, Beth Israel Deaconess Medical Center, Boston, MA

Introduction

The first report of acquired immunodeficiency syndrome (AIDS) appeared in the June 5, 1981, edition of *Morbidity and Mortality Weekly Report*. It described five men who had sex with men (MSM) diagnosed with *Pneumocystis carinii* pneumonia (PCP). In 1984, researchers reported the discovery of a retrovirus, now known as Human Immunodeficiency Virus, type 1 (HIV-1), associated with AIDS. In 1986, researchers described a second strain, HIV-2, which shares 42% genetic homology with HIV-1 but is less virulent. Based on genetic sequence analysis, scientists have concluded that HIV-1 originated in the African chimpanzee and HIV-2 in the African sooty mangabey.

What is the epidemiology of HIV infection?

World

According to recent estimates, 40 million people worldwide are infected with HIV, and 3 million have died of AIDS in the past year.

Sub-Saharan Africa has been most severely affected, with the highest prevalence in Botswana, South Africa, and Zimbabwe. In Botswana, 36% of the adult population is infected with HIV. By the end of 1999, an estimated 10.7 million African children had lost one or both of their parents to AIDS.

Asia has also been affected by the epidemic. Thailand experienced a dramatic increase in heterosexually acquired HIV cases in the mid-1980s. About 80% of injection drug users (IDUs) in China are HIV seropositive, and the epidemic in the heterosexual population in India is growing rapidly.

In Eastern Europe, injection drug use is the main means of acquiring HIV. Ukraine has reported the majority of cases. Given the sociopolitical instability of this region, the epidemic is expected to increase.

HIV and Psychiatry. A Training and Resource Manual, Second Edition, ed. Kenneth Citron, Marie-Josée Brouillette, and Alexandra Beckett. Published by Cambridge University Press.

In Latin America and the Caribbean region, HIV infection rates continue to increase over time, with a risk behavior profile similar to that of the USA (see below).

Globally, the HIV epidemic has disproportionately affected socially and economically disadvantaged persons. Frequent migration and low literacy rates have also impeded access to health care. While the availability of medical therapy has decreased the number of deaths attributable to HIV infection in the USA, Western Europe, and Brazil, antiretroviral drugs are not affordable in many developing countries, and the healthcare infrastructure required to properly monitor patients and maximize medication adherence does not exist.

Despite the lack of universal access to medications, some developing countries have reported decreases in HIV incidence after initiating intensive prevention programs. In Thailand, Uganda, Zambia, and Senegal, public education about safer sex, clean needle use, sexually transmitted disease (STD) prevention and treatment, and prenatal care has shown promise in curbing the spread of HIV infection.

USA

The first cases in the USA were primarily MSM. Over time, however, the epidemic has spread to injection drug users (IDUs), who contract HIV via contaminated drug equipment, and women, whose main risk behavior is heterosexual contact. A small but significant proportion of early HIV cases were in blood transfusion recipients and infants born to HIV-infected mothers but, with the screening of the blood supply and the widespread use of antiretroviral therapy in HIV-seropositive pregnant women, the incidence of infection attributed to these risk factors has decreased over time. In recent years, there has been an increased frequency of new cases of HIV infection in MSM of color, and the rate of heterosexual acquisition in women has been steadily rising.

AIDS incidence in the USA rose rapidly through the 1980s, peaked in the early 1990s, and then declined. As of December, 2001, 816,148 people with AIDS had been reported to the Centers for Disease Control and Prevention (CDC), and 57% of them had died. An estimated 40,000 new cases of HIV infection occur in the USA each year. Because of greater longevity, more people are alive with an AIDS diagnosis than ever before.

How is HIV transmitted?

Sexual

The overall risk of HIV transmission associated with unprotected sexual activity is estimated to range from 0.3 to as high as 30 in 1000 (Table 1.1). However, the per-episode risk associated with a specific sexual act has been difficult to quantify. Unprotected receptive anal intercourse is thought to be the highest risk sexual

Table 1.1. Estimates of per-contact risk of HIV infection

Activity	Risk
Needle-Sharing	6/1000 to 30/1000
Occupational Needle Stick	1/300
Receptive Anal Sex	8/1000 to 30/1000
Receptive Vaginal Sex	2/1000 to 8/1000
Insertive Anal or Vaginal Sex	3/10,000 to 10/10,000
Receptive Oral Sex	Unknown

Adapted from Table 1–2 in Libman H, Makadon HJ, eds. HIV, *Therapy Series, American College of Physicians, Philadelphia, PA, 2003.*

activity followed by unprotected receptive vaginal intercourse. Few data exist about the degree of risk associated with insertive anal or vaginal intercourse. In general, male-to-male and male-to-female transmission is more efficient than female-to-male and female-to-female transmission. Seroconversion as a result of oral sex has been reported, and recent information suggests that there is a tangible risk associated with this activity. The correct and consistent use of latex condoms can significantly reduce the risk of HIV transmission during anal, vaginal, and oral sex.

Injection drug use

The overall risk of HIV transmission associated with injection drug use is comparable to that of unprotected sexual activity, ranging from 6–30 in 1000. Needles and syringes are the primary drug equipment involved in transferring HIV-infected blood between drug injectors. Drug treatment and needle exchange programs are the most effective means of reducing HIV transmission in IDUs. However, if these are not accessible, IDUs should be instructed not to share drug equipment or to disinfect it prior to use with bleach.

Maternal–fetal

Approximately 70% of maternal–fetal transmissions occur in the peripartum period. Perinatal transmission rates in untreated mother–infant pairs vary geographically, with a 15–30% transmission rate in the USA, 13–15% in Europe, and 40–50% in Africa. Fetal passage through the birth canal is associated with most peripartum transmission through exposure to maternal blood. In 1994, a large study of zidovudine (ZDV, AZT) monotherapy in mother–infant pairs was stopped after interim analysis because ZDV decreased perinatal transmission rates from 25.5% to 8.3%. Although cesarean section has been shown to further decrease the perinatal transmission rate, its role in mothers whose viral load is suppressed on antiretroviral therapy has not been elucidated. HIV-infected

mothers are discouraged from nursing because of a 3.5–10.3% transmission risk, with the higher rate associated with a longer duration of breast-feeding.

Other considerations

Options for the HIV-seronegative woman who wishes to conceive with an infected partner are currently under investigation. Sperm washing, which involves removal of HIV from sperm prior to artificial insemination, is the most popular choice for risk reduction. The CDC has advised against sperm washing because of concerns about safety, but the procedure is currently being used in European countries with success.

There is no risk of HIV transmission from non-intimate household or routine work exposures. During phlebotomy or other invasive procedures, all patients should be managed using universal precautions regardless of their HIV serostatus.

The risk of HIV transmission in healthcare workers after exposure to HIV-infected blood is 0.3% per percutaneous exposure and 0.09% per mucous membrane exposure. The risk associated with body fluids other than blood has not been quantified but is thought to be substantially lower. The risk of transmission is increased with the inoculation of a large quantity of blood, visible blood on the device to which the worker was exposed, exposure to a needle that was inserted directly in a vessel, exposure to a hollow-bore needle, deep injury, and exposure to blood or secretions from an HIV-infected person with a high viral load. Postexposure prophylaxis (PEP) consists of a short course of antiretroviral therapy after a high-risk exposure. In general, PEP consists of 4 weeks of antiretroviral therapy instituted as soon as possible after exposure. For most exposures, a two-drug regimen, usually ZDV and lamivudine (3TC), is used. If the exposure is to a person thought likely to harbor resistant virus, a third agent, often indinavir or nelfinavir, is added. Non-occupational PEP, which might be used following rape or condom failure, consists of the same regimens.

What is the pathogenesis of HIV infection?

HIV is a cytopathic virus, composed of a central cylindrical core of RNA surrounded by a spherical lipid envelope. Through the binding of the HIV envelope glycoprotein gp120 to the receptor present on the surface of CD4+ T lymphocytes, the virus fuses with the cell membrane. Once within the cytoplasm of the host cell, the envelope of the virus is shed, and its contents are released. It is then that reverse transcription occurs: DNA is made from the viral RNA template, and the viral DNA inserts itself into the host cell genetic material. Infected cells remain in a dormant state for a variable period of time. When activation occurs, the proviral DNA transcribes genomic and messenger RNA. After viral proteins are synthesized, new virions are assembled and bud from the infected cell. For budding virions to become functional,

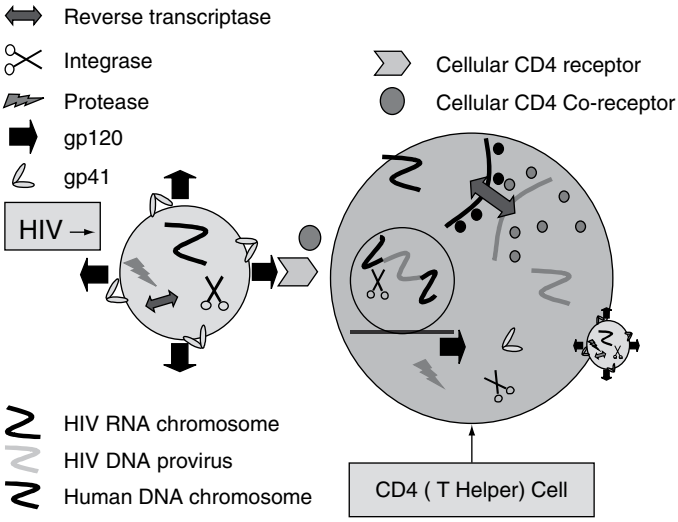

Figure 1.1. Schematic of HIV/CD4 cell interaction.

processing by a viral protease is required. Once this processing has been accomplished, the virions circulate until they identify new target cells (Figure 1.1).

How is a diagnosis of HIV infection made, and how is HIV infection classified?

A diagnosis of HIV infection is made by testing a patient for antibodies specific to HIV. Timing of the testing is important. HIV antibodies are not detectable using the standard serologic tests (i.e., enzyme-linked immunosorbent assay [ELISA] and Western blot [WB]) until approximately 3 weeks after infection. As part of antibody testing, the patient should receive standardized pretest and post-test counseling (see Appendix 1). HIV viral load testing, which is a direct measurement of HIV in the plasma, should never be used for the initial diagnosis of a suspected chronic infection because false-positive low titer results (usually < 2000 copies/ml) have been reported in acute non-HIV-related illnesses.

The CD4 cell count correlates highly with the progression of HIV disease and is the main surrogate marker for immunologic function. The CDC classification system for AIDS is based on the patient's CD4 cell count and clinical history: AIDS is defined as a CD4 count less than 200 cells/mm^3 or a history of opportunistic infections and malignancies that occur in the context of HIV infection (Table 1.2).

Without effective antiretroviral therapy, the average decline per year in CD4 count is 75 to 100 cells/mm^3. However, there is a great deal of variability among patients and in a given patient over time. A normal CD4 count is generally greater than 500 cells/mm^3 in healthy people, but it may be as low as 350 cells/mm^3. Although opportunistic infections usually do not occur with CD4 counts of

Table 1.2. Indicator conditions for case definition of AIDS

Candidiasis of bronchi, trachea, lungs or esophagus
Cervical cancer, invasive
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal
Cytomegalovirus disease (other than liver, spleen, or lymph nodes)
Encephalopathy, HIV-related
Herpes simplex: chronic ulcer(s) or bronchitis, pneumonitis, or esophagitis
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal
Kaposi's sarcoma
Lymphoma: Burkitt's, immunoblastic or primary (in brain)
Mycobacterium avium complex or *M. kansasii*, disseminated or extrapulmonary
Mycobacterium tuberculosis, any site
Pneumocystis carinii pneumonia
Pneumonia, recurrent
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain
Wasting syndrome, HIV-related

Adapted from Box 1.1 in Libman, H. and Makadon, H. J., eds. *HIV, Therapy Series*. American College of Physicians, Philadelphia, PA, 2003.

greater than 500 cells/mm^3, conventional bacterial infections, herpes simplex virus (HSV), varicella-zoster virus (VZV), thrush, tuberculosis (TB), Kaposi's sarcoma (KS), generalized lymphadenopathy, and chronic skin conditions may be seen as the count declines (Figure 1.2). A CD4 count of less than 200 cells/mm^3 indicates significant immunodeficiency with increased risk for serious opportunistic infections, such as PCP, toxoplasmosis, and cryptococcal meningitis. Patients with a count of less than 50 cells/mm^3 are also at risk for cytomegalovirus (CMV) and *Mycobacterium avium* complex (MAC) infection and for lymphoma. The highest risk for death in HIV-infected patients is in those with a CD4 count less than 50 cells/mm^3.

What are the clinical manifestations of HIV infection?

The clinical manifestations of HIV infection are listed in Table 1.3.

Primary HIV infection

At 2–6 weeks after exposure, the most common symptoms are fever, fatigue, rash, headache, lymphadenopathy, and pharyngitis. Neurologic manifestations of primary

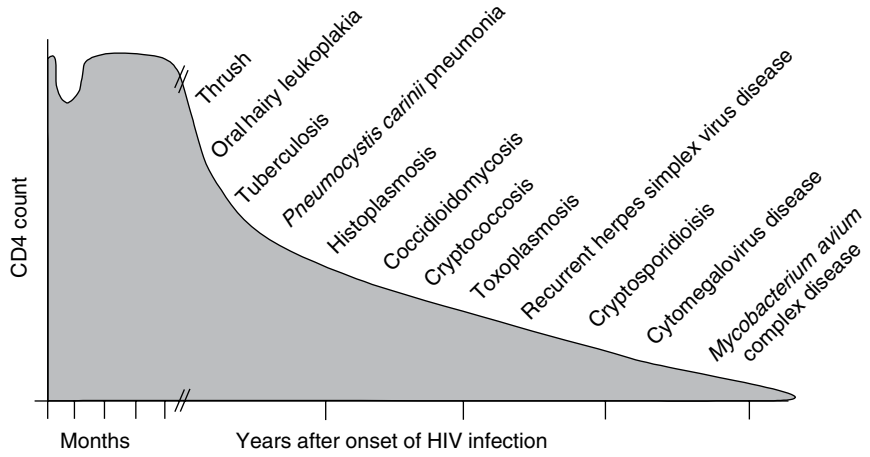

Figure 1.2. Opportunistic infections that occur as CD4 counts decline.

infection include aseptic meningitis, myelopathy, radiculopathy, peripheral neuropathy, meningoencephalitis, and Guillain–Barré syndrome. Between 40% and 90% of HIV-infected people can recall an illness suggestive of primary HIV infection. The syndrome of primary or acute HIV infection should be suspected in anyone who presents with an atypical or prolonged viral illness or an unexplained mononucleosis syndrome. A negative HIV antibody test in the presence of a high (i.e., $>$ 50 000 copies/ml) viral load is diagnostic of primary HIV infection.

Latency period

After primary HIV infection, there is a period of clinical latency before patients develop an AIDS-defining diagnosis. The latency period lasts 2 years in 5% of patients, 6 years in 20–25% of patients, and 10 years in 50% of patients. The single best predictive laboratory test for progression to AIDS is the HIV viral load measurement: a viral load of less than 10 000 copies/ml predicts the development of AIDS in fewer than 32% of patients at 6 years of follow-up, and a viral load of greater than 30 000 copies/ml predicts AIDS in 80%. Using both the CD4 count and HIV viral load values is even more helpful in determining an individual patient's prognosis.

Oral and skin manifestations

Oral lesions can occur throughout the course of HIV infection. Thrush and angular cheilitis are forms of oral candidiasis. Oral hairy leukoplakia is caused by the Epstein–Barr virus and is usually asymptomatic. Oral ulcerations are common in HIV disease and can be aphthous or caused by HSV or CMV. A severe and progressive form of gingivitis, acute necrotizing ulcerative gingivitis (ANUG),

Table 1.3. Clinical manifestations of HIV disease

Primary HIV infection
Latency period
Oral
Candidiasis
Hairy leukoplakia
Herpes simplex virus
Cytomegalovirus
Aphthous ulcers
Gingivitis
Kaposi's sarcoma
Skin
Seborrheic dermatitis
Bacterial folliculitis
Eosinophilic folliculitis
Herpes simplex virus
Varicella-zoster virus
Molluscum contagiosum
Human papillomavirus
Bacillary angiomatosis
Kaposi's sarcoma
Persistent generalized lymphadenopathy
Pulmonary
Community-acquired pneumonia
Pneumocystis carinii pneumonia
Tuberculosis
Kaposi's sarcoma
Lymphoma
Gastrointestinal
Esophagitis
Cholangiopathy
Hepatitis (A,B,C)
Pancreatitis
Diarrhea
Wasting syndrome
Multi-organ system disease
Cytomegalovirus
Mycobacterium avium complex
Lymphoma
Neurocognitive and neurologic
Progressive multifocal leukoencephalopathy
Toxoplasmosis

Primary CNS lymphoma
Cryptococcosis
Vacuolar myelopathy
Demyelinating polyradiculopathy
Peripheral neuropathy
HIV encephalopathy

often requires debridement and antibiotics. Oral nodules may represent KS, lymphoma, warts, or salivary gland enlargement.

The skin is commonly involved in HIV disease. Reactivation of VZV infection ("shingles") is often one of the earliest cutaneous manifestations. Molluscum contagiosum is caused by a poxvirus and presents as centrally umbilicated papules. Nodules, abscesses, ulcers, or lymphadenitis can manifest from histoplasmosis, cryptococcosis, and KS, as well as *Penicillium marneffei*, nontuberculous mycobacteria, and *Bartonella* infections. Human papillomavirus causes anogenital warts as well as cervical and anal dysplasia and carcinoma. Persistent generalized lymphadenopathy occurs in 50–70% of HIV-infected patients early in the course of disease and can recrudesce in patients who have initiated combination antiretroviral therapy as their CD4 counts recover.

Pulmonary manifestations

Pulmonary complications are a leading cause of morbidity and mortality in people with HIV infection. Of these, community-acquired pneumonia (CAP) is the most common and is caused by the usual respiratory pathogens. PCP was the first reported opportunistic infection. Most patients with PCP have a CD4 cell count less than 200 cells/mm^3. Tuberculosis and multidrug-resistant TB (MDRTB) are reported more frequently in AIDS. Although MAC and CMV are sometimes isolated from lung specimens in patients with HIV-associated respiratory illness, they are rarely the causative pathogens. Pulmonary KS and Hodgkin's and non-Hodgkin's lymphomas manifest in the chest as intrapulmonary nodules or mediastinal or hilar lymphadenopathy.

Gastrointestinal manifestations and multi-organ system disease

Esophagitis presenting as dysphagia and odynophagia can be caused by *Candida albicans*, CMV, or HSV, and is one of the more common gastrointestinal manifestations occurring in advanced HIV disease. Less frequent causes of esophageal symptoms include KS and lymphoma. AIDS cholangiopathy can be caused by CMV, *Cryptosporidium* species, microsporidial organisms, *Isospora belli*, or MAC, and is associated with very high alkaline phosphatase levels. People with HIV infection are at risk for hepatitis A (HAV), B (HBV), and C (HCV). Patients

co-infected with HIV and HCV are at risk for accelerated development of cirrhosis and increased mortality. Drug toxicity (e.g., ddI [didanosine], pentamidine) is the usual cause of pancreatitis. Diarrhea is common in people with HIV infection and most often related to infection or drug toxicity. HIV wasting syndrome, defined as loss of greater than 10% of baseline body weight associated with chronic diarrhea, weakness, or fever in the absence of a known cause, was one of the earliest recognized manifestations of AIDS. Opportunistic infections and malignancies including CMV, MAC, and lymphoma can cause multi-organ system disease in people with HIV infection.

Neurocognitive and neurologic manifestations

Neurocognitive and neurologic diseases are most prevalent in advanced HIV disease. Opportunistic infections and malignancies of the brain occur most often in patients with a CD4 cell count of less than 100 cells/mm^3. Progressive multifocal leukoencephalopathy (PML) manifests as slowly progressive neurocognitive deterioration associated with paresis, apraxia, aphasia, vertigo, ataxia, and/or diplopia. Brain MRI shows multiple non-enhancing white matter lesions adjacent to the cerebral cortex. Cerebral toxoplasmosis, caused by the parasite *Toxoplasma gondii*, generally presents subacutely with headaches, seizures, and/or focal neurologic findings. Computerized tomography with contrast or magnetic resonance imaging (MRI) scan shows multiple ring-enhancing lesions in the cortex, basal ganglia, or thalamus. Diagnosis is made by demonstration of serum antibodies to *T. gondii* and characteristic findings on neuroradiologic imaging. Primary central nervous system lymphoma (PCNSL) is a rapidly advancing brain malignancy manifesting as acute neurologic decompensation with imaging studies showing deep white matter lesions with weak contrast enhancement. Lesions associated with toxoplasmosis may be radiologically indistinguishable from those of PCNSL. Other opportunistic pathogens that can result in focal brain lesions in HIV disease include *Cryptococcus neoformans*, *Mycobacterium tuberculosis*, *Nocardia* species, and *Aspergillus* species. Diagnosis of these infections requires cerebrospinal fluid (CSF) examination and sometimes brain biopsy.

Meningoencephalitis is generally acute or subacute in presentation and most commonly caused by the fungus *C. neoformans*. Less frequent etiologies include the encapsulated bacteria *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Hemophilus influenzae*; and the viruses CMV, HSV, and VZV. Symptoms of meningoencephalitis include fever, headache, altered mental status, and meningismus. Diagnosis is generally made by CSF examination and appropriate microbiological studies.

Vacuolar myelopathy, which occurs in advanced HIV disease, is characterized by loss of motor function in the lower extremities. Dementia may or may not