CHAPTER 130

AIDS and HIV Infection

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PERSPECTIVE

History

The first cases of AIDS came to light in 1981, when reports of Kaposi's sarcoma (KS) and *Pneumocystis* pneumonia (PCP) in previously healthy homosexual men appeared in the literature. Shortly thereafter, it was recognized that these patients shared the common characteristic of a defect in cell-mediated immunity; accordingly, the clinical disease was designated the *acquired immunodeficiency syndrome* (AIDS). In 1983, a ribonucleic acid (RNA)–type retrovirus, the *human immunodeficiency virus* (HIV), was identified as the causative agent for the syndrome. The development of an antibody assay in 1985 permitted serologic diagnosis, allowing researchers to track the HIV epidemic and identify the principal modes of and risk factors for disease transmission. Significant therapeutic advances have occurred over the past 2 decades with institution of prophylaxis for opportunistic infections and introduction of highly active antiretroviral therapy (HAART) for slowing progression of disease. Despite these advances, HIV continues to be a major public health threat and is responsible for a large number of emergency department (ED) visits, for both acute and subacute conditions, each year.

Epidemiology

Most epidemiologic data regarding HIV infection are derived from studies in patients with illness that meets the definition of AIDS. The most up-to-date definition of AIDS, published in 1997 by the Centers for Disease Control and Prevention (CDC), is shown in Box 130-1.[1] Case definitions include either the presence of one or more AIDS-indicator conditions or laboratory evidence of severe immunosuppression as evidenced by a $CD4^+$ T lymphocyte count of less than 200 cells/μL.

Worldwide estimates indicate that approximately 39.5 million adults and 2.3 million children were living with HIV/AIDS at the end of 2006.[2] Cumulative HIV-related deaths totaled 25 million. Approximately 95% of HIV-infected persons live in the developing world. Sub-Saharan Africa has the highest levels of infection, with more than 25 million persons living with disease and more than 3 million newly reported cases in 2003 (representing approximately 60% of all incident cases). The medical and economic impacts of HIV and AIDS continue to devastate these areas, because these populations have the least access to the medical, social, and economic resources that might prevent new disease or delay the progression of HIV-related illnesses.

In developed countries significant progress has been made in controlling the HIV epidemic. In 1996, for the first time since HIV was recognized, there was a decline in the incidence of AIDS and the number of AIDS-related deaths,[3] attributed primarily to availability of new antiretroviral therapies. Unfortunately, the rates of decline in AIDS cases and AIDS deaths have slowed over the past several years.[4] In the United States an estimated 56,000 new cases of HIV were reported in 2007 and an estimated 1 million persons were living with HIV or AIDS.[4]

Within the United States, HIV-positive persons are concentrated primarily in large urban settings. Until 1987, New York City, Newark, Miami, San Francisco, and Los Angeles accounted for nearly 50% of AIDS cases. Although these cities still represent high-intensity pockets of infection, significant increases also have been seen in smaller metropolitan areas. The percentage distribution of AIDS cases by area of residence in 2001 was 81% from large metropolitan areas and 7% from nonmetropolitan areas. As of 2007 the ten states reporting the highest number of cumulative AIDS cases were New York, California, Florida, Texas, New Jersey, Pennsylvania, Illinois, Maryland, Georgia, and Massachusetts.

The incidence of HIV infection has remained relatively stable, at 40,000 new cases per year, although new methods of estimating HIV incidence currently under investigation suggest that this may be an underestimate. Approximately 80% of AIDS cases have occurred in adult men, 18% in adult women, and just over 1% in children. The proportion of adult women among those infected with HIV has increased over the past several years, with adult women now representing 26% of those living with HIV/AIDS.[2,4] Nearly one half of all people who are infected with HIV in the United States become infected before they turn 30, and the vast majority will die before reaching the age of 45 years. There is a disproportionate rate of infection among minority groups, with African Americans and Hispanics accounting for an ever-increasing proportion of new HIV cases and persons living with AIDS. In 2005, more than 70% of all AIDS cases diagnosed occurred in minority racial or ethnic groups.[4]

The primary risk factors associated with an increased likelihood of acquiring HIV infection include homosexual or bisexual orientation, intravenous drug use, heterosexual exposure to a partner at risk, blood transfusion before 1985, and vertical and horizontal maternal-neonatal transmission. A greater

BOX 130-1 AIDS-DEFINING ILLNESSES*

Laboratory-confirmed evidence of HIV infection *and*

Bacterial infections, multiple or recurrent
Candidiasis of bronchi, trachea, or lungs
Candidiasis of esophagus
CD4+ lymphocyte count of <200 cells/μL
Cervical cancer, invasive
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 month's duration)
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy, HIV related
Herpes simplex: chronic ulcers (>1 month's duration or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 month's duration)
Kaposi's sarcoma
Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex
Lymphoma, Burkitt (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
Mycobacterium tuberculosis of any site, pulmonary, disseminated, or extrapulmonary
Mycobacterium, other species of unidentified species, disseminated or extrapulmonary
Pneumocystis jiroveci pneumonia
Pneumonia, recurrent
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain, onset at age >1 month

*From the Centers for Disease Control: Revised surveillance case definitions for HIV infection among adults, adolescents, and children ages <18 months and for HIV infection and AIDS among children ages 18 months to <13 years—United States, 2008. MMWR: Recommendations and Reports 2008 (RR10), pp 1–8. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710al.htm?s_cid=rr5710al_e. Accessed April 4, 2009.

number of risk factors is associated with a greater likelihood of infection. CDC HIV surveillance data demonstrate significant changes in the distribution of newly acquired HIV cases over the past several years. A relative decrease in newly acquired HIV infection has been documented among homosexual and bisexual men, and a relative increase in incidence of infection has been noted among intravenous drug users and heterosexual contacts. The change in the distribution of AIDS cases in adults and adolescents by mechanism of transmission since the start of the HIV epidemic is shown in Figure 130-1.

During the past several years, the greatest percentage increase in reported AIDS cases has occurred among women (attributed principally to heterosexual exposure from an infected partner), in minority populations, and among children. Because these populations often lack access to primary health services and frequently are underinsured, an emerging trend has been toward increasing use of ED services by patients with HIV infection and AIDS. Surveillance data from centers in Baltimore, Chicago, Atlanta, and New York City indicate HIV seroprevalence rates ranging from 2 to 15%.[5]

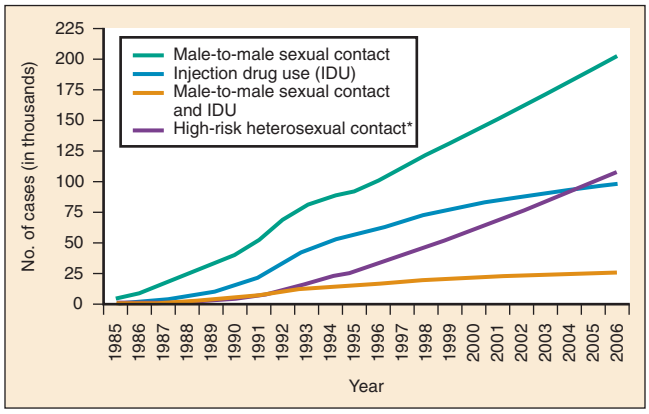

Figure 130-1. Proportions of AIDS cases among adults and adolescents by exposure category and year of diagnosis, 1985 to 2001, United States. (From Centers for Disease Control and Prevention: AIDS Surveillance—Trends [1985–2006]. Available at: http://www.cdc.gov/hiv/graphics/trends.htm.)

PRINCIPLES OF DISEASE

Pathophysiology

HIV is a cytopathic human retrovirus that belongs to the lentivirus subfamily. The two major subtypes of HIV are HIV-1 and HIV-2. HIV-1 is the predominant subtype worldwide and is the cause of AIDS. HIV-2 causes a similar immune syndrome but is rarely seen in the United States being restricted primarily to western Africa.

The HIV virion is composed of a central single-stranded RNA molecule and the enzyme reverse transcriptase. These are surrounded by a core protein and a lipid bilayer envelope that contain virally encoded transmembrane proteins critical for recognition and attachment to target host lymphocytes (predominantly $CD4^+$ cells). HIV-1 has been isolated from a variety of body fluids including blood, serum, semen, vaginal secretions, urine, cerebrospinal fluid (CSF), tears, breast milk, bone marrow, alveolar fluid, synovial fluid, amniotic fluid, and saliva. Only a few modes of transmission have been proved: in semen, vaginal secretions, blood or blood products, and breast milk and transplacental transmission in utero. There have been no instances of transmission by casual contact, although one case report described possible salivary transmission. The HIV virion is extremely labile and easily neutralized by heat and common disinfecting agents such as 50% ethanol, 35% isopropyl alcohol, 0.3% hydrogen peroxide, disinfectant (Lysol), or a 1:10 solution of household bleach (sodium hypochlorite).

HIV selectively attacks cells within the immune system (primarily T_H4 helper cells, but macrophages and monocytes also may be involved), a characteristic that accounts for much of the immunodeficiency it produces in affected persons. HIV-1 transmembrane proteins gp41 and gp120 play a critical role in recognition and attachment of HIV virions to receptors on host lymphocytes. After infection, viral RNA is reverse-transcribed into deoxyribonucleic acid (DNA) by reverse transcriptase, one of the critical enzymes required for HIV replication. The viral genome thus becomes permanently integrated into the host's genome. Once integrated, retroviral DNA may lie dormant, or it may be actively transcribed and translated to produce virally encoded proteins and new HIV virions. HIV protease is another critical retroviral enzyme in the life cycle of the virus, responsible for activation of viral protein precursors into the functional enzymes required for virion infectivity.

Primary HIV exposure is characterized by a transient viremia and a decrease in $CD4^+$ cell counts, followed by establishment of equilibrium between virus and host immunity. A persistent latent period, during which the virus lies dormant in the host genome, can last for years. The "set point" or steady-state viral load level in the blood of the patient allows prediction of long-term clinical outcomes. Lower levels of viremia correlate with longer clinical latency periods. In the later stages of HIV infection, a sudden increase of viremia correlates with a dramatic decrease in $CD4^+$ T lymphocytes. These hematologic changes are followed by the appearance of opportunistic infections or malignancies and ultimately death.

HIV-1 is highly heterogeneous. Multiple genetic subtypes exist in a variety of geographic and sociologic settings. Further genetic diversity exists within individual hosts owing to the highly mutable character of the virus. High error rates, which are associated with reverse transcription, ensure extensive viral diversity, a critical factor in the pathogenesis of infection and ongoing emergence of drug-resistant phenotypes.[6]

Tests for Human Immunodeficiency Virus Infection

General Approach

HIV infection most commonly is established by HIV serologic studies or by detection of antibodies to the virus. Testing involves sequential use of an enzyme immunoassay (EIA) and a Western blot assay. Criteria for positive results are positive results on EIA followed by Western blot assay. EIA detects the binding of specific serum antibodies to HIV antigens that are adherent to a microtiter plate. Western blot assay detects electrophoretically separated viral antigens in the patient's serum. A positive Western blot result requires detection of two of the following: p24, gp41, or gp120/160. Final HIV serology results are reported as positive, negative, or indeterminate. Overall sensitivity and specificity rates for HIV serologic testing are greater than 99.9%.

False-negative HIV test results are accounted for primarily by testing too early, during the "window period" (usually the first several months) of acute infection, after viral transmission but before the appearance of antibodies. Rates of false-negative testing range from 0.3% in high-prevalence populations to less than 0.001% in low-prevalence populations. Ninety-five percent of false-negative test results become positive by 3 months and 98% by 6 months. A less common explanation for false-negative results is seroreversion, which may occur in late-stage disease or in patients on HAART regimens, or in those harboring atypical strains of HIV-1 or with HIV-2 infection. False-positive test results are exceedingly rare (with a frequency of less than 0.0004%); they may occur in several clinical populations, including (1) recipients of transfused blood containing the HIV antibody; (2) children younger than 6 months of age, in whom a positive test result may be caused by transplacentally acquired antibodies; (3) patients with cross-reacting antibodies (e.g., antihepatitis A immunoglobulin M [IgM], antihepatitis B core IgM, antinuclear, anti-smooth muscle, anti-parietal cell, and antimitochondrial antibodies); and (4) patients with cross-reactive human lymphocyte antigens (HLAs) from the H9 cell line or other human retroviruses. In populations with a low prevalence of true-positive results (e.g., heterosexual men or women in low-seroprevalence areas), the frequency of false-positive results (on both EIA and Western blot assay) is increased. This finding has been cited as one of the reasons for not offering indiscriminate HIV screening in the ED.

Indeterminate results are most common with a positive EIA result and a single band (rather than two or three) on Western blot assay. In evaluating an indeterminate result on the latter, the patient's risk profile should be assessed. Low-risk patients with indeterminate results are rarely infected with HIV-1 or HIV-2, and repeat testing usually shows persistence of one band, with the cause rarely established. Referral to an infectious disease specialist and follow-up serologic testing at 3 months are indicated. Patients in higher-risk groups with indeterminate results usually are found to have definitively positive results on Western blot assay 3 or 6 months later and therefore should be counseled to follow appropriate risk-reduction behavior until follow-up definitive testing is completed.

Other methods for detection of HIV infection include detection of virus-specific antigens and assays for HIV nucleic acid. Neither of these techniques is considered superior to routine serologic tests in terms of accuracy, and they should be used only in patients with confusing serologic results requiring clarification; in the ED, the most common situation in which viral detection testing may be considered is in cases of suspected acute retroviral infection. Quantitative plasma HIV RNA assay is most commonly employed and is routinely used for HIV staging and monitoring of response to retroviral therapy. Test results are reported as copies per milliliter, with survival time directly correlated with viral burden. Sensitivity of the various viral detection methods varies with stages of diseases but generally is greater than 99% for DNA polymerase chain reaction (PCR) assay, 90 to 95% for quantitative HIV RNA assay, and 95 to 100% for viral culture of peripheral blood mononuclear cells.

The U.S. Food and Drug Administration (FDA) has approved a number of rapid HIV tests. These tests are easy to use and can be performed at the bedside or in a nearby satellite laboratory using saliva or fingerstick or whole blood specimens. Delivery of results is possible in as little as 10 to 20 minutes. Sensitivity and specificity is approximately 99%. Negative test results can be reported immediately as negative; reactive test results require confirmatory follow-up testing with a Western blot assay and should be reported as reactive. The first test to receive FDA approval is the OraQuick Rapid HIV-1 Antibody Test (OraSure Technologies, Inc., Bethlehem, Pennsylvania). Advantages of rapid test technologies include ease of specimen collection, reduced costs, rapid availability of results, and improved compliance with testing.

Human Immunodeficiency Virus Testing in the Emergency Department

Traditionally it has been thought that serologic testing of patients for HIV infection in the ED is not indicated. With the advent of rapid testing methodologies, the concept of ED testing for HIV infection is being reexamined. This is being driven by a number of factors, including the ease of the testing process, the recognized value of knowing a patient's HIV status if the acute clinical presentation raises suspicion for disease, and the now-widespread recognition that early detection of HIV infection (and early therapeutic intervention) provides a significant health benefit both for individual patients and for the community. Benefits to the infected patient include delaying progression of disease and reducing the risk of opportunistic infections; an important advantage for the community includes decreased disease transmission associated with reduction in high-risk behavior in persons who are aware of their HIV serostatus.

The most recent CDC guidelines for HIV testing, released in 2007, recommend that such testing be performed in health care settings.[7] These guidelines give special emphasis to the

role of the ED, driven largely by multiple studies showing that the ED is the most frequent site of encounter with the health care system for persons with unrecognized HIV infection (representing approximately 30% of all patients infected). Shortly after the CDC guidelines were published, the American College of Emergency Physicians (ACEP) released a corresponding policy statement supporting the availability of HIV testing for evaluation of related acute care conditions, indicating that testing and results should be available in an expeditious and efficient fashion, as with the management of other conditions. With regard to HIV *screening*, the policy suggests that individual institutions need to consider the appropriateness and feasibility of screening based on the particular characteristics of their ED and available resources. A list of important considerations that must be attended to before initiation of such a program is provided in the ACEP statement.[8] For institutions considering establishing ED-based HIV testing and screening programs, the American Hospital Association provides an online guide.[9]

A number of EDs around the country have implemented HIV testing using both rapid and traditional testing approaches.[10-12] Such HIV testing programs have included both routine, broad-based screening and focused testing based on clinical suspicion. Funding for implementation has been supported in part by the CDC as well as by state and local health departments. In spite of some success, barriers to implementing screening (more so than clinically based testing) remain. Most important among these barriers are time constraints, financial burdens, impact of testing on ED crowding, and concerns regarding the responsibility for ensuring follow-up care.[11,13,14]

Emergency physicians need to be aware of state laws and local regulations governing testing. Although separate informed consent or formal pretest counseling is no longer considered mandatory by the CDC,[15] many states have laws requiring informed consent before testing.[16] AIDS is a reportable disease in all 50 states, and HIV infection is reportable in most states. As of 2007, 47 states are conducting confidential name-based HIV infection reporting, based on the 2005 CDC recommendations.[17]

CLINICAL FEATURES

The broad spectrum of disease presentation for HIV-related disorders ranges widely from asymptomatic seropositive status to severe, life-threatening complications of AIDS. Included are a wide variety of opportunistic infections, malignancies, and other HIV-related diseases. Nearly every organ system may be affected by HIV infection and related conditions. Because the differential diagnosis is so broad in scope for many ED presentations, this chapter addresses clinical symptoms, signs, and focused information on some of the more common disorders.

Initial Evaluation of the Human Immunodeficiency Virus–Infected Patient

The initial evaluation and management of the HIV-infected patient consist of rapid and early assessment of stability. Any problems with airway, breathing, and circulation must be promptly identified and appropriate interventions performed. For unstable patients, intravenous access, cardiac monitoring, and administration of oxygen typically are indicated. After initial stabilization, the remainder of the history and physical examination may be conducted.

Relevant elements of the history include information pertinent to the chief complaint, including duration, location, qualities, characteristics, level of distress, and relieving or inciting factors. The past medical history should identify a previous history of similar problems, the time of diagnosis of HIV infection, previous AIDS-defining conditions, recent hospitalizations, past surgical history, current medications, and allergies. The existence of an advance directive may be important historical information, because many HIV-infected patients have expressed opinions about the level of intervention desired in various clinical settings, particularly in critical care settings and at the end of life.

Information regarding potential risk factors for HIV infection may be appropriate to gather in the ED evaluation in patients not known to be HIV-seropositive, particularly in endemic areas. The infection rate may be surprisingly high, even for those patients with presenting complaints not associated with HIV infection. Furthermore, inquiries about risk factors help direct the medical evaluation, remind ED personnel of the potential for occupational exposure to the virus, and afford the opportunity to offer referral for testing and counseling to persons who engage in high-risk behavior. Many cases of early HIV infection may not be detected during ED evaluation because of a low clinical suspicion for the disease, particularly in areas with a low prevalence of AIDS. Although inquiries regarding risk factors may be offensive to some patients, any difficulty usually can be averted by beginning with tactful inquiries about previous HIV testing or risk factors and indicating that these questions are routinely asked in the ED.

After initial stabilization and gathering of historical information, a focused physical examination should be conducted. In elements of the examination relevant to the chief complaint, special attention should be paid to the identification of potentially treatable disorders.

The universal goals of ED management are to rapidly and effectively assess the patient, identify potentially life-threatening disorders, administer urgent interventions, generate an appropriate differential diagnosis, and provide or arrange for appropriate initial therapy, consultation, and disposition.

Stages of Human Immunodeficiency Virus Infection

Several methods of classification and staging of HIV infection have been developed. The Walter Reed classification system is based on clinical and immunologic features. Other classifications are based on $CD4^+$ counts.[18] In 1993, the CDC case definition of AIDS incorporated $CD4^+$ counts of less than 200 cells/μL as an AIDS-defining condition. The median survival time for *untreated* patients with AIDS is 3.7 years for those with $CD4^+$ cell counts less than 200 cells/μL and 1.3 years for those with their first AIDS-defining complication (see Box 130-1).

Primary Human Immunodeficiency Virus Infection

Acute HIV syndrome (acute seroconversion syndrome) commonly follows primary exposure by 2 to 4 weeks and may be associated with nonspecific flulike symptoms and signs such as fever, adenopathy, fatigue, pharyngitis, diarrhea, weight loss, and rash. Additional signs and symptoms such as myopathy, peripheral neuropathy, or other neurologic or immunologic manifestations are less common.[19] These relatively nonspecific problems are seen in approximately 40 to 90% of patients and usually last 1 to 3 weeks. The differential diagnosis of acute HIV infection is broad in scope; considerations mainly include a wide variety of viral illnesses, such as Epstein-Barr virus (EBV) infection and viral hepatitis. Pres-

ence of a rash or mucocutaneous ulcers should raise suspicion for acute HIV seroconversion.

During the acute phase of HIV infection, results of standard HIV testing (enzyme-linked immunosorbent assay [ELISA] antibody testing) usually are negative, because the median time for seroconversion is approximately 2 months. If acute HIV infection is strongly suspected (on the basis of presentation and history of recent exposure), RNA viral load testing can be performed, either in the ED or by referral. Identification of acute HIV is important because HIV viral load is significantly higher during this phase of the illness and the risk of transmission is elevated. No current consensus has emerged among HIV experts, however, regarding the optimal timing and treatment regimen for acute HIV infection. Accordingly, any patient identified as having acute infection should be referred for urgent evaluation by an HIV specialist.

Predictors of Disease Progression

Although the rate of disease progression from initial HIV infection to development of AIDS-defining illnesses varies widely, the average time is 10 to 12 years. Some long-term nonprogressors have remained free of AIDS-defining conditions for more than 20 years. Clinical predictors of more rapid development of clinically significant immunodeficiency include oral candidiasis, oral hairy leukoplakia, dermatomal varicella, lymphadenopathy, and constitutional symptoms.[20,21] The best predictor of immunologic susceptibility to opportunistic infection is the $CD4^+$ cell count.[22] Other laboratory markers of disease progression include neutropenia and plasma HIV-1 RNA determinations.

Complications

Systemic Symptoms and Signs of Human Immunodeficiency Virus Infection

Systemic symptoms and signs such as fever, weight loss, and malaise are common among patients presenting to the ED. The differential diagnosis is lengthy and includes a variety of infectious causes, malignancy, and drug reactions (Box 130-2). Fever is a common presenting complaint in patients with AIDS. Evidence of an infectious cause or other reason for fever should be sought by careful history and physical examination. Initial workup for the cause of fever in an immunocompromised patient may include a complete blood count, electrolytes, comprehensive metabolic panel (CMP), chest radiograph, urinalysis and culture, and blood cultures (aerobic, anaerobic, mycobacterial, and fungal). Additional testing, based on current and past medical history and physical exam, may include stool (for culture, examination for ova and parasites, and Gram's stain), urine (for histoplasmosis and fungal and mycobacterial culture), and induced sputum (for smear fungal and mycobacterial culture) studies; erythrocyte sedimentation rate determination; liver function tests; serum cryptococcal antigen assay; and serologic tests for syphilis, *Toxoplasma*, and *Coccidioides*. In the absence of neurologic signs or symptoms or if no other source of fever is identified, lumbar puncture should be considered after a cranial computed tomography (CT) scan. Two of the most common causes of febrile illness in patients with later-stage HIV are disseminated atypical mycobacterial infections and cytomegalovirus (CMV) infection.

Atypical mycobacteral infections, caused by *Mycobacterium avium* complex or *M. kansasii*, cause disseminated disease in up to 50% of patients with AIDS and usually are associated with $CD4^+$ counts less than 100 cells/μL. Presentation typically includes severe weight loss, diarrhea, and various constitutional symptoms, such as fever, malaise, and anorexia. Anemia is common. Ziehl-Neelsen (acid-fast) stain of stool or other body fluids commonly yields positive findings, and the organism also can be cultured from blood. Treatment for *M. avium* complex infection consists of clarithromyin, 500 mg twice a day, and ethambutol, 15 mg/kg daily. Such regimens often reduce the degree of bacteremia and symptomatology but typically do not eradicate the organism. Clarithromycin or azithromycin should be used for prophylaxis in patients with $CD4^+$ counts below 50 cells/μL.

Disseminated CMV infections typically occur in patients with $CD4^+$ counts below 50 cells/μL. In addition to fever, patients often present with odonophagia, abdominal pain, and diarrhea secondary to esophagitis and colitis. Diagnosis usually requires endoscopy or colonoscopy for biopsy, because culture has poor sensitivity. Complications include gastrointestinal bleeding and perforation. Treatment includes immune restoration with antiretrovirals and a regimen of ganciclovir or foscarnet. Oral ganciclovir is used for prophylaxis.

Some patients with HIV infection and fever or other systemic symptoms may be managed on an outpatient basis if they are not severely immunosuppressed and not systemically ill. Requirements for discharge from the ED include ability to take oral fluids, assurance of timely follow-up including obtaining results of ED-initiated cultures, and capability of providing adequate self-care. Indications for hospital admission include

BOX 130-2 ETIOLOGY FOR SYSTEMIC SYMPTOMS IN HUMAN IMMUNODEFICIENCY VIRUS (HIV)–INFECTED PATIENTS

Infections
Primary HIV infection (e.g., acute retroviral syndrome, HIV wasting syndrome)

Protozoal Infections
Pneumocystis jiroveci pneumonia
Toxoplasmosis
Cryptosporidiosis

Bacterial Infections
Streptococcus pneumoniae infection
Haemophilus influenzae infection
Pseudomonas aeruginosa infection
Salmonellosis
Bacteremia (any organism)

Atypical Bacterial Infections
Mycobacterium avium-intracellulare (MAI) infection
Mycobacterium tuberculosis (MTB) infection

Fungal Infections
Histoplasmosis
Cryptococcosis
Coccidioidomycosis

Viral Infections
Herpes simplex virus infection
Herpes zoster virus infection
Cytomegalovirus infection
Hepatitis virus infections

Noninfectious Processes
Adverse drug reactions

Neoplasms
Kaposi's sarcoma
Lymphoma
Hodgkin's disease

toxic appearance, neutropenia with fever, active bleeding, or other need for urgent diagnosis and treatment. For patients with persistent fevers, in whom one or more of the discharge criteria are not met, hospitalization is warranted.

Pulmonary Involvement

Pulmonary manifestations of HIV infection are among the most common reasons for ED visits among patients with AIDS. Careful consideration is mandated to establish the diagnosis and initiate early treatment. The differential diagnosis of respiratory involvement is broad in scope; considerations include bacterial infections (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Chlamydia pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Mycobacterium tuberculosis* [MTB], *Mycobacterium avium-intracellulare* [MAI] complex), fungal infections (e.g., *Pneumocystis jiroveci* [formerly *Pneumocystis carinii*], *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Aspergillus fumigatus*, *Blastomyces dermatitides*), viral infections (e.g., cytomegalovirus, adenoviruses), protozoal infections (e.g., *Toxoplasma gondii*), malignancies (e.g., Kaposi's sarcoma, carcinoma, lymphoma), and others (e.g., lymphocytic interstitial pneumonitis, pulmonary hypertension, pulmonary embolism).

Occurrence of specific pulmonary infections often is related to $CD4^+$ counts. In patients with pulmonary involvement and $CD4^+$ counts greater than 500 cells/μL, encapsulated bacteria, tuberculosis, and malignancies are common. With lower $CD4^+$ counts, PCP, infections due to atypical mycobacteria, fungal infections, cytomegalovirus infection, lymphoma, lymphoproliferative disorders, and Kaposi's sarcoma are seen with increasing frequency.

Patients with fever and a productive cough are likely to have a bacterial pneumonia, whereas a nonproductive cough is more likely to accompany PCP, other fungal infections, or neoplasm. Hemoptysis often is associated with pneumococcal pneumonia and tuberculosis. Fulminant respiratory failure is most likely to be caused by *Pneumocystis jiroveci* (the agent of PCP) or CMV.

Diagnostic evaluation of patients with HIV infection and suspected pneumonia should routinely include pulse oximetry, chest radiography, and complete blood count. Additional testing based on the stage of disease and clinical presentation may include arterial blood gas (ABG) analysis, serum lactate dehydrogenase determination, assays for serum cryptococcal antigen and urine *Histoplasma* antigen, and induced sputum specimen studies including Gram stain, acid-fast bacillus (AFB) smear, and Gomori, Giemsa, or immunofluorescent antibody (IFA) staining for *Pneumocystis jiroveci*. Blood culture specimens should be obtained in the ED from all HIV-infected patients with suspected pneumonia; this component of the evaluation becomes increasingly important in patients with later-stage disease. Blood culture collection, however, should not delay the initiation of antimicrobial therapy.

Although radiographic findings in many pulmonary complications may be nondiagnostic, certain patterns may be suggestive of specific disorders. A focal infiltrate on the plain chest film often suggests bacterial pneumonia, whereas a diffuse interstitial or perihilar, granular pattern is associated with PCP. PCP is suggested by increased serum lactate dehydrogenase and hypoxia (especially exercise-induced), which may be more severe than expected from radiographic findings. Hilar adenopathy with diffuse pulmonary infiltrates suggests cryptococcosis, histoplasmosis, mycobacterial infection, or neoplasm. Kaposi's sarcoma (KS) can manifest with cough, fever, and dyspnea and may mimic PCP on the chest radiograph. Table 130-1 lists common radiographic findings and associated conditions in the HIV-infected patient.

Table 130-1 Chest Radiographic Abnormalities: Differential Diagnosis in the AIDS Patient

FINDING	POTENTIAL ETIOLOGIES
Diffuse interstitial infiltration	*Pneumocystis jiroveci* Cytomegalovirus *Mycobacterium tuberculosis* *Mycobacterium avium* complex Histoplasmosis Coccidioidomycosis Lymphoid interstitial pneumonitis *Mycoplasma pneumoniae*
Focal consolidation	Bacterial pneumonia *Mycoplasma pneumoniae* *Pneumocystis jiroveci* *Mycobacterium tuberculosis* *Mycobacterium avium* complex
Nodular lesions	Kaposi's sarcoma *Mycobacterium tuberculosis* *Mycobacterium avium* complex Fungal lesions Toxoplasmosis
Cavitary lesions	*Pneumocystis jiroveci* *Mycobacterium tuberculosis* Bacterial infection Fungal infection
Pleural effusion	Kaposi's sarcoma (small effusion may be associated with any infection)
Adenopathy	Kaposi's sarcoma Lymphoma *Mycobacterium tuberculosis* *Cryptococcus*
Pneumothorax	Kaposi's sarcoma
Normal radiograph	Histoplasmosis (40%) *Pneumocystis jiroveci* (20%) *Mycobacterium tuberculosis* Cryptococcosis Many other disease entities

As with all disease processes, ED management of pulmonary complications must first include stabilization with appropriate support of airway, breathing, and circulation. Definitive airway management may be indicated in severe cases. Volume repletion or pressors, or both, may be indicated for hypotension. Other treatment measures should include administration of supplemental oxygen and volume repletion if indicated. If the diagnosis can be ascertained or is strongly suspected, specific treatment should be instituted while the patient is in the ED, particularly if PCP is suspected. If the symptoms are of new onset or there has been a change from previous status, hospitalization should be considered. Decisions regarding patients with known pulmonary involvement are based on comparison with baseline status, the effectiveness of ongoing or previous treatment, and the individual's ability to obtain outpatient follow-up observation (see "Disposition"). The Pneumonia Outcomes Research Team (PORT) study did not include HIV-infected patients, and most experts suggest that hospital admission should be more readily considered for patients with HIV infection and pneumonia. Staging systems for predicting death from HIV-associated pneumonia found that clinical factors associated with increased mortality include the presence of neurologic symptoms, respiratory rate of 25 breaths per minute or less, and creatinine level greater than 1.2 mg/dL.[22]

Bacterial infections are the most frequent type of pulmonary infection among patients with AIDS and commonly are caused

by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and numerous other organisms.[23] Infections with *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* are relatively less common. *P. aeruginosa* is a more common pathogen in later stages of AIDS. Presentations of bacterial pneumonia may be typical or atypical in symptoms, duration, and severity. Severely ill patients with pneumonia being managed in an ICU should be treated with linezolid or vancomycin, an antipseudomonal agent, in addition to a macrolide or respiratory fluoroquinolone.

Pneumocystis Pneumonia

PCP is one of the most common opportunistic infections in AIDS. More than 80% of patients with AIDS acquire PCP at some time during their illness, and it is the initial opportunistic infection in many cases. As noted earlier, PCP is caused by the organism *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*[24]—the original basis for the "PC" in *PCP*, which remains in use to refer to *Pneumocystis* pneumonia). Although *P. jiroveci* traditionally is classified as a protozoan, its morphology has been suggested to closely resemble that of a fungus.[25] The incidence of PCP has declined since the widespread use of HAART.[26]

Patients typically present with an insidious cough (often nonproductive), dyspnea, unexplained fever for longer than 2 weeks, chest pain, and fatigue. The chest radiograph commonly shows a diffuse interstitial infiltrate but also may be normal in appearance or reveals asymmetry, nodules, cavitation, or bullae.[27] Considerations in the differential diagnosis include viral, bacterial, mycobacterial, fungal, and protozoal pneumonias, as well as malignancies. The more common causes to be considered in the differential diagnosis are shown in Box 130-2. Negative findings on the chest radiograph are reported in up to 20% of patients ultimately found to have PCP.[28] In situations in which a high clinical suspicion exists for PCP, chest CT should be performed; CT findings frequently are suggestive of PCP. Gallium scanning of the chest also offers improved sensitivity over that of chest radiography, but this modality generally is not available in the ED and is associated with a high false-positive rate. Serum LDH often is elevated in patients with PCP (sensitivity of approximately 90%) but, again, has poor specificity so it cannot be used for definitive diagnosis.

In the ED, a presumptive diagnosis of PCP can be made in a patient with later-stage HIV ($CD4^+$ count less than or in the range of 200 cells/μL) with unexplained hypoxia when other causes (e.g., pulmonary embolism) have been eliminated. The organism cannot be grown in the laboratory, so diagnosis relies on indirect IFA staining using monoclonal antibodies. Studies using induced sputum (often not practical to obtain in the ED) have a relatively low sensitivity. Accordingly, bronchoscopy (bronchoalveolar lavage, brush biopsy, or transbronchial biopsy) often is required for establishing the diagnosis. Establishment of a definitive diagnosis is not necessary before the initiation of treatment. Treatment should begin as early as possible with 15 to 20 mg/kg per day of trimethoprim and 75 mg/kg per day of sulfamethoxazole (TMP-SMX), given either orally or intravenously in two or three daily divided doses for a total of 21 days (e.g., two Bactrim DS tablets every 8 hours). Indications for intravenous therapy include tenuous respiratory status, an alveolar-arterial gradient above 45 mm Hg, and Pao_2 below 60 mm Hg. Other therapeutic agents that can be used with PCP include pentamidine isethionate, dapsone, clindamycin plus primaquine, atovaquone, and trimetrexate. Steroid treatment (prednisone 40 mg PO, twice daily for five days with a 3-week taper) is recommended for patients with a Pao_2 less than 70 mm Hg, or an alveolar-arterial gradient greater than 35 mm Hg.[29] Most patients (60 to 80%) respond to therapy, although *Pneumocystis* persists in the lungs of two thirds of patients. All patients requiring steroids should be hospitalized because clinical status in those with PCP typically will worsen a few days after the initiation of therapy.

Adverse effects of TMP-SMX occur in up to 65% of patients with AIDS and are 20 times more common than in the general population (Table 130-2); such effects generally become apparent after 7 to 14 days of therapy. The most common adverse effects are nausea, vomiting, rash, fever, neutropenia, thrombocytopenia, hyponatremia, and hepatitis. Pentamidine can cause nausea, vomiting, diarrhea, neutropenia, hypoglycemia, hyperglycemia, renal impairment, hepatic toxicity, and orthostatic hypotension.[30] Because sterile abscesses may develop at the injection site, intravenous infusion is preferred. Prophylaxis (with Bactrim DS, one tablet by mouth once daily) against PCP may be an important step in preventing reinfection and is recommended for patients with $CD4^+$ cell counts below 200 cells/μL.[31]

The mortality rate for PCP-associated respiratory failure is close to 60%. Patients requiring ventilatory support should be maintained on low tidal volumes and plateau pressures, because PCP is associated with an increased risk of pneumothorax. The presence of a pneumothorax in a patient with a low $CD4^+$ count should be presumed to be caused by PCP, although KS, intravenous drug use, toxoplasmosis, and viral, fungal, and mycobacterial infections also can cause pneumothoraces. Asymptomatic patients with a small pneumothorax (involving less than 20% of lung volume) may be treated with observation or insertion of a Heimlich valve.

Mycobacterium Tuberculosis Infection

The incidence of MTB infection in HIV-infected patients has increased dramatically, and it is estimated that over 10 million patients worldwide are co-infected with HIV and tuberculosis.[32] HIV-infected patients have an estimated 50- to 200-fold increased risk of acquiring tuberculosis over the general population.[33] The increase in tuberculosis among the HIV-infected population is thought to be due to a number of factors, including increased risk of reactivation of latent infection, high rates of infection after exposure, overlap in at-risk groups, and rapid progression to clinically significant disease. Tuberculosis may be a very early manifestation of AIDS.

Common presenting signs and symptoms include fever, cough, and hemoptysis, but in patients with immunosuppression, clinical manifestations are more atypical and extrapulmonary findings more common. Classic radiographic abnormalities are upper lobe alveolar lesions with cavitation accompanied by pleural effusions and mediastinal adenopathy.[34] Findings may vary considerably, however, and atypical features and absence of radiographic abnormalities are more common among patients with lower $CD4^+$ cell counts.[35] Central nervous system (CNS), bone, visceral, skin, pericardial, eye, pharynx, and lymph node involvement also may occur.

The diagnosis of tuberculosis is based on a number of factors, including risk of infection, clinical presentation, direct examination of patient specimens, and identification of mycobacteria from cultures.[36] Because a definitive diagnosis cannot be made in the ED, and the disease is transmitted by the aerosol route, isolation and hospital admission are indicated for any patient with suggestive clinical factors. Definitive laboratory diagnosis can be made by a nucleic acid amplification test (NAAT), an AFB smear, or culture evaluation of induced sputum specimens or samples obtained on bronchoscopy. NAAT has a higher sensitivity than AFB smear, and bronchoscopy or tissue biopsy a higher yield than induced sputum.

Table 130-2 Common Drug Reactions in HIV-Infected Persons*

	FEVER	RASH	N/V	DIARRHEA	H/A	ΔMS	NEUROPATHY	↑ LFT	↓ WBC	↓ HCT	↓ PLT	OTHER
Acyclovir		X	X	X								Vertigo
Amphotericin	X		X		X				X	X	X	Nephrotoxicity
Atovaquone	X	X	X	X	X				X	X		
Azithromycin		X	X	X	X							
Clarithromycin			X	X	X							
Clindamycin		X										
Clotrimazole			X	X								
Dapsone	X	X	X		X				X	X		Hepatitis
Didanosine		X	X	X	X	X	X					Pancreatitis
Fluconazole		X	X	X	X			X				
Foscarnet	X		X	X						X		Nephrotoxicity, seizures
Ganciclovir	X		X	X					X	X		
Ibuprofen		X	X	X				X	X	X		
Indinavir		X	X		X							Nephrolithiasis
Isoniazid	X	X	X				X	X	X	X	X	Hepatitis
Itraconazole		X	X	X	X			X				
Ketoconazole			X	X				X				
Lamivudine	X		X	X	X		X					Cough
Narcotics			X			X						
Pentamidine		X							X	X		Metallic taste
Pyrimethamine									X	X		
Rifabutin		X	X					X	X		X	Skin discoloration
Ritonavir			X	X	X							Paresthesias
Saquinivir		X	X	X								
TMP-SMX	X	X	X					X	X		X	Hepatotoxicity, ↓K
Zalcitabine	X	X	X	X	X		X					
Zidovudine	X	X	X	X	X	X			X	X		

*This table represents only a partial list of adverse drug reactions. An authoritative source should be consulted whenever adverse drug reactions are suspected.

Purified protein derivative (PPD) skin testing generally is not helpful, particularly in patients with more advanced immunosuppression, because negative PPD test results are common among those infected. Dissemination of pulmonary infection results in miliary tuberculosis, which can affect nearly every organ system.

Treatment of patients with suspected tuberculosis should be determined in conjunction with an infectious disease specialist, taking into consideration local resistance as well as individual susceptibility tests. Patients with AIDS found to have tuberculosis should receive a four-drug regimen consisting of isoniazid, rifampin, pyrazinamide, and ethambutol, for 6 months.[37,38] Second-line agents include ciprofloxacin, ofloxacin, kanamycin, amikacin, capreomycin, ethionamide, cycloserine, and para-aminosalicylic acid (PAS). Multidrug-resistant tuberculosis strains, resistant to multiple pharmacologic agents including isoniazid and rifampin, remain a concern.[39] Empirical treatment for tuberculosis should be provided for HIV-infected persons with close contact with a patient with active tuberculosis.[40] All HIV-infected patients with a positive result on PPD testing should receive tuberculosis prophylaxis with a regimen of isoniazid plus pyridoxine or rifampin plus pyrazinamide. Steps toward prevention of tuberculosis and its spread include the use of HAART, early identification of tuberculosis, early initiation of multidrug therapy, the use of respiratory isolation, and the use of personal respiratory protection devices.

Other Pulmonary Complications

Fungal pulmonary infections other than PCP may be seen in patients with AIDS. Such infections may include cryptococcosis, histoplasmosis, coccidioidomycosis, aspergillosis, nocardiosis, and blastomycosis.[41] *Cryptococcus neoformans* is the most common fungal pathogen in patients with AIDS after *Pneumocystis jiroveci*, typically causing infection in patients with $CD4^+$ counts less than 100 cells/μL. Radiographic findings often are nonspecific and may include consolidation, reticulonodular infiltrates, and nodules. Diagnosis is with serum cryptococcal antigen assay. Geographic regions with identified predilections for infection with specific pathogens include the eastern and central United States for *Histoplasma*, the south central and central United States for *Blastomyces*, and the southwestern United States for *Coccidioides*. Each of these pathogens is seen more commonly in late-stage HIV disease. In patients with cavitary lesions on chest radiographs, aspergillosis as well as tuberculosis and methicillin-resistant *Staphylococcus aureus* infection should be suspected.

Viral respiratory infections are common among HIV-infected patients. CMV infection is the most frequent, typically occurring with advanced immunosuppression. Radiographic findings may include alveolar consolidation or ground-glass opacities.

Pulmonary malignancies include Kaposi's sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease, and bronchogenic carcinoma. Kaposi's sarcoma typically is associated with hilar

peribronchovascular thickening, lower lobe reticulonodular opacities, adenopathy, pleural effusion, or focal consolidation.[42] Pulmonary Kaposi's sarcoma is treated with cytotoxic agents and HAART. Lymphoproliferative disorders also may have a pulmonary presentation among HIV-infected patients. Such disorders include lymphocytic interstitial pneumonia, nonspecific interstitial pneumonia, and bronchiolitis obliterans.

Patients hospitalized with pulmonary involvement in whom the diagnosis cannot be determined may require bronchoscopy, bronchial lavage, and possibly biopsy. If the clinical probability of PCP is high, treatment should begin before diagnostic bronchoscopy.

Neurologic Involvement

Neurologic diseases are the initial manifestation of AIDS in 10 to 20% of patients. The frequency of neurologic complications increases over the course of HIV infection, with cross-sectional studies showing a 75 to 90% prevalence of neurologic disorders in patients with AIDS.[43] The overall incidence rates of HIV-associated neurologic diseases and CNS opportunistic infections have been decreasing since the introduction of HAART, although this trend is expected to change as resistance to antiretroviral drugs emerges.[44]

Neurologic complications in the HIV-infected patient may be caused by both direct effects of HIV infection on the CNS and opportunistic infections and neoplasms occurring as a result of immunosuppression. In the early stages of HIV infection, aseptic meningitis, herpes zoster radiculitis, and inflammatory demyelinating polyneuropathy are common. Later stages of HIV infection are associated with cognitive dysfunction, dementia, opportunistic infections, cancers, and sensory neuropathies. The most common AIDS-defining neurologic complications are HIV encephalopathy (dementia), *C. neoformans* infection, toxoplasmosis, and primary CNS lymphoma. Less common CNS complications include bacterial meningitis, histoplasmosis (usually disseminated), CMV infection, progressive multifocal leukoencephalopathy, herpes simplex virus (HSV) infection, neurosyphilis, and tuberculosis. Noninfectious CNS processes include CNS lymphoma, cerebrovascular accidents, and metabolic encephalopathies.

Clinical presentations in patients with serious neurologic complications can be nonspecific, making the diagnosis and disposition challenging. The most common clinical manifestations of CNS pathology are seizures, meningismus, focal neurologic deficits, altered mental status, and headache (new or persistent). Infection accounts for a majority of neurologic disorders and most often is accompanied by fever.

Patients with $CD4^+$ cell counts greater than 200 cells/μL who present with fever and meningismus in the absence of focal neurologic deficits should have an immediate lumbar puncture performed. For those with focal deficits or new seizures, neuroimaging is recommended first, followed by lumbar puncture if neuroimaging is unrevealing. For patients with altered mental status or headache, diagnostic evaluation should proceed as in the non-HIV-infected population, with neuroimaging and lumbar puncture reserved for those cases in which another cause for the symptoms is not identified or with a clear indication for workup (e.g., patient complaint of "the worst headache of my life").[44] For patients with $CD4^+$ cell counts less than 200 cells/μL, a more aggressive approach is advocated, with any of the aforementioned findings demanding emergent imaging, usually followed by lumbar puncture[45,46] (Fig. 130-2).

Generally speaking, for those CNS processes that require immediate identification, CT without contrast is considered adequate.[47,48] If the entire ED evaluation is unrevealing, more advanced diagnostic imaging should be pursued immediately, usually in an inpatient setting, if the patient's symptoms are severe or if new neurologic findings are present. For all other cases, close follow-up is indicated with the patient's primary provider, because it has been demonstrated that more subtle lesions may be identified by contrast CT scan or magnetic resonance imaging (MRI). Cerebrospinal fluid (CSF) analysis should include determination of opening and closing pressures, cell count, measurement of glucose and protein, Gram's stain, and bacterial, viral, and fungal cultures. Testing for toxoplasmosis and cryptococcal antigens and coccidioidomycosis titer also are appropriate, particularly in patients with later-stage disease. A prudent measure is to direct the laboratory to hold excess CSF for further testing if the preliminary workup is unrevealing.

HIV Encephalopathy

HIV encephalopathy, or *AIDS dementia complex*, occurs in up to one third of patients with HIV, and is the initial manifestation of AIDS in 3% of affected adults.[43] It is a progressive process caused by direct HIV infection and commonly is heralded by impairment of recent memory or subtle cognitive deficits, such as difficulty concentrating. Traditionally, symptoms are expected to occur in patients with $CD4^+$ counts less than 200 cells/μL, although since 1996, increasing numbers of cases are being seen in patients with $CD4^+$ counts greater than 200 cells/μL.[3,49] Early stages of dementia may be easily confused with depression, the effects of psychoactive substances, or anxiety disorders. Deficits become more debilitating in later stages of disease and can include more obvious changes in mental status, seizures, frontal release signs, and hyperactive deep tendon reflexes; in such cases, physical examination usually reveals the hallmarks of advanced AIDS, including wasting, alopecia, generalized dermatitis, and lymphadenopathy. AIDS dementia is a diagnosis of exclusion: Even among patients with AIDS presenting to the ED with an established diagnosis of AIDS dementia, the appearance of progressive signs or symptoms requires immediate further evaluation to rule out other CNS processes. Neuroimaging findings in patients with HIV encephalopathy typically show atrophy and diffuse deep matter hyperintensities; MRI may reveal patchy punctate lesions in the white matter. Lumbar puncture findings typically are normal. Controlled trials in adults and children with HIV dementia have demonstrated benefit of high-dose zidovudine.[49]

Cryptococcus Neoformans Infection

C. neoformans is the agent of a fungal CNS infection that causes either focal cerebral lesions or diffuse meningoencephalitis. It occurs in up to 10% of patients with HIV infection but most commonly in those with $CD4^+$ counts less than 100 cells/μL. The most frequent initial symptoms are fever and headache, often accompanied by nausea and vomiting. Less frequent manifestations are visual changes, dizziness, seizures, and cranial nerve deficits.[50] The brainstem and basal ganglia are typical locations; high intracranial pressure and sudden clinical deterioration from herniation are relatively common. The mortality rate approaches 30%.

Patients with *C. neoformans* infection usually have no significant changes on CT. Definitive diagnosis relies on finding cryptococcal antigen in the CSF, which is nearly 100% sensitive and specific; other diagnostic tests include India ink staining (60 to 80% sensitive), fungal culture (95% sensitive), and serum cryptococcal antigen (95% sensitive). All patients with a positive result on serum cryptococcal antigen assay should undergo lumbar puncture to rule out neurologic involvement.

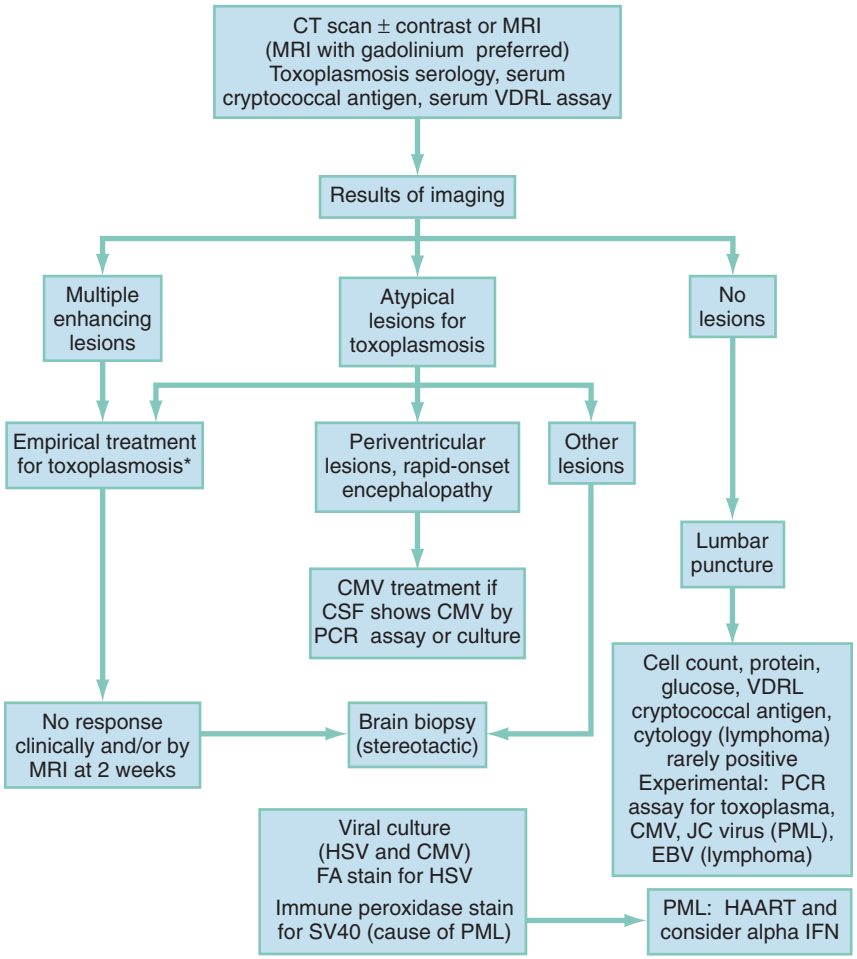

Figure 130-2. Approach to the evaluation of patients presenting to the emergency department with advanced HIV disease plus altered mental status, new-onset seizures, headache (severe or persistent), or focal neurologic deficits. CMV, cytomegalovirus; CSF, cerebrospinal fluid; CT, computed tomography; EBV, Epstein-Barr virus; FA, fluorescent antibody; HAART, highly active antiretroviral therapy; HSV, herpes simplex virus; IFN, interferon; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PML, progressive multifocal leukoencephalopathy; SV40, simian virus 40; VDRL, Venereal Disease Research Laboratory. (Modified from McArthur J, Bartlett JG: Headache in patients with AIDS. In Bartlett JG [ed]: 1999 Medical Management of HIV Infection. Baltimore, Port City Press, 1999, p 333.)

*Serology for *Toxoplasma gondii* is positive 85–90% with toxoplasmic encephalitis. Clinical response to empirical treatment is anticipated within 1 week. Negative serology, atypical presentation, and/or delayed clinical response should prompt early biopsy.

Additional findings associated with cryptococcal infection include elevated CSF opening pressure and a mononuclear pleocytosis. Treatment requires hospital admission for administration of intravenous amphotericin B (0.7 mg/kg per day) plus 5-flucytosine (100 mg/kg per day) for 2 weeks, followed by oral fluconazole (400 mg per day) for 8 weeks or until the CSF is sterile. The most clinically significant adverse effect of treatment for cryptococcal meningitis is bone marrow suppression due to flucytosine; amphotericin B also may cause fever and renal dysfunction. After successful treatment, chronic suppressive therapy with lower doses of oral fluconazole is indicated because of the high relapse rate (approximately 50%). This therapy can be discontinued in patients with immune reconstitution.

Toxoplasma Gondii Infection

T. gondii is the most common cause of focal intracranial mass lesions in patients with HIV infection, with an incidence of 3 to 4%.[43,49] In most cases, symptomatic disease is a result of reactivation of latent infection. Common signs and symptoms include headache, fever, altered mental status, and seizures. Focal neurologic deficits are found in up to 80% of cases. Serologic testing is not useful, because up to 30% of the U.S. population has antibodies to *T. gondii*. Diagnosis most often is made by the presence of multiple subcortical lesions on CT. Noncontrast CT often is used as the initial study in the ED, because addition of contrast has been shown to be of marginal value in patients with completely normal findings on noncontrast CT scans.[48] In those patients with suspicious lesions, or those with clinical findings strongly suggestive of a pathologic process but equivocal or negative findings on noncontrast scans, a contrast CT or MRI study may be helpful. In the presence of contrast, toxoplasmosis lesions are ring-enhancing with surrounding edema. MRI is considered even more sensitive than contrast CT in delineating the extent of lesions but usually is not indicated in the ED setting.[51]

Clinical and radiologic features often cannot reliably distinguish CNS toxoplasmosis from a wide variety of other potential causative disorders (e.g., lymphoma, cerebral tuberculosis, fungal infections, progressive multifocal leukoencephalopathy, CMV infection, KS, hemorrhage). Toxoplasmosis more typically is characterized by a greater number of lesions with a predilection for the basal ganglia and corticomedullary area, whereas lymphomas more often are singular lesions located in the periventricular matter or corpus callosum. Tuberculosis is characterized by an inflammatory appearance on the CT scan, with a thick isodense exudate filling the basal cisterns.

Patients with suspected toxoplasmosis should be hospitalized and treated with pyrimethamine (200 mg loading dose, then 50 to 75 mg/day) plus sulfadiazine (4 to 6 g/day). Folinic acid (leucovorin, 10 mg/day) should be added to reduce the incidence of pancytopenia. Alternative agents to sufadiazine include sulfisoxazole, clindamycin, azithromycin, atovaquone,

or doxycycline and often are required due to the relatively high frequency of side effects associated with sulfadiazine. Dexamethasone (4 mg IV) may be used in cases with the radiographic finding of midline shift, critically elevated intracranial pressure (ICP), or clinical deterioration. Seizure prophylaxis is not recommended. Bactrim is indicated for chronic suppressive therapy after initial treatment as well as for prophylaxis in patients with a positive result on serologic testing and a $CD4^+$ cell count less than 100 cells/μL. Failure to respond to treatment suggests an alternate diagnosis, which may necessitate biopsy.

Primary Central Nervous System Lymphoma

A previously rare disorder, primary CNS lymphoma occurs in up to 3% of patients with HIV infection, typically in those with $CD4^+$ cell counts less than 50 cells/μL. Incidence has decreased slightly since 1996 with the introduction of HAART.[49] Primary CNS lymphomas originate from B cells that express Epstein-Barr virus (EBV). Patients present with headache, aphasia, memory loss, hemiparesis, or seizure. Diagnosis usually is based on CT findings, which show hyperdense or isodense round or multiple lesions that enhance with contrast, and have a predilection for the periventricular region. Differentiation from toxoplasmosis can be challenging and often is made after failure to respond to therapy for that infection. PCR assay for EBV is a helpful diagnostic adjunct, but definitive diagnosis often necessitates biopsy. Prognosis for lymphoma is poor, with median survival time of less than 1 month. Life expectancy may be extended to several months with whole-brain irradiation along with corticosteroids and chemotherapy.[49]

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy occurs in approximately 1 to 3% of patients with AIDS and is caused by reactivation of the polyomavirus (JC virus). The most common presenting features are weakness, speech disturbances, cognitive dysfunction, and headaches. CT or MRI scans show hypodense white matter disease. JC virus PCR assay is approximately 80% sensitive. Progressive multifocal leukoencephalopathy carries a poor prognosis unless immune reconstitution can occur.

Tuberculosis Meningitis

Mycobacterium avium-intracellulare (MAI) infection is the most common cause of tuberculosis meningitis; it occurs in less than 1% of patients with AIDS and may be associated with intracranial abscesses or spinal cord absesses. CT findings in MAI infection may suggest toxoplasmosis. Because findings on CSF analysis may be negative, definitive diagnosis often requires brain biopsy. Four-drug therapy for at least 9 months is required for cure.[49]

Human Immunodeficiency Virus Neuropathy

HIV infection also is associated with a variety of disorders of the peripheral nervous system. These disorders rarely are emergent but necessitate appropriate referral. The most common peripheral nervous system disorder is HIV neuropathy, which occurs in up to 50% of HIV-infected patients and is characterized by painful sensory symptoms in the feet. Treatment in the ED should be directed toward analgesia. Ibuprofen may be used for first-line therapy, although narcotics may be required in more severe cases. Amitriptyline and phenytoin have been shown to be helpful but should be used judiciously because of their potential for causing delirium in patients with concurrent HIV dementia.

Gastrointestinal Involvement

Most patients with AIDS have gastrointestinal signs or symptoms at some time during the course of their illness. The most common clinical manifestations are diarrhea, weight loss, malabsorption, abdominal pain, bleeding, esophageal symptoms, and hepatobiliary symptoms.[52] Nonspecific findings may include nausea, vomiting, and abdominal pain as common adverse effects of antiretroviral therapy.[53] Evaluation for a specific causative disorder often is difficult until objective studies are performed. More than one source of infection often is present, which may further complicate the diagnosis. Treatment in the ED focuses on supportive care, fluid and electrolyte repletion, and obtaining appropriate studies for further investigation.

Oropharynx

Oral involvement is common in AIDS and may manifest as a variety of problems, including fungal infections (oral candidiasis, histoplasmosis, cryptococcosis, penicillinosis), viral lesions (herpes simplex, herpes zoster, cytomegalovirus, hairy leukoplakia, papillomavirus infection), bacterial lesions (periodontal disease, necrotizing stomatitis, tuberculosis, *Mycobacterium avium* complex [MAC], bacillary angiomatosis), neoplasms (Kaposi's sarcoma, lymphoma, Hodgkin's lymphoma), and autoimmune or idiopathic lesions (salivary gland disease, aphthous ulcers). Presence of oral lesions may be an indicator of disease progression.[54]

Oral candidiasis affects more than 80% of patients with AIDS. *Candida albicans* infection, the most common fungal infection in HIV-infected patients, typically involves the tongue and buccal mucosa and may be asymptomatic. Symptoms may include soreness, burning, and dysphagia. Candidiasis can be distinguished from hairy leukoplakia by its characteristic whitish, lacy plaques, which are easily scraped away from an erythematous base. Any of three forms of candidiasis may be seen: pseudomembranous candidiasis (thrush), erythematous candidiasis, and angular cheilitis. Microscopic examination with a potassium hydroxide smear can confirm the diagnosis in the ED. Most oral lesions can be managed symptomatically on an outpatient basis. Preferred treatment is with clotrimazole troches, 10 mg, PO, five times daily for 14 days. Other treatment options include nystatin vaginal tablets, one tablet dissolved slowly in the mouth four times daily, and nystatin pastilles, two dissolved in the mouth five times daily. Systemic therapy with fluconazole, ketoconazole, or itraconazole may be used for resistant lesions.

Hairy leukoplakia also is commonly seen, typically manifesting as white, corrugated or filiform, thickened lesions on the lateral aspects of the tongue. Because it often is asymptomatic, therapy is not necessary, but when indicated, treatment is with acyclovir, 800 mg PO five times a day for 2 to 3 weeks.

Painful oral and perioral ulcerations may be caused by HSV. HSV infection can be diagnosed in the ED by the identification of multinucleated giant cells in scrapings of the lesions. Definitive diagnosis is by culture. Therapy is with acyclovir, 400 mg PO three times daily for 7 to 10 days. MAC also may cause painful oral ulcerative lesions. Diagnosis is by acid-fast stain. Oral Kaposi's sarcoma may appear as nontender, well-circumscribed, slightly raised, violaceous or erythematous lesions anywhere in the oropharynx. Definitive diagnosis requires biopsy. Treatment may include surgical excision, localized chemotherapy, sclerosing agents, or radiation therapy.

Periodontal disease, including gingival erythema and necrotizing periodontal disease, may be seen in up to 10% of

patients. Outpatient treatment, including local irrigation and mouth rinses and oral antibiotics such as amoxicillin-clavulanate or clindamycin, may be instituted. Dental follow-up care is essential.

Aphthous ulcerations, often painful and recurrent, are small crateriform ulcers with white to yellow membranes surrounded by an erythematous ulcer. The etiology is unknown but is thought to involve immune deficiency. Other potential causes of ulcerations, such as fungal or mycobacterial infection, HSV or CMV infection, and lymphoma, should be excluded. Aphthous ulcers usually respond to topical steroids, such as 0.05% flucinomide ointment mixed 50-50 with an oral topical anesthetic such as benzocaine preparations (e.g., Orabase).

Esophagus

In HIV infected patients with dysphagia or odynophagia and a $CD4^+$ count greater than 200 cells/μL, non-HIV-related causes of esophagitis, such as gastroesophageal reflux disease or medications, must be considered. In patients with a $CD4^+$ count below 200 cells/μL, *Candida* is responsible for 50 to 70% of esophagitis cases. Other etiologic disorders include HSV and CMV infection, Kaposi's sarcoma, *Mycobacterium avium* complex disease, and reflux esophagitis, as well as idiopathic esophagitis.

The most cost-effective approach to the evaluation of patients with esophageal complaints is to initiate empirical therapy with fluconazole (100 to 200 mg PO daily for 2 to 3 weeks). Alternative agents include clotrimazole, ketoconazole, and itraconazole. Endoscopy, fungal stains, viral cultures, and occasionally biopsy may be required to definitively establish diagnosis in nonresponders. On endoscopy, *Candida* infection is associated with an ulcerative pattern with plaques separated by normal mucosa compared with herpes, which typically produces "punched-out" ulcerations without plaques.

Relapses are common after cessation of treatment, and intravenous amphotericin B is recommended in these cases. Disseminated candidiasis is managed with intravenous amphotericin B and flucytosine. Fluconazole has been shown to be effective for prophylaxis against fungal infections in patients with a $CD4^+$ count less than 100/μL, although survival is unaffected by prophylactic therapy.[55]

Diarrhea

Diarrhea is the most common gastrointestinal complaint in AIDS, occurring in 50 to 90% of patients. Diarrhea can vary in severity, ranging from a few loose stools per day to massive fluid loss with prostration, fever, chills, and weight loss. Medication side effects should be considered, because use of antiretroviral agents is associated with a high incidence of gastrointestinal adverse effects. Potential pathogens include parasites (*Cryptosporidium parvum*, *Enterocytozoon bieneusi*, *Isospora belli*, *Giardia lamblia*, *Entamoeba histolytica*, *Microsporidia*, *Cyclospora*, and others), bacteria (*Salmonella*, *Shigella*, *Campylobacter*, *Helicobacter pylori*, MTB, *Mycobacterium avium* complex, *Clostridium difficile*, and others), viruses (CMV, herpes simplex virus, HIV, and others), and fungi (*Histoplasma capsulatum*, *Cryptococcus neoformans*, *Coccidioides immitis*, and others). Opportunistic infections are more commonly seen among patients with $CD4^+$ cell counts less than 100 cells/μL. Significant gastrointestinal bleeding and dehydration have been associated with many pathogens, particularly CMV. *Salmonella* infection can be of particular concern in HIV-infected patients because it often produces recurrent bacteremia. Neoplastic gastrointestinal tract involvement with Kaposi's sarcoma or lymphoma may produce dysphagia, obstruction, intussusception, or diarrhea.

ED management of diarrhea should be directed toward stabilization, hydration, and obtaining appropriate diagnostic studies. Initial studies should include blood cultures (for MAC and salmonellae), stool cultures, microscopic examination of stool for ova and parasites, trichrome stain for microsporidia, *Giardia* EIA, and *C. difficile* assay for toxins A and B. If indicated, colonoscopy or sigmoidoscopy (with or without biopsy) may be arranged for patients who require further evaluation.[56] Often, no definitive diagnosis of the cause of diarrhea can be made in patients with AIDS. Management of severe diarrhea not necessitating specific therapy may include attapulgite (Kaopectate), psyllium (Metamucil), diet modification, or diphenoxylate hydrochloride with atropine (Lomotil).

Cryptosporidium and *Isospora* infections commonly are associated with HIV infection, and both organisms may produce prolonged watery diarrhea.[57] Diagnosis may be sought using acid-fast staining of stool samples, monoclonal antibody assay, or ELISA. Treatment of these disorders is variably successful. Symptoms may be managed with diet modification or loperamide. *Cryptosporidium* infections may be treated with some success using paromomycin or azithromycin. *Isospora* infections often are successfully treated with TMP-SMX. Pyrimethamine or metronidazole may be used as alternative agents. HAART also may reduce duration and severity of symptomatology.

Viruses causing diarrhea include CMV, adenovirus, astrovirus, rotavirus, and others.[58] CMV colitis most commonly is seen in patients with $CD4^+$ cell counts below 50 cells/μL. Diarrhea is associated with weight loss and abdominal pain; CT shows colonic thickening. Complications include hemorrhage and perforation. Treatment is with intravenous ganciclovir, valganciclovir, or foscarnet.

C. difficile is responsible for approximately 50% of cases of diarrhea in HIV-infected patients. The typical history is one of watery diarrhea and recent antibiotic use. *C. difficile* testing should be performed. Treatment is with oral metronidazole (Flagyl) or vancomycin.

MAC consists of *M. avium* and *M. intracellulare*, acquired by ingestion or inhalation. The typical presentation is that of fever, night sweats, and diarrhea in patients with $CD4^+$ counts less than 100 cells/μL. Diagnosis can be made by stool or blood cultures, results of which may take up to weeks to turn positive. Treatment is with oral clarithromycin, 500 mg twice a day, plus ethambutol, 15 mg/kg per day. Prophylaxis is indicated in patients with $CD4^+$ cell counts less than 50 cells/μL.

Malabsorption syndromes are relatively common with HIV infection. Delayed gastric emptying and intestinal infections may contribute and lead to significant weight loss. Treatment includes nutritional counseling, parenteral nutrition, and adjunctive agents such as dronabinol, megestrol acetate, and human growth hormone.[59]

Liver Involvement

Hepatomegaly is seen in up to 50% of patients with AIDS. Jaundice is less common. Hepatitis B and hepatitis C are common among these patients, especially among intravenous drug users. Previous hepatitis B virus infection may become reactivated after HIV infection or may be acquired with increased frequency after HIV infection. Several opportunistic organisms, including CMV, MAI, *M. tuberculosis*, *Histoplasma capsulatum*, and *Cryptosporidium*, also can produce hepatitis-like disease in patients with HIV infection. Typically, an elevation in the alkaline phosphatase level occurs that is disproportionate to levels of other liver enzymes. Hepatotoxicity also may result from a variety of medications, including indinavir.

Complete examination of the anus and rectum is important in diagnosing such disorders. Fissures, masses, infection, and inflammation will be detected by inspection, palpation, digital examination, anoscopy, and, when indicated, sigmoidoscopy. Proctocolitis is common in patients with AIDS and may be caused by any of several organisms, including *Campylobacter jejuni*, *Shigella* species, *Salmonella* species, *Giardia*, HSV, *Entamoeba histolytica*, *Chlamydia*, and *Neisseria gonorrhoeae*. Diagnostic tests include anoscopy with evaluation of stool for blood, leukocytes, ova, and parasites. Additionally, bacterial cultures, an HSV culture or Tzanck preparation, a rapid plasma reagin (RPR) test, and appropriate assays for detection of *N. gonorrhoeae* and *Chlamydia* may be useful. The diagnosis of anal gonorrhea can be confirmed on a Gram's stain of stool showing leukocytes and intracellular organisms. HSV infection can be diagnosed by viral cultures or by identification of multinucleated giant cells on scrapings of anal lesions.

Cutaneous Involvement

Several common cutaneous manifestations of AIDS are likely to be seen in the ED. Preexisting dermatologic conditions may be exacerbated by HIV infection. Common infections and conditions may manifest in an atypical fashion. Generalized cutaneous complaints such as xerosis (dry skin) and pruritus are common and may be manifested before an AIDS-defining illness. Treatment for these conditions is identical to that in patients who do not have AIDS. Xerosis may be treated with emollients. Pruritus may be treated with oatmeal baths and, if necessary, antihistamines.

Kaposi's sarcoma is the second most common manifestation of AIDS. It is found commonly among homosexual or bisexual men and is caused by human herpesvirus-8 (HHV-8). The disease usually is widely disseminated with mucous membrane involvement. Kaposi's sarcoma typically manifests in HIV-infected patients with any variation of mucocutaneous involvement, lymph node involvement, or involvement of the gastrointestinal tract or other organs. The typical appearance includes pink, red, or purple papules, plaques, nodules, and tumors. Treatment is based on site and extent of involvement. Kaposi's sarcoma is incurable but rarely is fatal. Palliative therapies include cryotherapy, radiotherapy, infrared coagulation, sclerosing agents, intralesional vinblastine, and systemic chemotherapy with doxorubicin (Adriamycin), bleomycin, and vincristine.[60]

Varicella-zoster (VZ) eruptions are nearly 27 times more likely in HIV-infected patients than the general population, and multidermatomal involvement is more frequent in those with AIDS.[61] In the HIV-infected patient with simple dermatomal zoster infection, outpatient management options include oral famciclovir (500 mg three times a day), acyclovir (800 mg fives times daily), and valacyclovir (1000 mg three times daily).[62] Hospital admission to an isolation bed for administration of intravenous acyclovir (10 mg/kg every 8 hours) is warranted for any patient with systemic involvement, ophthalmic zoster, or severe dermatomal zoster.[63] Varicella immune globulin may be useful in patients with primary infection and visceral involvement.

HSV infections are highly prevalent among HIV-infected patients. Both HSV-1 and HSV-2 infections may occur as localized infection or systemic disease. HSV infections commonly manifest with fever, adenopathy, malaise, and ulcerative lesions of mucosal and cutaneous sites. Common sites of involvement include oral mucosa, genital areas, and rectum. HSV and HZV infections may be difficult to distinguish clinically, and cultures may be required for differentiation of the two conditions. Reactivation is common. Mucocutaneous HSV infection responds well to oral famciclovir (750 mg three times daily) or acyclovir (200 mg five times daily for 10 days). For disseminated infection or neurologic involvement, intravenous acyclovir is recommended (5 to 10 mg/kg every 8 hours for 7 to 21 days). Famciclovir, penciclovir, foscarnet, or valacyclovir also may be used. Suppressive therapy is effective in decreasing rates of recurrence. Patients with these viral infections should be assigned to isolation beds in the hospital.

Molluscum contagiosum manifests with small flesh-colored papules with a whitish core (see Fig. 151-4). The condition is difficult to cure; cryotherapy or curettage is reserved for symptomatic lesions. Intertriginous infections with either *Candida* or *Trichophyton* are common and may be diagnosed by microscopic examination of scrapings in potassium hydroxide. Treatment may include topical imidazole creams (e.g., clotrimazole, miconazole, ketoconazole).

Scabies should be considered in all HIV-infected patients, particularly those with dermatitis complicated by excoriations or pruritus. Microscopic identification of mites is diagnostic. Preferred treatment is with single application 5% permethrin. Sexual and household contacts also should be treated. Norwegian scabies is particularly resistant to treatment and should be considered if lesions consistent with scabies fail to respond to traditional therapy. Treatment should be undertaken in consultation with an infectious disease specialist.

Seborrheic dermatitis is common, particularly among patients with AIDS-associated dementia. Lesions are erythematous, hyperkeratotic scaling plaques involving the scalp, face (especially the nasolabial folds), ears, chest, and genitalia. Treatment with topical steroids often is effective, although less so than in the general population. Alternative therapy includes topical or oral ketoconazole.

Human papillomavirus infections occur with increased frequency in immunocompromised patients. Treatment is cosmetic or symptomatic and may include cryotherapy, topical agents, or, in extreme cases, laser therapy.

Other dermatologic disorders, including psoriasis, atopic dermatitis, and alopecia, occur with increased frequency in patients with AIDS. Any preexisting dermatologic disorder may be exacerbated by HIV infection.

Ophthalmologic Manifestations

Ocular findings are common in the HIV-infected patient. Cotton-wool spots in the retina are the most common eye finding and do not require intervention. Other common ophthalmologic manifestations of HIV include CMV retinitis, herpes zoster ophthalmicus, and Kaposi's sarcoma of eyelids or conjunctiva.

CMV retinitis occurs in 10 to 30% of HIV-infected patients and is the most common cause of blindness in patients with AIDS. With advances in HAART, reduced incidences of CMV retinitis have been observed, but discontinuation of HAART may result in intraocular inflammation.[64] CMV retinitis typically produces severe necrotic vasculitis and retinitis. This may be asymptomatic or may manifest as blurred vision, a change in visual acuity, "floaters," flashes of light, photophobia, scotoma, redness, or pain.[65] Funduscopic examination typically shows fluffy white perivascular lesions with areas of hemorrhage that may be confused with retinal cotton-wool spots, a benign condition with no prognostic implications for those with AIDS. Considerations in the differential diagnosis also include toxoplasmosis, syphilis, HSV infection, VZV infection, and tuberculosis. Because of the risk of rapid progression and blindness, any patient in whom ophthalmic CMV

infection is a possibility requires immediate evaluation by an ophthalmologist. Treatment is with intravenous ganciclovir (5 mg/kg every 12 hours for 2 weeks, followed by 6 mg/kg/day maintenance therapy) or foscarnet (90 mg/kg every 12 hours). Intravitreal injections of fomivirsen also may be used for patients unresponsive to traditional therapy.[66] Similar rates of efficacy are achieved with ganciclovir and foscarnet. Ganciclovir-containing intravitreal implants constitute another therapeutic option that provides higher intravitreal concentrations and is associated with reduced risk for CMV-related retinal detachment. Immune recovery uveitis may occur as a complication of treatment during the recovery phase.[67] Chronic suppressive therapy with ganciclovir or foscarnet may be indicated.

Patients with serum anti-*Toxoplasma* antibodies and $CD4^+$ cell counts below 100 cells/μL should receive prophylaxis with TMP-SMX.[68] Herpes zoster ophthalmicus is another common cause of ocular damage in patients with HIV infection. The typical presentation is pain or paresthesia in the distribution of cranial nerve V_1, followed by the emergence of the vesicular zoster skin rash. Complications include conjunctivitis, episcleritis, iritis, keratitis, secondary glaucoma, and, rarely, retinitis. As with CMV infection, early recognition and treatment can prevent morbidity. All patients with suspected zoster ophthalmicus require immediate ophthalmologic consultation and may need hospital admission. Treatment should be initiated with oral or intravenous acyclovir, famciclovir, or valcyclovir.

Cardiovascular Manifestations

Cardiac manifestations of AIDS may include pericardial effusion, cardiomyopathy, increased left ventricular mass, myocarditis, endocarditis, malignancy, and cardiotoxicity of medications.[69] The pericardium is the most common site of cardiac involvement, although many patients have clinically insignificant effusions. Pericardial effusions may be secondary to malignancies, uremia, lymphatic obstruction, or infections such as with *Mycobacterium tuberculosis*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, or a host of other bacterial, viral, fungal, or protozoal pathogens. Infective endocarditis occurs commonly in HIV-infected patients with a history of intravenous drug use and should be considered in all injection drug users presenting with febrile illnesses. Cardiac neoplasms also may occur, typically as either Kaposi's sarcoma or lymphoma. Such neoplasms may be clinically silent or may manifest congestive heart failure, tamponade, or arrhythmias or other clinical syndromes. Some antiretroviral agents are associated with a fat redistribution syndrome and diabetes, which may increase the risk of coronary artery disease. Patients with HIV infection also have higher rates of dilated cardiomyopathy. Etiologic categories include primary HIV infection; viral, mycobacterial, fungal, or protozoal infection; drug-induced; immunologic; and ischemic. Patients present with typical signs and symptoms of congestive heart failure; echocardiography shows left ventricular diastolic dysfunction with decreased ejection fraction. These patients are at an increased risk for arrhythmias.

Renal Manifestations

Renal insufficiency in the patient with AIDS may be associated with a variety of underlying disorders, but initial ED presentation may include general malaise, edema, or oliguria. Prerenal azotemia is the most common renal abnormality, especially in conjunction with volume loss related to systemic or gastrointestinal infection. It is diagnosed and treated by evaluation and therapy of fluid status. Acute renal failure also may occur and often is secondary to drug nephrotoxicity (e.g., from pentamidine, aminoglycosides, sulfa drugs, foscarnet, rifampin, dapsone, or amphotericin B). HIV-associated nephropathy (HIVAN) typically is a cause of chronic renal insufficiency in the late stages of immunosuppression, but may occur earlier in disease progression.[70] Vasculitis, tuberculosis, or other systemic infections also may contribute to renal insufficiency. Postrenal azotemia may result from tubular, ureteral, or pelvis obstruction or from lymphoma, stones, fungus ball, blood clot, or sloughed papillae. ED evaluation should include urinalysis, assessment of fluid status, and determination of blood urea nitrogen and serum creatinine. If indicated, ultrasonography or intravenous pyelography may demonstrate the site and degree of obstruction. Renal biopsy may be indicated for patients with proteinuria and undiagnosed renal disease. Treatment depends on the causative agent. Therapies that have demonstrated limited benefit in HIVAN include corticosteroids, angiotensin-converting enzyme inhibitors, and dialysis and should be initiated in consultation with a nephrologist.

Psychiatric Considerations

HIV-infected patients may present with a variety of social and emotional issues complicated by neuropsychiatric and cognitive impairments. The diagnosis of AIDS may dramatically alter interactions with family and friends, and patients may be devastated by the prospect of confronting chronic illness and death. Although psychiatric issues are common among HIV-infected patients, many do not receive optimal care.[71]

Depression is common among AIDS patients and often is responsive to hospitalization and psychosocial intervention. It has been estimated that 60% of HIV-infected patients experience depression during their illness.[71] Patients with depression generally have lower $CD4^+$ counts and may report more AIDS-related symptoms.[72] Referral for antidepressant therapy should be considered if symptoms have lasted for longer than 2 weeks. Depression may result in suicidal ideation and may bring the patient to the attention of the ED for medical treatment after a suicide attempt. Other psychiatric disorders may be seen, including personality disorders, addiction disorders, and adjustment disorders.

Delirium suggests the presence of a primary physiologic disease state. Considerations in the differential diagnosis include CNS, toxic, and metabolic derangements. AIDS psychosis commonly manifests with psychiatric symptoms such as hallucinations, delusions, or other abnormal behavioral changes. Treatment should be undertaken with traditional antipsychotic agents.

Sexually Transmitted Diseases

Sexually transmitted diseases (STDs) are common among HIV-infected patients, and the prevalence of STDs, including syphilis, is increasing.[73] Syphilis is associated with increased susceptibility to HIV seroconversion by an unknown mechanism.[74] For EDs that are able to institute screening for HIV, combined testing for both HIV and other STDs may be most cost-effective.[75]

Common STDs include gonorrhea, chlamydial infection, herpes, and syphilis. Serologic testing for syphilis should be performed for all HIV-infected patients with a suspected STD. Empirical therapy for syphilis may be instituted even without laboratory proof of infection. Recommended treatment for primary or secondary syphilis of less than 12 months' duration is with a single intramuscular dose of benzathine penicillin (2.4 million units). For latent syphilis or unknown

duration of secondary syphilis, three weekly injections are recommended. Patients with known or suspected syphilis should be evaluated for the presence of neurosyphilis, which has an increasing incidence among HIV-infected persons. Patients with neurosyphilis should be treated with penicillin G, 12 to 24 million units IV daily for 10 to 14 days.

Hematologic Complications

Hematopoiesis may be adversely affected by HIV infection, tumor, infection, or HIV medications. Anemia in AIDS is independently associated with an increased risk of death. Chronic anemia in AIDS characteristically is of the normocytic, normochromic type, with a low reticulocyte count and low erythropoietin level. HAART usually results in improvement.

Pediatric Considerations

HIV/AIDS in pediatric patients may have a variety of ED presentations, including recurrent or severe bacterial infections, chronic diarrhea, candidiasis, opportunistic infections, and numerous other clinical syndromes. In addition to stabilization, diagnostic tests, and definitive management, close follow-up and communication with family members and primary physicians are imperative in this population.

Drug Reactions

Drug reactions are extremely common among HIV-infected patients; these patients commonly are treated with a variety of drugs known to produce adverse effects in some people. In addition, for unclear reasons, HIV-infected persons often experience more frequent or more severe reactions to commonly used medications than noninfected patients. Dermatologic reactions are particularly common. Antimicrobial drugs frequently are implicated. Drug reactions must *always* be considered as a possible cause of new symptoms in HIV-infected patients. Table 130-2 presents a brief summary of common drug reactions in the HIV-infected patient.

Table 130-3 Antiretroviral Drugs Approved by FDA for Treatment of HIV Disease

DRUG CLASS	GENERIC NAME	TRADE NAME
NRTIs[a]	Zidovudine (AZT, ZDV)	Retrovir
		Combivir (AZT + 3TC)
		Trizivir (AZT+3TC + ABC)
	Didanosine (ddI)	Videx and Videx EC
	Zalcitabine (ddC)	Hivid
	Stavudine (d4T)	Zerit
	Lamivudine (3TC)	Epivir
		Epzicom (3TC + ABC)
	Abacavir (ABC)	Ziagen
	Emtricitabine (FTC)	Emtriva
		Atripla (FTC + EFV + TDF)
		Truvada (FTC + TDF)
	Tenofovir (TDF)	Viread
NNRTIs[b]	Nevirapine (NVP)	Viramune
	Delavirdine (DLV)	Rescriptor
	Efavirenz (EFV)	Susitiva
PIs[c]	Indinavir	Crixivan
	Tipranavir (TPV)	Aptivus
	Darunavir (DRV)	Prezista
	Fosamprenavir (FPV)	Lexiva
	Ritonavir (RTV)	Norvir
	Saquinavir (SQV)	Invirase
	Nelfinavir (NFV)	Viracept
	Atazanavir (ATV)	Reyataz
	Lopinavir/ritonavir	Kaletra
EIs[d]	Enfuvirtide (T20)	Fuzeon
	Maraviroc (MVC)	Selzentry
II[e]	Raltegravir (RAL)	Isentress

[a]Nucleoside analog reverse transcriptase inhibitors
[b]Nonnucleoside reverse transcriptase inhibitors
[c]Protease inhibitors
[d]Entry inhibitors
[e]Integrase inhibitor

■ MANAGEMENT

Antiretroviral Therapy and Chemoprophylaxis

The introduction of HAART in 1996 has had dramatic effects on the clinical consequences of HIV infection in the developed world. The incidence of AIDS-defining illnesses and death rate declined rapidly through 1998.[3] Reports of high levels of treatment failure due to serious adverse effects, emergence of drug resistance, and difficulties in maintaining long-term adherence have raised concerns regarding the continued success of HAART; however, recent studies suggest that the reduction in morbidity and mortality associated with HAART has been sustained.[76] The U.S. Department of Health and Human Services (DHHS) has published guidelines for use of antiretroviral agents in HIV-infected adults and adolescents.[77]

Antiretroviral therapy for HIV infection is constantly evolving, and optimal decisions regarding such therapy will require a basic understanding of the classes of drugs available, the rationale for initiating treatment, and the common adverse drug reactions. The five classes of antiretroviral drugs currently in use are listed in Table 130-3. Each class of drugs independently interrupts the normal life cycle of the HIV. When used with appropriate timing and in combination, these agents have been shown to significantly delay progression of disease and prolong life.

The first drug demonstrated to have antiretroviral activity was an nucleoside analogue reverse transcriptase inhibitor (NRTI), a competitive inhibitor of the viral enzyme reverse transcriptase. Several controlled trials showed that zidovudine (azidothymidine [AZT], Retrovir) decreases the number and severity of opportunistic infections.[78,79] Although zidovudine also was found to decrease the rate of AIDS progression in patients with early symptomatic HIV infection, no significant change in survival was found.[80] This finding, coupled with the recognition of the emergence of drug resistance and the appearance of significant side effects, led to the development of other NRTIs. Combination therapy, with zidovudine and another NRTI, resulted in not only prevention of disease progression but also decreased mortality.[81] The FDA has since approved multiple agents in this class, each with its own unique adverse effect profile. The most common side effects are bone marrow suppression with zidovudine; distal sensory peripheral neuropathy with didanosine (Videx), stavudine (Zerit), and zalcitabine (Hivid); and pancreatitis with didanosine.[81]

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) are noncompetitive inhibitors of reverse transcriptase and block RNA-dependent and deoxyribonucleic acid (DNA)–dependent DNA polymerase activity. Three NNRTIs are currently available; the most commonly used agents are nevirapine (Viramune) and efavirenz (Sustiva). Target organ-

isms have a high propensity for developing resistance to these agents, which are recommended for use only as part of a three-drug (or more) regimen. Rash is the most common side effect associated with use of the NNRTIs, with the development of Stevens-Johnson syndrome seen in a small minority of patients (less than 5%).[82] Symptomatic hepatitis, including fatal hepatic necrosis, has been reported with use of nevirapine.[83]

The enzyme HIV protease activates the HIV proteins that are required for infectivity by cleaving the inactive viral polypeptide precursors. Protease-inhibiting agents block this step, thereby preventing HIV particles from becoming infectious. Ten protease inhibitors currently are approved for clinical use in the United States. Introduction of this class of drugs is believed to be responsible in large part for the marked decline in mortality rates for HIV infection, which was first realized in 1996. Protease inhibitors are expensive, however, and they also have been associated with a high frequency of side effects. Short-term effects are principally gastrointestinal (including nausea, diarrhea, and bloating); long-term effects are metabolic, the most common of which are hyperglycemia, hyperlipidemia, and fat redistribution.

Additional newer classes of drugs include entry inhibitors and integrase inhibitors. Entry inhibitors prevent HIV entry into cells by targeting specific viral surface proteins or their corresponding receptors.[84] Enfuvirtide and maraviroc are two entry inhibitors currently approved for use in combination with other antiviral agents only in treatment-experienced patients. Major side effects include local injection site reactions and increased rate of bacterial pneumonia (with enfuvirtide). Integrase inhibitors work by blocking integrase, a protein required by HIV to allow it to insert its viral genetic material into the genetic material of an infected cell.[85] Raltegravir is the only integrase inhibitor currently approved for use, restricted to patients who have limited or no treatment options. Common side effects include diarrhea, nausea, headache, and fever.

The DHHS recently published updated guidelines for use of antiretroviral agents in HIV-infected adults and adolescents.[77] In general, the goals of antiretroviral therapy are virologic, immunologic, clinical, and therapeutic. Because virologic (HIV RNA levels) and immunologic ($CD4^+$ cell count) parameters are independent predictors of clinical outcomes, therapeutic recommendations are based on both of these factors. The *virologic* goal is to reduce viral load as much as possible, halt disease progression, and prevent development of resistant HIV variants. *Immunologic* goals are to achieve both quantitative ($CD4^+$ cell count) and qualitative (pathogen-specific immune response) immune reconstitution. The principal *clinical* goals are to prolong and improve the quality of life. The *therapeutic* goal is to achieve the other three goals by choosing a sequence of drugs that maintains therapeutic options, minimizes side effects, and optimizes the likelihood of patient compliance with the chosen regimen.

Expert consensus on the timing of initiation of HAART continues to evolve. The current consensus recommends mandatory treatment for HIV-infected patients with $CD4^+$ counts below 350 cells/μL or with history of AIDS-defining illness. Other patient populations in whom initiation of antiretroviral therapy is indicated regardless of $CD4^+$ count include pregnant women, patients with HIVAN, and patients with HBV co-infection requiring treatment. Similarly, in patients with recognized primary HIV infection, antiretroviral therapy is recommended, because early treatment is believed to decrease the number of infected cells, maintain or restore immune response, and perhaps lower the viral "set point," resulting in improved course of the disease.[81] Therapy may be considered in some patients with $CD4^+$ greater than 350 cells/μL, given some evidence suggesting that higher $CD4^+$ counts can be achieved with early therapy; however, initiation of treatment in these patients should be individualized in accordance with the willingness and readiness of the person to begin therapy, the potential benefits and risks of initiating therapy in an asymptomatic person, and the likelihood of compliance with the prescribed treatment regimen.

Selection of an appropriate combination of drugs also is a complex issue for which no definitive recommendations exist. Twenty-eight antiretroviral drugs are currently approved by the FDA. A complete list and up-to-date guide for their use can be found on the NIH website (AIDSinfo.nih.gov). The current DHHS recommended first-line HAART regimens include NNRTI-based regimens (one NNRTI and two NRTIs), or protease inhibitor–based regimens (one or two protease inhibitors and two NRTIs).[77] Triple-NRTI regimens are recommended as second-line regimens. Therapy should be individualized with consideration of tolerability, comorbid conditions, adverse effect profile, likely drug-drug interactions, convenience, and likelihood of adherence.

Pregnancy should not preclude women from receiving optimal treatment regimens; however, issues relating to prevention of mother-to-child transmission as well as maternal and fetal safety deserve special considerations. Previous studies have shown that HAART reduces perinatal transmission to 1 to 2%, and the rate is strongly correlated with viral load at the time of delivery.[86,87] On the basis of these observations, HAART should be recommended for any pregnant woman. Selection of antiretroviral combinations should take into account known safety efficacy and pharmacokinetic data for each agent during pregnancy. Efavirenz-containing regimens should be avoided in pregnancy or in women of reproductive age owing to potential teratogenic effects. Elective cesarean section has established merit in reducing prenatal transmission if done at 38 weeks of gestation with a maternal viral load greater than 1000 copies/mL.[88]

The goal of the antiretroviral therapy is to produce long-term viral suppression. Clinical situations that should prompt consideration for changing therapy include drug toxicity or intolerance, difficulty with adherence, and failure to suppress viral infection. Decisions regarding alternative treatment regimens should be made in consultation with infectious disease experts to assess potential cross resistance from previously used drugs. With advances in genotypic and phenotypic analysis of HIV strains, selection of a drug regimen based on drug resistance patterns will soon become an essential part of therapeutic decision-making.

Chemoprophylaxis is directed toward preventing initial and subsequent episodes of certain opportunistic infections (i.e., primary and secondary prophylaxis). Emphasis on measures to prevent opportunistic infections is critical because of the inherent limitations of HAART and the recognition that these infections constitute a cause of significant morbidity and mortality in the HIV-positive population. The $CD4^+$ cell count is the best predictor of the risk for opportunistic infections and is used most often in making decisions about initiating or maintaining antimicrobial prophylaxis. The most serious and common infections for which antimicrobial prophylaxis has been shown to be effective include PCP, toxoplasmosis, tuberculosis, and MAC infection. Specific timing and choice of agents are described in earlier clinical sections of this chapter; a more comprehensive review can be found in the Public Health Service and Infectious Disease Society Revised Guidelines for the Prevention of Opportunistic Infections.[89] The emergency physician can play a critical role in recognizing those patients requiring initiation of chemoprophylaxis and then should work closely with the patient's

primary care doctors or an infectious disease consultant to begin therapy.

Immunizations for Human Immunodeficiency Virus–Infected Patients

Response to immunizations may be variable among HIV-infected patients. Many such patients mount an adequate antibody response to immunizations, but the immune response is not predictable.[90] Most routine immunizations recommendations are the same as for the non-HIV-infected patients.[91] However, HIV-infected patients should not receive live virus or live bacterial vaccines. Pneumococcal vaccine is recommended for all patients older than 2 years of age[92]; however, immunization is recommended early in the disease course to optimize antibody development.[93] Hepatitis B vaccine is indicated for patients at risk of exposure, although owing to variable immune response, follow-up serologic testing is indicated. Hepatitis A vaccination also should be considered because of increased risk of severe liver damage among patients previously infected with hepatitis B or C.[94] Influenza vaccination is considered safe and is routinely recommended.[95] Measles-mumps-rubella (MMR) vaccine may be considered because studies have not documented an increased incidence of adverse effects. If polio vaccine is indicated, enhanced inactivated polio vaccine may be administered. Although evidence suggests that the expression of HIV may be transiently increased by administration of tetanus toxoid,[96] the clinical significance of this observation is unknown; current recommendations include providing a booster every 10 years for patients who have completed their primary series. Because the smallpox vaccine has not been rigorously studied in the HIV-infected population, the adverse effects and immune response are unknown, and some experts currently advise against its use.[97] The potential risks and benefits of immunization in the HIV-infected patient should be considered in decisions regarding immunization.

DISPOSITION

When questions remain about specific diagnostic or management options, consultation with specialists is appropriate. Consultations with an infectious disease specialist, neurologist, psychiatrist, AIDS specialist, and others may be indicated. Although symptomatic patients are cared for predominantly by AIDS specialists, the increasing numbers of symptomatic patients are shifting the focus of primary care to nonspecialists.

Disposition decisions for HIV-infected patients are based, as for any patient, on clinical condition, availability of outpatient resources, and ability to arrange adequate follow-up observation. Any patient to be discharged must demonstrate capability for self-care or have sufficient in-home assistance available. In the AIDS population, particular attention should be given to ability to ambulate and to tolerate oral intake, as well as availability of timely and appropriate medical follow-up care.

Although the AIDS epidemic has raised concerns regarding the economic impact of the disease, financial considerations should not be a factor in determining management or disposition. Guidelines for hospital admission and discharge are presented in Box 130-3.

BOX 130-3 GENERAL EMERGENCY DEPARTMENT (ED) DISCHARGE REQUIREMENTS

- Stable medical condition
- Normal or baseline vital signs
- Appropriate follow-up arrangements have been made
- Appropriate consultations and referrals have been made
- Patient understands discharge instructions
- Patient or caregiver is able to comply with discharge instructions
- Patient or caregiver understands warning signs indicating the need for repeat ED evaluation

ETHICAL CONSIDERATIONS

Numerous ethical issues arise in the management of HIV-infected patients. General issues relevant to many patients may include issues of confidentiality, discrimination, access to health care, justice, informed consent, respect for autonomy, and advance directives. Additionally, concerns specific to HIV infection may arise, such as questions related to prenatal testing, abortion, euthanasia, suicide, access to experimental therapies, and role in clinical trials. In general, commonly accepted principles of medical ethics may be applied, which include principles of beneficence, nonmaleficence, respect for autonomy, and justice. Additionally, codes of ethical conduct developed by the define and the Society for Academic Emergency Medicine (SAEM) may provide general guidance.[98,99]

Testing of patients to detect HIV infection has some controversial aspects. Routine HIV testing initiated in the ED often is not appropriate because of difficulties in ensuring appropriate pre- and post-test counseling and confidentiality issues. However, recommendations and referral for testing often are indicated for patients with risk factors or with clinical evidence of HIV infection. Each institution should have appropriate mechanisms arranged for these referrals.

Occupational exposures to blood and body fluids may necessitate testing of patients and health care workers in the ED to expedite initiation of antiretroviral therapy. In such cases, institutions not only must comply with state guidelines but should implement uniform policies and procedures for testing that ensure pretest and post-test counseling and confidentiality of results.

Confidentiality of the patient's identity and medical data are of paramount importance in the ED, particularly for HIV-infected patients, for whom breached confidentiality may have numerous clinical, social, psychological, career, and insurability effects.

Public health responsibilities may at times override the duty of the physician to maintain strict confidentiality. AIDS is a reportable disease in most states, and state guidelines for reporting should be followed as a public health measure, even if this breaches confidentiality, as in cases of child abuse, gunshot wounds, or other infectious diseases. Moreover, the physician who is aware of potentially contagious practices of an infected patient has an obligation to provide appropriate counseling for that person. Additionally, infected patients should be encouraged to divulge their disease state with sexual or needle-sharing partners. In many states, the physician has the discretion to inform public health officials about the culpable practices, to allow partners potentially at risk to be informed.[100]

The potential value of aggressive interventions in critical care settings must be determined on an individual case basis. Some clinicians believe that in the advanced stages of AIDS, resuscitative measures are not appropriate because of the uniformly poor prognosis. Many patients may agree as they approach the terminal stages of their disease. Appropriate advance directives should be completed before the patient

enters the resuscitation setting. However, many patients fail to provide such documentation. Decisions regarding the withholding of extraordinary resuscitation efforts may be difficult to make in the ED because of insufficient information about an individual patient, his or her wishes, the specific disease state, prognosis, and the judgment and intentions of the primary care and consultant physicians. Although some ethicists argue against the excessive use of extensive resources for this class of patients, decisions in the ED should be largely unbiased and based on the appropriate factors relevant to the individual case. As with all patients with clinical indications for invasive monitoring or interventions, decisions should be based on factors including the patient's wishes (if known) or a surrogate's assessment of the patient's wishes, expected outcome of the intervention, and potential risks of the intervention. Interventions should not be withheld or discontinued merely because of the presence of AIDS.

If certain diagnostic and therapeutic interventions are withheld, particular attention should be made to ensure adequate control of pain and other symptoms. Psychosocial, religious, and cultural needs also should be addressed.

The courts have addressed increasing numbers and varieties of cases regarding the treatment of AIDS and HIV-related illness. The AIDS Litigation Project (a review of cases) has shown increasing cases of litigation involving areas of AIDS education, blood supply, epidemiologic surveillance, criminal law, public places, products and fraud, torts, court system, family law, confidentiality, prisons, military, fear of exposure, homelessness, and discrimination.[101]

In general, the same ethical principles of respect for autonomy, beneficence, nonmaleficence, justice, confidentiality, communication, informed consent, and research ethics should be honored in the treatment of HIV-infected patients as for all ED patients.

PRECAUTIONS AND POSTEXPOSURE PROPHYLAXIS FOR HEALTH CARE WORKERS

Precautions and Exposures

Health care workers often are exposed to the blood and body secretions of HIV-infected patients or of other persons who are at high risk of harboring HIV and other infectious pathogens. The overall risk of having any occupational blood exposure is not insignificant, with more than one half of emergency physicians reporting at least one occupational exposure during a 2-year period.[102]

The overall risk of contracting HIV infection remains small. As of December 2006, the CDC had received reports of 57 documented cases of HIV seroconversion that were temporally associated with occupational exposure to HIV among U.S. health care workers.[103] An additional 140 infections among health care workers were considered to represent possible cases of occupational transmission. No new documented cases of occupationally acquired HIV/AIDS have been reported since December 2001. Global surveillance data is less reliable, so the overall rates of occupational transmission are not known. A majority of cases occurred in nurses; less frequently affected were laboratory technicians and physicians.[102] Of all transmissions, a majority were percutaneous, followed by mucocutaneous or both. There have been no confirmed seroconversions to date with exposures to a suture needle. Efficacy of transmission is estimated at 0.3% for percutaneous exposure and 0.09% for mucocutaneous exposure.[104]

The proportion of patients infected with a pathogen varies by geographic setting and practice locale. A survey conducted at a Baltimore inner city hospital found that up to 11% of patients were infected with HIV and nearly 24% were infected with HIV or hepatitis B or C.[105] Numerous studies have demonstrated that a substantial number of patients in the ED have previously undiagnosed HIV infection, and HIV seroreactivity cannot be accurately predicted even with the aid of risk factor assessment. Because asymptomatic persons who are HIV antibody–positive can transmit the disease, *all* contacts with patients' blood or body secretions must be considered to be potentially infectious by ED personnel.

HIV transmission by health care workers to patients appears to be extremely rare. Only seven cases have been reported to date, six of which occurred from a single dentist's practice, and one from a patient who apparently acquired HIV during orthopedic surgery. At present, routine screening of health care personnel is not indicated.

Numerous studies have demonstrated that health care workers can significantly reduce their risk of exposure to blood-borne pathogens by following universal precautions. CDC guidelines for universal precautions include the use of protective equipment (including gloves, gown, mask, and eye protection) for any situation in which the potential for exposure exists. Protective equipment is indicated for most ED procedures, including examination of the bleeding patient, chest tube placement, lumbar puncture, and other commonly performed procedures in which contact with blood or body fluids is likely. Although significant improvement has been made in observance of universal precautions in the ED setting, studies have indicated that continued education and improvements in work environments are required to ensure consistent compliance.[106,107]

Postexposure Prophylaxis

Occupational Exposures

Postexposure prophylaxis (PEP) reduces the risk of HIV transmission and seroconversion.[108] The CDC provides explicit guidelines for institution of PEP for occupational exposure to HIV.[104] Current guidelines advise case-by-case determination of exposure risk to resolve whether PEP should be recommended. Recommendations are based on two primary factors: (1) type of exposure and (2) HIV status of the source (or, if the source status is unknown, evaluation of risk status of the source). Separate recommendations are provided by the CDC for percutaneous and mucus membrane or nonintact skin exposures. Exposures involving contact between intact skin and blood or other body fluids contaminated by HIV are not indications for therapy. Higher-risk percutaneous exposures associated with an increased likelihood of transmission include those involving deep injuries, visible blood on a device, and injuries sustained during placement of a catheter in a vein or artery; lower-risk percutaneous exposures are superficial or involve solid needles. High-risk sources are patients with symptomatic HIV infection, AIDS, acute seroconversion, or high viral load; low-risk sources are patients with asymptomatic HIV infection or viral load of less than 1500 copies/mL.[109] When the serostatus of the source is not known (i.e., no recent positive or negative results on serologic tests), rapid testing should be performed. A negative result on EIA (using either SUDS or OraQuick) is adequate for a decision to withhold or discontinue therapy if initiated. Some states allow testing the source patient without informed consent. Confidentiality should be rigorously protected while still ensuring that the appropriate information is provided to all exposed persons. In unusual circumstances in which the source patient has an illness consistent with acute

HIV infection, testing should include assay of HIV RNA levels.

Current public health guidelines recommend a 4-week regimen of two drugs for most HIV exposures given by percutaneous or mucous membrane routes.[104] Two-drug therapy options include zidovudine plus lamivudine (available as Combivir), lamivudine plus stavudine, and didanosine plus stavudine. For highest-risk exposures, an expanded PEP regimen with the addition of a protease inhibitor (preferably lopinavir plus ritonavir) is advised. When the source is known to be infected with a resistant HIV strain, the selection of PEP drugs to which the source's virus is unlikely to be resistant is recommended.

PEP should be initiated as soon as possible, preferably within hours rather than days of exposure; in general, antiretroviral therapy is not indicated in patients presenting more than 36 hours after exposure. The optimal duration of PEP is 4 weeks, if tolerated. Constitutional and gastrointestinal side effects may be significant and often lead to early termination of treatment. Initial treatment should never be delayed during the wait for information regarding final determination of overall risk of exposure, because therapy subsequently can be altered or stopped after the first dose. If the source person's HIV infection status is unknown at the time of exposure, use of PEP should be decided on a case-by-case basis, with type of exposure and likelihood of HIV infection in the source taken into consideration. If the findings suggest a possibility for HIV transmission and the result of HIV testing of the source person is pending, a two-drug PEP regimen should be initiated until laboratory results become available. PEP should be discontinued if the source patient is determined to be HIV-seronegative. In addition to the evaluation and management of HIV exposure risk, all patients should be tested and treated for other highly infectious diseases, such as hepatitis.

Patients often present to the ED seeking PEP because services are available at any time and early initiation of PEP is critical for efficacy. Many EDs are developing protocols and starter treatment packets for PEP. If possible, however, the choice of intervention and regimen usually is best accomplished in consultation with an infectious disease specialist and the patient's primary physician, to allow arrangement for appropriate medical follow-up and counseling.

Nonoccupational Exposure

Recent interest in the use of PEP for nonoccupational exposure has emerged, because the probability of HIV transmission by certain sexual or injection drug exposures is of the same order of magnitude as for percutaneous exposures, for which the CDC recommends PEP. The current DHHS recommendations regarding nonoccupational postexposure prophylaxis (nPEP) are as follows[110]: (1) For persons seeking care at 72 hours or earlier after nonoccupational exposure to blood, genital secretions, or other potentially infectious body fluids of a person known to be HIV-infected, when that exposure represents a substantial risk for transmission, a 28-day course of a HAART regimen is recommended, and antiretroviral medications should be initiated as soon as possible after exposure. (2) For persons seeking care at 72 hours or earlier after nonoccupational exposure to blood, genital secretions, or other potentially infectious body fluids of a person of unknown HIV status, when such exposure would represent a substantial risk for transmission if the source were HIV-infected, no recommendations are made for the use of nPEP. (3) For persons with an exposure history that represents no substantial risk for HIV transmission or who seek care later than 72 hours after exposure, DHHS does not recommend the use of nPEP. (4) Clinicians may consider prescribing nPEP for exposures conferring a serious risk for transmission, even if the person seeks care later than 72 hours after exposure if, in their judgment, the diminished potential benefit of nPEP outweighs the risks for transmission and adverse events. All patients seeking care after HIV exposure should be tested for the presence of HIV antibodies at baseline and at 4 to 6 weeks, 3 months, and 6 months after exposure to determine whether HIV infection has occurred. In addition, testing for STDs, hepatitis B and C, and pregnancy should be offered. Early experience with implementation of these guidelines indicates that challenges exist in ensuring routine implementation.[111]

For most cases in which a patient with recent exposure is likely to have continuing risk for exposure, the CDC recommends providing basic risk reduction counseling and referral to risk reduction programs rather than offering PEP. Additional resources should be used whenever possible to assist with decision making and follow-up services; in-house infectious disease consultation should be sought. Other useful resources for information on both occupational and nonoccupational exposure include the CDC/University of California–San Francisco (UCSF) National Clinicians PEP Hotline (1-888-448-4911), providing 24-hour assistance, and the University of California at Los Angeles (UCLA)'s online decision-making support (http://www.needlestick.mednet.ucla.edu).

KEY CONCEPTS

- The seroprevalence of HIV infection and AIDS among patients presenting to EDs serving large metropolitan areas is 2 to 15%. Many of these are undiagnosed cases, so compliance of ED personnel with universal precautions is extremely important.
- Acute HIV seroconversion syndrome commonly follows exposure by 2 to 6 weeks and manifests with common nonspecific signs and symptoms such as fever, fatigue, diarrhea, weight loss, adenopathy, and rash. Patients fitting this profile should be screened for HIV risk factors and appropriately referred for HIV testing.
- PCP is the most common opportunistic infection in patients with AIDS. It often manifests as progressive dyspnea on exertion associated with a nonproductive cough. The chest radiograph commonly shows a diffuse interstitial infiltrate but may be normal in appearance. Blood gas analysis usually reveals hypoxemia that often is more pronounced after exercise.
- CNS disease is common in HIV-infected patients and may be caused by the disease itself, opportunistic infections, or malignancy. An algorithm for the evaluation of HIV-infected patients with severe or prolonged headache, altered mentation, new-onset seizures, or focal neurologic deficits is presented in Figure 130-2.
- The evaluation and management of HIV-infected patients with acute symptoms often are complex and best accomplished either in the hospital or in the outpatient setting with close follow-up.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.