

Virtual Mentor

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CLINICAL PEARL

Managing the Care of Patients with HIV Infection

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HIV/AIDS refers to all cases of HIV infection, whether or not the infection has progressed to AIDS. The diagnosis of AIDS is based on surveillance case definitions established by the Centers for Disease Control and Prevention (CDC), which are the same for adults, adolescents, and children.

Definitive AIDS Diagnosis

(With or without laboratory evidence of HIV infection.)

- Candidiasis of esophagus, trachea, bronchi, or lungs.
- Cryptococcosis, extrapulmonary.
- Cryptosporidiosis with diarrhea persisting for more than 1 month.
- Cytomegalovirus infection of an organ other than the liver, spleen, or lymph nodes.
- Herpes simplex virus infection causing a mucocutaneous ulcer that persists more than 1 month, or bronchitis, pneumonia, or esophagitis of any duration.
- Kaposi sarcoma in a patient less than 60 years of age.
- Lymphoma of the brain (primary) in a patient less than 60 years of age.
- *Mycobacterium avium* complex or *Mycobacterium kansasii* infection, disseminated (at a site other than or in addition to the lungs, skin, or cervical or hilar lymph nodes).
- *Pneumocystis jiroveci* pneumonia.
- Progressive multifocal leukoencephalopathy.
- Toxoplasmosis of the brain.

Definitive AIDS Diagnosis

(With laboratory evidence of HIV infection.)

- Coccidioidomycosis, disseminated (at a site other than or in addition to the lungs or cervical or hilar lymph nodes).
- HIV encephalopathy.
- Histoplasmosis, disseminated (at a site other than or in addition to the lungs or cervical or hilar lymph nodes).
- Isosporiasis with diarrhea persisting more than 1 month.
- Kaposi sarcoma at any age.
- Lymphoma of the brain (primary) at any age.
- Other non-Hodgkin lymphoma of B cell or unknown immunologic phenotype.

- Any mycobacterial disease caused by mycobacteria other than *Mycobacterium tuberculosis*, disseminated (at a site other than or in addition to the lungs, skin, or cervical or hilar lymph nodes).
- Disease caused by extrapulmonary *M. tuberculosis*.
- Salmonella (nontyphoid) septicemia, recurrent.
- HIV wasting syndrome.
- CD4 cell count less than 200/uL or a CD4 lymphocyte percentage below 14 percent.
- Pulmonary tuberculosis.
- Recurrent pneumonia.
- Invasive cervical cancer.

Presumptive AIDS Diagnosis

(With laboratory evidence of HIV infection.)

- Candidiasis of esophagus: (a) recent onset of retrosternal pain on swallowing, and (b) oral candidiasis.
- Cytomegalovirus retinitis: characteristic appearance on serial ophthalmoscopic examinations.
- Mycobacteriosis: specimen from stool or normally sterile body fluids or tissue from a site other than the lungs, skin, or cervical or hilar lymph nodes showing acid-fast bacilli of a species not identified by culture.
- Kaposi sarcoma: erythematous or violaceous plaque-like lesion on skin or mucous membrane.
- *Pneumocystis jiroveci* pneumonia: (a) a history of dyspnea on exertion or nonproductive cough of recent onset (within the past 3 months); and (b) chest radiograph evidence of diffuse bilateral interstitial infiltrates or gallium scan evidence of diffuse bilateral pulmonary disease; and (c) arterial blood gas analysis showing an arterial blood PO₂ of less than 70 mm Hg or a low respiratory diffusing capacity (DLCO) of less than 80 percent of predicted value or an increase in the alveolar-arterial oxygen tension gradient; and (d) no evidence of bacterial pneumonia.
- Toxoplasmosis of the brain: (a) recent onset of a focal neurologic abnormality consistent with intracranial disease or a reduced level of consciousness; and (b) brain imaging evidence of a lesion having a mass effect or the radiographic appearance of which is enhanced by injection of contrast medium; and (c) serum antibody to toxoplasmosis or successful response to therapy for toxoplasmosis.
- Recurrent pneumonia: (a) more than one episode in a 1-year period; and (b) acute pneumonia (new symptoms, signs, or radiographic evidence not presented earlier) diagnosed on clinical or radiographic grounds by the patient's physician.
- Pulmonary tuberculosis: (a) apical or miliary infiltrates and (b) radiographic and clinical response to antituberculosis therapy.

Initiation of Care

Ideally, the initial encounter occurs in the outpatient setting with an asymptomatic person who has been electively tested and found to be positive for HIV. In actual fact, however, the first encounter often occurs in the office or hospital following the development of signs and symptoms of immune compromise or opportunistic infection. In this setting, some patients may not be aware of their HIV status.

After HIV-positive status is confirmed, the initial evaluation includes a complete history and physical examination. The patient's social support system should be evaluated, and his or her reaction to learning about HIV infection should be explored because anxiety, depression, and adjustment disorders commonly occur early in the course of infection. If the patient has a previously established diagnosis of HIV/AIDS, a complete antiretroviral treatment history should be obtained. The patient should be educated about precautions needed to avoid virus transmission as well as the indications and goals of antiretroviral therapy and the need for preventive care. Patients should have some knowledge of resistance mechanisms and understand the importance of adhering to the treatment regimen. Providing appropriate counseling and education generally requires several visits.

Laboratory Testing

Laboratory testing is performed to assess immune status and rule out concomitant diseases or exposure to previous infections possibly requiring treatment, prophylaxis, or immunization. Assessment of liver, bone marrow, and kidney function is important. Serum lipid levels should be measured before beginning antiretroviral therapy because hyperlipidemia can be a complication of HIV infection or antiretroviral therapy. Testing also includes a CD4 count, which should be monitored every 3 to 4 months and guides prophylaxis therapy as well as initiation of treatment.

Viral load testing, which measures the amount of HIV-1 RNA present in the plasma, is also undertaken at baseline and every 3 to 4 months. The plasma HIV RNA viral load is the best predictor of prognosis and the rate of decline of CD4 lymphocytes and is used to assess and monitor the efficacy of antiretroviral medications and to guide ongoing treatment decisions. It should be checked 4 weeks after antiretroviral therapy is initiated or changed. An "undetectable" viral load refers to a result that is below the lower threshold of the test, generally less than 50 copies/mL. An undetectable viral load does not mean that virus is no longer present in the body or that cure has been achieved. Individuals with undetectable viral loads are still considered infectious.

Preventive Care

A number of preventive measures contribute to disease avoidance for patients with HIV infection. These include routine immunizations, cervical cancer screening, and medications for primary and secondary prophylaxis of opportunistic diseases. Routine immunizations include pneumococcal vaccine every 5 years and influenza vaccine annually. Hepatitis A and B vaccines should be administered unless the presence of protective antibodies is documented.

A tuberculin skin test using purified protein derivative should be performed annually. In patients with HIV infection, a skin test resulting in 5 or more mm of induration is considered positive. At baseline a patient should also be screened for hepatitis B and hepatitis C, *Toxoplasma* IgG antibody, cytomegalovirus IgG antibody and syphilis using the RPR test. Women with HIV infection have a higher incidence of cervical dysplasia and invasive cervical carcinoma, and many experts therefore suggest more frequent Pap smear screenings in these patients.

Several drugs have been shown to provide effective prophylaxis against opportunistic infections in patients with HIV infection and to prolong life in some patients. The CD4 cell count is an indicator of immune competence. Recommendations regarding when to initiate prophylaxis are based on CD4 cell count levels below which these infections are likely to occur.

Opportunistic Infections

Opportunistic infections remain a significant cause of morbidity and mortality in patients with HIV/AIDS. These infections result from an imbalance in cell-mediated immunity. The immune system is no longer able to maintain control in patients with HIV infection, allowing fungi, bacteria, and viruses to invade impaired hosts and cause disease. Healthy persons infected with these pathogens may experience mild illness followed by recovery; those infected with HIV can become severely ill. The major AIDS-defining opportunistic infections are cryptococcal infection, cytomegalovirus infection, *Pneumocystis jiroveci* pneumonia, *Mycobacterium avium* complex infection, and toxoplasmosis.

Cryptococcal Infections. Cryptococcal meningitis is the most common form of meningitis in patients with AIDS, typically causing symptoms that mimic other disorders such as headache, irritability, and nausea. Most patients have a CD4 cell count of less than 100/uL. The diagnosis is based on detection of cryptococcal antigen or culture of *Cryptococcus neoformans* in the cerebrospinal fluid (CSF). Treatment is divided into three phases (induction, consolidation, and maintenance). The usual induction therapy is amphotericin B, with or without flucytosine, for 14 days followed by fluconazole for 8 weeks during the consolidation phase. Therapy during the maintenance phase is continuous fluconazole until the patient has successfully completed a course of initial therapy, has no signs and symptoms of cryptococcosis, and has a documented sustained increase in the CD4 count (more than 200 cells/uL for more than 6 months).

Cytomegalovirus Infection. Cytomegalovirus is a common pathogen that occurs in late stages of HIV infection, usually in patients with a CD4 cell count of less than 50/uL. It can be associated with either disseminated or localized end-organ disease. Many organs may be involved, including the retina, gastrointestinal tract, and nervous system. Cytomegalovirus only rarely invades the lungs in patients with HIV infection. Treatment involves the use of ganciclovir induction followed by maintenance therapy. In patients who are intolerant to ganciclovir or have dose-

limiting toxicity, foscarnet and cidofovir have been used. The length and type of treatment depends on the specific organ system involved.

Mycobacterium avium Complex Infection. Disseminated *Mycobacterium avium* (MAI) complex infection is common in patients with advanced-stage HIV infection and a CD4 cell count of less than 50/uL. Weekly azithromycin is the standard regimen for MAI prophylaxis. Symptoms are fever, weight loss, hepatosplenomegaly, malaise, and abdominal pain. The diagnosis is generally confirmed by recovering the pathogen from a sterile tissue (usually blood). Treatment consists of a combination of a macrolide and ethambutol with or without rifampin.

Pneumocystis jiroveci Pneumonia. *Pneumocystis jiroveci* pneumonia (PCP) remains the most common AIDS-defining illness and cause of death in patients with AIDS. The diagnosis should be considered in any patient with a CD4 cell count of less than 200/uL who has fever, dry cough, and dyspnea developing over several days or weeks. The chest radiograph typically shows bilateral interstitial infiltrates, but findings can vary from a normal film to consolidation or a pneumothorax. The diagnosis is established by silver stain examination of induced sputum or a bronchoscopic sample showing characteristic cysts. A 3-week course of trimethoprim-sulfamethoxazole (TMP-SMX) is the standard treatment. Corticosteroids are required for patients with evidence of hypoxia (arterial blood PO₂ of less than 70 mm Hg or an alveolar-arterial gradient greater than 35 mm Hg) and should be continued for the entire course of treatment. Daily TMP-SMX is the medication of choice for prophylaxis against PCP when a patient has a CD4 count less than 200/uL.

Toxoplasmosis. Toxoplasmosis almost always presents as reactivation disease in patients with HIV infection and typically occurs when the CD4 cell count is less than 100/uL. Additional findings are fever, neurologic deficits, and an MRI showing ring-enhancing lesions. Sulfadiazine plus pyrimethamine and folinic acid are given initially. Daily TMP-SMX is the standard prophylaxis for toxoplasmosis.

Treatment of HIV Infection

The U.S. Department of Health and Human Services (DHHS) and the International AIDS Society–USA (IAS-USA) frequently update guidelines for use of antiretroviral therapy in patients with HIV infection [1, 2].

The goals of antiretroviral therapy are to prolong life, avoid destruction or allow reconstitution of the immune system, prevent opportunistic infections, and provide improved quality of life by reducing HIV-related symptoms. Effective therapy aims to lower the HIV RNA viral load to less than 50 copies/mL. Such dramatic reductions in viral load improve prognosis, minimize the development of resistance, and prolong the duration of the antiretroviral response.

The most appropriate time to begin treating patients with HIV infection is an issue of great debate. Current guidelines recommend initiating antiretroviral therapy in patients with a history of an AIDS-defining illness or a CD4 cell count of less than 350/uL. Strong evidence from clinical trials suggests that treating patients with an AIDS-defining illness and a CD4 cell count of less than 200/uL improves survival and reduces disease progression. The guidelines have recently been changed to include the recommendation to treat all patients with HIV infection, regardless of their CD4 cell count, who have evidence of HIV nephropathy or hepatitis B co-infection that requires treatment or are pregnant.

Antiretroviral Agents. Twenty-five antiretroviral agents are currently approved for treating HIV infection. Six different antiretroviral drug classes are licensed. These are nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, fusion inhibitors, integrase inhibitors, and co-receptor antagonists. The NRTIs are nucleoside/nucleotide analogues and act as chain terminators that impair the transcription of viral RNA into DNA. The NNRTIs inhibit reverse transcriptase by binding to the enzyme. Protease inhibitors impair the packaging of viral particles into a mature virus capable of budding from the cell and productively infecting additional lymphocytes. The fusion inhibitors impair membrane fusion of HIV to T cells, thus preventing one of the key steps in entry. Coreceptor antagonists block a second major step in entry by binding to the chemokine receptors (CCR5 or CXCR4), and integrase inhibitors prevent incorporation of viral DNA into the host cell genome. Recommended first-line regimens include two NRTIs plus either a NNRTI or a protease inhibitor.

Resistance Testing. Two types of resistance tests, genotype and phenotype, are used in clinical practice. Genotype testing identifies mutations in reverse transcriptase and protease genes. Phenotype testing measures the ability of HIV to grow in the presence of varying concentrations of antiretroviral drugs. This procedure involves recombining the patient's gene sequences with a laboratory HIV clone and measuring the replication of the virus in different drug concentrations. Resistance testing is recommended for patients who develop acute HIV infection (within 6 to 12 months of virus transmission), compliant patients who fail to benefit from adequate therapy, and treatment-naïve patients with chronic HIV infection.

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Further Reading

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