HIV Infection: The Role of Primary Care

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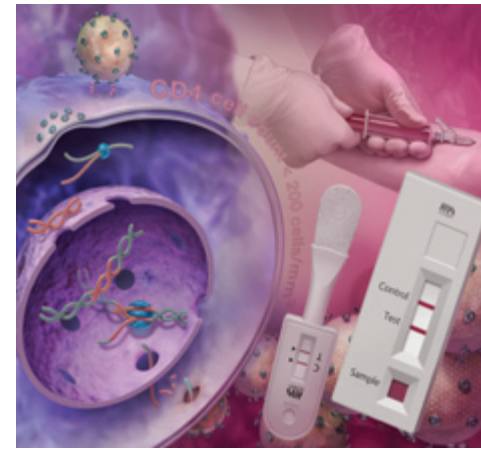
Human immunodeficiency virus infection was first documented in the United States in 1981. Since that time, significant strides have been made in the prevention and treatment of the condition. Screening is paramount in identifying early infection and is now a routine component of primary care. Primary care physicians are also often involved in monitoring patients with the infection. Diagnosis can occur at any stage of human immunodeficiency virus infection. The acute retroviral syndrome that occurs shortly after infection is characterized by constitutional symptoms and is often difficult to differentiate from common community-acquired viruses. Appropriate management with combination antiretroviral therapy often extends the patient's life, sometimes for many years. Selection of pharmacotherapy is usually based on genotypic or phenotypic resistance testing. Therapy is lifelong and complicated by pill burden, cost, adverse effects, and drug interactions. (*Am Fam Physician*. 2009;80(9):946-952. Copyright © 2009 American Academy of Family Physicians.)



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Prevention and treatment of human immunodeficiency virus (HIV) infection have changed considerably in the past few years. Updated screening recommendations give family physicians an important role in assessing patients at risk of HIV infection, detecting those who are infected, and recommending treatment options. Although family physicians may elect to refer some patients to an HIV subspecialist for therapeutic interventions, they may continue to provide intermittent or chronic care for these patients.[1] Additionally, it is important for family physicians to recognize complications of therapy and potential medication interactions.

Disease Course and Transmission

HIV is a retrovirus with a remarkable capacity to replicate and mutate.[2,3] The virus gains access to CD4 cells via sequential binding with a CD4 cell receptor and one of two coreceptors (CCR5 or CXCR4).[2,3] The clinical course of HIV infection varies substantially from person to person. Within days of being infected, at least 40 to 90 percent of persons develop an acute retroviral syndrome characterized by symptoms such as low-grade fever, rash, diarrhea, nausea and vomiting, pharyngitis, aseptic meningitis, and headache.[2] After acute seroconversion and the initial immune response, patients may be symptom free for many years before the infection progresses.[1] Progression is associated with sustained increases in viral load (plasma HIV RNA) and associated declines in CD4 cell counts. As CD4 cell counts decline, patients become increasingly susceptible to opportunistic diseases, including certain, more pathogenic conditions recognized as AIDS-defining illnesses *(Table 1)*.[4]

In the United States, sexual contact remains the primary mode of HIV transmission. The infection is most commonly transmitted among men who have sex with men, followed by persons who engage in high-risk heterosexual contact and persons who use injection drugs. New groups at risk include persons younger than 20 years, certain racial and ethnic minorities, and persons residing outside metropolitan areas.[5,6] Receptive anal intercourse is associated with the highest incidence of HIV infection, followed by insertive anal intercourse and receptive vaginal intercourse. Although transmission from oral sex is possible, the risk is considered

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Routine HIV screening should be considered for patients 13 to 64 years of age and for pregnant women, particularly if the prevalence of undiagnosed infection in the physician's patient population is documented to be 0.1 percent or more.	C	11
Patients with HIV infection who have a CD4 cell count of less than 350 cells per mm^3 (350×10^9 per L) should undergo genotypic or phenotypic resistance testing before appropriate antiretroviral pharmacotherapy is selected.	B	15
Initial antiretroviral regimens for HIV infection should include a combination of three agents, typically two nucleoside reverse transcriptase inhibitors, plus one nonnucleoside reverse transcriptase inhibitor or one protease inhibitor. The primary goal of antiretroviral therapy should be achieving an undetectable viral load (plasma HIV RNA of less than 48 copies per mL).	A	1, 4, 14, 15
CD4 cell count thresholds should be used to determine the need for antimicrobial prophylaxis against opportunistic infections in patients with HIV infection. Patients with CD4 cell counts of less than 200 cells per mm^3 (200×10^9 per L) require prophylaxis.	B	4
Primary care for patients with newly diagnosed HIV infection should include screening for opportunistic diseases and sexually transmitted infections. Annual tuberculin testing also should be performed, and vaccination histories should be updated at each office visit.	C	1, 4, 15, 21

HIV = human immunodeficiency virus.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

Table 1. AIDS-Defining Illnesses

Candidiasis of the bronchi, trachea, or lungs
Cervical cancer, invasive
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (persisting for more than one month)
Cytomegalovirus disease (other than liver, spleen, or nodes) and retinitis with vision loss
Encephalopathy, HIV-related
Herpes simplex virus (chronic ulcer persisting for more than one month, bronchitis, pneumonitis, esophagitis)
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (persisting for more than one month)
Kaposi sarcoma
Lymphoma (Burkitt, immunoblastic, or primary lymphoma; lymphoma of the brain)
Mycobacterium avium complex disease; infection with *Mycobacterium kansasii* or other species, disseminated or extrapulmonary
Mycobacterium tuberculosis infection at any site, pulmonary or extrapulmonary
Pneumonia, bacterial and recurrent (*Pneumocystis jiroveci* pneumonia)
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain
Wasting syndrome, HIV-related

HIV = human immunodeficiency virus.

Information from reference 4.

very low and of consequence only in the context of receptive oral sex. Risk of sexual transmission of HIV infection is increased in the presence of another sexually transmitted infection, which may compromise natural barriers to infection.[5,6]

Screening and Prevention

More than 40,000 new cases of HIV infection are estimated to occur annually in the United States, and this rate has not diminished in the past few years.[5,6] More than 25 percent of those infected are thought to be unaware of their status.[7] Early and regular screening increases life expectancy because treatment is initiated earlier. Screening of pregnant women and treatment of those who are HIV-positive significantly reduce vertical transmission. New guidelines may further reduce the rate of perinatal HIV infection in the United States to less than 2 percent of HIV-associated pregnancies per year.[8]

Primary care physicians play an important role in screening and prevention. Addressing HIV in the primary care setting may also reduce the stigma associated with the disease and HIV clinics. Adolescent patients in particular may prefer to receive prevention information from their primary care physician rather than from parents,

teachers, or friends.[9] Transmission from injection drug use has decreased because of needle exchange programs and over-the-counter sales of clean needles.[5,6] The use of latex condoms is also an essential component of disease prevention[10]; polyurethane condoms are an option for patients who are allergic to latex. Condoms should be used with water-based lubricants to lessen the risk of breakage.

In 2006, the Centers for Disease Control and Prevention issued new HIV screening recommendations *(Table 2)*.[11] Standard screening for HIV consists of an enzyme immunoassay (EIA), followed by the confirmatory Western blot test. Low-risk patients with indeterminate test results should be reassured, and the Western blot should be performed again after three months. In patients with risk factors, repeat tests after one, two, and six months are advised. Tests to screen blood, plasma, and oral secretions have virtually equal reliability (greater than 99 percent sensitivity and specificity).[11] Several screening tests, such as Oraquick, Uni-Gold, and Recombigen, are widely available in primary care offices. Oraquick is a clinical laboratory improvement amendments–waived test with a 20-minute turnaround time. If an acute retroviral syndrome is suspected, testing of viral load should be performed in conjunction with an EIA, because the EIA may take weeks or months to convert.[11] Several other organizations have also released guidelines to assist physicians in making screening decisions *(Table 3)*.[11-14]

Diagnosis

The symptoms associated with initial HIV infection may be difficult to differentiate from common community-acquired viruses, such as mononucleosis. Regardless of initial symptoms, most patients subsequently enter a prolonged asymptomatic phase characterized by reduced viral load and some viral steady state or set point. Unpredictably, viral replication may eventually exceed immune response, leading to persistently elevated viremia with associated drops in CD4 cell counts. A patient may be HIV

Table 2. Centers for Disease Control and Prevention Recommendations for HIV Screening

Adults and adolescents
In all health care settings, screening for HIV infection should be performed routinely in patients 13 to 64 years of age. Physicians should initiate screening, unless prevalence of undiagnosed HIV infection in their patients has been documented to be less than 0.1 percent. In the absence of existing data for HIV prevalence, physicians should initiate voluntary HIV screening until they establish that the diagnostic yield is less than one per 1,000 patients screened, at which point such screening is no longer warranted.
All patients initiating treatment for tuberculosis should be screened routinely for HIV infection.
Patients at high risk of HIV infection should be screened at least annually.
All patients seeking treatment for STIs, including all patients attending STI clinics, should be screened routinely for HIV during each visit for a new complaint, regardless of whether the patient is known or suspected to have specific behavioral risks for HIV infection.
HIV screening is recommended after the patient is notified that testing will be performed unless the patient declines (opt-out screening).
Separate written consent for HIV testing should not be required; general consent for medical care should be considered sufficient to encompass consent for HIV testing.
Pregnant women
HIV screening should be included in the routine panel of prenatal screening tests for all pregnant women.
Repeat screening in the third trimester is recommended in certain jurisdictions with elevated rates of HIV infection among pregnant women.

HIV = human immunodeficiency virus; STI = sexually transmitted infection.

Information from reference 11.

Table 3. Comparison of Key Recommendations for HIV Screening

American Academy of Family Physicians[12]
Routine HIV screening is recommended for all pregnant women and for persons at high risk (e.g., men who have sex with men, persons who have unprotected sex with multiple partners, injection drug users).
American College of Physicians[13]
Physicians should adopt routine HIV screening and encourage patients to be tested. Repeat testing should be determined on an individual basis.
Centers for Disease Control and Prevention[11]
In all health care settings, screening for HIV infection should be performed routinely in patients 13 to 64 years of age. All pregnant women should be screened. See Table 2 for more detailed guidelines.
U.S. Preventive Services Task Force[14]
HIV screening is strongly recommended in all adolescents and adults at increased risk of HIV infection; there is no recommendation for or against routine screening in those who are not at increased risk. All pregnant women should be screened.

HIV = human immunodeficiency virus.

Information from references 11 through 14.

seropositive without having AIDS. AIDS is diagnosed in HIV-seropositive patients who have had a CD4 cell count of less than 200 cells per mm^3 (200×10^9 per L) or at least one AIDS-defining illness, such as *Pneumocystis jiroveci* pneumonia (formerly *Pneumocystis carinii* pneumonia), toxoplasmosis, or Kaposi sarcoma.[4]

Treatment

Several classes of antiretroviral drugs, which inhibit viral replication at distinct sites, are available *(Table 4[15-17])*. Treatment with a combination of three antiretroviral drugs is recommended for HIV infection, most often two nucleoside reverse transcriptase inhibitors plus one nonnucleoside reverse transcriptase inhibitor or protease inhibitor; this regimen may be boosted with ritonavir (Norvir).[15] Other antiretroviral classes (e.g., fusion inhibitors, integrase inhibitors, coreceptor antagonists) are usually reserved for more treatment-experienced patients who have a greater likelihood of acquired resistance.

INITIAL TREATMENT

Before selecting an initial or salvage drug regimen, genotypic or phenotypic resistance testing is recommended. Usually, genotypic assays are preferred early in disease, whereas phenotypic assays are reserved for patients with more complicated disease.[15] Not all patients with HIV infection are candidates for antiretroviral treatment. Decisions about the best time to initiate drug therapy should consider drug cost, psychosocial factors, comorbid diagnoses, implications of drug-induced resistance, and the potential toxicity of antiretrovirals. Additionally, some patients are known to have slowly progressing disease and may have relatively low levels of viremia with sustained CD4 cell counts for several years after infection.[18]

Treatment is generally initiated when the CD4 cell count falls to less than 350 cells per mm^3 (350×10^9 per L).[15] In certain instances, treatment may be initiated regardless of CD4 cell count (e.g., pregnancy, HIV-associated nephropathy, hepatitis B infection). New data have led to earlier initiation

Table 4. Antiretroviral Medications for the Treatment of HIV Infection

Agent	*Common adverse effects*
Nucleoside reverse transcriptase inhibitors	
Abacavir (Ziagen)	Hypersensitivity reaction
Didanosine (Videx EC)	Pancreatitis, peripheral neuropathy
Emtricitabine (Emtriva)	Headache, nausea, vomiting
Lamivudine (Epivir)	Headache, nausea, vomiting
Stavudine (Zerit)	Pancreatitis, peripheral neuropathy
Zidovudine (Retrovir)	Anemia
Lamivudine/abacavir (Epzicom)	See individual agents
Zidovudine/lamivudine (Combivir)	See individual agents
Zidovudine/lamivudine/abacavir (Trizivir)	See individual agents
Nucleotide reverse transcriptase inhibitor	
Tenofovir DF (Viread)	Bloating, renal dysfunction
Nonnucleoside reverse transcriptase inhibitors	
Delavirdine (Rescriptor)	Rash
Efavirenz (Sustiva)	Dizziness, impaired concentration, vivid dreams
Etravirine (Intelence)	Diarrhea, rash
Nevirapine (Viramune)	Rash
Protease inhibitors*	
Atazanavir (Reyataz)	Hyperbilirubinemia
Darunavir (Prezista)	Diarrhea, nausea, vomiting, rash
Fosamprenavir (Lexiva)	Nausea, vomiting, rash
Indinavir (Crixivan)	Nephrolithiasis
Lopinavir/ritonavir (Kaletra)	Gastrointestinal upset, nausea, vomiting
Nelfinavir (Viracept)	Diarrhea
Ritonavir (Norvir)	Gastrointestinal upset, nausea, vomiting
Saquinavir, hard gel (Invirase)	Nausea, vomiting
Tipranavir (Aptivus)	Diarrhea, nausea, vomiting, rash
Other	
Coreceptor antagonist: maraviroc (Selzentry)†	Nausea, vomiting, rash
Fusion inhibitor: enfuvirtide (Fuzeon)†	Injection site reactions
Integrase inhibitor: raltegravir (Isentress)†	Headache, nausea, vomiting
Multiple-class inhibitors: efavirenz/emtricitabine/tenofovir (Atripla); emtricitabine/tenofovir (Truvada)	See individual agents

NOTE: *Treatment with a combination of three antiretroviral drugs is recommended for HIV infection, most often two nucleoside reverse transcriptase inhibitors plus one nonnucleoside reverse transcriptase inhibitor or protease inhibitor. A protease inhibitor–based regimen may be boosted with ritonavir.*

HIV = human immunodeficiency virus.

**—With the exception of atazanavir, all protease inhibitors have been associated with varying degrees of hyperlipidemia and insulin resistance.*

†*—Usually reserved for more treatment-experienced patients with a greater likelihood of acquired resistance.*

Information from references 15 through 17.

of antiretroviral therapy in selected patients.[19] A recent observational study found mortality benefit with earlier initiation of therapy.[20] Once therapy is initiated, the primary goal is achieving an undetectable viral load (less than 48 copies per mL), which usually occurs within 12 to 24 weeks. A secondary goal is sustaining increased CD4 cell counts.[15]

TREATMENT FAILURE

Treatment failure is defined as not achieving an undetectable viral load within 12 to 24 weeks of drug therapy, or development of viremia in patients who previously had an undetectable viral load. In patients with treatment failure, modifiable factors, such as drug interactions and nonadherence, should initially be considered. In the absence of modifiable factors to explain treatment failure, a change in drug therapy should be guided by resistance testing, potentially with subspecialist consultation. Over time, some treatment-experienced patients may develop high levels of resistance to many of the available antiretroviral agents, and salvage therapy may be warranted.[15]

PROPHYLAXIS

Patients with CD4 cell counts of less than 200 cells per mm^3 require antimicrobial prophylaxis against various opportunistic infections. Specific CD4 cell count thresholds are used to predict when certain opportunistic infections are likely to occur, thus guiding the initiation of primary prophylaxis *(Table 5)*.[4] Physicians may consider discontinuing primary prophylaxis when a patient's CD4 cell count remains above the threshold for at least three months in concordance with an undetectable viral load.[4] Some physicians are more conservative in the discontinuation of secondary prophylaxis that is initiated following actual infection and treatment.

NEW DRUG DEVELOPMENTS

Recent developments in HIV pharmacotherapy have focused on new agents with reduced pill burdens, improved tolerability, and fewer drug interactions. Combination products, such as emtricitabine/tenofovir (Truvada) and efavirenz/emtricitabine/tenofovir (Atripla), have been introduced to make it easier for patients to adhere to the regimens. Boosting antiretroviral therapies with ritonavir is now common practice in HIV pharmacotherapy.[16] Ritonavir, an older protease inhibitor, is a potent inhibitor of cytochrome P450; however, adverse drug interactions often preclude its use at full dosages with antiretroviral regimens. More commonly, ritonavir is used in low dosages (100 to 200 mg per day) in combination with other protease inhibitors to produce favorable drug interactions that allow for reduced or simplified dosing of the substrate antiretroviral. Boosting dosages of ritonavir are not considered components of a three-drug regimen.[15,16] Research has also focused on the discovery of new targets for the inhibition of viral replication. Recently, two new classes of antiretroviral drugs have been introduced (i.e., coreceptor antagonists and integrase inhibitors).[17,21]

Monitoring Patients with HIV Infection

A thorough history and physical examination should be performed in patients with newly diagnosed HIV infection, and counseling should be offered.[22] Patients should also be evaluated for risk of opportunistic infections and receive appropriate immunizations and baseline testing *(Table 6*[1,4,15,21]*)*.

Table 5. Prophylaxis Regimens for Common Opportunistic Infections in Persons with HIV Infection

Opportunistic infection	*CD4 cell count**	*Prophylaxis regimen*
Pneumocystis jiroveci pneumonia	< 200 cells per mm^3 (200 × 10^9 per L)	Trimethoprim/sulfamethoxazole (Bactrim, Septra), double-strength tablet once per day
		Alternative: Dapsone, 100 mg orally once per day (screen for G6PD deficiency)
Toxoplasmosis	< 100 cells per mm^3 (100 × 10^9 per L)	Trimethoprim/sulfamethoxazole, double-strength tablet once per day
Mycobacterium avium complex disease	< 50 cells per mm^3 (50 × 10^9 per L)	Azithromycin (Zithromax), 1,200 mg orally per week

G6PD = glucose-6-phosphate dehydrogenase; HIV = human immunodeficiency virus.

**—Initiation of primary prophylaxis is recommended at these thresholds.*

Information from reference 4.

Table 6. Baseline Testing for Patients with Newly Diagnosed HIV Infection

Complete blood count
Chemistry profile
Blood urea nitrogen and creatinine levels
Transaminase levels
Hepatitis A, B, and C serologies
Fasting blood glucose and serum lipid levels (in patients at risk of cardiovascular disease or before initiation of antiretroviral therapy)
Urinalysis
Tuberculin test (unless patient has history of positive test or tuberculosis)
Chest radiography (in patients with pulmonary symptoms or positive tuberculin test results)
Pap smear in women (some experts advocate anal Pap smear in men)
HIV antibody testing (if prior documentation is not available or if HIV RNA level, or viral load, is undetectable [less than 48 copies per mL])
CD4 cell count
Plasma HIV RNA level
Genotypic resistance testing (if pretreatment HIV RNA level is greater than 1,000 copies per mL)
Anti-*Toxoplasma gondii* titer
Syphilis, *Chlamydia trachomatis*, and *Neisseria gonorrhoeae* testing

HIV = human immunodeficiency virus; Pap = Papanicolaou.

Information from references 1, 4, 15, and 21.

DRUG ADHERENCE AND ADVERSE EFFECTS

After the initiation of a new antiretroviral regimen, follow-up and monitoring usually occur every 30 days, and every 90 days after the patient is stable. Monitoring may be extended to every six months in patients with slowly progressing disease.[18,22] Physicians should be especially cognizant of patient adherence because of the potential for drug resistance.[15] In patients with HIV infection, adherence is often complicated by pill burdens associated with the use of multiple drugs (i.e., antiretrovirals, medications for the prophylaxis and treatment of opportunistic infection, and therapy for any ongoing disease states).[15]

Antiretroviral therapy is associated with known adverse effects that require monitoring.[15] Metabolic effects (e.g., hyperglycemia, hyperlipidemia), which may be accompanied by morphologic changes, are common.[15,23-25] Less common effects include osteopenia, which may be a complication of HIV infection itself, and lactic acidosis.[23-25] Hyperlipidemia should be managed according to standard guidelines for patients without HIV infection; many patients require therapy with statins or fibrates.[15,26] The addition of pharmacotherapy in patients with HIV infection warrants close attention to potential drug interactions because they may compromise antiretroviral effectiveness, or lead to resistance or deleterious adverse effects. Physicians should consult appropriate resources or subspecialists to evaluate the potential for drug interactions when additions or deletions are made to drug regimens.

IMMUNIZATION RECOMMENDATIONS

Vaccination histories should be updated at each office visit. Patients with HIV infection may receive killed/inactivated vaccines. However, an appropriate immune response may not occur in patients with severe immune compromise (CD4 cell count of less than 100 cells per mm^3 [100×10^9 per L]) or uncontrolled viremia, and revaccination when CD4 cell counts are more robust may be indicated. Patients should receive yearly influenza vaccinations, pneumococcal vaccination once before 65 years of age (additional boosters can be considered every five years), and tetanus boosters (e.g., pertussis, tetanus, and diphtheria [DTaP]; tetanus and diphtheria [Td]) every 10 years. Patients who have not been exposed to hepatitis A or B should complete the normal vaccination series for each.[4,22]

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