MAYO CLINIC

# Human Immunodeficiency Virus: What Primary Care Clinicians Need to Know

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## CME Activity

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## Abstract

Human immunodeficiency virus (HIV) has evolved from an illness that consistently led to death to a chronic disease that can be medically managed. Primary care clinicians can provide beneficial care to the individual patient and potentially decrease the transmission of HIV to others through appropriate HIV screening and recognition of clinical clues to both chronic and acute HIV. Most patients who take combination antiretroviral therapy experience immune reconstitution and resume normal lives. These patients benefit from the care of an experienced primary care clinician in addition to a clinician with HIV expertise. Primary care clinicians have expertise providing preventive care, including counseling regarding healthier lifestyle choices and managing cardiovascular risk factors, osteoporosis, hypertension, and diabetes, all of which have become increasingly important for individuals with HIV as they age. This article reviews the many important roles of primary care clinicians with regard to the HIV epidemic and care of patients with HIV.

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Human immunodeficiency virus (HIV) infection in the United States has morphed over the past 3 decades from an untreatable illness that predictably led to death to a chronic disease in which life expectancy for many patients is similar to that for the general population. This change has led to new challenges and opportunities for primary care clinicians who are on the front line of preventing, recognizing, and diagnosing HIV infection. Primary care clinicians have expertise in managing chronic medical problems and are increasingly comanaging patients with HIV alongside the HIV specialist. This article follows a primary care physician through a busy month of clinic work and highlights HIV-related issues pertinent to primary care clinicians.

*Dr Smith's clinic has recently added appropriate HIV screening as a quality measure. She reviews the appointment schedule and makes a note as to which patients should have screening.*

## WHO SHOULD BE SCREENED FOR HIV?

Since 2006, the Centers for Disease Control and Prevention (CDC) has recommended that everyone between the ages of 13 and 64 years be screened for HIV infection at least once by using an opt-out approach, and high-risk patients be screened at least annually. An *opt-out approach* is defined by the CDC as notifying the patient that HIV screening will be performed, presuming consent, and providing screening unless the patient specifically declines.[1] The US Preventive Services Task Force also recommends HIV screening of all adolescents and adults aged 15 through 65 years, younger adolescents and older adults at increased risk of infection, and pregnant women.[2] The HIV Medicine Association and the American Geriatric Society have issued a joint statement that recommends screening of all adults 65 years and older.[3]

*Dr Smith's second patient, Mr C, is a 42-year-old man with a painful rash consistent with shingles. His medical history is unremarkable except for recurrent genital herpes. He denies risk factors for HIV infection and reports having a negative HIV test result about 7 years ago.*

## WHAT SIGNS AND SYMPTOMS SHOULD RAISE CONCERN FOR CHRONIC HIV?

Table 1 lists common signs and symptoms of chronic HIV infection.[4] Many patients are reluctant to admit to high-risk behaviors for acquiring HIV infection because of the stigma attached to these behaviors, so patients with the conditions mentioned in Table 1 should be screened even in the absence of known risk factors for HIV. Mr C should be screened for HIV despite his history of a negative test result and denial of risk factors.

*Dr Smith's fourth patient, Ms E, is a 34-year-old woman who would like to have screening for sexually transmitted diseases. She had multiple sexual encounters using a condom over the past year with a partner who is HIV infected but did not use a condom 3 weeks ago. She reports that an over-the-counter HIV test result was negative the previous week and asks whether she should be retested.*

## HOW SHOULD PATIENTS BE SCREENED FOR HIV, AND WHAT IS THE ROLE OF RAPID HIV TESTS?

In 2013, 3 methods are available for HIV screening: traditional laboratory testing obtained at a health care facility, rapid HIV testing obtained at patient point of care, and home testing with an over-the-counter HIV test. Screening for HIV in the clinical setting is usually performed with a serum antibody test, an enzyme immunoassay (EIA), or a chemiluminescence immunoassay. Results are typically available in 1 to 4 days. Rapid HIV antibody testing is convenient in many settings, including community screening events, emergency departments, and during labor and delivery when the HIV status of the mother is unknown. One available rapid test uses an oral fluid sample, whereas other rapid tests use whole blood obtained from a finger prick. The body fluid sample is placed on a test strip, and results are available within 30 minutes, indicated by a color or symbol change on the test strip.[5] The US Food and Drug Administration (FDA) approved the first over-the-counter rapid HIV screening test, the OraQuick in-home oral HIV test, in 2012. Individuals collect an oral fluid sample by swabbing their gums and obtain results within 20 to 40 minutes in the privacy of their homes.[6] Another in-home option is a kit that requires a finger-prick blood sample that is mailed to a laboratory for traditional antibody testing.

All positive screening test results must be confirmed with a more specific test, usually the Western blot antibody test, regardless of which initial test is used. Ms E reports a negative home screening test result the previous week, so she does not need to be retested that day. She reports not using a condom 3 weeks ago, and a negative antibody test result is expected during the "window period" before seroconversion. Seroconversion usually occurs 3 to 6 weeks after infection but can remain negative up to 12 weeks and rarely longer. Ms E's negative test result 2 weeks after exposure to an infected partner is helpful as a baseline, but it does not provide any information

**TABLE 1. Common Clinical Signs and Symptoms of Chronic Human Immunodeficiency Virus Infection**

| |
|---|
| Active tuberculosis |
| Herpes zoster in a healthy person younger than 50 y |
| New severe psoriasis or other new unexplained severe skin disorder |
| History of hepatitis B or C |
| Cervical cancer |
| Thrush not related to recent antibiotic use |
| Unexplained cachexia or weight loss |
| Diffuse lymphadenopathy |
| Unexplained thrombocytopenia, leukopenia, or anemia |
| History of an opportunistic or unusual infection in an otherwise healthy individual |
| Prolonged unexplained illness despite evaluation |
| Any history of sexually transmitted infection |

Adapted from *Mayo Clinic Proceedings*.[4]

regarding the recent exposure. She needs to be followed up and retested. Recommendations are for antibody testing at baseline and 6, 12, and 24 weeks after HIV exposure.[2]

## WHAT METHODS, OTHER THAN ABSTINENCE, PROVIDE PROTECTION AGAINST ACQUIRING HIV?

The use of latex or polyurethane condoms continues to provide excellent protection against the transmission of HIV. Meta-analysis suggests that the consistent use of latex condoms is 80% to 95% protective.[7] Nonoxynol-9 spermicide has been associated with an increased risk of HIV transmission and should ideally be avoided.[8] Water-based lubrication is recommended because oil- and petroleum-based products make latex condoms more susceptible to breakage. Ms E's use of condoms should be supported and inquiries made to ensure she understands how to most effectively use a condom. She should receive additional counseling regarding what to do in case of condom slippage or breakage, including the possibility of postexposure prophylaxis against HIV. Postexposure prophylaxis entails taking 3 antiretroviral drugs for 28 days and should begin within 72 hours of the exposure. An HIV specialist can assist with providing counseling, prescribing medications, and ordering laboratory tests. In this case, Ms E should be reassured that the likelihood of acquiring HIV from a single sexual exposure involving receptive vaginal intercourse is extremely low, approximately 1 in 1000. The risk of acquiring HIV is higher for both women and men who are exposed through receptive anal intercourse, approximately 5 in 1000. The risk of HIV acquisition with insertive anal or vaginal intercourse is much lower, approximately 6 to 7 in 10,000. The highest behavioral risk of HIV acquisition is with exposure related to intravenous drug abuse, at approximately 6 to 7 in 1000.[9]

If Ms E continues to have sexual intercourse with a partner who is infected with HIV, preexposure prophylaxis (PrEP) may be an option for her. In 2012, the FDA approved Truvada (tenofovir/emtricitabine) for PrEP in high-risk adults who are HIV negative and have ongoing sexual activity with a partner who is infected with HIV or indulges in other high-risk behaviors. Because of concerns of resistance and toxicity, patients considering PrEP should be evaluated by a caregiver who is knowledgeable regarding appropriate screening and follow-up.[10]

*The following day, Dr Smith sees Mr H, a 45-year-old married man with fever, nausea, anorexia, and headache for the past 5 days. On questioning, he reluctantly admits to having sex in Thailand with a "hostess" while on a recent business trip. His examination is remarkable for pharyngeal erythema, shotty cervical and axillary lymphadenopathy, and temperature of 39°C. He has a subtle macular rash.*

## WHAT SIGNS AND SYMPTOMS SHOULD PROMPT TESTING FOR ACUTE HIV?

The signs and symptoms of acute HIV infection are nonspecific and diverse. The primary care clinician cannot rely on patients admitting to high-risk behaviors for acquiring HIV. Clinicians should have a high index of suspicion for acute HIV in febrile patients with a viral syndrome because acute HIV is a major cause of the ongoing epidemic in the United States owing to the high viral load at a time when patients are actively engaging in behaviors that favor transmission. A febrile illness with oral or genital ulcers is highly suggestive of acute HIV, although most patients with acute HIV do not develop ulcers. Rash, diarrhea, headache, sore throat, and lymphadenopathy are common but not always present. Patients can present with a diffuse array of neurological symptoms, predominant gastrointestinal symptoms, elevated results of liver function tests (LFTs), thrombocytopenia, or leukopenia.


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Aseptic meningitis and heterophile-negative mononucleosis are commonly recognized manifestations of acute HIV.[11] Mr H admitted to a high-risk sexual encounter. However, even without this history, he should undergo testing for acute HIV infection because of his symptoms.

## HOW DOES ONE TEST FOR ACUTE HIV?

Patients suspected of having acute HIV should have plasma HIV RNA quantification in addition to a screening HIV EIA blood test. In acute infection, the plasma HIV RNA level is usually more than 50,000 copies/mL and the EIA test result is negative. Low HIV RNA values with a negative antibody test result should be repeated because false-positive viral RNA results have been reported.[11] Recently proposed testing guidelines suggest using a fourth-generation combination HIV p24 antigen and HIV-1/2 antibody test. The fourth-generation HIV antigen/antibody test, which was approved by the FDA in 2010, can detect the p24 antigen of the HIV virus as early as 14 days after infection. It should be followed by confirmatory testing, according to the proposed guidelines.[12]

*Mrs O had an HIV antibody test done as part of the new screening guidelines, and unfortunately, her screening and confirmatory test results for HIV are positive. She returns for a follow-up appointment with Dr Smith, who has a long discussion with Mrs O. At the end of the visit, Dr Smith orders baseline laboratory testing and refers Mrs O to an HIV specialist.*

## WHAT LABORATORY TESTS SHOULD BE ORDERED WITH A NEW HIV DIAGNOSIS?

Laboratory testing that should be ordered for Mrs O includes a complete blood cell count with differential, electrolyte panel, liver enzymes, bilirubin level, lipid panel, HIV RNA quantification, HIV genotype, CD4 lymphocyte count, and urinalysis. All patients who receive a diagnosis of HIV require screening for other sexually transmitted infections, including chlamydia, gonorrhea, and syphilis. Screening for tuberculosis and serologies for toxoplasma and viral hepatitis are also indicated. All women need a cervical Papanicolaou test, and premenopausal women should have a pregnancy test.[13]

*Dr Smith reviews the laboratory data for Mrs O. Her CD4 lymphocyte count is 550 cells/μL, and her HIV RNA level is 67,000 copies/mL. She wonders whether Mrs O is a candidate for antiretroviral treatment and whether any medication is necessary to prevent pneumocystis pneumonia or other opportunistic infections.*

## WHEN SHOULD HIV TREATMENT BE INITIATED?

### Antiretroviral Treatment

Antiretroviral treatment is now recommended for all patients with HIV regardless of their CD4 lymphocyte count to prevent both progression and spread of the disease.[14] The goal of initiating combination antiretroviral treatment (cART), which consists of 3 active HIV drugs from at least 2 classes of medications used in treatment-naive patients, must be balanced with the patient's readiness to begin treatment. Antiretroviral treatment is a lifelong commitment, and nonadherence can result in HIV-resistant strains that complicate future treatment regimens. Antiretroviral treatment is not urgent in asymptomatic patients with chronic HIV infection. The HIV specialist will review the patient's viral genotype, comorbidities, medications, and lifestyle when making cART recommendations. For young women, pregnancy plans will also affect cART choice.

Fortunately, in 2013, many treatment options and classes of medications are available for individuals with HIV. The nucleoside reverse transcriptase inhibitors remain the backbone of most regimens. Additional classes include nonnucleoside reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, fusion inhibitors, and entry blockers. There are multiple fixed-dose combination pills that provide ease of dosing, less pill burden, and decreased risk of development of HIV resistance. Table 2 lists the recommended starting regimens for treatment naive adults without any evidence of resistance in their HIV genotyping.[14]

### Opportunistic Infection Prophylaxis

Pneumocystis pneumonia prophylaxis should be prescribed for patients with a CD4 lymphocyte count below 200 cells/μL or if oropharyngeal candidiasis is present, and it should be continued until the CD4 lymphocyte count

**TABLE 2. Preferred Starting Regimens for Treatment Naive and Nonpregnant Adults Without Human Immunodeficiency Virus Resistance on Genotyping**

| |
|---|
| Nonnucleoside reverse transcriptase inhibitor—based regimen |
| • Atripla (tenofovir/emtricitabine/efavirenz) |
| Protease inhibitor—based regimens |
| • Truvada (tenofovir/emtricitabine) + ritonavir + atazanavir |
| • Truvada (tenofovir/emtricitabine) + ritonavir + darunavir |
| Integrase inhibitor—based regimen |
| • Truvada (tenofovir/emtricitabine) + raltegravir |

Adapted from the Department of Health and Human Services.[14]

remains above 200 cells/μL for at least 3 months. *Mycobacterium avium* complex prophylaxis should be prescribed for patients with a CD4 lymphocyte count below 50 cells/μL and continued until it reaches 100 cells/μL. Prior to initiating MAC prophylaxis, active infection must be ruled out. Trimethoprim-sulfamethoxazole daily remains the preferred prophylaxis for pneumocystis pneumonia and azithromycin for *Mycobacterium avium* complex prophylaxis. For patients with a positive toxoplasma serology result and CD4 lymphocyte count below 100 cells/μL, trimethoprim-sulfamethoxazole double strength daily is the appropriate prophylaxis.[15] Dr Smith notes that Mrs O's CD4 lymphocyte count is 550 cells/μL, so no opportunistic infection prophylaxis is indicated.

*The following week, Mr W, a 56-year-old homosexual man with HIV, returns to see Dr Smith for his hypertension management. His HIV has been well controlled on Atripla (tenofovir/emtricitabine/efavirenz) combination pill for many years.*

## WHAT IS THE ROLE OF THE PRIMARY CARE CLINICIAN IN THE COMANAGEMENT OF PATIENTS WITH HIV?

Since 1996, when cART became the standard of care, AIDS—related deaths have decreased dramatically.[16] With the advent of cART, the US population infected with HIV is beginning to age and have comorbidities similar to those of patients without HIV. Because of this success, it is estimated that by 2015 at least 50% of the people living with HIV in the US will be aged 50 years or older.[17] These patients are at increased risk for developing multiple comorbidities at younger ages than is the general population, likely owing to a combination of factors including HIV-associated inflammation, antiretrovirals, and lifestyle decisions. As a result, primary care clinicians are playing an increasingly important role in the care of patients with HIV. Primary care clinicians have expertise in the prevention and management of chronic diseases, including cardiovascular disease, osteoporosis, diabetes mellitus, mental illness, and cancer, which are becoming increasingly common as individuals with HIV age.

### Cardiovascular Disease

Cardiovascular disease has become a leading cause of death in the US population infected with HIV. It is likely that inflammation associated with untreated HIV infection and adverse effects of cART, including dyslipidemia and metabolic disorders, contribute. However, other risk factors appear to be similar to those of the general population, including elevated low-density lipoprotein cholesterol level, smoking, diabetes mellitus, and hypertension.[18] Regardless of age, all individuals with HIV should have lipid screening yearly and more often if abnormalities are identified.[13] Treatment goals are the same as for individuals who are not infected with HIV, although drug interactions, particularly between statins and antiretrovirals, need to be considered. Dr Smith notes that Mr W has not had a lipid screening in 15 months and places the order to have it completed.

### Kidney Disease

Both acute kidney disease and chronic kidney disease are more common in patients with HIV than in patients without HIV. Since the advent of cART, we have seen a decline in HIV-associated nephropathy but an increase in chronic kidney disease related to the nephrotoxicity of HIV medications, particularly tenofovir, and to comorbidities such as diabetes and hypertension.[19,20] Renal function should be evaluated at the time of initial diagnosis with the measurement of creatinine, estimated glomerular filtration rate, and urinalysis. Renal function monitoring is recommended every 3 to 12 months, depending on the patient's baseline renal function and antiretroviral regimen. The primary care clinician should be alert to the possibility of renal complications in patients with HIV.[13]


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### Bone Mass

Patients with HIV are more likely to have a low bone density and higher rates of bone fracture than patients who are not infected with HIV. HIV-specific risk factors associated with osteoporosis include some cART medications (particularly tenofovir), chronic immune activation, and hypogonadism. Dual-energy x-ray absorptiometry should be considered for all patients aged 50 years regardless of sex. The cost-benefit of performing dual-energy x-ray absorptiometry in younger patients with HIV, less than 60 years old, has not yet been reported.[21]

### Liver Disease

Individuals with HIV have a higher rate of chronic infection with hepatitis B and hepatitis C than the general population. Coinfected patients are at increased risk of progression to cirrhosis. All patients with HIV should be screened for viral hepatitis and should undergo baseline LFTs at the time of their HIV diagnosis. Coinfected patients should be monitored closely by the HIV specialist, and such patients can frequently benefit from the involvement of a liver specialist. In addition, in the cART era, both alcoholic liver disease and nonalcoholic steatohepatitis are increasing in the population infected with HIV. These patients are also at risk for medication toxicity from their antiretroviral treatment.[22] Liver functions tests should be performed every 3 to 6 months in patients with HIV, and any unexplained increase in LFT results should be investigated. For patients with well-controlled HIV infection and progression to end-stage liver disease, liver transplant is an option.[23]

### Malignancies Other Than AIDS-Defining Malignancies

AIDS-defining malignancies, including Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer, are declining in patients with HIV infection, whereas non-AIDS–defining cancers, including anal cancer, Hodgkin lymphoma, hepatocellular carcinoma, skin cancer, head and neck cancer, and lung cancer, are increasing.[24] Clinicians should perform routine malignancy screening and should be alert for symptoms of malignancy at younger ages. Anal Papanicolaou tests should be considered at baseline in all patients with HIV. Cervical Papanicolaou tests are still recommended yearly in all women with HIV. Patients with HIV have a higher rate of abnormal cytology and are more likely to have progression to dysplasia or cancer in the presence of human papillomavirus infection.[13]

*During his visit, Mr W mentions that he has been experiencing heartburn multiple nights per week and that the over-the-counter omeprazole is not effective.*

## WHAT DRUG INTERACTIONS WITH HIV MEDICATIONS ARE COMMON IN PRIMARY CARE?

Multiple HIV medications in the nonnucleoside reverse transcriptase inhibitor and protease inhibitor classes are metabolized by the cytochrome P450 system, including the CYP3A4 system, and interactions should be reviewed before administering any new medication. The most common classes of medications used in primary care that are CYP3A4 metabolized include benzodiazepines; cholesterol-lowering, antiseizure, and erectile dysfunction agents; and warfarin. Herbal drugs that adversely interact with HIV medications include St John's wort and garlic supplements.[25] In this case, Dr Smith notes that acid-reducing medications can reduce the absorption of some HIV medications, but fortunately this is not an issue with the medications that make up Atripla. Dr Smith reminds Mr W of the importance of consulting with his HIV physician or pharmacist before taking any over-the-counter medications or supplements.

## CONCLUSION

Primary care clinicians have many important roles in the care of patients with HIV. Incorporating HIV screening into routine preventive health care for all adults younger than 65 years as recommended by the CDC and the US Preventive Services Task Force will lead to earlier diagnosis and better long-term health of patients with HIV. Recognizing and testing for acute HIV benefits both the individual patient and the community by decreasing transmission rates during this highly contagious period of the infection. Primary care clinicians have been taking a more active role in the comanagement of patients with HIV since the advent of cART, which has resulted in the reduced mortality of patients with HIV and an increase in comorbidities that develop at a younger age

than in the general population. Patients who are receiving stable cART are best served when primary care clinicians and HIV specialists work together in the interest of the individual patient's health.

**Abbreviations and Acronyms:** **cART** = combination antiretroviral treatment; **CDC** = Centers for Disease Control and Prevention; **EIA** = enzyme immunoassay; **FDA** = Food and Drug Administration; **HIV** = human immunodeficiency virus; **LFT** = liver function test; **PrEP** = preexposure prophylaxis

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