Care of Patients With HIV Infection

April 2016

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pp 11-15

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Foreword

The first patients with HIV infection in the United States were reported in 1981. In reading this edition of FP Essentials™, the faces of patients with AIDS that I cared for in the early years of the epidemic came to mind: a young gay man severely ill with *Pneumocystis jirovecii* pneumonia whose partner was constantly by his side in the hospital, a middle-aged woman infected with HIV years earlier via a blood transfusion who died of encephalitis with her family surrounding her, and a young man with a history of intravenous drug use seen in his small apartment during a visit with his home care nurse as he tried to manage the pill burden and adverse effects of early antiretroviral therapy.

Treatment for patients with HIV infection has significantly improved. With appropriate care, as outlined in this edition of FP Essentials, HIV infection and AIDS have become chronic conditions to be managed, rather than the death sentence they used to be. The Centers for Disease Control and Prevention estimates that approximately 1.2 million individuals in the United States are infected with HIV, so approximately 1 in 258 patients in my practice and yours is likely to be HIV-positive. However, we may not be aware of these patients; only approximately 87% have been diagnosed, and only approximately 30% are receiving the care necessary to fully suppress the virus. My electronic medical record shows I have about 3,000 patients in my practice, so I should have approximately 12 patients with HIV infection, but I know of only two who are receiving antiretroviral therapy. We can do better. I found this edition quite educational. I hope you do, too.

Please provide feedback. We look forward to reading your comments. And if you are interested in writing for FP Essentials, please visit our website, where calls for authors are posted three times per year: http://www.aafp.org/cme/subscriptions/fp-essentials/authors.html.

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Learning Objectives

1. Screen appropriate patients for HIV infection.
2. Assess for HIV infection in patients with symptoms consistent with acute HIV infection.
3. Obtain appropriate initial and follow-up testing for patients with HIV infection.
4. Initiate antiretroviral therapy for all patients with HIV infection who are able to consent, commit, and adhere to treatment, regardless of CD4 count or viral load.
5. Initiate evidence-based prophylaxis for opportunistic infections in patients with HIV infection, appropriate CD4 counts, and risk factors.
6. Apply current guidelines when selecting an initial antiretroviral treatment regimen.
7. Screen all patients with HIV infection for sexually transmitted infections as recommended in current guidelines.
8. Recommend appropriate vaccinations for patients with HIV infection.
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The mission of FP Essentials is to provide practicing family physicians, family medicine residents, and other clinicians and trainees with high-quality, cost-effective educational content that emphasizes new advances in clinical practice.

Objectives
1. To provide learners with information on advances in clinical practice to aid them in providing up-to-date care for their patients.
2. To assist learners in preparing for the American Board of Family Medicine (ABFM) certification and recertification examinations. Each monthly edition of FP Essentials is part of a 9-year curriculum that presents topics with areas of emphasis similar to those on the ABFM examinations.
3. To provide learners with content that meets their CME needs and requirements.
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1. According to the Centers for Disease Control and Prevention, which one of the following percentages of the 1.2 million individuals with HIV infection in the United States are unaware of their condition?
   ❑ A. 1% to 5%.
   ❑ B. 6% to 10%.
   ❑ C. 11% to 15%.
   ❑ D. 16% to 20%.
   ❑ E. 21% to 25%.

2. The US Preventive Services Task Force recommends universal HIV screening regardless of risk for which one of the following groups?
   ❑ A. Adolescents and adults ages 15 to 65 years.
   ❑ B. Pregnant women.
   ❑ C. Women with unknown HIV status who present in labor.
   ❑ D. All of the above.

3. Which one of the following statements about acute HIV infection is true?
   ❑ A. Leukopenia or thrombocytopenia occurs in approximately 51% of patients.
   ❑ B. It produces a clinical illness in 10% to 15% of patients.
   ❑ C. Rhinorrhea, nasal congestion, and cough are common symptoms.
   ❑ D. Symptoms begin 2 to 3 days after infection.

4. A patient with HIV infection, who grew up in Puerto Rico, has a CD4 count of 100 cells/mm$^3$ as well as fever, diarrhea, leukopenia, and mouth ulcers. Urine antigen testing should be used to diagnose or rule out which one of the following opportunistic infections?
   ❑ A. Coccidioidomycosis.
   ❑ B. Cryptococcosis.
   ❑ C. Histoplasmosis.
   ❑ D. Toxoplasmosis.

5. At which one of the following CD4 counts should antiretroviral therapy be offered to patients with HIV infection who are able to consent, commit, and adhere to treatment?
   ❑ A. Less than 200 cells/mm$^3$.
   ❑ B. Less than 500 cells/mm$^3$.
   ❑ C. Less than 1,000 cells/mm$^3$.
   ❑ D. Any count.

6. To prevent chelation, which one of the following drugs should not be taken with antacids or supplements containing magnesium, aluminum, iron, calcium, or zinc?
   ❑ A. Cobicistat.
   ❑ B. Darunavir.
   ❑ C. Dolutegravir.
   ❑ D. Maraviroc.

7. Which one of the following vaccinations is recommended routinely for a 35-year-old woman with HIV infection and a viral load of 20,000 copies/mL, a CD4 count less than 200 cells/mm$^3$, and a history of childhood varicella?
   ❑ A. Inactivated influenza.
   ❑ B. Live influenza.
   ❑ C. Varicella.
   ❑ D. Zoster.

8. A candidate for preexposure prophylaxis with emtricitabine-tenofovir would be HIV-negative and have which one of the following characteristics?
   ❑ A. A creatinine clearance less than 60 mL/min/1.73m$^2$.
   ❑ B. A history of osteoporosis.
   ❑ C. Active intravenous drug use.
   ❑ D. An HIV-negative partner.
Pretest Answers

Question 1: The correct answer is C.
The Centers for Disease Control and Prevention estimates that approximately 87% of the 1.2 million individuals infected with HIV in the United States have been diagnosed, which means that approximately 14% (156,000 individuals) are unaware that they are infected. See page 11.

Question 2: The correct answer is D.
The US Preventive Services Task Force (USPSTF) recommends screening adolescents and adults ages 15 to 65 years at least once for HIV infection regardless of risk level. For pregnant women, the Centers for Disease Control and Prevention, USPSTF, and American College of Obstetricians and Gynecologists endorse universal HIV screening regardless of risk to decrease mother to child transmission of HIV. Patients presenting in labor with unknown HIV status should undergo rapid HIV testing. See pages 11-12.

Question 3: The correct answer is A.
Leukopenia or thrombocytopenia occurs in approximately 51% of patients with acute HIV infection. See page 16.

Question 4: The correct answer is C.
Disseminated histoplasmosis occurs in patients with HIV infection who have lived in areas in which the Histoplasma capsulatum fungus is endemic, including states bordering the Ohio River valley and the lower Mississippi River; Puerto Rico; and many countries in Central America and South America. Fever, diarrhea, leukopenia, and oral ulcers are common symptoms. This condition typically occurs in patients with CD4 counts less than 150 cells/mm³. Urine antigen testing is used to make the diagnosis. See page 21.

Question 5: The correct answer is D.
The Department of Health and Human Services recommends antiretroviral therapy for all patients with HIV infection who are able to consent, commit, and adhere to treatment regardless of CD4 count or viral load. See page 23.

Question 6: The correct answer is C.
Dolutegravir must be taken 2 hours before or 6 hours after antacids or supplements containing magnesium, aluminum, iron, calcium, or zinc, to prevent chelation. See page 24.

Question 7: The correct answer is A.
The inactivated influenza vaccine is recommended for all patients with HIV infection. See page 34.

Question 8: The correct answer is C.
Characteristics of candidates for preexposure prophylaxis include HIV-negative status and active intravenous drug use. See Table 11.
Key Practice Recommendations

1. Screen all patients ages 15 to 65 years for HIV infection at least once, regardless of risk factors.

2. Screen for HIV infection using the fourth-generation tests listed in the Centers for Disease Control and Prevention's recommended HIV testing algorithm (ie, p24 antigen/antibody combination immunoassay, antibody differentiation assay, nucleic acid amplification test).

3. Monitoring of CD4 count may be discontinued in patients with HIV infection who have a CD4 count greater than 500 cells/mm$^3$ and demonstrate consistent viral suppression (ie, viral load of less than 200 copies/mL) for more than 2 years.

4. For patients with HIV infection, assess lipid and A1c or fasting blood glucose levels on entry into care and before initiating or modifying antiretroviral therapy.

5. For adults with HIV infection, initiate prophylaxis for *Pneumocystis jirovecii* pneumonia in patients with CD4 counts less than 200 cells/mm$^3$ or a history of oropharyngeal candidiasis; toxoplasmic encephalitis in patients with CD4 counts of less than 100 cells/mm$^3$ and positive serum *Toxoplasma gondii* immunoglobulin G antibody results; disseminated *Mycobacterium avium* complex disease in patients with CD4 counts less than 50 cells/mm$^3$.

6. Offer antiretroviral therapy to all HIV-positive patients able to consent, commit, and adhere to treatment, regardless of CD4 count or viral load.

7. Screen all patients with HIV infection for sexually transmitted infections (ie, chlamydia and gonorrhea in men and women, trichomoniasis in all women) on initiation of care and annually thereafter if risk factors are present.

Resources

1. **Strength of evidence: SORT A**
   - **Source:** US Preventive Services Task Force, reference 9.

2. **Strength of evidence: SORT A**
   - **Source:** Centers for Disease Control and Prevention, reference 12.
   - **Website:** http://stacks.cdc.gov/view/cdc/23447

3. **Strength of evidence: SORT C**
   - **Source:** Dept of Health and Human Services, reference 31.
   - **Website:** https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf

4. **Strength of evidence: SORT B**
   - **Source:** Dept of Health and Human Services, reference 31.
   - **Website:** https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf

5. **Strength of evidence: SORT A**
   - **Source:** Centers for Disease Control and Prevention, National Institutes of Health, HIV Medicine Association of the Infectious Diseases Society of America, reference 42.
   - **Website:** http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_o.pdf

6. **Strength of evidence: SORT A**
   - **Source:** Dept of Health and Human Services, reference 31.
   - **Website:** https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf

7. **Strength of evidence: SORT A**
   - **Source:** *Clin Infect Dis*, reference 109.
   - **Website:** http://cid.oxfordjournals.org/content/58/1/1.full
### Strength of Recommendation Taxonomy (SORT)

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>• Recommendation based on consistent and good-quality patient-oriented evidence.¹</td>
</tr>
<tr>
<td>B</td>
<td>• Recommendation based on inconsistent or limited-quality patient-oriented evidence.¹</td>
</tr>
<tr>
<td>C</td>
<td>• Recommendation based on consensus, usual practice, opinion, disease-oriented evidence,² or case series for studies of diagnosis, treatment, prevention, or screening.</td>
</tr>
</tbody>
</table>

¹Patient-oriented evidence measures outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life. Disease-oriented evidence measures intermediate, physiologic, or surrogate end points that may or may not reflect improvement in patient outcomes (eg, blood pressure, blood chemistry, physiologic function, pathologic findings).


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**AAFP FP Essentials™ Approved as CME Clinical Content**

This enduring material activity, *FP Essentials™*, has been reviewed and is acceptable for up to 60 Prescribed credits by the American Academy of Family Physicians. AAFP certification begins June 1, 2014. Term of approval is for two years from this date. Each monograph is approved for 5 Prescribed credits. Credit may be claimed for two years from the date of each monograph. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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The American Academy of Family Physicians designates this enduring material activity for a maximum of 60 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.
Case 1. James is a 24-year-old black man who presents to your office. He says he has not seen a physician recently. He works as a cook and lives with his wife and two young children. He uses fluticasone and albuterol inhalers for mild persistent asthma but has no other significant medical history. He smokes marijuana but does not drink alcohol or use other drugs. When asked if he has sex with men, women, or both, he says “both,” although he identifies as “straight.” He uses condoms as birth control with his wife, but does not use them regularly with others. He has lost weight in the past year, always feels tired, and is concerned. The result of an in-home HIV test was positive, and he was referred to your office for confirmatory testing. He wants to know if the positive result of the in-home HIV test is correct.

The new face of the HIV epidemic in the United States is that of young black men who have sex with men and are poorly connected to and historically not well served by the health care system. The annual rate of new diagnoses of HIV infection per 100,000 individuals in the US population decreased by 33% from 2002 to 2011. However, the incidence of HIV infection increased in the 13- to 24-year-old age range, particularly among men who have sex with men, in whom it rose 12% from 2008 to 2010. Among them, blacks ages 13 to 24 years had the highest rate of increase. Although blacks account for only 12% of the US population, they comprised 41% of individuals living with HIV infection in the United States in 2011. Among patients with HIV infection who were receiving care, a 2015 longitudinal cohort study showed the 10-year mortality risk for black men and women was 7.2% and 7.9% higher, respectively, than that for white men.

Establishment of a personal connection between patients and the health care team has been shown to be a key factor in retaining patients with HIV infection in medical care. It also has been shown that use of multidisciplinary care teams supported by the federal Ryan White CARE Act can improve patient retention and viral suppression rates.

Candidates for Screening

The Centers for Disease Control and Prevention (CDC) estimates that approximately 87% of the 1.2 million individuals infected with HIV in the United States have been diagnosed (Figure 1), which means that approximately 14% (156,000 individuals) are unaware that they are infected. Widespread screening is needed to achieve the Joint United Nations Programme on HIV/AIDS goal of Getting to Zero (ie, zero new infections, zero AIDS-related mortalities, zero discrimination), with renewed focus on difficult-to-screen populations with higher rates of HIV transmission. The US Preventive Services Task Force (USPSTF) recommends screening adolescents and adults ages 15 to 65 years at least once for HIV infection regardless of risk level. The CDC recommends routine testing of patients...
as young as 13 years because of the recent increase in infection rates among adolescents. Screening outside of this age range and repeat testing are recommended for patients at higher risk (Table 1). It is unclear how frequently patients at higher risk should be tested, but it is reasonable to test annually or more frequently, based on risk level. Risk factors may change over time, so these should be reassessed regularly. Patients may be reluctant to disclose sensitive personal information related to screening. A strong physician-patient relationship built on continuity and trust can increase the likelihood of an honest discussion of risk factors.

For pregnant women, the CDC, USPSTF, and American College of Obstetricians and Gynecologists endorse universal HIV screening regardless of risk to decrease mother to child transmission of HIV. In high-incidence areas (ie, those with at least 1 pregnant woman with HIV/1,000 women screened) or in patients with ongoing risks for exposure, repeat testing in the third trimester is recommended. Patients presenting in labor with unknown HIV status should undergo rapid testing. To reduce the risk of perinatal transmission, positive test results should trigger initiation of antiretroviral therapy without waiting for confirmatory test results.

**Screening Methods**

Screening for HIV infection has evolved significantly in the past few years, with the changes affecting clinic-, hospital-, community-, and home-based testing. In 2014, the CDC recommended adoption of fourth-generation HIV tests. These tests have a shorter window period (ie, time between infection and a positive test result), which decreases the number of false-negative and indeterminate results. The recommended algorithm uses an HIV antibody assay and a p24 antigen test. The presence of p24 antigen can be detected as early as 14 days after infection, which is 1 to 2 weeks before the emergence of HIV antibody. If one of these test results is positive, the sample is then tested with an HIV-1/HIV-2 antibody differentiation assay. Samples that show a positive initial antibody/antigen test result but a negative or indeterminate HIV-1/HIV-2 differentiation assay result are tested with a nucleic acid test.

Because early treatment significantly improves patient outcomes and reduces HIV transmission rates, it is essential to identify patients as early in the course of infection as possible. Fourth-generation testing allows for improved differentiation between HIV-1 and HIV-2, which can affect the clinical course and drug choices. Potential disadvantages of fourth-generation

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**Figure 1. Individuals Living With Diagnosed or Undiagnosed HIV Infection, 2012**

**National HIV Surveillance System:** Estimated number of persons aged ≥13 years living with diagnosed or undiagnosed HIV infection (prevalence) in the United States at the end of 2012. The estimated number of persons with diagnosed HIV infection was calculated as part of the overall prevalence estimate.

**Medical Monitoring Project:** Estimated number of persons aged ≥18 years who received HIV medical care during January to April of 2012, were prescribed ART, or whose most recent VL in the previous year was undetectable or <200 copies/mL—United States and Puerto Rico.

HIV tests are that they require venous blood sample collection and follow-up to disclose results.

For some testing sites, third-generation antibody tests are more practical. These test results are available more rapidly, and third-generation tests have sensitivities and specificities greater than 98%. When managing occupational exposures or testing pregnant patients in active labor, the shorter time to results (eg, 20 minutes or less) of rapid third-generation antibody testing may be preferred.

Although the stigma of HIV infection has diminished, some individuals may hesitate to seek facility-based testing and instead use anonymous in-home tests. The Home Access HIV-1 Test System is a Food and Drug Administration-approved antibody-based finger-stick blood sampling test with results available the next business day. Samples with positive test results undergo confirmatory testing and posttest counseling is offered, with referral for treatment if necessary. The cost ranges from $44 to $60, the latter for next-day results. The second approved in-home testing kit, the OraQuick In-Home HIV Test, costs approximately $40. It uses a mouth swab, tests for HIV-1 and HIV-2 antibodies, and produces results in 20 to 40 minutes. Although OraQuick has high sensitivity (99.3%) and specificity (99.8%), its results and those of other rapid HIV tests must be confirmed with a fourth-generation HIV test or a Western blot. OraQuick offers confidential posttest counseling via telephone and referral to a confirmatory testing site.

Advantages of in-home testing include increased access to screening by eliminating potential barriers such as obligatory posttest counseling or lack of access to a testing site. Concerns regarding in-home tests include the risk of false-negative results during the window period, possible lack of follow-up for posttest counseling and referral for care, and a lack of data on use among adolescents. In-home testing is not covered by many health care insurance companies and may be cost-prohibitive for some individuals. Nevertheless, physicians should be aware that in-home HIV tests may be widely used among certain populations.

Case 1, cont’d. You obtain a fourth-generation HIV test to confirm James’ previous positive test results, and schedule a follow-up visit with him in 1 week to review the results.

### Table 1

<table>
<thead>
<tr>
<th>Risk Factors Warranting Frequent HIV Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homelessness</td>
</tr>
<tr>
<td>Incarceration</td>
</tr>
<tr>
<td>Inconsistent condom use</td>
</tr>
<tr>
<td>Injection drug use</td>
</tr>
<tr>
<td>Men who have sex with men</td>
</tr>
<tr>
<td>Multiple partners</td>
</tr>
<tr>
<td>Seropositive partner</td>
</tr>
<tr>
<td>Sexually transmitted infections</td>
</tr>
</tbody>
</table>


### HIV-Specific Laws

Many HIV-specific laws reflect the stigma associated with HIV infection and AIDS. State laws vary widely regarding HIV testing and criminalization of HIV exposure and transmission, and many such laws have created barriers to testing. In 2006, the CDC recommended that “separate written consent for HIV testing should not be required,” instead, an opt-out approach should be taken, in which “general consent for medical care should be considered sufficient to encompass consent for HIV testing.” The CDC also recommended that “prevention counseling—defined as an interactive process of assessing risk of infection, recognizing specific behaviors that increase this risk, and developing a plan to reduce risk—should not be required with HIV diagnostic testing or as part of HIV screening programs in health care settings.” As CDC recommendations have evolved to endorse universal screening, some state laws also have changed to decrease barriers to testing. A full review of such laws is beyond the scope of this edition of FP Essentials.
However, because state laws regarding HIV vary widely and are subject to change, physicians should consult the government website of their state for information on applicable laws.  

Laws on criminalization of HIV exposure and transmission are varied, complex, and occasionally outdated. For example, in some states it is a felony to expose an individual to HIV without warning of the risk. Such laws were enacted in hopes of deterring risky behaviors and preventing intentional exposures. Opponents of these laws claim there is no evidence that the laws have achieved their objectives. Many statutes date from a time when transmission risk was poorly understood. For example, although it is now estimated that viral suppression with antiretroviral therapy (to a viral load of less than 200 copies/mL) for more than 6 months reduces the risk of sexual transmission of HIV to 1 in approximately 100,000 sex acts without condoms, some states still consider such sex acts criminal. Widespread use of preexposure prophylaxis has further prevented HIV transmission.

**Positive HIV Test Results**

Although awareness of HIV has significantly improved in recent years, it is essential for the clinician to assess each patient’s knowledge and educate in a culturally sensitive manner. This should include a discussion of partner notification and testing, which requires awareness of local mandates and resources available to aid in partner notification. A useful resource for this is InSpot.org, which allows patients to send anonymous e-cards informing their partners of the need to be tested for a sexually transmitted infection. (Available at http://www.inspot.org/.)

It should be emphasized to patients that with current treatments, HIV infection is now a chronic condition that can be managed with appropriate medical care. Oftentimes, a discussion of a cure may arise in the initial visit. Intensive research in this area has yet to yield a cure. However, current treatments allow patients with HIV infection to live healthy lives with life expectancies similar to those of patients without HIV infection.

**Case 1, cont’d.** When James returns for the follow-up visit, you notify him that the result of the confirmatory HIV test is positive. You ask about his understanding of the implications of this result, give him time to share his reactions, and offer him the opportunity to speak with a behavioral health staff member. Blood tests are necessary before initiating therapy, so you obtain samples and schedule a follow-up appointment in 2 weeks. This allows time for the baseline genotype and other pretreatment laboratory test results to return, and gives James time to consider all of this new information and to prepare to begin treatment.

**Monitoring**

The CD4 T lymphocyte is the target of HIV infection, and the CD4 count is regularly used in patient monitoring. CD4 counts typically show massive depletion at the time of initial infection, followed by partial recovery, and then a steady decline over 5 to 15 years (an average of 10 years) before crossing the AIDS threshold, which is defined as a CD4 count of less than 200 cells/mm³ for an adult. The rate of decline varies based on the genetic and immunologic characteristics of the host and the virus.

The CD4 count is the product of the total white blood cell count, the percentage of white blood cells that are lymphocytes, and the percentage of lymphocytes in the peripheral blood expressing the CD4 receptor. Thus, the CD4 count is profoundly affected by changes in the differential white blood cell count. For example, the CD4 count can be reduced by the lymphocyte depletion produced by steroid therapy, by the reduction in total white cells in some non-HIV infections, or by the shift to neutrophil and neutrophil precursor predominance in acute bacterial infections.

One or more of these factors often is present when a patient presents to the emergency department or is admitted to the hospital for acute illness, so CD4 counts obtained at these times may grossly overestimate the degree of immunodeficiency. In such situations, it is preferable to use the last value obtained in an outpatient setting when the patient was in stable condition.

The other test used in monitoring, the plasma HIV RNA or viral load, is performed in most laboratories using an ultrasensitive RNA polymerase chain reaction test, with lower limits of detection ranging from less than 20 to 75 copies/mL. These tests may detect low levels of virus present in many patients who may be accustomed to undetectable viral loads using older, less sensitive tests. Although the goal of antiretroviral therapy is achieving an undetectable viral load, guidelines typically define viral suppression as a viral load of less than 200 copies/mL, and virologic failure as inability to achieve or maintain a viral load of 200 copies/mL or greater.

Recommendations for initial tests for patients with HIV infection are shown in Table 2. Detailed
recommendations for ongoing monitoring are available online in the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (available at https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf). These recommendations address testing for comorbid conditions commonly seen in patients with HIV infection, antiretroviral efficacy, and drug toxicities that may affect decisions about treatment and prophylaxis.

As treatments have become more tolerated and more likely to provide viral suppression, guidelines have loosened regarding the frequency and extent of monitoring. Per 2015 guidelines, CD4 count monitoring is considered optional for patients with CD4 counts consistently greater than 500 cells/mm³ with more than 2 years of viral suppression.

Viral loads should be evaluated 2 to 8 weeks after regimen initiation or changes, and then should be assessed every 3 to 6 months, or sooner if clinically indicated. A CD4 count should be obtained every 3 to 6 months for patients who are not receiving treatment, who are receiving treatment but have detectable viral loads, or who have a CD4 count less than 300 cells/mm³.

Other laboratory tests should be obtained periodically, as shown in the guidelines.

---

Table 2
Initial Testing for Patients With HIV Infection

<table>
<thead>
<tr>
<th>Tests</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic metabolic panel, urinalysis</td>
<td>Assess for underlying renal dysfunction that could affect choice of antiretroviral therapy, such as tenofovir</td>
</tr>
<tr>
<td>CD4 count, CD4 percent</td>
<td>Stage the degree of immunosuppression</td>
</tr>
<tr>
<td>Cervical Papanicolaou test</td>
<td>Screen for cervical cancer</td>
</tr>
<tr>
<td>Chlamydia and gonorrhea tests</td>
<td>Initiate treatment if positive</td>
</tr>
<tr>
<td>Complete blood count</td>
<td>Assess for underlying hematopoietic dysfunctions, such as with HIV-related immune thrombocytopenic purpura, or cirrhosis-related etiologies</td>
</tr>
<tr>
<td>Glucose-6-phosphate dehydrogenase</td>
<td>Identify patients at risk of methemoglobinemia with use of drugs, such as dapsone</td>
</tr>
<tr>
<td>Hepatitis A IgG</td>
<td>Immunization recommended for certain populations; consider immunization for all patients if nonimmune</td>
</tr>
<tr>
<td>Hepatitis B sAg, sAb, cAb</td>
<td>Immune if nonimmune; evaluate if long-term infection is present, and choose antiretroviral therapy appropriately</td>
</tr>
<tr>
<td>Hepatitis C Ab</td>
<td>If positive, measure hepatitis C viral load and consider drug interactions with hepatitis C antivirals when choosing antiretroviral therapy</td>
</tr>
<tr>
<td>HIV genotypic resistance testing</td>
<td>Assess for baseline transmitted resistance mutations</td>
</tr>
<tr>
<td>HIV RNA quantitative (viral load)</td>
<td>Assess the degree of native immune viral suppression</td>
</tr>
<tr>
<td>HLA-B*5701</td>
<td>Identify patients at risk of abacavir hypersensitivity reaction</td>
</tr>
<tr>
<td>Lipid profile, A1c</td>
<td>Assess for underlying dyslipidemia or diabetes</td>
</tr>
<tr>
<td>Liver function tests</td>
<td>Assess for underlying hepatic inflammation or dysfunction</td>
</tr>
<tr>
<td>Syphilis IgG</td>
<td>Initiate treatment if positive; obtain lumbar puncture if the patient has neurologic symptoms</td>
</tr>
<tr>
<td>Toxoplasma IgG, cytomegalovirus IgG</td>
<td>Assess for latent toxoplasmosis or cytomegalovirus infection, which might affect evaluation of opportunistic infections</td>
</tr>
<tr>
<td>Tuberculin skin test or interferon-gamma release assay</td>
<td>Assess for latent tuberculosis, initiate treatment if detected</td>
</tr>
</tbody>
</table>

*Recommended for all men who have sex with men and other patients with indications (eg, injection drug users, travelers to countries of high prevalence, patients with chronic liver disease, patients with hepatitis B and/or C infection).

Ab = antibody; Ag = antigen; c = core; Ig = immunoglobulin; s = surface.

SECTION TWO
Medical Complications and Comorbidities

Care of patients with HIV infection starts with diagnosis as soon as possible, preferably at or near the time of acute infection. Opportunistic infections, malignancies, and other conditions develop progressively over time, particularly in untreated patients. The AIDS-defining opportunistic infections most common in the United States include *Pneumocystis jirovecii* pneumonia, *Candida* esophagitis, toxoplasmic encephalitis, tuberculosis, disseminated *Mycobacterium avium* complex, cryptococcal meningitis, and cytomegalovirus retinitis. Specific prophylaxis regimens exist for several opportunistic infections, and effective antiretroviral therapy reduces the risk of most others. Other AIDS-defining conditions include wasting syndrome and HIV encephalopathy. AIDS-defining malignancies include Kaposi sarcoma, systemic non-Hodgkin lymphoma, primary central nervous system lymphoma, and invasive cervical cancer. Although not an AIDS-defining condition, anal cancer is common in patients with HIV infection. Other HIV-related conditions include thrombocytopenia, recurrent bacterial respiratory infections, HIV-associated nephropathy, and HIV-associated neurocognitive disorder.

**Acute Retroviral Syndrome**

Recognition of acute HIV infection is a critical step in improving the health of patients and limiting spread of the virus. The likelihood that the CD4 count will return to normal with treatment is greatest for patients who start therapy within 4 months of acquiring HIV infection, and the risk of transmission is greatest in the earliest weeks when the viral load is highest. Studies show that individuals who are aware of their HIV infection are more likely to take measures to protect their sexual and drug-using partners. HIV infection results in a clinical illness in as many as 89% of patients. Acute retroviral syndrome starts as early as 7 to 10 days after infection with HIV, and commonly includes fever, headache, pharyngitis, oral ulcers, diarrhea (related to massive depletion of gut-associated lymphoid cells), arthralgias, myalgias, rash, and lymphadenopathy. It does not produce rhinorrhea, nasal congestion, or cough, so symptoms more closely resemble those of mononucleosis than the common cold. Some patients experience neurologic manifestations, including aseptic meningitis, Bell palsy, Guillain-Barré syndrome, brachial neuritis, encephalitis, or psychosis. Leukopenia or thrombocytopenia occurs in approximately 51% of patients with acute HIV infection. When present, either should increase the level of suspicion, as should the presence or a history of genital ulcers. Weight loss is one of the most common signs within the first 6 months of HIV infection (ie, early infection). Table 3 shows the frequency with which clinical signs and symptoms occur.

Some patients with acute HIV infection may be sufficiently ill to warrant hospitalization, others have nondescript illnesses that may be recognized in retrospect, but might have been identified as acute HIV infection earlier had the level of suspicion been higher. Clinicians must consider acute HIV infection in the differential diagnosis of patients with these symptoms and approach testing of patients in an open, nonjudgmental manner.

Case 1, cont’d. James comes to your office reporting shortness of breath starting 3 days ago and a temperature of 37.9°C (100.2°F) last night. He has a nonproductive cough but no chest pain, myalgias, or other symptoms. He reports no contact with ill individuals at home or work. On physical examination, he does not appear acutely ill. His temperature is 37.0°C (98.6°F), blood pressure is 100/62 mm Hg, heart rate is 86 beats/min, and respiratory rate is 18 breaths/min. He has no thrush, oral hairy leukoplakia, or pharyngeal erythema, and breath sounds are normal. The oxygen saturation level is 97% at rest, but when he walks down the hallway, it decreases to 83% and the heart rate increases to 110 beats/min. You decide to send James to your affiliated hospital’s pulmonary clinic for a chest x-ray, arterial blood gas measurement, and collection of induced sputum for *Pneumocystis jirovecii* testing.
AIDS-Defining Opportunistic Infections

Opportunistic infections among patients with HIV infection are markedly less common today than in the earlier days of the HIV epidemic. Recommended regimens for treatment and primary and secondary prophylaxis are detailed in Department of Health and Human Services (DHHS) guidelines. These guidelines are updated frequently and should be consulted often in the management of opportunistic infections. The guidelines provide specific information about when to initiate antiretroviral therapy for treatment-naive patients with opportunistic infections.

The AIDS-defining opportunistic infections discussed here are the ones most commonly encountered in the United States. Patients with AIDS may have more than one opportunistic infection, and symptoms of opportunistic infections being managed or yet undiagnosed may manifest after initiation of antiretroviral therapy and subsequent increase in CD4 count, a process called immune reconstitution inflammatory syndrome (IRIS). Table 4 provides a list of AIDS-defining conditions.

Antiretroviral therapy is the most effective method of preventing opportunistic infections. However, for patients with CD4 counts below certain thresholds, primary prophylaxis is recommended as shown in Table 5. The strongest recommendations are to initiate primary prophylaxis for *Pneumocystis jirovecii* pneumonia in patients with CD4 counts less than 200 cells/mm³ or a history of oropharyngeal candidiasis, for toxoplasmic encephalitis in patients with CD4 counts less than 100 cells/mm³ and positive serum *Toxoplasma gondii* immunoglobulin (Ig) G results, and for disseminated *Mycobacterium avium* complex in patients with CD4 counts less than 50 cells/mm³. There also is a weaker recommendation for primary prophylaxis of histoplasmosis for patients with CD4 counts less than 150 cells/mm³ who live in highly endemic areas or have occupational exposure. Clinicians should consult the DHHS guidelines for specific information about transitioning patients from opportunistic infection management to secondary prophylaxis.

**Pneumocystis jirovecii Pneumonia**

Often referred to as PCP, *P jirovecii* (previously *carinii*) pneumonia is a fungal infection that typically follows a subacute course of progressive dyspnea and nonproductive cough. Patients frequently experience chest pain that is more pressure than pleuritic in nature, except when a bleb or cyst ruptures and causes pneumothorax. The cough often is provoked by deep inspiration. Fever is mild, if present, and the upper respiratory prodrome seen in many patients with community-acquired pneumonia is absent.

Before the advent of antiretroviral therapy, most patients with *P jirovecii* pneumonia died within 2 years. Treatment of *P jirovecii* pneumonia in children with acute lymphocytic leukemia proved the effectiveness of trimethoprim-sulfamethoxazole, making this a treatable opportunistic infection. Early studies in patients with AIDS found that adding pred-

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**Table 3**

<table>
<thead>
<tr>
<th>Sign or Symptom</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>97</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>77</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>73</td>
</tr>
<tr>
<td>Rash</td>
<td>70</td>
</tr>
<tr>
<td>Myalgia or arthralgia</td>
<td>58</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>51</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>38</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33</td>
</tr>
<tr>
<td>Headache</td>
<td>30</td>
</tr>
<tr>
<td>Elevated serum aminotransferase levels</td>
<td>23</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>20</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>17</td>
</tr>
<tr>
<td>Oral thrush</td>
<td>10</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>8</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>8</td>
</tr>
</tbody>
</table>

*As identified in a review of 139 reported cases.*

*Also reported, though less frequently, were esophageal ulceration, esophageal candidiasis, nephritis, rhabdomyolysis with acute renal failure, hypoxemia, and fatal aplastic anemia. Reprinted with permission from Clark SJ, Saag MS, Decker WD, et al. High titers of cytopathic virus in plasma of patients with symptomatic primary HIV-1 infection. N Engl J Med. 1991;324(14):954-960.*
nisone for those with oxygen saturation levels less than approximately 70% on room air (for whom the mortality rate was at least 50%) decreased the early deterioration that frequently developed after initiation of therapy and significantly reduced mortality rates.44-46 (This is an off-label use of prednisone.) However, the addition of folic acid to prevent bone marrow toxicity from trimethoprim-sulfamethoxazole was shown to impair response to therapy.47

A high level of suspicion combined with oxygen desaturation on exercise have proven to be sensitive indicators of this infection.44-46 Lung examination results often are normal, although fine dry crackles occasionally are audible. The presence of wheezing, rhonchi, or wet rales does not support a diagnosis of P jirovecii pneumonia. The CD4 count most often is less than 200 cells/mm³ in patients with this infection but can be higher in patients with oropharyngeal candidiasis and in patients who were receiving but discontinued antiretroviral therapy.

The classic sign of P jirovecii pneumonia on chest x-ray is diffuse reticulonodular opacities but the x-ray results may be normal or show almost any type of abnormality.48,49 Sputum induced by inhaling 3% saline can be directly stained for detection of the organism. Positive stain results are diagnostic, but if results are negative, bronchoalveolar lavage (which has 95% sensitivity) should be obtained if necessary.42,48 Elevation of the serum beta-d-glucan level is highly sensitive for Pneumocystis infection, and normal levels have a high negative predictive value.50

### Table 4
#### AIDS-Defining Conditions

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
</table>
| **Bacterial** | *Mycobacterium tuberculosis*: of any site, pulmonary, disseminated, or extrapulmonary  
*Mycobacterium avium complex* or *Mycobacterium kansasii*: disseminated or extrapulmonary  
*Mycobacterium, other species* or unidentified species: disseminated or extrapulmonary  
Recurrent *Salmonella* sepsis  
Recurrent bacterial pneumonia (≥1 episode in 1 year)  
Multiple or recurrent infections |
| **Fungal** | *Pneumocystis jirovecii* pneumonia  
*Candidiasis*: esophagus, bronchi, trachea, or lungs  
Cryptococcosis: extrapulmonary  
Histoplasmosis: disseminated or extrapulmonary  
Coccidioidomycosis: disseminated or extrapulmonary |
| **Neoplasms** | Invasive cervical cancer  
Kaposi sarcoma  
Lymphoma: primary central nervous system, systemic non-Hodgkin (Burkitt, immunoblastic) |
| **Other** | HIV-related wasting syndrome  
HIV-related encephalopathy |
| **Parasites/ protozoa** | Toxoplasmosis: brain, onset at age ≥1 month  
Cryptosporidiosis: chronic intestinal ≥1 month duration  
Isosporiasis: chronic intestinal ≥1 month duration |
| **Viral** | Cytomegalovirus: retinitis or disease (other than liver, spleen, or lymph nodes), onset at age ≥1 month  
Herpes simplex: chronic ulcers ≥1 month duration or bronchitis, pneumonitis, or esophagitis; onset at age ≥1 month  
Progressive multifocal leukoencephalopathy (JC virus) |

*Only among adults, adolescents, and children ages ≥6 years.  
Only among children ages <6 years.  
on the clinical presentation and response to empiric fluconazole. However, nonresponse to treatment may be attributable to drug resistance or esophagitis due to other etiologies (eg, herpes simplex, cytomegalovirus infection, HIV-related aphthous ulcers). A definitive diagnosis requires esophagogastroduodenoscopy with biopsies.

**Toxoplasmic Encephalitis**

Toxoplasmic encephalitis occurs predominantly in patients with CD4 counts less than 100 cells/mm$^3$ who also have preexisting antibody to *T. gondii*, indicative of prior infection and the presence of cysts in the brain (and occasionally the retina) that can reactivate. These patients have ring-enhancing lesions on brain imaging and may have focal neurologic deficits, headache, or seizures. Empiric treatment for toxoplasmosis typically is begun immediately and should produce a clinical response within 14 days. Brain biopsy for alternative diagnoses typically is reserved for patients who do not improve with empiric therapy.

### Table 5
**Opportunistic Infection Screening and Primary Prophylaxis for Patients With HIV Infection**

<table>
<thead>
<tr>
<th>Infection or Infecting Organism</th>
<th>Indication for Prophylaxis</th>
<th>Recommendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus</td>
<td>CMV antibody-negative</td>
<td>Transfuse CMV antibody-negative blood</td>
<td>Screening serology is not indicated in men who have sex with men or intravenous drug users (assumed positive)</td>
</tr>
<tr>
<td></td>
<td>CMV antibody-positive and CD4 count &lt;50 cells/mm$^3$</td>
<td>Funduscopic examination monthly</td>
<td></td>
</tr>
<tr>
<td><strong>Mycobacterium avium complex</strong></td>
<td>CD4 count &lt;50 cells/mm$^3$</td>
<td>Azithromycin 1,200 mg/ week or clarithromycin 500 mg 2 times/day or azithromycin 600 mg 2 times/week</td>
<td>Discontinue PPX when CD4 count &gt;100 cells/mm$^3$ for ≥3 months in response to ART</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>Positive tuberculin skin test ≥5 mm, prior positive tuberculin skin test without treatment, positive IGRA result, or close contact with infectious tuberculosis case</td>
<td>Treat according to CDC guidelines</td>
<td>Must rule out active tuberculosis, obtain IGRA in patients with history of BCG vaccine, repeat testing is indicated if initial test was obtained when CD4 count &lt;200 cells/mm$^3$</td>
</tr>
<tr>
<td>Pneumocystis jirovecii pneumonia</td>
<td>CD4 count &lt;200 cells/mm$^3$ or history of oropharyngeal candidiasis</td>
<td>TMP-SMX DS/day or SS/day$^a$</td>
<td>Discontinue PPX when CD4 count ≥200 cells/mm$^3$ for &gt;3 months in response to ART</td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td>Toxoplasma IgG-positive with CD4 count &lt;100 cells/mm$^3$</td>
<td>TMP-SMX DS/day$^{a,c}$</td>
<td>Discontinue PPX when CD4 count &gt;200 cells/mm$^3$ for &gt;3 months in response to ART Repeat testing when CD4 count decreases to &lt;100 cells/mm$^3$</td>
</tr>
<tr>
<td></td>
<td>Toxoplasma IgG-negative</td>
<td>Counsel on prevention</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Alternative regimen: dapsone$^c$ 100 mg/day (if G6PD level normal) or atovaquone 1,500 mg/day or aerosolized pentamidine 300 mg/month

$^b$Alternative regimen: dapsone$^c$ 50 mg/day plus pyrimethamine$^c$ 50 mg/week and leucovorin$^c$ 25 mg/week or atovaquone$^c$ 1,500 mg/day

$^c$This is an off-label use of this drug.

ART = antiretroviral therapy; CDC = Centers for Disease Control and Prevention; CMV = cytomegalovirus; DS = double strength; G6PD = glucose-6-phosphate dehydrogenase; Ig = immunoglobulin; IGRA = interferon-gamma release assay; PPX = primary prophylaxis; SS = single strength; TMP-SMX = trimethoprim-sulfamethoxazole.

Information from Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents; Centers for Disease Control and Prevention; National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.
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**Tuberculosis**

Tuberculosis is more common in patients from countries with high rates of endemic tuberculosis, and more common in patients with HIV infection than in patients without HIV infection. In patients with HIV infection ages 6 years or older, pulmonary tuberculosis is considered an AIDS-defining opportunistic infection at any CD4 count.42

Extrapulmonary tuberculosis (including tuberculous meningitis) and unusual presentations, such as lower lobe instead of apical involvement of the lungs, are more often seen in patients with HIV infection.42 The lower the CD4 count, the more extrapulmonary and atypical manifestations are seen. Patients with HIV infection can have normal chest x-ray results and still have pulmonary tuberculosis with positive sputum smear and culture results. Overall, however, sputum smear results are more often negative than positive, even in patients whose cultures eventually yield *Mycobacterium tuberculosis*.

Nucleic acid amplification testing for tuberculosis is more sensitive than a smear for acid-fast bacilli, with positive results in 50% to 80% of sputum specimens that eventually test positive on culture.42 Therefore, nucleic acid amplification testing should be obtained for at least one sputum specimen from each patient with suspected tuberculosis. Cultures for *Mycobacterium tuberculosis* rarely have positive results in less than 3 weeks and are not declared negative until after 8 weeks of incubation, so treatment for tuberculosis typically must be initiated on the basis of clinical suspicion rather than delayed while waiting for test results.

Drug interactions, adverse effects, and overall pill burden make management of tuberculosis difficult. However, a recent study has shown a decreased mortality rate if antiretroviral therapy is started within the first 2 weeks of pulmonary tuberculosis therapy in patients with CD4 counts less than 50 cells/mm$^3$ and within 8 to 12 weeks for all others.51 There is no clear guidance on when to start antiretroviral therapy in patients with tuberculosis meningitis, which is associated with a higher risk of IRIS. Although many experts suggest waiting 8 to 12 weeks regardless of CD4 count, physicians should consult the current DHHS opportunistic infection guidelines and consult an HIV specialist.42

Primary tuberculosis prophylaxis for a patient with HIV infection with a positive tuberculin skin test or interferon-gamma release assay result consists of isoniazid or rifampin, after appropriate evaluation has ruled out active tuberculous disease.42

**Disseminated Mycobacterium avium Complex**

Predominantly seen in patients with CD4 counts less than 50 cells/mm$^3$, disseminated *M avium complex* (MAC) produces fever, diarrhea, anemia, and weight loss.42 Symptoms may include abdominal pain related to retroperitoneal or mesenteric lymphadenopathy or right upper quadrant pain from involvement of the biliary tract. MAC includes several atypical bacteria found in soil and water. Unlike *M tuberculosis*, MAC is not transmissible between individuals.

Disseminated MAC is identified by isolating organisms from blood or an aspirate of bone marrow or abdominal lymph nodes; a positive stool stain for acid-fast bacilli also supports this diagnosis.52 Isolation of MAC from sputum cultures is nonspecific and may occur in patients with no infection. Treatment typically is with azithromycin or clarithromycin (the latter has fewer interactions with antiretroviral therapy) plus ethambutol. (This is an off-label use of ethambutol.) Azithromycin or clarithromycin prophylaxis is recommended for patients with CD4 counts less than 50 cells/mm$^3$. When considering drug interactions and dosing frequency in choosing between these drugs, azithromycin often is preferred.

**Cryptococcal Meningitis**

Cryptococcal meningitis typically occurs in patients with CD4 counts less than 100 cells/mm$^3$.42 It produces severe headaches, but the classic signs and symptoms of meningitis (eg, neck stiffness, photophobia) are present only in approximately 25% to 33% of cases. Some patients have Cryptococcus involvement elsewhere, including skin lesions that appear similar to large molluscum.

Serum cryptococcal antigen testing is highly sensitive and specific.52 Results of cerebrospinal fluid evaluation may be normal except for the presence of cryptococcal antigen, but opening pressure often is elevated, occasionally severely, and may require repeat lumbar puncture even in patients who are improving with therapy.42 Ventriculoperitoneal shunts should be considered for patients who cannot tolerate repeat lumbar punctures or in whom signs and symptoms of cerebral edema persist after multiple lumbar taps.

The preferred initial therapy is a combination of amphotericin B and flucytosine, followed by a prolonged course of fluconazole.42 Initiation of antiretroviral therapy should be delayed for 2 to 10 weeks because of the risk of IRIS affecting the central nervous system.53
Cytomegalovirus Retinitis

Cytomegalovirus retinitis is a viral infection of the retina that progresses to blindness if not managed. It typically occurs in patients with CD4 counts less than 50 cells/mm$^3$. Diagnostic symptoms are visual floaters, blind spots, or blurred vision. A visual field examination may identify visual field defects the patient finds difficult to describe. Classic findings on fundus examination are yellow-white retinal exudates with bleeding.

Diagnosis is an urgent priority and requires examination by an ophthalmology subspecialist experienced in the diagnosis and management of this condition. Treatment is with oral valganciclovir, with the addition of intravitreal injections of ganciclovir or foscarnet for immediately sight-threatening lesions.

Disseminated Histoplasmosis

Disseminated histoplasmosis occurs in patients with HIV infection who have lived in areas in which the *Histoplasma capsulatum* fungus is endemic, including states bordering the Ohio River valley and the lower Mississippi River; Puerto Rico; and many countries in Central America and South America. Fever, diarrhea, leukopenia, and oral ulcers are common symptoms. This condition typically occurs in patients with CD4 counts less than 150 cells/mm$^3$. Urine antigen testing is used to make the diagnosis. Antifungal therapy consists of liposomal amphotericin B or oral itraconazole, depending on disease severity and specific organ involvement. (This is an off-label use of liposomal amphotericin.)

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare, typically fatal disease of brain white matter caused by JC virus infection. It is more common in patients in whom the CD4 count is less than 200 cells/mm$^3$ but may occur in patients with higher CD4 counts. PML manifests as focal neurologic deficits that evolve over a period of several weeks. Headache and fever are not typically present, except in patients with IRIS.

Diagnosis is based on characteristic magnetic resonance imaging study results and is confirmed by the finding of JC virus in cerebrospinal fluid using polymerase chain reaction. Initiation of antiretroviral therapy is associated with the greatest likelihood of neurologic improvement and survival but is not uniformly effective. None of the other therapies studied has proven effective, although corticosteroids may improve symptoms in the inflammatory form of PML.

Case 1, cont’d. James’ chest x-ray results are normal and you obtain a complete blood count with differential, basic metabolic panel, viral load, genotype resistance test, CD4 count, and beta-d-glucan assay. The arterial blood gas measurement shows a PaO$_2$ of 65 mm Hg and the induced sputum test result is positive for *P* jiroveci. Respiratory viral study results are negative. The beta-d-glucan level is elevated at greater than 500 pg/mL, viral load is 200,000 copies/mL, and CD4 count is 100 cells/mm$^3$. You diagnose *P* jiroveci pneumonia and prescribe a 21-day course of trimethoprim-sulfamethoxazole and prednisone.

Other AIDS-Defining Conditions

Low CD4 Count

In patients with HIV infection, a low CD4 count is considered an AIDS-defining condition, with the threshold depending on the patient’s age. In infants younger than 1 year, a CD4 count less than 750 cells/mm$^3$ is AIDS-defining; in children ages 1 to 5 years, a CD4 count less than 500 cells/mm$^3$ is AIDS-defining; and in patients 6 years or older, a CD4 count less than 200 cells/mm$^3$ is considered AIDS-defining (Table 4). CD4 counts obtained during acute illness may significantly overestimate the degree of immunodeficiency, so clinicians should use a value obtained in an outpatient setting when the patient is in stable condition.

Wasting Syndrome

Wasting syndrome is defined as the involuntary loss of more than 10% of body weight accompanied by diarrhea or weakness and fever (the latter can be intermittent) persisting at least 30 days that is not attributable to another definable infection or malignancy. Tests should include evaluation for tuberculosis, disseminated MAC, disseminated fungal infection, and cancer.

HIV Encephalopathy

Also referred to as AIDS dementia complex and HIV-associated dementia, HIV encephalopathy is a relatively rapid (eg, weeks to months) progressive loss of cognitive and/or motor function resulting in dementia. HIV encephalopathy was much more common in patients with HIV infection before use of combination antiretroviral therapy.

AIDS-Defining Malignancies

Kaposi Sarcoma

Kaposi sarcoma is an AIDS-defining malignancy that produces blue to black nodular lesions on the
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Skin and mucosal lesions are prevalent, with nodular to macular lesions on the mucosa, particularly of the mouth and gastrointestinal and respiratory tracts. These lesions are highly vascular, and mucosal lesions may bleed. Kaposi sarcoma is caused by human herpesvirus 8 infection and is seen most commonly in men who have sex with men.

Systemic Non-Hodgkin Lymphomas

Systemic non-Hodgkin lymphomas, primarily Burkitt and immunoblastic B-cell lymphomas, are AIDS-defining malignancies that can develop at any CD4 count. The roles of Epstein-Barr virus and HIV in causing these lymphomas are still under investigation.

Primary Central Nervous System Lymphoma

Primary central nervous system lymphoma typically is related to Epstein-Barr virus infection and unrelated to non-Hodgkin lymphoma. Patients with this condition respond poorly to treatment. The presence of a single ring-enhancing lesion is more likely to indicate central nervous system lymphoma rather than toxoplasmic encephalitis, but multiple lesions may occur with central nervous system lymphoma.

Invasive Cervical Cancer

Invasive cervical cancer is another virus-associated AIDS-defining malignancy in patients with HIV infection. It is caused by certain high-risk types of human papillomavirus, particularly types 16 and 18.

HIV-Associated Malignancies

The incidence of several non-AIDS-defining malignancies is significantly higher among patients with HIV infection. A large meta-analysis showed elevated standardized incidence ratios of laryngeal (1.5), kidney (1.7), lung (2.6), liver (5.6), and anal cancers (28) and Hodgkin lymphoma (11) in patients with HIV infection. Although there are no screening recommendations in the DHHS guidelines for any of these cancers, many experts recommend screening for anal cancer using anal Papanicolaou (Pap) tests and nucleic testing for high-risk human papillomavirus types.

Other Clinical Manifestations

Between initial HIV infection and before development of AIDS (previously referred to as the latent period), patients who do not receive antiretroviral therapy will experience progressive HIV infection, particularly in the central nervous system, and other distinctive non-AIDS-defining conditions may develop.

Thrombocytopenia

Thrombocytopenia is an HIV-related condition that may be profound, and patients may not respond to conventional treatments such as corticosteroids. All patients with acquired thrombocytopenia should be tested for HIV infection. Antiretroviral therapy typically results in a rapid increase in the platelet count; however, recovery occasionally will take longer, and the platelet count typically decreases again if the patient discontinues therapy.

Recurrent Bacterial Respiratory Infections

Recurrent bacterial respiratory infections, such as sinusitis, are common in patients with HIV infection and can occur at any CD4 count. Antiretroviral therapy can decrease the frequency of these infections and markedly improve patient responsiveness to treatment. More than one episode of bacterial pneumonia within 1 year qualifies as an AIDS-defining condition. Despite the well-known association between P. jirovecii pneumonia and AIDS, Streptococcus pneumoniae is the most common etiology of bacterial pneumonia in patients with HIV infection.

HIV-Associated Nephropathy

HIV-associated nephropathy is a major etiology of renal failure that occurs disproportionately in black patients with CD4 counts less than 200 cells/mm³. The condition is characterized by proteinuria and focal glomerulosclerosis with collapse of the glomerular tuft and tubular dilatation. Direct HIV infection of renal epithelial cells has been shown, and it is theorized that antiretroviral therapy has reduced the incidence of this condition significantly, such that it is now rare.

HIV-Associated Neurocognitive Disorder

HIV-associated neurocognitive disorder is a characteristic slowing of mental processing. Manifestations range from asymptomatic (ie, detected on screening) to severe dementia. Motor retardation such as slow gait may accompany the neurocognitive changes. Antiretroviral therapy has been shown to produce long-term improvement in patients with neurocognitive impairments.
The advent of combination antiretroviral drug regimens has transformed HIV infection from a fatal illness into a manageable chronic condition. All patients with HIV infection should be considered for antiretroviral therapy, regardless of CD4 count or HIV viral load, for individual benefit and to prevent HIV transmission. Antiretroviral drugs affect HIV in several ways: entry inhibitors block HIV entry into CD4 T cells; nucleotide and nucleoside reverse transcriptase inhibitors prevent reverse transcription from RNA to DNA via chain-terminating proteins; nonnucleoside reverse transcriptase inhibitors prevent reverse transcription through enzymatic inhibition; integrase strand transfer inhibitors block integration of viral DNA into cellular DNA; protease inhibitors block maturation and production of the virus. Current guidelines recommend six combination regimens for initial therapy. Five are based on tenofovir and emtricitabine; the other uses abacavir and lamivudine. Five include integrase strand transfer inhibitors. HIV specialists should assist with treating patients with complicated HIV infection, including patients with treatment-resistant HIV infection, coinfection with hepatitis B or C virus, pregnancy, childhood infections, severe opportunistic infections, complex drug interactions, significant drug toxicity, or comorbidities. Family physicians can treat most patients with HIV infection effectively by choosing appropriate treatment regimens, monitoring patients closely, and retaining patients in care.

**Background**

In 1996, the development of triple therapy antiretroviral regimens transformed HIV infection from an almost universally fatal illness into a manageable chronic condition. However, these early drugs were associated with a significant burden of adverse effects. Current regimens are simpler and better tolerated. Still, in the United States as of 2011, only 40% of the 1.2 million individuals with HIV infection/AIDS were receiving care, 37% were prescribed antiretroviral therapy, and 30% had achieved viral suppression.

The National HIV/AIDS Strategy: Updated to 2020 calls for reducing the rate of new HIV infections, increasing access to care and improving health outcomes, reducing disparities in care and health inequities, and improving the coordination of national efforts. With an increasing prevalence of chronic HIV infection, a diminishing workforce of HIV specialists, and the transformation of HIV infection into a manageable chronic condition, family physicians have a key role in achieving these goals.

Although this section reviews the most recent developments and recommendations regarding antiretroviral therapy, in particular the selection of an initial treatment regimen, it is not a comprehensive guide to prescribing. As antiretroviral drugs have become less toxic and more potent, the challenges in prescribing them have shifted toward retaining patients in medical care. As most patients with HIV can achieve durable viral suppression with a recommended initial antiretroviral regimen, family physicians who can choose and manage initial regimens will be able to care for a majority of patients with HIV infection.

Case 1, cont’d. James returns for a review of the laboratory test results. The CD4 count is 100 cells/mm³ and viral load is 200,000 copies/mL. Results of liver function tests, basic metabolic panel, phosphorus, complete blood count, and urinalysis are normal. Test results for syphilis, gonorrhea, chlamydia, cytomegalovirus immunoglobulin (Ig) G, and Toxoplasma IgG are negative. The HIV genotype is wild type, indicating that there currently are no mutations that might cause treatment resistance. The HLA-B^*5701 test result is negative, and the glucose-6-phosphate dehydrogenase level is normal. You prepare to treat him and consult the appropriate guidelines.

The Department of Health and Human Services (DHHS) recommends antiretroviral therapy for all patients with HIV infection who are able to consent, commit, and adhere to treatment regardless of CD4 count or viral load. Patients or clinicians may elect to delay therapy based on clinical or psychosocial...
Case 1, cont’d. You discuss James’ acceptance and understanding of the diagnosis, treatment options, and his desire and ability to adhere to a drug regimen. He does not report any significant barriers to adherence or with mental health, substance abuse, health care insurance, or financial issues. However, he plans to keep his condition a secret from his wife and family. He says he needs to be discreet about taking the drugs, and wants a single-tablet regimen with minimal to no adverse effects.

Although you recommend that James disclose his HIV status to his wife and other sexual partners, he instead plans to prevent transmitting HIV by using condoms with all of his partners and by starting antiretroviral therapy. In your state, there is no law requiring him to disclose his HIV status to his partners.

**Recommended Initial Regimens**

Antiretroviral drugs affect HIV in various ways. Entry inhibitors block HIV entry into CD4 T cells. Nucleotide and nucleoside reverse transcriptase inhibitors prevent reverse transcription from RNA to DNA via chain-terminating proteins, and nonnucleoside reverse transcriptase inhibitors prevent reverse transcription through enzymatic inhibition. Integrase strand transfer inhibitors prevent integration of viral DNA into cellular DNA, and protease inhibitors prevent maturation and production of the virus.

Over the years, treatment regimens for HIV infection have evolved from ineffective to effective but toxic and challenging to administer, to the current state of potent, simple, and well-tolerated. All recommended antiretroviral therapy regimens comprise two nucleoside/nucleotide reverse transcriptase inhibitors and a third drug from a different class. Table 6 and Table 7 list the most commonly used antiretroviral drugs currently available in the United States, along with their significant features. Many previous regimens are no longer recommended due to toxicity, pill burden, drug interactions, food restrictions, or a combination of these factors.

Current guidelines recommend six preferred regimens for initial therapy (Table 8). Three of the six use tenofovir-emtricitabine nucleoside/nucleotide reverse transcriptase inhibitors (the other uses abacavir-lamivudine); and five of the six use the newest class of drugs, integrase strand transfer inhibitors. Only one regimen is based on a protease inhibitor, owing to the issues with pill burden, drug interactions, gastrointestinal adverse effects, and lipid level abnormalities. Nonetheless, protease inhibitors play a key role in second- and third-line antiretroviral therapy regimens and as an initial regimen in patients with adherence issues.

**Dolutegravir-Abacavir-Lamivudine**

Dolutegravir-abacavir-lamivudine (Triumeq) is the only single-tablet regimen based on abacavir-lamivudine. Before starting abacavir, patients must be confirmed to be HLA-B*5701-negative and thus at low risk of abacavir hypersensitivity reaction. Abacavir hypersensitivity reaction is rare in HLA-B*5701-negative patients but physicians should be aware of its features (eg, fever, rash, nausea, vomiting, diarrhea, abdominal pain, fatigue, occasionally pharyngitis, tachypnea, cough). Patients with abacavir hypersensitivity reaction can experience fatal anaphylaxis on rechallenge and should never take abacavir in any form (ie, Epzicom, Trumeq, Trizivir, Ziagen).

Given the likely increased cardiovascular risk with abacavir, DHHS guidelines advise avoiding abacavir for patients with elevated cardiovascular risk. Another concern with dolutegravir-abacavir-lamivudine is that dolutegravir must be taken 2 hours before or 6 hours after antacids or supplements containing magnesium, aluminum, iron, calcium, or zinc, to prevent chelation. Iron or calcium supplements may be administered with dolutegravir if also taken with food. Overall, dolutegravir-abacavir-lamivudine is a well-tolerated regimen that avoids the renal risk
## Table 6
### Recommended Antiretroviral Drugs for Management of HIV Infection

<table>
<thead>
<tr>
<th>Class</th>
<th>Renal Dosing</th>
<th>Take With Food</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacokinetic enhancers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir (Norvir)</td>
<td>No</td>
<td>Yes</td>
<td>Take with food&lt;br&gt;Potent CYP3A4 inhibitor&lt;br&gt;Dose ranges from 100 mg to 200 mg&lt;br&gt;Ritonavir is a PI but is administered only as a boosting agent&lt;br&gt;Capsules (but not tablets) must be refrigerated&lt;br&gt;Many adverse effects and toxicities (eg, nausea, diarrhea, asthenia, hyperlipidemia, hepatitis, lipodystrophy)</td>
</tr>
<tr>
<td>Cobicistat (Tybost)</td>
<td>No</td>
<td>Yes</td>
<td>Take with food&lt;br&gt;Potent CYP3A4 inhibitor with no antiretroviral activity&lt;br&gt;Creatinine level increase of ≤4 mg/mL is common, but increase &gt;4 mg/mL raises concerns for tubulopathy</td>
</tr>
<tr>
<td><strong>Nucleoside/tide reverse transcriptase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine (Epivir)</td>
<td>Yes</td>
<td>No</td>
<td>Minimal adverse effects or toxicity&lt;br&gt;Has anti-HBV activity; do not administer without tenofovir or entecavir in HBsAg-positive patients</td>
</tr>
<tr>
<td>Emtricitabine (Emtriva)</td>
<td>Yes</td>
<td>No</td>
<td>Minimal adverse effects or toxicity&lt;br&gt;Has anti-HBV activity; do not administer without tenofovir or entecavir in HBsAg-positive patients</td>
</tr>
<tr>
<td>Tenofovir (Viread)</td>
<td>Yes</td>
<td>No</td>
<td>Some adverse effects (eg, asthenia, headache, nausea, diarrhea), renal and bone toxicity&lt;br&gt;Has anti-HBV activity; may be administered alone in HBsAg-positive patients as potent anti-HBV therapy</td>
</tr>
<tr>
<td>Abacavir (Ziagen)</td>
<td>No</td>
<td>No</td>
<td>Patient must be HLA-B*5701-negative to use&lt;br&gt;Few adverse effects but might increase cardiac risk&lt;br&gt;Do not use if Child-Pugh score &gt;6&lt;br&gt;Adjust dosage for hepatic insufficiency</td>
</tr>
<tr>
<td><strong>Nonnucleoside reverse transcriptase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz (Sustiva)</td>
<td>No</td>
<td>Yes</td>
<td>Take on empty stomach to reduce adverse effects (eg, vivid dreams, drowsiness, impaired thinking)&lt;br&gt;Effects related to toxicity include rash, hyperlipidemia, transaminitis, possible teratogenicity in the first 8 weeks of pregnancy&lt;br&gt;Prescribe with caution or avoid in patients with depression</td>
</tr>
<tr>
<td>Rilpivirine (Edurant)</td>
<td>No</td>
<td>Yes</td>
<td>Take with a meal&lt;br&gt;Needs acidic pH for absorption, so cannot use with PPI&lt;br&gt;Adverse effects and toxicities not common but some reported (eg, rash, hepatotoxicity, headache, insomnia, depression)</td>
</tr>
</tbody>
</table>

*Taken 1 time/day.<br>†Taken 2 times/day.

Note: The drugs most frequently used in their most common forms appear in bold typeface. The drugs in regular typeface are drugs and formulations used less commonly. Several drugs that were mainstays of early antiretroviral regimens are not listed and their use is no longer recommended because of toxicity, pill burden, drug interactions, meal restrictions, or a combination of these factors. A full listing of these drugs, including less common drugs and regimens, is available at http://www.aidsinfo.nih.gov/contentfiles/adultandadolescentgl.pdf.

CYP = cytochrome P450; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; PI = protease inhibitor; PPI = proton pump inhibitor.
### Table 6 (continued)
#### Recommended Antiretroviral Drugs for Management of HIV Infection

<table>
<thead>
<tr>
<th>Class</th>
<th>Renal Dosing</th>
<th>Take With Food</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Integrase strand transfer inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dolutegravir (Tivicay)</td>
<td></td>
<td></td>
<td>Use 2 times/day with prior raltegravir or elvitegravir resistance or when coadministering with efavirenz, fosamprenavir-ritonavir,</td>
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<tr>
<td>50 mg&lt;sup&gt;a,b&lt;/sup&gt;</td>
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<td></td>
<td>tipranavir-ritonavir, rifampin, or carbamazepine</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Significantly increases metformin levels (maximum dose 1 g/day)</td>
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<td></td>
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<td></td>
<td>Take 2 hours before or 6 hours after cations (eg, magnesium, aluminum, iron, calcium, zinc)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Calcium or iron supplements can be taken with dolutegravir if taken with food</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low incidence of adverse effects (eg, insomnia, headache, possible depression, hypersensitivity reaction with rash, constitutional</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>symptoms, hepatotoxicity)</td>
</tr>
<tr>
<td>Elvitegravir (Vitekta)</td>
<td></td>
<td></td>
<td>Take with food</td>
</tr>
<tr>
<td>150 mg&lt;sup&gt;a&lt;/sup&gt; or 85 mg&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>Yes</td>
<td>Requires boosting, usually with cobicistat as in Stribild or Genvoya</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Take 2 hours before or 6 hours after cations (eg, magnesium, aluminum, iron, calcium, zinc)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Use 85 mg&lt;sup&gt;a&lt;/sup&gt; when taken with atazanavir-ritonavir or lopinavir-ritonavir</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adverse effects include nausea, diarrhea</td>
</tr>
<tr>
<td>Raltegravir (Isentress)</td>
<td></td>
<td></td>
<td>Do not coadminister with aluminum or magnesium antacids</td>
</tr>
<tr>
<td>400 mg&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>Otherwise few drug interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adverse effects not common, but some reported (ie, rash [rare Stevens-Johnson syndrome, toxic epidermal necrolysis], nausea,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>headache, diarrhea, pyrexia)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Toxicities reported (ie, rhabdomyolysis, rare hypersensitivity reaction)</td>
</tr>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darunavir (Prezista)</td>
<td></td>
<td></td>
<td>Take with food</td>
</tr>
<tr>
<td>600 mg&lt;sup&gt;a&lt;/sup&gt; or 800 mg&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>Yes</td>
<td>Use 2 times/day 600 mg darunavir + 100 mg ritonavir if the patient has ≥1 darunavir-associated mutations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Must boost with ritonavir or cobicistat</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prescribe with caution in patients with sulfa allergy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Typical PI adverse effects (ie, hepatotoxicity, diarrhea, nausea, hyperlipidemia, hyperglycemia, lipodystrophy, transaminitis) plus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>rash (ie, Stevens-Johnson syndrome, toxic epidermal necrolysis)</td>
</tr>
<tr>
<td>Atazanavir (Reyataz)</td>
<td></td>
<td></td>
<td>Take with food</td>
</tr>
<tr>
<td>300 mg&lt;sup&gt;a&lt;/sup&gt; if with ritonavir</td>
<td></td>
<td>Yes</td>
<td>Must boost when administered with tenofovir or in antiretroviral drug-experienced patients</td>
</tr>
<tr>
<td>400 mg&lt;sup&gt;a&lt;/sup&gt; without ritonavir; 400 mg&lt;sup&gt;a&lt;/sup&gt; + ritonavir when taken with efavirenz or when pregnant in 2nd/3rd trimesters</td>
<td></td>
<td></td>
<td>Adjust dosage for hepatic insufficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Needs acidic pH for absorption, so cannot be taken with PPIs, and doses must be separate from histamine&lt;sub&gt;2&lt;/sub&gt; blockers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(consult guidelines)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Causes benign indirect hyperbilirubinemia in all patients; also nephrolithiasis, renal insufficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Typical PI adverse effects</td>
</tr>
</tbody>
</table>

<sup>a</sup>Taken 1 time/day.
<sup>b</sup>Taken 2 times/day.

CYP = cytochrome P450; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; PI = protease inhibitor; PPI = proton pump inhibitor.

Information from Panel on Antiretroviral Guidelines for Adults and Adolescents; Dept of Health and Human Services, Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Appendix B. Available at http://www.aidsinfo.nih.gov/contentfiles/adultandadolescentgl.pdf.
of tenofovir-based regimens; has relatively few adverse
effects, toxicities, or drug interactions; and no food
requirements when not taken with polyvalent cations.

Although transmitted resistance to integrase inhibi-
tors is not common, and has not yet been found with
dolutegravir, integrase resistance
testing should be obtained before
initiating a drug regimen. Finally, because hepatitis B virus (HBV)
develops resistance to lamivudine in most patients within 4 years,
patients with HBV coinfection who take dolutegravir-abacavir-
lamivudine should receive an
additional drug for management of
HBV infection, such as entecavir.

**Elvitegravir-Cobicistat-
Tenofovir-Emtricitabine**

Elvitegravir-cobicistat-tenofovir-
emtricitabine (Stribild) is a
single-tablet regimen that uses
cobicistat, a strong inhibitor of
the cytochrome P450 (CYP) 3A4
enzyme, as a booster to increase
elvitegravir levels. This introduces
potential drug interactions with a
variety of other drugs metabolized
by CYP3A4, such as azole antifun-
gals, antiepileptics, some statins
(eg, simvastatin, lovastatin), and
calcium channel blockers.

Tenofovir in its original form,
tenofovir disoproxil fumarate
(TDF), can cause renal tubular dys-
function, phosphate wasting, and
decreased bone density. It typi-
cally causes renal issues in conjunc-
tion with other conditions, such as
diabetic or hypertensive nephropa-
thy. Patients with preexisting
chronic kidney disease should avoid
taking TDF if possible. A new form
of tenofovir recently has become
available as part of Genvoya, a com-
bination drug that uses tenofovir
alafenamide (TAF) instead of TDF.

TAF achieves higher intracellular
levels than TDF in CD4 cells but
not in renal tubular cells, thereby requiring lower doses
and incurring less renal and bone toxicity.

Cobicistat increases the serum creatinine level without
true nephropathy, confounding typical means of
renal function measurement. Thus, considering this

---

### Table 7

<table>
<thead>
<tr>
<th>Fixed-Dose Combination Drug</th>
<th>Trade Name</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF-FTC</td>
<td>Truvada</td>
<td>Most common dual-NRTI combination pill</td>
</tr>
<tr>
<td>ABC-3TC</td>
<td>Epzicom</td>
<td>Second most common dual-NRTI combination pill</td>
</tr>
<tr>
<td>EFV-TDF-FTC</td>
<td>Atripla</td>
<td>First single-tablet regimen</td>
</tr>
<tr>
<td>RPV-TDF-FTC</td>
<td>Compla</td>
<td>Take on empty stomach</td>
</tr>
<tr>
<td>DTG-ABC-3TC</td>
<td>Triumeq</td>
<td>Patients must be HLA-B*5701 negative to use</td>
</tr>
<tr>
<td>EVGc-TAF-FTC or EVGc-TDF-FTC</td>
<td>Genvoya, Stribild</td>
<td>Do not prescribe if CrCl &lt;30 mL/min/1.73 m² (Genvoya) or &lt;70 mL/min/1.73 m² (Stribild)</td>
</tr>
<tr>
<td>DRVc</td>
<td>Prezcobix</td>
<td>Do not prescribe if CrCl &lt;70 mL/min/1.73 m² or darunavir mutations present</td>
</tr>
<tr>
<td>ATVc</td>
<td>Evotaz</td>
<td>Do not prescribe if CrCl &lt;70 mL/min/1.73 m²</td>
</tr>
</tbody>
</table>

*Taken 1 time/day.

**Refer to component drugs for information on adverse effects and toxicities.

3TC = lamivudine; ABC = abacavir; ATV = atazanavir; c = cobicistat; CrCl = creatinine clearance; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; NRTI = nucleoside reverse transcriptase inhibitor; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

together with the potential for tenofovir nephrotoxicity, Stribild is not recommended for patients with creatinine clearance rates less than 70 mL/min/1.73 m², whereas Genvoya is approved for use in patients with clearance rates as low as 30 mL/min/1.73 m². Along with dolutegravir-abacavir-lamivudine, Stribild is the only other recommended single-tablet regimen for initial therapy because it typically is well tolerated, with rare adverse effects, low toxicity, and no known cardiovascular risk. Because of its lower toxicity, Genvoya is likely to replace Stribild in the next DHHS guideline update.

New drugs are expected to be available soon, with TAF instead of TDF in Complera (rilpivirine-tenofovir-emtricitabine) and Truvada (emtricitabine-tenofovir), as well as TAF in place of Viread (TDF). However, there will be no replacement for the TDF in Atripla (emtricitabine-efavirenz-tenofovir).

**Dolutegravir-Tenofovir-Emtricitabine**

Dolutegravir-tenofovir-emtricitabine (Tivicay-Truvada) is a two-tablet once-daily regimen for patients with normal renal function. It is an alternative for patients with CYP3A4 drug interactions who cannot take cobicistat or who cannot take abacavir because of HLA-B*5701-positive status or cardiac risk. There are few adverse effects or toxicities aside from potential nephrotoxicity with tenofovir, and few drug interactions or food requirements, except for the previously discussed issues regarding dolutegravir and polyvalent cations.

**Raltegravir-Tenofovir-Emtricitabine**

Raltegravir-tenofovir-emtricitabine (Isentress-Truvada) is similar to dolutegravir-tenofovir-emtricitabine, except that raltegravir is taken twice daily instead of once daily. The overall pill burden is still low at three tablets/day; there are few adverse effects, toxicities (except renal, as previously discussed), or drug interactions; and there are no food requirements. The genetic barrier to resistance to raltegravir is lower than that of dolutegravir, thus, this would not be a recommended regimen for patients unlikely to adhere to a twice-daily drug regimen. Use of aluminum- or magnesium-containing antacids can reduce absorption of raltegravir, and is not recommended. Raltegravir must be administered 2 hours before or 6 hours after supplements containing polyvalent cations.

**Darunavir-Ritonavir-Tenofovir-Emtricitabine**

Darunavir-ritonavir-tenofovir-emtricitabine (Prezista-Norvir-Truvada) is the only initial regimen based on a protease inhibitor. It can be taken as three tablets once daily as an initial regimen if there is no significant transmitted protease inhibitor resistance. Darunavir, like atazanavir (Reyataz), does not increase lipid levels as much as older protease inhibitors. It does not increase the serum bilirubin level or have drug interactions with antacids, two disadvantages of atazanavir. Like all protease inhibitors, it has a high genetic barrier to resistance, thus this regimen may be preferred for patients for whom daily drug adherence is a concern.

Darunavir must be boosted with ritonavir or cobicistat, thus raising the potential for CYP3A4 drug interactions as previously discussed. Adverse effects of ritonavir (eg, nausea, diarrhea, flatulence) typically are mild and self-limiting with the 100 mg/day dosage used in this regimen, and are less common if tablets are prescribed instead of capsules.

Darunavir is now available combined with cobicistat (Prezcobix), obviating the need for a separate ritonavir tablet and reducing this to a two-pill/day regimen. There are promising results from a phase II trial of
single-tablet darunavir-cobicistat-emtricitabine-TAF, which would be the first single-tablet regimen based on protease inhibitors, and phase III trials are under way.99

**Alternative Regimens**

**Efavirenz-Tenofovir-Emtricitabine**

The initial most widely prescribed single-tablet regimen, efavirenz-tenofovir-emtricitabine (Atripla), became an alternative regimen in April 2015.31 A trial of dolutegravir- and efavirenz-based regimens showed superiority of dolutegravir in an intent-to-treat analysis because of central nervous system adverse effects (eg, dizziness, abnormal dreams, insomnia) with efavirenz.71

A large meta-analysis found a twofold greater hazard ratio of suicidality in patients taking efavirenz compared with those taking other antiretroviral drugs.80 Although patients taking Atripla who have no depression, central nervous system adverse effects, hyperlipidemia, or CYP3A4 induction conditions need not be switched to another drug, it is no longer a preferred choice for initial therapy.31

**Rilpivirine-Tenofovir-Emtricitabine**

Rilpivirine-tenofovir-emtricitabine (Complera), the second single-tablet regimen to enter the market, is not recommended because gastric acid-decreasing drugs impair rilpivirine absorption, and higher rates of virologic failure have been found among patients with CD4 counts less than 200 cells/mm³ or viral loads greater than 100,000 copies/mL.31 However, in patients without these issues, Complera is well tolerated in patients with no preexisting renal disease who desire a single-tablet regimen and cannot take abacavir, efavirenz, or cobicistat.

**Atazanavir-Ritonavir-Tenofovir-Emtricitabine**

Atazanavir-ritonavir-tenofovir-emtricitabine (Reyataz-Norvir-Truvada) became an alternative regimen in April 2015, after a trial comparing it with darunavir showed a higher rate of toxicity-related discontinuation with the atazanavir formulation.31,81

*Case 1, cont’d.* James cannot take ritonavir or cobicistat because these can lead to adverse drug interactions when taken with fluconazole. Thus, elvitegravir-cobicistat-tenofovir-emtricitabine (Stribild) is not an option, unless he switches his inhaled steroid to beclomethasone. The viral load is greater than 100,000 copies/mL and the CD4 count is less than 200 cells/mm³, there are contraindications to rilpivirine-tenofovir-emtricitabine (Complera), and he is reluctant to take efavirenz-tenofovir-emtricitabine (Atripla) because of the central nervous system adverse effects.

He is HLA-B*5701-negative and has no cardiac risk factors, and thus can safely take abacavir. He takes no polyvalent cation supplements (eg, magnesium, aluminum, iron, calcium, zinc), so he should absorb dolutegravir properly. He has no renal insufficiency requiring dose adjustment of lamivudine and does not have chronic hepatitis B or C virus infection. Therefore, you decide to initiate therapy using dolutegravir-abacavir-lamivudine (Triumeq). James meets with the nurse after picking up his prescription to confirm that he has the correct drug, understands how to take it, and has a plan for how he will remember to take it every day.

You obtain a CD4 count, viral load, liver function tests, and basic metabolic panel for James at 1 and 3 months after starting therapy, then every 3 to 4 months for the next year. The viral load decreases to less than 20 copies/mL by 3 months, and the CD4 count increases to more than 200 cells/mm³ by 3 months, so you tell James he can discontinue the trimethoprim-sulfamethoxazole he was taking for *P. jirovecii* pneumonia secondary prophylaxis.

One year later, James has missed two consecutive appointments, and after an 8-month lapse in care he returns with a viral load of 200,000 copies/mL. The genotype test (including integrase resistance test, as he is taking dolutegravir) results still show no resistance mutations. The CD4 count is now 100 cells/mm³. He feels weak and tired, is losing weight, and has oral candidiasis with painful swallowing. James admits he has discontinued taking dolutegravir-abacavir-lamivudine.

The oral and esophageal candidiasis is the result of his HIV-weakened immune system, and he is again at risk of *P. jirovecii* pneumonia. James resumes taking dolutegravir-abacavir-lamivudine, and within 3 months the viral load is again undetectable. The candidiasis improves with a course of fluconazole, and he reports feeling better. He is restarted on trimethoprim-sulfamethoxazole until the CD4 count is greater than 200 cells/mm³ for more than 3 months.

**Consultation With HIV Specialists**

Specialists with experience in HIV infection management should assist with the care of patients with more complicated cases. Issues may include treatment resistance, coinfection with HBV or hepatitis C virus (HCV), pregnancy, childhood HIV infection, complex
or severe opportunistic infections, complicated drug interactions, significant drug toxicity, and medical comorbidities.

Mutations from baseline or subsequent genotypes can be entered into the Stanford HIV Drug Resistance Database to assess which drugs may no longer be effective, but physicians should have experience in interpreting this analysis before using it to select regimens.

Tenofovir, lamivudine, and emtricitabine have activity against HBV; therefore, assistance should be sought from an HBV infection specialist before initiating an antiretroviral therapy regimen for a patient with HBV-HIV coinfection. Similarly, the anti-HBV drug entecavir has partial anti-HIV activity and can select for HIV-resistant mutations, so its use should be avoided in patients with HIV infection who are not taking antiretroviral therapy. Many of the new drugs for HCV infection have interactions with drugs for HIV infection, so HCV infection management plans must be considered before choosing drugs for HIV infection.

The DHHS has issued a comprehensive guideline for the care of pregnant patients with HIV infection and their newborns and infants, and for children with HIV infection. These topics are beyond the scope of this edition. Clinicians should consult these guidelines and seek support from pediatric subspecialists and perinatal HIV specialists when caring for such patients.

Clinicians also should seek assistance from a multidisciplinary team in the care of patients with HIV infection. In a large Veterans Health Administration HIV cohort study, the number of missed appointments was the only retention measure that predicted all primary and secondary outcomes (eg, CD4 count less than 500 cells/mm³, progression to AIDS, emergency department visits, hospitalization).

A team-based focus on eliminating barriers to care access will yield positive clinical results for individual patients. It is also critical for the greater community, as roughly three-fourths of new HIV infections are transmitted by previously diagnosed individuals, and improved care retention is likely to be a more influential factor in reducing numbers of new infections than widespread screening.

Case 1, cont’d. Over the next year, James remains connected to care and maintains viral suppression. During his visits, you gently but persistently reiterate the importance of spouse testing for HIV infection. Ultimately, he is able to disclose his condition to his wife, and her HIV test result is negative.
With the advent of antiretroviral therapy and improved access to care, the average life expectancy of patients with HIV infection receiving optimal treatment approaches that of patients in the general population. AIDS-related opportunistic infections and malignancies are no longer the primary issues; instead, traditional age- and lifestyle-related conditions are a growing concern. Patients with HIV infection are at higher risk of cardiovascular disease, diabetes, hypertension, and some non-AIDS-related cancers than patients in the general population. Family physicians need to be knowledgeable about screening for and managing chronic comorbid conditions as this population ages. Health maintenance, including appropriate vaccinations, prophylaxis against opportunistic infections, and routine screening for sexually transmitted infections, remains an important part of care. As HIV infection becomes a chronic condition, emerging strategies in prevention, including preexposure prophylaxis, fall within the scope of practice of the family physician.

Case 1, cont’d. James, who was diagnosed with HIV infection and began antiretroviral treatment 10 years ago, is now age 34 years and is visiting your office for a scheduled health maintenance examination. He has been adherent to his drug regimen. He is now monogamous, continues to use condoms, and his wife’s HIV status remains negative. He is busy managing a restaurant, and he has gained weight. Recently, he developed type 2 diabetes, for which he takes metformin. He has low-grade anal dysplasia that was evaluated 1 year ago with high-resolution anoscopy. He is due for an annual influenza vaccine and wants to talk to you about having another child with his wife.

Background

The epidemiology of HIV infection has significantly shifted with the development of antiretroviral therapy and improved access to care. The decline in rates of opportunistic infections and AIDS-related malignancies has led to decreased mortality rates, and the life expectancy of patients with HIV infection receiving optimal treatment approaches that of patients in the general population. Inpatient health care use by patients with HIV infection has decreased, with studies showing lower rates of hospitalization and shorter lengths of stay.

However, coincident with this success has been a concurrent increase in age- and lifestyle-related conditions in patients with HIV infection, including cardiovascular disease, chronic obstructive pulmonary disease, diabetes, chronic kidney disease, hepatitis C infection, cirrhosis, and non-AIDS-related malignancies. As many as 45% of patients with HIV infection may have metabolic syndrome, with some studies linking protease inhibitors with increased risk. Age-related bone mineral density loss also is common in these patients, particularly among patients taking tenofovir.

The causes of the overall increase in non-AIDS morbidity are complex and likely due to a combination of normal aging, proinflammatory effects of HIV infection, adverse effects of antiretroviral therapy, and risk factors common in HIV-positive populations (eg, smoking, intravenous drug use). The growing incidence of chronic comorbid conditions has led to an increasing role for family physicians in caring for patients with HIV infection.

Cardiovascular Disease

Patients with HIV infection have a 1.5- to 2-fold increased risk of acute myocardial infarction, and as the population of patients with HIV infection ages, cardiovascular disease is emerging as a leading contributor to all-cause mortality. Toxicity from antiretroviral drugs, inflammation, HIV infection, kidney disease, and common lifestyle risk factors likely have contributing roles.

One of the main observational studies of metabolic complications in patients with HIV infection, Data Collection on Adverse Events of Anti-HIV Drugs (DAD), showed a quadrupling of myocardial infarction incidence in patients exposed to protease inhibitors for more than 6 years versus in unexposed controls, for an incidence increase of 1.53 to
Care of Patients With HIV Infection

6.01/1,000 person-years. More recent studies have confirmed the link between antiretroviral therapy and cardiovascular disease, with abacavir showing the strongest association. Immune activation related to HIV infection likely contributes to the pathophysiology of cardiovascular disease in these patients. One study showed that even the low levels of inflammation observed in patients with viral suppression appear to spur formation of high-risk unstable arterial plaques.

The most important intervention to reduce cardiovascular disease risk is traditional risk factor modification. For patients with HIV infection, smoking cessation is one of the most important. Smoking is twice as common in patients with HIV infection, and their smoking-related cardiovascular disease risk is nearly three times that of patients without HIV infection. Management of diabetes, hypertension, hyperlipidemia, and alcohol and substance abuse are also key in limiting cardiovascular disease risk in aging patients with HIV infection.

Calculating cardiovascular disease risk to determine the need for statin use in patients with HIV infection is not yet completely understood. Guidelines from the Infectious Diseases Society of America (IDSA) recommend that fasting lipid levels should be evaluated at initiation of care, again within 1 to 3 months after initiating antiretroviral therapy, and then managed according to National Cholesterol Education Program (NCEP) guidelines.

Risk calculators, such as the Framingham Risk Score, may underestimate the higher cardiovascular disease risk of patients with HIV infection. The more recent Atherosclerotic Cardiovascular Disease Risk Estimator from the American College of Cardiology/American Heart Association does not account for HIV infection. The DAD score may be more accurate in predicting risk for these patients because it factors in viral load, history of antiretroviral therapy, and immune status. However, the DAD score is not extensively validated or paired with treatment recommendations. (Online Resources lists several online risk calculators.)

The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) currently is enrolling patients to investigate the use of statins for cardiovascular disease risk reduction for patients with HIV infection. The trial will focus on patients with 10-year atherosclerotic cardiovascular disease risk scores of 10% or less. Until study results are published, patients with HIV infection should be counseled on modification of traditional risk factors and use of statins as are patients without HIV infection.

**Insulin Resistance and Diabetes**

Patients with HIV infection are at higher risk of insulin resistance and diabetes compared with patients in the general population, with some studies indicating a greater than fourfold increase in the incidence of diabetes in patients receiving antiretroviral therapy. The association of antiretroviral therapy with the development of insulin resistance and diabetes is well established, with older protease inhibitors and nucleoside/nucleotide reverse transcriptase inhibitors most frequently implicated. As with cardiovascular disease, diabetes also has been associated with HIV infection.

All patients with HIV infection should undergo screening for diabetes at initiation of care and annually thereafter, also before and 1 to 3 months after initiation or modification of antiretroviral therapy. Diabetes should be managed as in patients without HIV infection. There is no optimal antiretroviral therapy regimen or data to suggest that switching drugs is beneficial in patients with impaired glucose tolerance or diabetes. Metformin is a safe first-line oral drug, as the known link to lactic acidosis primarily was seen with older antiretroviral drugs, such as stavudine and didanosine. However, dolutegravir increases metformin levels, so the total metformin dosage should be limited to 1,000 mg/day when metformin is taken with dolutegravir.

**Hypertension**

As with cardiovascular disease and diabetes, there is a higher incidence of hypertension in patients with HIV infection compared with patients in the general population, and many patients are undertreated or untreated. One large study showed that minor reductions in blood pressure in patients with HIV infection resulted in fewer cardiovascular events. All patients should undergo blood pressure evaluation at least annually, with therapy initiated based on current guidelines as for patients without HIV infection. Although there are no specific antihypertensive regimens recommended for patients with HIV infection, the boosting agents ritonavir and cobicistat inhibit excretion of calcium channel blockers, so patients taking these drugs should be monitored closely or changed to alternative antihypertensive drugs when possible.
Cancer Screening

The incidence of AIDS-defining malignancies, including Kaposi sarcoma, systemic non-Hodgkin lymphoma, and invasive cervical cancer, is decreasing among patients with HIV infection, whereas the incidence of non-AIDS-defining cancers, including anal cancer, Hodgkin lymphoma, hepatocellular carcinoma, head and neck cancer, and lung cancer, is increasing.118 Although some studies show that patients with HIV infection have overall malignancy rates more than 3 times greater than those of patients in the general population,119 there are no specific guidelines for screening patients with HIV infection differently from those in the general population for breast, colon, prostate, and lung cancer. Nevertheless, clinicians should perform all routinely recommended screenings for these cancers in patients with HIV infection.

Screening with cervical Papanicolaou (Pap) testing for human papillomavirus-related neoplasia is an integral part of care for women with HIV infection. Invasive cervical cancer is an AIDS-defining condition that was widely prevalent in the early era of HIV management. The cervical cancer screening guidelines for women with HIV infection were revised in September 2015.42 Previously, it was recommended that all women undergo annual Pap testing; new guidelines recommend screening intervals based on results (Figure 2, Figure 3). The guidelines differ significantly based on patient age, with human papillomavirus cotesting recommended only for women 30 years or older. There currently is no evidence-based guidance on whether Pap testing in women with HIV infection can be safely discontinued after hysterectomy for benign disease or for patients older than 65 years.

Patients with HIV infection are at increased risk of anal dysplasia and anal cancer based on data from numerous observational studies.120-122 However, there is no consensus on screening guidelines due to a lack of definitive data linking anal Pap screening with decreased mortality rates. The IDSA recommends anal

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**Figure 2. Cervical Cancer Screening Algorithm for Women Younger Than 30 Years With HIV Infection**

> ASC-US = atypical squamous cells; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; Pap = Papanicolaou.

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Pap tests for men who have sex with men, women with a history of receptive anal intercourse or abnormal cervical Pap test results, and all patients with HIV infection and genital warts. Abnormal results warrant follow-up with high-resolution anoscopy. Though not yet validated in clinical trials, annual screening typically is accepted as the current standard of care in the management of HIV infection.

**Vaccinations**

Most vaccines are safe and effective in patients with HIV infection. Inactivated vaccines are safe for all patients with HIV infection. Live virus vaccines (eg, varicella, measles-mumps-rubella) only should be administered to patients with viral suppression (ie, viral load less than 200 copies/mL) and a CD4 count 200 cells/mm$^3$ or greater. The exception to this rule is live influenza vaccine, which should be avoided in all patients with HIV infection, whereas the inactivated influenza vaccine is recommended for all patients with HIV infection. Table 9 summarizes current recommendations for routine vaccination.

Because of evidence of decreased efficacy of vaccination overall in patients with immunocompromise, many experts recommend revaccination after CD4 counts are greater than 200 cells/mm$^3$. In the future, there may be expanded use of the human papillomavirus vaccine in patients with HIV infection based on studies currently investigating its efficacy in high-risk patients.

**Opportunistic Infection Prophylaxis and Sexually Transmitted Infection Screening**

Sexually transmitted infections are common in patients with HIV infection given shared routes of transmission. Many such infections are asymptomatic but can be associated with significant morbidity. Screening and treatment are critical components of HIV prevention because HIV transmission may increase in the presence of infection.

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**Figure 3. Cervical Cancer Screening Algorithm for Women 30 Years and Older With HIV Infection**

Some experts recommend repeating 6 months after initiation of care.

AGC = atypical glandular cells; ASC-H = atypical squamous cells, cannot exclude HSIL; ASC-US = atypical squamous cells of undetermined significance; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; Pap = Papanicolaou.

of concurrent sexually transmitted infections.\textsuperscript{123} Periodic testing for sexually transmitted infections at relevant anatomic sites based on sexual history is recommended for all patients with HIV infection.\textsuperscript{109} Table 10 provides a summary of these recommendations.

Despite their decreasing incidence, opportunistic infections still contribute to substantial morbidity and mortality in patients with HIV infection, and many patients present with an opportunistic infection as the first indicator of the condition.\textsuperscript{124} A \textit{Toxoplasma gondii} immunoglobulin (Ig) G test should be obtained on intake for all patients.\textsuperscript{42} \textit{Toxoplasma} IgG-negative patients should be counseled on handwashing and prevention of exposure from cat feces, undercooked or raw meat, or gardening without gloves.\textsuperscript{42} While HIV-positive men who have sex with men or injection drug users may be assumed to have been exposed to cytomegalovirus, other patients should be tested at initiation of care for latent infection with cytomegalovirus IgG.\textsuperscript{109}

All patients should be screened on intake for \textit{Mycobacterium tuberculosis} infection with a tuberculin

<table>
<thead>
<tr>
<th>Table 9</th>
<th>Routine Vaccinations for Patients With HIV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine</td>
<td>CD4 count &lt;200 cells/mm(^3)</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Certain populations(^a) 2 doses</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>3 doses (screen first for immunity and active infection)</td>
</tr>
<tr>
<td>Human papillomavirus, males and females ages 9 to 26 years</td>
<td>3 doses</td>
</tr>
<tr>
<td>Influenza</td>
<td>1 dose/year (live vaccine contraindicated)</td>
</tr>
<tr>
<td>Measles-mumps-rubella</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>Certain populations(^b) 1 or more doses</td>
</tr>
<tr>
<td>Pneumococcal conjugate(^c)</td>
<td>1 dose</td>
</tr>
<tr>
<td>Pneumococcal polysaccharide(^c)</td>
<td>1 dose followed by 1 more dose at 5 years</td>
</tr>
<tr>
<td>Tetanus toxoid</td>
<td>Substitute 1-time dose Tdap for Td booster, then Td every 10 years</td>
</tr>
<tr>
<td>Varicella</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Zoster</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

\(^a\)Patients ages 11 to 18 years, first-year college students living in communal housing, patients with asplenia, travelers to endemic areas.

\(^b\)Men who have sex with men, intravenous drug users, travelers to endemic areas, patients with chronic liver disease or hepatitis B or C infection.

\(^c\)One dose of PCV13 followed by a dose of PPV23 at least 8 weeks later. If previously vaccinated with PPV23, administer PCV13 at least 1 year after PPV23.

PCV13 = 13-valent pneumococcal conjugate vaccine; PPV23 = polyvalent pneumococcal polysaccharide vaccine; Td = tetanus toxoid, reduced diphtheria; Tdap = tetanus toxoid, reduced diphtheria, acellular pertussis.

skin test or interferon-gamma release assay. Annual testing for latent tuberculosis is recommended only for patients with HIV infection with a high risk of repeated or ongoing exposure to individuals with active tuberculosis. Patients with a positive tuberculin skin test or interferon gamma-release assay result and no symptoms or chest x-ray evidence of active tuberculosis infection should receive 9 months of isoniazid treatment for latent tuberculosis infection. Table 5 includes a summary of recommendations for opportunistic infection screening and primary prophylaxis.

**Preexposure Prophylaxis**

A major development in prevention of HIV transmission is the Food and Drug Administration approval of emtricitabine-tenofovir (Truvada) for preexposure prophylaxis (PrEP). The efficacy of PrEP is well established based on multiple clinical trials performed in men who have sex with men, serodiscordant heterosexual couples, heterosexual adults, and intravenous drug users. The key determinant of PrEP efficacy is strict daily drug adherence, with the reduction in transmission rates varying from approximately 40% to 90% based on degree of adherence.

In addition to daily emtricitabine-tenofovir, PrEP comprises repeated condom provision, sexual risk reduction counseling, and diagnosis and treatment of sexually transmitted infections. Candidates for PrEP are patients without HIV infection and with substantial risk factors for HIV acquisition who are willing to adhere to a daily drug regimen and frequent follow-up (Table 11). Although PrEP only is approved for use in adults, trials currently are under way in adolescents.

The safety of PrEP in women who are breastfeeding has not been adequately studied. However, data from studies of infants born to mothers with HIV infection and exposed to tenofovir or emtricitabine through breast milk suggest limited drug exposure. Therefore, clinicians should discuss the potential risks and benefits of initiating or continuing PrEP with these women so an informed decision can be made.

Before PrEP initiation, patients must be screened for symptoms of acute HIV infection. Verification of hepatitis B infection status also is crucial, given that tenofovir has activity against hepatitis B virus, and its abrupt discontinuation can lead to an episode of viral hepatitis. Emtricitabine-tenofovir is typically

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**Table 10**  
**Sexually Transmitted Infection Screening for Patients With HIV Infection**

<table>
<thead>
<tr>
<th>Males</th>
<th>Females</th>
<th>Males and Females With High-Risk Behaviors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia urine NAAT</td>
<td>Chlamydia vaginal swab (preferred) or urine NAAT</td>
<td>If receptive anal sex, obtain rectal chlamydia and gonorrhea NAAT</td>
</tr>
<tr>
<td>Gonorrhea urine NAAT</td>
<td>Gonorrhea vaginal swab (preferred) or urine NAAT</td>
<td>If receptive oral sex, obtain oropharyngeal gonorrhea NAAT</td>
</tr>
<tr>
<td>Syphilis EIA, FTA, RPR, or VDRL</td>
<td>Syphilis EIA, FTA, RPR, or VDRL</td>
<td></td>
</tr>
<tr>
<td>Trichomoniasis vaginal swab or NAAT</td>
<td>Trichomoniasis vaginal swab or NAAT</td>
<td></td>
</tr>
</tbody>
</table>

**Screening Intervals**

Test at initial visit and annually thereafter, with more frequent testing at the site of exposure for patients with high-risk behaviors, including multiple or anonymous partners, inconsistent condom use, substance abuse (particularly methamphetamine), and exchange of sex for drugs or money.

Retest all patients treated for chlamydia and gonorrhea and all women with trichomoniasis at the relevant site of infection within 3 months after treatment.

EIA = enzyme immunoassay; FTA = fluorescent treponemal antibody; NAAT = nucleic acid amplification test; RPR = rapid plasma reagin; VDRL = Venereal Disease Research Laboratory.

well tolerated, but can cause bone loss and impaired renal function and little is known about adverse effects from long-term use. The risks and benefits of PrEP should be explained before prescribing, so each patient can make an informed decision about its use. Further guidance on the use of PrEP, including tools for screening candidates for PrEP, are available.129,131

Some argue against the use of PrEP based on its expense compared with condom use, although economic analyses suggest that PrEP is cost-effective, particularly in men who have sex with men. Another concern is the potential for development of viral resistance in the setting of drug nonadherence, but this has yet to be observed outside of rare case reports. Some studies show that patients receiving PrEP may engage in higher-risk behaviors, such as less condom use,132 potentially leading to higher rates of other sexually transmitted infections, although this has not been observed in the referenced studies of PrEP. Nevertheless, this concern highlights the importance of behavioral risk reduction counseling as an integral part of PrEP.

**Case 1, cont’d.** After asking James about continued adherence to the antiretroviral therapy regimen, you focus on his recent A1c level of 9.5%. You cannot increase his dosage of metformin, which is 500 mg 2 times/day, because he is taking dolutegravir. You explain that he may eventually need insulin. You encourage him to pursue a healthy diet, regular exercise, and weight loss, and you refer him to a nutritionist.

James is taking lisinopril 10 mg/day and atorvastatin 20 mg/day, and his blood pressure today is 125/85 mm Hg. You administer the annual inactivated influenza vaccine, and you verify that his other vaccinations are current. Results of the anal Papanicolaou test this year are normal, and you plan to repeat the test again next year. You confirm that he continues to use condoms with his wife because she prefers that to taking preexposure prophylaxis. Finally, you discuss he and his wife’s desire for another child, and you give him information about the merits of sperm washing versus timed unprotected intercourse, given the near-zero risk of HIV transmission with long-term viral suppression. He plans to discuss this with his wife and schedules a follow-up appointment in 3 months.
References


References

35. Marks G, Crepaz N, Janssen RS. Estimating sexual transmission of HIV from persons aware and unaware that they are infected with the virus in the USA. AIDS. 2006;20(10):1447-1450.


Care of Patients With HIV Infection


Online Resources

American College of Cardiology/American Heart Association Atherosclerotic Cardiovascular Disease Risk Estimator Website: http://tools.acc.org/ASCVD-Risk-Estimator/

Center for HIV Law and Policy Website: http://www.hivlawandpolicy.org/

Clinician Consultation Center Telephone consultation service provides information and assistance for occupational and nonoccupational postexposure prophylaxis, preexposure prophylaxis, perinatal HIV management, and general HIV management Website: http://nccc.ucsf.edu/


Dept of Health and Human Services Guidelines for prevention and treatment of opportunistic infections Website: https://aidsinfo.nih.gov/guidelines

Internet Sexuality Information Services Website: http://www.inspot.org

National Heart, Lung, and Blood Institute Framingham Risk Score Website: http://cvdrisk.nhlbi.nih.gov/

NEJM Journal Watch HIV/AIDS Website: http://www.jwatch.org/hiv-aids

Suggested Reading


Websites accessed March 2016
1. According to the Centers for Disease Control and Prevention, which one of the following percentages of the 1.2 million individuals with HIV infection in the United States are unaware of their condition?
   - A. 1% to 5%.
   - B. 6% to 10%.
   - C. 11% to 15%.
   - D. 16% to 20%.
   - E. 21% to 25%.

2. The US Preventive Services Task Force recommends universal HIV screening regardless of risk for which one of the following groups?
   - A. Adolescents and adults ages 15 to 65 years.
   - B. Pregnant women.
   - C. Women with unknown HIV status who present in labor.
   - D. All of the above.

3. The algorithm for HIV testing recommended by the Centers for Disease Control and Prevention uses fourth-generation tests, including HIV antibody assay, p24 antigen test, antibody differentiation assay, and nucleic acid test. Which one of the following statements is true of fourth-generation HIV tests?
   - A. The test results are available more rapidly than those for third-generation antibody tests.
   - B. They are Food and Drug Administration-approved for in-home testing.
   - C. They have a shorter window period.
   - D. They use finger-stick blood sampling.

4. State laws regarding HIV testing vary. Which one of the following has the Centers for Disease Control and Prevention recommended be eliminated for all states?
   - A. Anonymous testing requirements.
   - B. Partner notification requirements.
   - C. Separate written consent for HIV testing requirements.
   - D. None of the above.

5. The initial laboratory evaluation for a patient with HIV infection should include HLA-B*5701 testing for which one of the following reasons?
   - A. To assess for latent tuberculosis infection.
   - B. To assess the degree of native immune virologic control.
   - C. To detect risk of methemoglobinemia in patients taking dapsone.
   - D. To identify patients at risk of abacavir hypersensitivity reaction.

6. When a patient is being treated for HIV infection with antiretroviral therapy, in which one of the following cases could CD4 count monitoring be considered optional?
   - A. The CD4 count has been greater than 200 cells/mm$^3$ with a viral load less than 500 copies/mL for more than 1 year.
   - B. The CD4 count has been greater than 200 cells/mm$^3$ with a viral load less than 500 copies/mL for more than 2 years.
   - C. The CD4 count has been greater than 500 cells/mm$^3$ with a viral load less than 200 copies/mL for more than 1 year.
   - D. The CD4 count has been greater than 500 cells/mm$^3$ with a viral load less than 200 copies/mL for more than 2 years.

7. Which one of the following statements about acute HIV infection is true?
   - A. Leukopenia or thrombocytopenia occurs in approximately 51% of patients.
   - B. It produces a clinical illness in 10% to 15% of patients.
   - C. Rhinorrhea, nasal congestion, and cough are common symptoms.
   - D. Symptoms begin 2 to 3 days after infection.

8. An adult with HIV infection presents with oral candidiasis, a CD4 count of 170 cells/mm$^3$, a positive cytomegalovirus immunoglobulin (Ig) G test result, and a negative Toxoplasma gondii IgG result. In this patient, primary prophylaxis is recommended for which one of the following opportunistic infections?
   - A. Cytomegalovirus infection.
   - B. Histoplasmosis.
   - C. Mycobacterium avium complex.
   - D. Pneumocystis jirovecii pneumonia.

Complete the online quiz at http://www.aafp.org/fpequiz.
9. Which one of the following pulmonary infections is considered an AIDS-defining condition in an adult with HIV infection with any CD4 count?
   - A. Coccidioidomycosis.
   - B. Cryptococcosis.
   - C. Histoplasmosis.
   - D. Tuberculosis.

10. When assessing patients with HIV infection for active pulmonary tuberculosis, 8 weeks may be needed to obtain the results of which one of the following tests?
   - A. Interferon-gamma release assay.
   - B. Nucleic acid amplification test on sputum specimen.
   - C. Sputum culture for *Mycobacterium tuberculosis*.
   - D. Sputum smear for acid-fast bacilli.

11. A patient with HIV infection, who grew up in Puerto Rico, has a CD4 count of 100 cells/mm³ as well as fever, diarrhea, leukopenia, and mouth ulcers. Urine antigen testing should be used to diagnose or rule out which one of the following opportunistic infections?
   - A. Coccidioidomycosis.
   - B. Cryptococcosis.
   - C. Histoplasmosis.
   - D. Toxoplasmosis.

12. A CD4 count of 600 cells/mm³ is considered to be an AIDS-defining condition for patients with HIV infection at which one of the following ages?
   - A. 4 months.
   - B. 4 years.
   - C. 14 years.
   - D. 24 years.

13. Which one of the following is considered an AIDS-defining condition in an adult with HIV infection with any CD4 count?
   - A. Burkitt lymphoma.
   - B. Cytomegalovirus of the lymph nodes.
   - C. Oral candidiasis.
   - D. Pulmonary *Mycobacterium avium* complex.

14. At which one of the following CD4 counts should antiretroviral therapy be offered to patients with HIV infection who are able to consent, commit, and adhere to treatment?
   - A. Less than 200 cells/mm³.
   - B. Less than 500 cells/mm³.
   - C. Less than 1,000 cells/mm³.
   - D. Any count.

15. Which one of the following statements is true of the action of protease inhibitors regarding HIV?
   - A. They block entry of HIV into CD4 T cells.
   - B. They block maturation and production of HIV.
   - C. They block reverse transcription of HIV from RNA to DNA using enzymatic inhibition.
   - D. They block reverse transcription of HIV from RNA to DNA via chain-terminating proteins.

16. To prevent chelation, which one of the following drugs should not be taken with antacids or supplements containing magnesium, aluminum, iron, calcium, or zinc?
   - A. Cobicistat.
   - B. Darunavir.
   - C. Dolutegravir.
   - D. Maraviroc.

17. Which one of the following initial antiretroviral therapy regimens is preferred in patients with HIV infection and preexisting chronic kidney disease?
   - B. Dolutegravir-abacavir-lamivudine.
   - C. Dolutegravir-tenofovir-emtricitabine.
   - D. Elvitegravir-cobicistat-tenofovir-emtricitabine.
   - E. Raltegravir-tenofovir-emtricitabine.

18. Coinfection with hepatitis B virus can complicate management of HIV infection. Which one of the following is an antihepatitis B virus drug that has partial anti-HIV activity, can select for HIV-resistant mutations, and whose use should be avoided in patients with HIV infection who are not receiving antiretroviral therapy?
   - A. Abacavir.
   - B. Elvitegravir.
   - C. Entecavir.
   - D. Raltegravir.
19. Which one of the following vaccinations is recommended routinely for a 35-year-old woman with HIV infection and a viral load of 20,000 copies/mL, a CD4 count less than 200 cells/mm$^3$, and a history of childhood varicella?

- A. Inactivated influenza.
- B. Live influenza.
- C. Varicella.
- D. Zoster.

20. A candidate for preexposure prophylaxis with emtricitabine-tenofovir would be HIV-negative and have which one of the following characteristics?

- A. A creatinine clearance less than 60 mL/min/1.73 m$^2$.
- B. A history of osteoporosis.
- C. Active intravenous drug use.
- D. An HIV-negative partner.
Question 1: The correct answer is C.
The Centers for Disease Control and Prevention estimates that approximately 87% of the 1.2 million individuals infected with HIV in the United States have been diagnosed, which means that approximately 14% (156,000 individuals) are unaware that they are infected. See page 11.

Question 2: The correct answer is D.
The US Preventive Services Task Force (USPSTF) recommends screening adolescents and adults ages 15 to 65 years for HIV infection regardless of risk level. For pregnant women, the Centers for Disease Control and Prevention, USPSTF, and American College of Obstetricians and Gynecologists endorse universal HIV screening regardless of risk to decrease mother to child transmission of HIV. Patients presenting in labor with unknown HIV status should undergo rapid HIV testing. See pages 11-12.

Question 3: The correct answer is C.
In 2014, the Centers for Disease Control and Prevention recommended adoption of fourth-generation HIV tests. These tests have a shorter window period (ie, time between infection and a positive test result), which decreases the number of false-negative and indeterminate results. See page 12.

Question 4: The correct answer is C.
State laws vary widely regarding HIV testing and criminalization of HIV exposure and transmission, and many such laws have created barriers to testing. In 2006, the Centers for Disease Control and Prevention recommended that "separate written consent for HIV testing should not be required," instead, an opt-out approach should be taken, in which "general consent for medical care should be considered sufficient to encompass consent for HIV testing." See page 13.

Question 5: The correct answer is D.
Initial testing for patients with HIV infection should include HLA-B*5701 testing to identify patients at risk of abacavir hypersensitivity reaction. See Table 2.

Question 6: The correct answer is D.
Per 2015 guidelines, CD4 count monitoring is considered optional for patients with CD4 counts consistently greater than 500 cells/mm³ with more than 2 years of viral suppression. See page 15.

Question 7: The correct answer is A.
Leukopenia or thrombocytopenia occurs in approximately 51% of patients with acute HIV infection. See page 16.

Question 8: The correct answer is D.
The strongest recommendations are to initiate primary prophylaxis for Pneumocystis jirovecii pneumonia in patients with CD4 counts less than 200 cells/mm³ or a history of oropharyngeal candidiasis, for toxoplastic encephalitis in patients with CD4 counts less than 100 cells/mm³ and positive serum Toxoplasma gondii immunoglobulin (Ig) G results, and for disseminated Mycobacterium avium complex in patients with CD4 counts less than 50 cells/mm³. See page 17.

Question 9: The correct answer is D.
In patients with HIV infection ages 6 years or older, pulmonary tuberculosis is considered an AIDS-defining opportunistic infection at any CD4 count. See page 20.

Question 10: The correct answer is C.
Cultures for Mycobacterium tuberculosis rarely have positive results in less than 3 weeks and are not declared negative until after 8 weeks of incubation See page 20.

Question 11: The correct answer is C.
Disseminated histoplasmosis occurs in patients with HIV infection who have lived in areas in which the Histoplasma capsulatum fungus is endemic, including states bordering the Ohio River valley and the lower Mississippi River; Puerto Rico; and many countries in Central America and South America. Fever, diarrhea, leukopenia, and oral ulcers are common symptoms. This condition typically occurs in patients with CD4 counts less than 150 cells/mm³. Urine antigen testing is used to make the diagnosis. See page 21.

Question 12: The correct answer is A.
In patients with HIV infection, a low CD4 count is considered an AIDS-defining condition, with the threshold depending on the patient’s age. In infants younger than 1 year, a CD4 count less than 750 cells/mm³ is AIDS-defining. See page 21.

Question 13: The correct answer is A.
Systemic non-Hodgkin lymphomas, primarily Burkitt and immunoblastic B-cell lymphomas, are AIDS-defining malignancies that can develop at any CD4 count. See page 22.
Question 14: The correct answer is D.
The Department of Health and Human Services recommends antiretroviral therapy for all patients with HIV infection who are able to consent, commit, and adhere to treatment regardless of CD4 count or viral load. See page 23.

Question 15: The correct answer is B.
Protease inhibitors prevent maturation and production of the virus. See page 24.

Question 16: The correct answer is C.
Dolutegravir must be taken 2 hours before or 6 hours after antacids or supplements containing magnesium, aluminum, iron, calcium, or zinc, to prevent chelation. See page 24.

Question 17: The correct answer is B.
Overall, dolutegravir-abacavir-lamivudine is a well-tolerated regimen that avoids the renal risk of tenofovir-based regimens. Patients with preexisting chronic kidney disease should avoid taking tenofovir if possible. See pages 24-27.

Question 18: The correct answer is C.
The antihepatitis B virus drug entecavir has partial anti-HIV activity and can select for HIV-resistant mutations, so its use should be avoided in patients with HIV infection who are not taking antiretroviral therapy. See page 30.

Question 19: The correct answer is A.
The inactivated influenza vaccine is recommended for all patients with HIV infection. See page 34.

Question 20: The correct answer is C.
Characteristics of candidates for preexposure prophylaxis include HIV-negative status and active intravenous drug use. See Table 11.
The following topics appear in this month’s edition of the AAFP FP Audio™ program:

**Clinical Topic:** New Congestive Heart Failure Agents

**Clinical Topic:** Top Articles of 2015: Diagnosis

**Journal Notes:** Lower Extremity Revascularization in Nursing Home Patients

**Editor’s Q&A:** Familial Hypercholesterolemia

The next edition of AAFP FP Essentials™ will be:

**Nephrology Update**