The care of the HIV-infected patient in the emergency department has changed since the development of highly active antiretroviral therapy. This therapy has resulted in longer life expectancies and increased quality of life for HIV-infected patients, and in cases of treatment compliance and success, virtual elimination of AIDS-associated opportunistic infections. As a result, the emergency clinician is now more often confronted with adverse events related to medication and the diseases associated with aging and chronic disease. This issue focuses on the differences in evaluation of HIV patients on long-term therapy and patients with medication non-compliance and low CD4 counts, as well as recognition of life-threatening and rare opportunistic infections. Disease processes related to the effect of longstanding HIV infection, even with good control, on many organ systems are addressed. 

**Abstract**

1. Recognize the more common system-based diseases and problems status and whether they are on highly active antiretroviral therapy.
2. Recognize common side effects of antiretroviral drugs.
3. Initiation of and long-term treatment with antiretroviral drugs.

Prior to beginning this activity, see "Physician CME Information" on the back page.
Case Presentations

You arrive for your ED shift and are presented with 3 HIV-infected patients with various chief complaints. The first patient is a 28-year-old man with 1 day of right flank pain, nausea, vomiting, and hematuria. He had a kidney stone a year ago with identical pain, and a point-of-care ultrasound shows asymmetric hydronephrosis; however, a nonenhanced CT scan demonstrates hydronephrosis and hydroureter without a stone. You wonder if the CT eliminates an impacted stone or if there is another explanation.

The second patient is a 42-year-old HIV-infected woman complaining of as many as 3 episodes a day of diarrhea for the past 3 weeks. She denies pain, melena, rectal bleeding, and fevers. Her laboratory test results are unremarkable. You wonder if additional testing is needed and whether sending her home is appropriate.

The third patient presents because her family has noticed that she has been acting increasingly “sad.” She denies any suicidal or homicidal ideation, but does corroborate that since initiation of an SSRI antidepressant drug 6 months ago, she has not noticed any improvement in her mood. In the absence of suicidal ideation, you wonder if she can be sent home.

You are reminded that caring for the HIV-infected patient is not so simple, and you realize quickly that you are dealing with 3 very different presentations related to the same disease and must prioritize where to begin.

Introduction

The human immunodeficiency virus (HIV) causes a progressive failure of the immune system, ultimately leading to acquired immunodeficiency syndrome (AIDS) in the absence of treatment. Although under different nomenclature, AIDS was first described in the early 1980s when clusters of patients developed opportunistic infections (OIs) not seen in patients with intact immune systems. HIV has spread to every country in the world, creating a global pandemic. In 2012, there were 35.3 million people living with HIV worldwide and 2.3 million new diagnoses that year.1

The development of highly active antiretroviral therapy (HAART) in 1996 dramatically increased life expectancy for HIV-infected patients. Due to the effectiveness of HAART, by the early 2000s, life expectancy of HIV-infected patients in developed countries was equivalent to that of comparable persons who were not HIV-infected.2,3

Current guidelines from the United States Department of Health and Human Services recommend the treatment of all HIV-infected patients with antiretroviral medications (ARVs).4 These current recommendations are based on evidence that ARVs reduce the risk of disease progression in all patients with CD4 T lymphocyte (CD4) count < 350 cells/mm³, CD4 count 350 to 500 cells/mm³, and CD4 count > 500 cells/mm³. This recommen-

inflammatory syndrome. Because of the large number of articles retrieved in these searches, the initial focus was on review articles with cross-referencing primary literature cited in the bibliographies. Relevant guidelines by the World Health Organization, the United States Department of Health and Human Services, and the American College of Emergency Physicians were also reviewed.

Now, nearly 20 years after the advent of HAART, considerable literature exists on the subject of HIV both in terms of the OIs patients experience and the chronic effects of longstanding illness and treatment. This literature provides strong evidence to support the practice recommendations made in this article.

**Epidemiology And Pathophysiology**

In 2012, there were an estimated 1.2 million persons in the United States aged > 12 years infected with HIV. This estimate includes approximately 160,000 persons (14%) who were unaware of their diagnosis. The high prevalence of undiagnosed HIV underscores the importance of routine HIV testing. Based on 2009-2010 National Hospital Ambulatory Medical Care Survey data, HIV-infected patients accounted for 5 in 1000 emergency department (ED) visits. Although they had similar acuity to non–HIV-infected patients, they received more diagnostic testing, had longer lengths of stay, and were more likely to be admitted.

In order to become infected with HIV, an individual must be exposed to an infected body fluid, typically through either direct inoculation into the bloodstream or via a disrupted mucosal barrier. As a medium, blood carries the highest risk of infection; however, exposure to other fluids such as semen, vaginal secretions, breast milk, and cerebrospinal fluid also carry risk. Risk of infection is determined by 2 key factors: the viral load of the source patient and the method of exposure. Several days after infection, the virus moves beyond the local site of infection into the bloodstream with rapid replication. Approximately 75% to 90% of patients experience an acute illness during this time. Patients develop a fever, with additional symptoms typical of many viral syndromes including lymphadenopathy, sore throat, and gastrointestinal symptoms (such as vomiting and diarrhea). Some more-distinctive features include genital or mucocutaneous ulcers and a relatively nondescript macular rash that mimics a viral exanthem often seen in children with viral illnesses. The syndrome typically lasts for weeks, and patients seek evaluation by a medical provider, often in the ED. There is a notable absence of pulmonary symptoms during the illness, and this may help clinicians in their diagnostic approach to the febrile patient. This constellation of signs and symptoms is known by several names, including acute seroconversion, primary HIV infection, or acute retroviral syndrome.

During the seroconversion syndrome, there may be an acute drop in CD4 count (leading, rarely, to an OI), which typically rebounds when the body gains some control over the virus. The diagnosis of acute seroconversion is challenging, because current rapid HIV antibody testing technology may not detect the presence of the infection. Fourth-generation tests that combine detection of the HIV antibody as well as the p24 antigen on the surface of HIV identify infection as early as 2 weeks after exposure. However, with negative rapid testing and with a diagnosis of an acute HIV infection suspected, an HIV viral load must be obtained. Diagnosis is critical, as patients with acute infection have extremely high viral loads and are more infectious than those with chronic infection. Additionally, identification of acute infection allows for prompt referral to an HIV clinician, allowing initiation of ARV therapy. After the acute illness is over, patients experience a period of chronic (or latent) HIV infection without AIDS. AIDS is defined by a CD4 count < 200 cells/mm³ or development of certain OIs or cancers. The average time from HIV infection to a CD4 count < 200 cells/mm³ is 8 to 10 years. Most individuals remain asymptomatic during this chronic (or latent) phase, although many have lymphadenopathy. Considering the high infectivity and then clinical silence, if the diagnosis is missed, emergency clinicians must maintain a high index of suspicion for this illness in patients presenting with typical features and risk factors for HIV exposure in the weeks preceding their evaluation.

Although patients may survive for years without developing OIs, chronic infection with the virus in the absence of HAART is not without detrimental effects on the body. Infection causes a chronic inflammatory state, which may predispose patients to numerous conditions, including coronary artery disease, venous thromboembolism, and chronic obstructive pulmonary disease. Once patients begin treatment with HAART, measurable inflammatory markers decrease, as does the risk for adverse sequelae from the HIV infection itself. However, patients taking HAART are at risk for adverse medication effects as well as regular age-related conditions that have become more prevalent as HIV-infected patients live longer.

**Prehospital Care**

The primary goal for providers in the prehospital care of the HIV-infected patient is safe transfer to the receiving facility and careful attention to personal protection. Resuscitation and stabilization of the HIV-infected patient follows the same principles as a non–HIV-infected individual. High-risk procedures for exposure to bodily fluids occur often, and the
prehospital provider must take caution for his or her own safety, strictly adhering to universal precautions. In the event that a blood or body fluid exposure does occur, the provider should seek immediate care. Treatment with postexposure prophylaxis (PEP) (a 28-day course of treatment with HIV medication) is effective at decreasing rates of HIV acquisition.

### Emergency Department Evaluation

#### History
Chronic HIV infection can affect nearly every organ system, highlighting the importance of a thorough history and physical examination. First, providers should evaluate the status of the HIV infection (eg, CD4 count and viral load), the treatment regimen, and the patient’s medication compliance. After an overall sense of disease status is obtained, emergency clinicians should focus on evaluation of the chief complaint and its relevance to HIV infection or treatment taken for the HIV infection.

Initial questions for an HIV-infected patient include inquiring about the patient’s most recent CD4 count, viral load (or at least whether the viral load is undetectable), and any recent travel history or exposure to sick contacts. Asking about a patient’s prior OIs is also important, as patients may have sequelae from OIs that alter their physical examination. If the patient is on HAART, determine the specific drugs taken, the patient’s compliance, and ask about the characteristic side-effect profiles of some medications. (See Table 1.) These questions help frame an understanding of the patient’s baseline HIV infection status.

Questions related to the patient’s chief complaint should be guided by whether or not the patient is under the care of a clinician for his or her HIV infection and is compliant with the prescribed medication regimen. Patients unaware of their CD4 count or viral load or who are not engaged in their care should be considered at higher risk for OIs and other complications of AIDS. Therefore, a thorough history of these patients includes questions regarding infectious symptoms such as fevers, chills, and diaphoresis. Patients compliant with treatment regimens are at higher risk for conditions related to chronic infection and adverse reactions from medication. A thorough review of systems may uncover symptoms related to chronic infection that the patient may not have thought relevant to their presenting complaint (eg, changes in skin, sleep, bowel or bladder habits, or psychiatric disturbance).

#### Physical Examination
A complete physical examination is critical for patients with HIV. Physical examination findings related to specific conditions are discussed in the following tables.

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#### Table 1. Major Adverse Effects Of Antiretroviral Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside Reverse Transcriptase Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>Hypersensitivity reaction, Stevens-Johnson syndrome, lactic acidosis, increased risk of myocardial infarction</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Stevens-Johnson syndrome, lactic acidosis, pancreatitis, peripheral neuropathy</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Lactic acidosis, hyperpigmentation/skin discoloration</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Lactic acidosis</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Lactic acidosis, pancreatitis, peripheral neuropathy</td>
</tr>
<tr>
<td>Tenofovir*</td>
<td>Lactic acidosis, Fanconi syndrome, accelerated osteoporosis</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Stevens-Johnson syndrome, lactic acidosis, bone marrow suppression</td>
</tr>
<tr>
<td><strong>Nonnucleoside Reverse Transcriptase Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Stevens-Johnson syndrome, transaminitis</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Stevens-Johnson syndrome, psychosis, depression</td>
</tr>
<tr>
<td>Etravirine</td>
<td>Stevens-Johnson syndrome, hypersensitivity reactions</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Stevens-Johnson syndrome, hepatic necrosis</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Stevens-Johnson syndrome, depression</td>
</tr>
<tr>
<td><strong>Protease Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Hyperbilirubinemia (indirect), PR interval prolongation/atrioventricular block</td>
</tr>
<tr>
<td>Darunavir</td>
<td>Gastrointestinal upset, sulfonamide hypersensitivity, Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Rash, sulfonamide hypersensitivity, transaminits</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Nephrotoxicity, urolithiasis</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>Pancreatitis, PR and QT interval prolongation, transaminits, gastrointestinal intolerance</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Gastrointestinal intolerance</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Gastrointestinal intolerance, metabolic syndrome, paresthesia (circumoral and extremities), asthenia</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Metabolic syndrome, PR and QT interval prolongation</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>Hepatotoxicity, intracranial hemorrhage, skin rash</td>
</tr>
<tr>
<td><strong>Integrase Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>Hypersensitivity reactions</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>Nephrotoxicity, gastrointestinal intolerance</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Stevens-Johnson syndrome, creatine phosphokinase elevation, pyrexia</td>
</tr>
<tr>
<td><strong>Fusion/Entry Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>Hypersensitivity reaction, increased incidence of pneumonia</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>Hepatotoxicity, abdominal pain, pyrexia, upper respiratory tract infections</td>
</tr>
</tbody>
</table>

*Nucleotide reverse transcriptase inhibitor.
lowing sections. Because HIV has many dermatologic manifestations, a comprehensive skin examination should be included in addition to a complaint-based physical examination.

**Diagnostic Testing**

**Laboratory Testing**

In general, laboratory testing plays an important role in the screening and diagnosis of HIV-related metabolic and infectious diseases. A study published in 2013 suggested that HIV-infected patients received 4.5 laboratory tests per ED visit compared to 3.5 tests for the non–HIV-infected individual. These tests included complete blood count, basic metabolic panel, and hepatic function testing. Lactic acidosis is a complication of nucleoside reverse transcriptase inhibitor (NRTI) use and, when acutely worsened, is associated with higher mortality. Serum lactic acid measurement is appropriate in patients with an anion gap metabolic acidosis or severe illness. HIV-infected patients are not only tested more often than noninfected patients, but are admitted more frequently. Therefore, it appears that having a lower threshold for testing is appropriate in these patients.

When infectious complications are suspected, appropriate cultures (sometimes for atypical organisms or OIs) should be ordered. If recent HIV-specific testing results are not available, the emergency clinician can order a CD4 count and viral load; however, timely results are not typically available for decision-making. CD4 counts and viral load results help to narrow the differential diagnosis in HIV-infected patients. In cases where patients have not had or do not know these values, an absolute lymphocyte count may be used as a surrogate for CD4 count. An absolute lymphocyte count < 950 cells/mm³ is associated with a total CD4 count < 200 cells/mm³ (sensitivity, 76%; 95% confidence interval [CI] 73%-79%; specificity, 93%; 95% CI, 87%-96%; positive likelihood ratio, 10.1; 95% CI, 8.2-14). When infectious complications are suspected, appropriate cultures (sometimes for atypical organisms or OIs) should be ordered. If recent HIV-specific testing results are not available, the emergency clinician can order a CD4 count and viral load; however, timely results are not typically available for decision-making. CD4 counts and viral load results help to narrow the differential diagnosis in HIV-infected patients. In cases where patients have not had or do not know these values, an absolute lymphocyte count may be used as a surrogate for CD4 count. An absolute lymphocyte count < 950 cells/mm³ is associated with a total CD4 count < 200 cells/mm³ (sensitivity, 76%; 95% confidence interval [CI] 73%-79%; specificity, 93%; 95% CI, 87%-96%; positive likelihood ratio, 10.1; 95% CI, 8.2-14).

HIV testing should be conducted in individuals who might be infected with HIV if they show signs or symptoms of diagnoses consistent with OIs or AIDS-related complications. Rapid HIV antibody testing is available using either oral swabs or blood samples. Most currently available HIV antibody tests have sensitivities of 100% and specificities > 99%. Fourth-generation HIV tests identify both antibodies as well as the p24 antigen on the surface of HIV, which appears to permit earlier diagnosis of an HIV infection. If an acute HIV infection is suspected, then measurement of a viral load can help to make the diagnosis.

**Imaging**

Radiologic imaging tests should be directed at the patient’s complaints and immune status. The emergency clinician should have a low bar for imaging, especially low-risk and low-cost tests (such as x-ray and ultrasound), where appropriate. Other modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) should also be used, when appropriate. For example, an immunocompetent HIV-infected patient with headache probably does not need a CT of the brain; however, with decreasing CD4 counts, the chance of OIs or malignancy in the brain increases, and neuroimaging is indicated.

**Medication Side Effects**

**Highly Active Antiretroviral Therapy**

The first promising antiretroviral medication against HIV was the NRTI, zidovudine (AZT/ZDV), which was approved by the United States Food and Drug Administration (FDA) in 1987. In the years following, several more NRTIs were developed; however, the virus’s rapid rate of mutation created drug resistance, and mortality remained high. In 1996, the addition of protease inhibitors (PIs) revolutionized HIV treatment. Two landmark studies demonstrated a 60% to 80% decrease in AIDS, associated hospitalization, and mortality in patients treated with this drug combination, HAART. In addition, nonnucleoside reverse transcriptase inhibitors (NNRTI), integrase inhibitors, fusion inhibitors, entry inhibitors, and pharmacokinetic enhancers have been introduced as treatment, each directed at a different stage of viral reproduction. Medications are often administered in combination therapy through single pills. This section will discuss each of these drug classes and some of the more common adverse reactions and side effects associated with each.

**Nucleoside Reverse Transcriptase Inhibitors And Nucleotide Reverse Transcriptase Inhibitors**

The NRTIs and nucleotide reverse transcriptase inhibitors (NtRTIs) inhibit reverse transcription of HIV RNA into DNA, thereby preventing viral replication. These classes of medications are relatively well tolerated and have a mild side-effect profile, including gastrointestinal upset, headache, and insomnia. The most severe toxic effect is dose-dependent bone marrow suppression, causing anemia and leukopenia. Transaminitis and severe lactic acidosis have also been reported and are more common in patients with liver disease. Abacavir, one of the most commonly prescribed NRTIs, is associated with a potentially severe hypersensitivity reaction in 3% to 5% of patients. Certain HLA alleles are susceptible to this reaction and guidelines have been developed for screening and
dosing before prescribing this medication, which reduces or eliminates its occurrence.\textsuperscript{15,16} Symptoms of the hypersensitivity reaction include fever, rash, and gastrointestinal and respiratory symptoms, which usually occur within the first 6 weeks of drug exposure. Abacavir is also associated with an increased risk of myocardial infarction in patients with risk factors for cardiovascular disease.\textsuperscript{17}

For patients with liver disease who are taking NRTIs, discontinuation of agents effective against both HIV and hepatitis B virus (e.g., emtricitabine, lamivudine, and tenofovir) can precipitate a severe and sometimes fatal flare in hepatitis. When presented with this clinical concern, the emergency clinician should provide supportive care and consult an infectious disease specialist for treatment options.

Tenofovir, another commonly prescribed NRTI, is associated with development of Fanconi syndrome in some patients.\textsuperscript{18} Patients with impaired renal function prior to initiation of the drug are most at risk. Patients with this syndrome can develop polyuria, polydipsia, and dehydration. Laboratory tests may demonstrate acidemia, hypercholaemia, hypokalemia, and hyperphosphatemia due to loss of bicarbonate, glucose, amino acids, and phosphate in the urine. Urinalysis demonstrates glucosuria and proteinuria. Tenofovir can also cause bone density loss and fractures, either alone or as part of Fanconi syndrome. The syndrome is usually avoided by stopping tenofovir at the time of abnormal creatinine measurements.

Some medications in this class have less common, but important, side effects. According to animal studies, AZT/ZDV may cause endothelial dysfunction leading to cardiovascular complications.\textsuperscript{19} Didanosine and stavudine have been associated with a rare incidence of pancreatitis, which can be fatal and has led to an FDA black box warning.

**Nonnucleoside Reverse Transcriptase Inhibitors**

NNRTIs also inhibit HIV reverse transcriptase. Examples of NNRTIs include nevirapine, efavirenz, etravirine, and rilpivirine. Efavirenz is associated with vivid dreams, nightmares, insomnia, and confusion, which often resolve after the first several weeks of treatment.\textsuperscript{20} However, more-severe neuropsychiatric complications, including severe psychosis, have been reported, and for this reason, efavirenz is often avoided in patients with a psychiatric history. Immediate discontinuation of the medication is recommended if such severe psychosis occurs. Rarely, rilpivirine is also associated with insomnia and depression.

Rash, gastrointestinal upset, headache, and dizziness are common with all medications in this class. Infrequently (though more commonly with nevirapine), patients can experience Stevens-Johnson syndrome, toxic epidermal necrolysis, or erythema multiforme. Nevirapine has also been associated with liver injury and failure, which led to an FDA black box warning in 2000. This complication is most frequent in the first 6 weeks of treatment and in patients with a history of chronic hepatitis and in male patients with CD4 counts > 400/\text{mm}^3.\textsuperscript{21}

**Protease Inhibitors**

PIs prevent budding of the mature HIV virion from the host membrane, making the virus largely noninfectious. The most commonly used PIs are atazanavir, darunavir, lopinavir/ritonavir, and nelfinavir. Common side effects associated with PIs are mild gastrointestinal upset, including nausea, diarrhea, and abdominal discomfort. Other potentially more severe metabolic alterations include lipodystrophy, dyslipidemia, hypertriglyceridemia, and type 2 diabetes mellitus.\textsuperscript{22} Rarely, hypertriglyceridemia can precipitate pancreatitis. Atazanavir is associated with hyperbilirubinemia and jaundice, which may prompt patients to present to the ED; however, this condition is not dangerous and resolves when the drug is discontinued.

Many of the PIs inhibit, and some induce, isoforms of the cytochrome P 450 enzyme system. As a result, numerous other classes of medications interact with PIs, including proton pump inhibitors, anticoagulants, HMGCoA reductase inhibitors, corticosteroids, antiarrhythmics, antiepileptics, antimalarials, and antidepressants. Therefore, it is imperative to cross-check interactions prior to administering or prescribing other medications to patients taking PIs.\textsuperscript{23}

**Integrase Inhibitors**

Integrase inhibitors, first approved by the FDA in 2007, prevent the incorporation of viral DNA into the human host DNA. Examples of integrase inhibitors include raltegravir, dolutegravir, and elvitegravir. This class of medications is usually well tolerated, with side effects usually mild and including nausea and headache.

**Fusion Inhibitors**

In order for HIV to gain entry into the host CD4 cell, glycoprotein 120 on the surface of HIV must attach to host receptors and other glycoproteins, ultimately allowing the cells to fuse. Currently, the only fusion (sometimes called entry) inhibitors available are enfuvirtide and maraviroc. Enfuvirtide is administered by injection only because the acidic pH of the stomach destroys the protein component of this medication. Side effects are primarily limited to local erythema and nodules at the injection site. Rarely, patients develop neutropenia.

**System-Based Disease And Medication Effects**

**Cardiovascular Disease**

As the life expectancy of HIV-infected patients has increased, so have observed rates of traditional age-related cardiovascular disease.
related conditions (such as cardiovascular disease) increased among this population. A recent study estimated the increased relative risk of myocardial infarction among HIV-infected persons to be 1.75 (95% CI, 1.51-2.02) compared to patients not HIV-infected.\textsuperscript{23} The pathophysiology of this increase involves not only traditional risk factors such as age and smoking, but also HAART. As mentioned previously, HAART causes metabolic side effects that also likely contribute the increased risk of cardiovascular disease.\textsuperscript{17,25-27}

**Pulmonary Disease**

Prior to HAART, *Pneumocystis* pneumonia used to be one of the most common opportunistic pulmonary infections. Patients with *Pneumocystis* pneumonia classically present with an indolent, nonproductive cough and exertional dyspnea. On x-ray, a perihilar or “batwing” infiltrate is seen. (See Figure 1.) Lactate dehydrogenase (LDH) is typically elevated in patients with *Pneumocystis* pneumonia, and a normal value is helpful in ruling out the disease.\textsuperscript{28} Patients infected with HIV are at increased risk of tuberculosis (TB), (both novel infection and reactivation) after diagnosis with HIV because of the depletion of TB-specific T-cells. With poorly controlled HIV infection, the risk of TB increases. In the developed world (where there are lower rates of TB in general), the disease is not seen as frequently, but it must remain on the differential in HIV-infected patients with possible exposures.

Today, patients with well-controlled HIV on HAART more commonly develop the traditional pulmonary infections of immunocompetent patients, of which, *Streptococcus* pneumonia is most common.\textsuperscript{29} Treatment for common pneumonias is the same as for non–HIV-infected patients, using antibiotics and fluid resuscitation or other supportive measures. Patients with immunosuppressive disease are at risk for drug-resistant organisms, and the emergency clinician should consider expanding therapy in those patients whose disease is not well-controlled.

Guidance on the disposition of HIV-infected patients with pneumonia from the ED likely can mirror practice for patients without an HIV infection, although there are no evidence-based guidelines on this topic. However, patients with good social support who are followed closely by a primary care provider and known to be compliant with treatment are likely to be good candidates for outpatient treatment.\textsuperscript{30}

Chronic obstructive pulmonary disease (COPD) is an increasing concern in HIV patients. Higher rates of smoking in HIV-infected patients, lung injury from previous OIs, and drug effects are all risk factors for the development of COPD.\textsuperscript{31} Treatment for COPD is the same as for noninfected patients. Some data suggest that chronic HIV infection itself may also be an independent risk factor for the disease.\textsuperscript{32} The higher risk could be related to the chronic systemic inflammatory response present in longstanding infection. This inflammatory state is also associated with hypercoagulability, leading to higher rates of venous thromboembolism and pulmonary embolism in this population.\textsuperscript{33} The Pulmonary Embolism Rule-out Criteria (PERC) did not report HIV status on the participants of the study, so it is difficult to conclude whether these criteria can be applied to HIV-infected individuals.

Emergency clinicians should have a high index of suspicion for concomitant conditions in the context of a patient’s CD4 count and be prepared to evaluate patients with laboratory and radiologic studies, as appropriate. Imaging with chest x-ray should be considered in all patients with HIV and pulmonary complaints.

**Renal Disease**

Renal disease in HIV patients can be caused both by the HIV infection itself as well as the nephrotoxicity of HAART. Patients present with acute kidney injury similar to non–HIV-infected patients, and their treatment is the same. Nephrotoxic medications should be withheld temporarily while the patient is resuscitated.
Clinical Pathway For Management Of Weakness In HIV-Infected Patients

HIV-infected patient presents with weakness

Rapidly assess for possible stroke syndrome. Perform a comprehensive physical and neurologic examination, focusing on:
- Focal vs generalized findings
- Upper vs lower extremity asymmetry
- Cranial nerves
- Muscle tone and strength
- Upper and lower motor neuron findings

Is the weakness focal?

Consider CNS causes of unilateral weakness:
- Stroke
- Tumor
- Spinal cord lesion

If the CD4 count is < 200 cells/mm³:
- Toxoplasmosis
- CNS lymphoma
- Abscess
- Tuberculosis (Class III)

Weakness is associated with upper motor neuron findings

Consider:
- Spinal cord lesion
- Spinal epidural abscess

If the CD4 count is < 200 cells/mm³:
- HIV myelopathy (Class III)

Weakness is associated with lower motor neuron findings (reflexes, fasciculations)

Consider:
- Guillain-Barré syndrome
- Cauda equina
- Radiculopathy

If the CD4 count is < 200 cells/mm³:
- HIV polyneuropathy (Class III)

Weakness is generalized

Consider:
- Electrolyte abnormalities
- Sepsis
- Hypothyroid
- Adrenal insufficiency
- Acute coronary syndromes
- Dehydration
- Myasthenia gravis
- Botulism (Class III)

Patient is on HAART

Consider medication-specific effects:
- Renal impairment
- Lactic acidosis
- Anemia/bone marrow suppression
- Dehydration from diarrhea (Class III)

Abbreviations: CD4, CD4 T lymphocyte; CNS, central nervous system; CT, computed tomography; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging.

Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

**Class I**
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

*Level of Evidence:*
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

**Class II**
- Safe, acceptable
- Probably useful
- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

**Class III**
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

*Level of Evidence:*
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

**Indeterminate**
- Continuing area of research
- No recommendations until further research

*Level of Evidence:*
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient’s individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

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Nephrolithiasis and urolithiasis are common side effects of PIs, particularly indinavir (although few HIV-infected patients take this medication and, instead, take one of the newer PIs). PIs have poor solubility and significant urinary excretion that leads to stone formation. Urinalysis will most likely demonstrate hematuria; however, stones comprised of indinavir deposits are typically radiolucent and may be missed by standard radiologic imaging. Therefore, secondary signs of obstruction, such as hydroutere and perinephric stranding, may be the only findings on imaging. Discussion with the patient’s HIV provider regarding the continuation or cessation of indinavir is advised. Treatment of nephrolithiasis and urolithiasis are the same as for the non–HIV-infected patient.

### Neurologic Disease

Evaluation of the HIV-infected patient with a neurologic complaint should be guided by the CD4 count. Patients with HIV infection, even if it is well-controlled, have a slightly higher risk of cerebrovascular disease due to the chronic inflammatory state, accelerated atherosclerosis, and metabolic effects of medications. The evaluation of patients with focal neurologic deficits should follow typical stroke algorithms.

Rates of central nervous system OIs, such as cryptococcal meningitis, toxoplasmosis, progressive multifocal leukoencephalopathy, and *Cytomegalovirus* have decreased significantly with treatment adherence. However, if a patient with a low CD4 count is identified, imaging and, possibly, lumbar puncture aimed at the identification of OI is indicated. CT of the head may require contrast in order to better identify infectious processes or central nervous system malignancy, such as lymphoma. MRI provides identification of smaller lesions and evaluates leptomeningeal enhancement better than CT.

HIV myelopathy may develop at the end stages of untreated disease. Patients develop lower extremity weakness associated with sensory abnormalities, imbalance, and incontinence. Patients are hyperreflexic, with normal imaging studies and abnormalities on electrophysiologic testing.

The prevalence of HIV-associated dementia has also decreased since the introduction of HAART. Rates of milder neurocognitive disorders also appear to decrease with longer periods of undetectable virus.

### Gastrointestinal And Hepatobiliary Disease

Gastrointestinal symptoms, especially diarrhea, are some of the most common presentations of HIV-infected patients in the ED. In a large cohort study, 40% of HIV infected adults on HAART reported at least 1 episode of diarrhea in the past month, with 3% reporting severe diarrhea (defined as > 6 stools per day). Etiologies include infectious diseases, malignancies, and medication-induced diarrhea.

The pathogenesis of gastrointestinal symptoms depends on the degree of immunocompromise. Common pathogens that cause diarrhea in healthy individuals will also do so in HIV-infected patients on HAART. In the pre-HAART era, *Clostridium difficile* was the most common pathogen isolated in HIV-infected patients with diarrhea; however, with successful treatment with HAART, the frequency of hospitalizations and diagnosis of AIDS are both decreased. Therefore, *C. difficile* may not be the most frequent infection, though it is more common in HIV-infected individuals than in non–HIV-infected individuals.

As the CD4 count drops, the patient is at risk for OIs such as Cryptococcus, *Cytomegalovirus*, microsporidiosis, and *Mycobacterium avium* complex. In many cases, initiation of HAART to restore the gastrointestinal immune system will help eradicate these infections. Stool laboratory studies are guided based on the patient’s stage of disease.

Hepatobiliary complaints are also common in HIV-infected patients and may be caused by a variety of etiologies from infectious to infiltrative to medication-related problems. Co-infection with hepatitis C virus affects 30% to 80% of HIV patients and chronic hepatitis B virus affects 5% to 10% of patients. Co-infection with either virus increases a patient’s risk of developing chronic hepatitis 2 to 3 times compared to non–HIV-infected patients with hepatitis B virus or hepatitis C virus. Nearly all of the HAART medications have potential hepatotoxicity that can be worsened by co-infection with hepatitis B virus or hepatitis C virus.

Patients with hepatobiliary complaints should be asked about their medication regimens and any co-infections with hepatitis B virus or hepatitis C virus. Laboratory evaluations should include transaminases, bilirubin, and lipase.

### Hematologic Disease

Cytopenias of all cell lines are common in HIV-infected patients. Patients with an uncontrolled HIV infection may develop pancytopenia, as bone marrow production is suppressed. Anemia may be caused by a primary HIV infection or as a result of medication use. Medication-induced anemia is often macrocytic, although in the ED evaluation, this is a diagnosis of exclusion.

The rate of HIV-associated thrombocytopenia increases with decreasing CD4 count. Initiation of HAART, particularly AZT/ZDV, is the mainstay of treatment. These medications are rarely initiated in the ED, and patients with severe or symptomatic thrombocytopenia should be evaluated in consultation with the appropriate specialists.

HIV-infected patients also have higher rates of thrombocytopenia than the non–HIV-infected patient.
of thromboembolic disease, with a large prospective study estimating the rate to be 2.6 per 1000 patient-years. The chronic inflammatory state of HIV infection appears to be a risk factor for thromboembolic disease. In HIV-infected patients without well-controlled disease, factors associated with thrombotic complications include lower CD4 count, higher viral load, presence of OI, malignancy, and indwelling central venous catheters. Thrombotic thrombocytopenic purpura occurs in HIV-infected patients, although its prevalence has decreased in the HAART era. Patients with hemolytic anemia and thrombocytopenia should be evaluated for thrombotic thrombocytopenic purpura.

### Endocrine Disease

HAART is associated with dyslipidemia and truncal obesity. This pattern of central fat accumulation and peripheral fat loss has been termed **HIV-associated lipodystrophy syndrome**. Prevalence of lipodystrophy ranges from 10% to 80%, depending on the definition of lipodystrophy. The most important risk factor for development of this condition appears to be NRTI use.

Prior to widespread use of HAART, endocrine complications of OIs were much more prevalent. These complications included glandular infection and infiltration of the pituitary, adrenal, and, rarely, thyroid glands. Although these conditions are much less common now because of HAART, they should still be considered, especially in patients not on HAART or patients with AIDS. Glucocorticoid deficiency can result from adrenal involvement, and while it is usually subclinical, it should be considered in patients with AIDS and hypotension or critical illness. Treatment for these patients is the same as for non–HIV-infected patients.

Patients on HAART are at risk for developing thyrotoxicosis in association with immune reconstitution inflammatory syndrome due to autoim-

### Risk Management Pitfalls For Managing HIV-Infected Patients In The Emergency Department (Continued on page 11)

1. "I know he had long-standing HIV, but he was only 42 years old, and I thought that was too young to have acute coronary syndromes.”

2. “This patient presented with fever, generalized lymphadenopathy, sore throat, and a macular rash. He is concerned about HIV infection, but his rapid HIV test is negative.”

3. “My patient presented with generalized weakness but recently had a high CD4 count.”

4. “My patient has a history of migraines; I assumed this headache was a migraine as well.”

5. “My patient complained of diarrhea for the past 2 weeks since starting HAART, and the symptoms were interfering with her ability to work. I thought it would be OK to temporarily stop her medications until her primary care provider could adjust them.”

Inconsistent compliance with HAART can cause viral resistance to the medications. Therefore, there are very few scenarios in which a patient should stop HAART treatment. Stevens-Johnson syndrome and nevirapine-associated hepatic failure are indications to stop HAART. The patient’s primary care provider or an HIV medicine consultant should be involved in all decisions to terminate HAART.
and more significant pathology. Infectious complications (such as septic arthritis) are less common with improved control of the disease. As the CD4 count drops, septic arthritis, osteomyelitis, and discitis must be considered with appropriate evaluation, including laboratory testing and imaging studies.  

**Psychiatric Disease**

Neuropsychiatric illness is prevalent and multifactorial in HIV-infected individuals. Direct effects of the virus, underlying mental illness, and the social implications of an HIV diagnosis all contribute to psychiatric illness. Medication effects, notably efavirenz, also contribute. Depression is one of the most common diagnoses in HIV-infected patients and is associated with decreased medication compliance.  

Demoralization syndrome is similar to depression in that patients experience a sense of hopelessness or sadness. However, it is different from depression because it is not associated with an immune activation against the thyroid. Patients generally present months to years after starting HAART with symptoms of Grave disease, weight loss, and tachycardia.  

Disorders of glucose metabolism are associated with the use of HAART, particularly PIs. Additionally, the disease itself is associated with an increased incidence of diabetes as a result of chronic inflammation leading to insulin resistance.  

**Musculoskeletal Disease**

Patients with longstanding HIV infection who are on treatment have lower bone mineral density when compared with noninfected individuals of similar age. Therefore, HIV-infected patients are at increased risk of fracture. HIV itself, as well as antiretroviral medications, are implicated in higher rates of avascular necrosis. Benign musculoskeletal and joint complaints of pain are common in the HIV-infected patient, and the emergency clinician must differentiate between these and other etiologies of pain.  

**Risk Management Pitfalls For Managing HIV-Infected Patients In The Emergency Department** (Continued from page 10)

6. “A patient with a history of HIV infection and COPD presented with shortness of breath and mild pleuritic chest pain. He said that the pain was not characteristic of his COPD exacerbations. Oxygen saturation was normal and his lungs were clear to auscultation.” Consider pulmonary embolism in a patient like this. HIV infection causes a chronic inflammatory state, which is associated with increased risk of venous thromboembolism.

7. “The patient frequently had loose stools, so I thought his diarrhea was the same old thing.” Diarrhea is a frequent complaint in HIV-infected patients and can often be caused by medications. However, dangerous etiologies occur frequently, as well. It is important to question patients about changes in bowel movements, recent travel history, recent antibiotic use, and previous history of gastrointestinal infections, and to assess for infectious etiologies before blaming a medication side effect.

8. “There was no history of OI and he just started HAART. I never thought he could have TB.” Initiation of HAART treatment places patients at risk of unmasking previously unrecognized OI. Although it may seem counterintuitive, starting treatment can actually be dangerous in patients with very low CD4 counts. When these patients present to the ED, OIs and medication side effects should both be considered as etiologies of their complaints.

9. “The patient complained of feeling 'off balance.' She had mild ataxia, but the CT scan was normal. I never expected a cerebellar lesion.” Remember the limitations of nonenhanced CT scans. Patients with poorly controlled HIV are at higher risk for central nervous system infections, including toxoplasmosis, which may be missed on this type of CT scan. Patients with a concerning history or physical examination should receive additional testing when a nonenhanced CT scan is negative.

10. “He recently discontinued his tenofovir. The liver function tests were high. I still don't understand what happened.” Tenofovir, emtricitabine, and lamivudine are also active against hepatitis B virus. Termination of these agents in patients with co-infection can precipitate a severe and sometimes fatal hepatitis flare that must be included in the differential diagnosis of this patient. Along with evaluating other etiologies of hepatitis, consultation with an HIV medicine specialist about reinitiating these medications is suggested.
Dermatologic Disease

Dermatologic complaints are common in HIV-infected patients. HAART is associated with a high rate of drug-related skin reactions, which can lead to medication noncompliance. Dermatologic hypersensitivity and photosensitivity are both common with HAART.

Although treatment with HAART seems to be associated with a lower risk of infectious dermatologic conditions, rates of these infections remain high. Folliculitis is likely the most common of these, with Staphylococcus aureus being the most common pathogen, particularly the methicillin-resistant strain. Other common infectious dermatologic complaints, including herpes zoster, human papillomavirus-associated warts, seborrheic dermatitis, and molluscum contagiosum, are more common in HIV-infected patients, with treatment considerations being the same as in non–HIV-infected patients.

Special Circumstances

HIV-infected patients with sexual partners, or patients with a sexual partner of unknown status, may present to the ED after sexual encounters during which barrier methods of protection are compromised, ie, condom breakage or lack of condom usage. In these instances, the emergency clinician must counsel the patient regarding PEP and potentially initiate treatment. The ED is also a frequent portal of entry for healthcare workers and others with potential exposures to HIV through percutaneous or mucous membrane exposure. The risk of HIV transmission depends on both the type of exposure and stage of illness in the source of the exposure (if known).

PEP is most effective when administered soon after the exposure, ideally within 2 hours. The United States Centers for Disease Control and Prevention recommend that PEP be initiated as soon as possible, preferably within 72 hours of the exposure.

Individual states may have different guidelines, and emergency clinicians should be aware of local regulations. The exposed patient should have baseline HIV testing performed. A multidrug regimen is recommended, extrapolating the success of using combination therapy in the treatment of HIV. Randomized data on the success of PEP are not available; however, rates of seroconversion remain low when therapy is initiated early with full compliance.

Summary

When evaluating the HIV-infected ED patient, the first step is an assessment of the status of disease. The differential diagnosis of a patient’s symptoms will change significantly based on the CD4 count and viral load. Patients with low CD4 counts (< 200 cells/mm³) must have a complete history, review of systems, and physical examination in order to identify any OIs. When the CD4 count is unknown, the absolute lymphocyte count might be a helpful surrogate. HIV-infected patients with well-controlled disease taking medications are living longer and are now experiencing side effects possibly due to the chronic inflammatory state of HIV and adverse drug reactions. It is critical to understand the organ-specific complications of chronic HIV infection and more common adverse medication effects. In particular, patients with longstanding HIV infection are likely at higher risk of coronary artery disease, thromboembolic disease, and COPD. Commonly used HIV medications carry the risk of multiple drug interactions, and emergency clinicians must cross-check ED therapy and new prescriptions with the patient’s home medication regimen.

Key Points

- A thorough history should include the patient’s most recent CD4 count, CD4 nadir, viral load, and a list of the patient’s medications.
- HAART (especially PI's) increase triglycerides and LDL (low-density lipoprotein) and lower HDL (high-density lipoprotein) levels, causing higher risk of coronary artery disease.
- Systemic inflammatory response associated with chronic HIV leads to coronary artery disease, hypercoagulability, and venous thromboembolism.
- Ritonavir increases bioavailability of corticosteroids and can lead to iatrogenic Cushing syndrome.
- Nonenhanced CT scans can miss nephrolithiasis caused by radiolucent indinavir stones.
- Laboratory-based fourth-generation rapid HIV tests have sensitivities > 90%, even in the acute phase.
- HIV-infected patients with low CD4 counts are
at risk for several central nervous system infections and diseases, such as progressive multifocal leukoencephalopathy. Maintain a low threshold for nonenhanced CT scans of the brain.

- Although diarrhea is very common in HIV-infected patients and may have a benign etiology, *C. difficile* is also very common, so dangerous etiologies of diarrhea should be excluded.
- Cytopenias of all cell lines are common in HIV-infected patients.
- Demoralization syndrome presents similarly to depression but is not improved by antidepressants. Ask patients with psychiatric complaints about suicidal and homicidal ideation.
- PEP is most effective if it is administered as close to the time of exposure as possible. It is not recommended after 72 hours postexposure.

**Case Conclusions**

After reviewing the CT scan for the 28-year-old man with flank pain and no identifiable stone, you decided to treat him presumptively. You remembered that in patients taking indinavir, CT scans may not demonstrate the stone and may show only secondary signs. The patient had ongoing pain and urology was consulted. He was taken to the operating room for ureteral stent in the context of an obstructing radiolucent stone.

The 42-year-old woman’s laboratory test results were notable for a leukocytosis of 14,000 cells/mm³. On further questioning, she said that, although she was on HAART and Pneumocystis pneumonia prophylaxis with trimethoprim-sulfamethoxazole, she had not been able to see a physician in over a year because of insurance problems. She did not remember the last time she had her CD4 count or viral load checked. You decided that this patient was at high risk for *C. difficile* infection. You started metronidazole and admitted her to the hospital.

Upon speaking with the third patient, you realized that she was most likely not responding to antidepressants because she suffered from demoralization. She reported that she had not been taking her HAART consistently because, “What’s the point?” While she did not require emergent psychiatric evaluation, you conferred with her and her family members, and they agreed that she would follow up with her psychiatrist to discuss her demoralization and to pursue therapy. You reiterated the importance of HAART compliance and counseled her that therapy and proper treatment for demoralization may improve her mood and her compliance with treatment.

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**References**

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study are included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, are noted by an asterisk (*) next to the number of the reference.


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1. The United States Department of Health and Human Services recommends treatment with HAART for which of the following groups of HIV-infected patients?
   a. Patients with CD4 count < 350 cells/mm³
   b. Patients with CD4 count < 500 cells/mm³ without opportunistic infection
   c. Patients with CD4 count > 500 cells/mm³ with previous opportunistic infection
   d. All of the above

2. Which of the following factors is NOT implicated in the increased risk of cardiovascular disease seen in patients with HIV?
   a. History of smoking
   b. A systemic inflammatory response associated with HIV infection
   c. HAART
   d. Opportunistic infection

3. The most common cause of community-acquired pneumonia in HIV patients on HAART is:
   a. Pneumocystis jiroveci
   b. Streptococcus pneumoniae
   c. Influenza A
   d. Haemophilus influenzae

4. Nephrolithiasis is strongly associated with which of the following HAART medications?
   a. Protease inhibitors
   b. Reverse transcriptase inhibitors
   c. Integrase inhibitors
   d. Nephrolithiasis is not a known complication of HAART

5. Which of the following is associated with increased risk of cerebrovascular accidents in patients with HIV?
   a. Progressive multifocal leukoencephalopathy
   b. Atherosclerosis
   c. Central nervous system lymphoma
   d. Higher CD4 counts

6. Which of the following is NOT a common etiology of diarrhea in HIV-infected patients on HAART?
   a. Clostridium difficile
   b. Adverse medication effect
   c. Viral gastroenteritis
   d. Mycobacterium avium complex

7. Which of the following statements about hepatobiliary disease in HIV infection is FALSE?
   a. Co-infection with either hepatitis B or hepatitis C increases a person’s risk of chronic hepatitis by 2 to 3 times compared to non–HIV-infected patients.
   b. HIV-infected patients with hepatobiliary complaints in the ED should receive laboratory testing with transaminases, bilirubin, and lipase.
   c. Hepatobiliary disease in HIV patients only occurs in the presence of co-infection with hepatitis B or hepatitis C.
   d. Co-infection with hepatitis C affects up to 80% of HIV patients, depending on risk factors.

8. Anemia is common in patients with HIV on HAART. This is likely secondary to which of the following?
   a. Medication side effect
   b. Hemolysis
   c. A response to thrombocytopenia
   d. Disseminated intravascular coagulation
9. Factors associated with thromboembolic disease include all of the following EXCEPT:
   a. Anemia
   b. Low CD4 count
   c. High viral load
   d. Indwelling central venous catheters

10. A person presents after having an unexpected exposure to HIV when the condom of his HIV-infected partner broke during sexual intercourse. Which of the following is true?
   a. Initiation of treatment with antiretroviral medication is contraindicated after 36 hours postexposure.
   b. A negative HIV viral load in the exposed person excludes exposure to infection.
   c. PEP is most effective within 2 hours of exposure.
   d. PEP is only effective within 24 hours of exposure.

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