

# Care of the HIV-Positive Patient in the Emergency Department in the Era of Highly Active Antiretroviral Therapy

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More than 1 million individuals in the United States are HIV positive, with greater than 40,000 new patients being diagnosed per year. With the advent of highly active antiretroviral therapy (HAART), HIV-infected patients in the United States are living longer. HIV-infected patients receiving HAART now more commonly have noninfectious and nonopportunistic complications of their disease. This review article will discuss the assessment and treatment of HIV-positive patients in the era of HAART, with an emphasis on the noninfectious and changing infectious complications that require emergency care. [Ann Emerg Med. 2008;52:274-285.]

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## INTRODUCTION

More than 1 million individuals in the United States are HIV positive,<sup>1</sup> with greater than 40,000 new patients being diagnosed per year.<sup>2</sup> With the advent of highly active antiretroviral therapy (HAART) in 1995, HIV-infected patients in the United States and those with access to HAART worldwide are living longer.<sup>3,4</sup> Since the beginning of the HIV epidemic, HIV-infected patients have commonly presented to the emergency department (ED). As a result, the emergency medicine literature from the pre-HAART era includes extensive reviews of the infectious complications, both opportunistic and otherwise, that can bring these individuals to the ED.<sup>5-7</sup>

Since widespread use of HAART, the spectrum of illness and medication-related complications in HIV-infected patients have changed. It has become more common to see emergency presentations and hospitalizations because of complications unrelated to opportunistic infections. Illness related to cardiovascular disease, medication adverse effects, and malignancies have become more prevalent in patients with HIV.<sup>8,9</sup> With these changes in presentation, the challenges for emergency physicians caring for HIV-infected patients have become more complex.

This article will review the major emergency complications of patients with HIV in the HAART era, with an emphasis on the noninfectious and changing infectious disease processes that require emergency care. The organ-based approach used in this article will allow emergency physicians to more easily assess and

treat HIV-infected patients who present to the ED in early and close consultation with their primary care and infectious disease physicians.

## Changing Epidemiology of Disease Burden in HIV-Infected Patients

With the emergence of AIDS in the 1980s, emergency physicians were required to evaluate HIV-positive patients for the presence of numerous opportunistic infections. Before HAART, hospitalizations in the HIV population were predominantly due to opportunistic infections and conditions related to the HIV-infected patient's poor immune response to nonopportunistic pathogens. According to data from the National Hospital Discharge Survey published in 1993, 23.3% of all HIV-related admissions carried a concurrent diagnosis of infectious or parasitic disease caused by opportunistic pathogens, predominantly *Pneumocystis jirovecii* (previously *carinii*), *Candida albicans*, *Mycobacterium* species (*tuberculosis*, *avium*, and *intracellulare*), *Cytomegalovirus*, and *Cryptococcus neoformans*. An additional 10.1% of HIV-infected patients were hospitalized because of respiratory ailments, predominantly pneumonia that was uncharacterized.<sup>10</sup>

More recent studies have found that although the number of hospital discharges among known HIV-positive patients has decreased from 249,000 in 1995 to 173,000 in 2004, the majority of such hospitalizations are now in patients older than 40 years (67%).<sup>11</sup> Hospitalized HIV-infected patients are also

showing a different spectrum of illness. In a single-center study in a high-prevalence area, conducted from 2000 to 2005, the percentage of admissions because of *M avium* complex, *Cryptosporidium parvum*, and other late opportunistic pathogens decreased significantly, whereas those related to renal, oncologic (primarily lymphoma), and psychiatric ailments, as well as medication adverse effects, increased.<sup>9</sup> This concurs with earlier research that showed that mortality caused by opportunistic infections in patients with advanced HIV has markedly decreased because of HAART.<sup>4,8</sup>

In the pre-HAART era, hospitalizations were primarily in the population younger than 40 years.<sup>10,11</sup> The aging of the hospitalized HIV population is largely due to improved life expectancy in HIV-infected patients who are receiving HAART. For a 20-year-old HIV-infected patient, mean life expectancy has increased from 9.1 years ( $\pm 2.3$  years) in 1993 to 1995 to 23.6 years ( $\pm 4.4$  years) in 2002 to 2004.<sup>3</sup>

No published study has examined whether these changes in the epidemiology of HIV have translated to ED chief complaints and diagnoses in HIV-positive patients. However, they do point to the need for emergency physicians to evaluate these patients for disease that extends beyond opportunistic infections, whether because of aging of this population, medication adverse effects, or other causes.

#### HAART Regimens, Adverse Events, and Drug Interactions

The decision to initiate HAART for an HIV-positive patient is usually made according to the CD4 count, as well as other clinical factors, including the presence of AIDS-defining illness and comorbid conditions that might be exacerbated by the initiation of treatment. In general, all HIV-positive patients with a CD4 count less than 350 cells/mL should begin receiving HAART. The data supporting this recommendation from the Department of Health and Human Services are strongest for those patients with a CD4 count less than 200 cells/mL. Pregnant HIV-positive patients, patients with HIV-associated nephropathy, patients with a history of an AIDS-defining illness, and patients coinfecting with hepatitis B who will begin treatment for that condition should also begin receiving HAART. For HIV-infected individuals with a CD4 count greater than 350 cells/mL, the decision about when to initiate HAART is not well defined. This decision is based on the risks and benefits of therapy for the individual patient and whether compliance can be maintained for the long term. Viral load testing can be used as a factor in the decision to initiate HAART but is more useful in the monitoring of the efficacy of therapy, with a goal of reaching an undetectable HIV ribonucleic acid level on polymerase chain reaction.<sup>12</sup>

With the initiation of HAART, patients receive a combination of 2 nucleoside-analog reverse transcriptase inhibitors and either a non-nucleoside reverse transcriptase inhibitor or protease inhibitor. The Department of Health and Human Services recommends an initial regimen with the combination of tenofovir/emtricitabine or zidovudine/lamivudine as the nucleoside-analog reverse

transcriptase inhibitors and either efavirenz as a non-nucleoside reverse transcriptase inhibitor or atazanavir with ritonavir, fosamprenavir with ritonavir, or lopinavir/ritonavir as the protease inhibitor.<sup>12</sup> Table 1 shows the currently available antiretroviral medications and their major adverse effects. Table 2 provides information on the drug interactions relevant to emergency physicians that can occur with the medications used in HAART.

Emergency physicians should be aware that all antiretroviral medications, regardless of class, have the potential for hepatotoxicity, manifesting anywhere from asymptomatic increase in transaminase levels to fulminant hepatic failure. However, the incidence of this complication varies by medication, with nevirapine, didanosine, and stavudine recognized as most toxic.<sup>12,13</sup> Lactic acidosis represents another important complication requiring recognition by emergency physicians. Because of mitochondrial toxicity mediated by nucleoside reverse transcriptase inhibitors, most commonly didanosine and stavudine, lactic acidosis will present with nonspecific symptoms, including fatigue, vomiting, and myalgias, and is confirmed by evaluation of serum lactic acid level. Levels above 10 mM/dL are potentially life threatening, requiring aggressive intravenous hydration, mechanical ventilation, and dialysis. Time to recovery can be as long as 28 weeks.<sup>13,14</sup>

Patients with advanced HIV with multiple drug resistance may require salvage therapy. Enfuvirtide, a fusion inhibitor that prevents HIV from fusing to the surface of the CD4 cell, was approved by the Food and Drug Administration in 2003. More recently, maraviroc, a coreceptor-binding entry inhibitor, and raltegravir, the first integrase inhibitor that prevents HIV from integrating into the DNA of CD4 cells, were approved in 2007. Currently, these are second-line agents, initiated if the patient fails to respond to standard HAART regimens, but there is active research into using these agents in first-line therapy. The fusion inhibitor enfuvirtide is a subcutaneously injected medication, and its most common adverse effects include local skin reaction with painful nodules at the site of injection, as well as an increased risk of bacterial pneumonia. Maraviroc is the only oral entry inhibitor, and its most common dose-limiting adverse effect is postural hypotension.<sup>12,15</sup> Raltegravir is an oral medication, and its most common adverse effects appear to be gastrointestinal (including nausea, diarrhea, and increased flatulence) and headache.<sup>16</sup>

#### Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome represents a unique consequence of the initiation of HAART. The reconstitution of the immune system response by HAART can exacerbate otherwise dormant opportunistic pathogens or aggravate the symptoms of clinically apparent opportunistic disease. The most common infectious pathogen associated with immune reconstitution inflammatory syndrome is *M avium* complex, with clinical manifestations including lymphadenitis, pneumonitis, hepatosplenomegaly, and hypercalcemia. Nearly

**Table 1.** Antiretroviral medications and major adverse effects.

Antiretroviral Medications	Adverse Effects
<b>Nucleoside reverse transcriptase inhibitors</b>	
Abacavir	Hypersensitivity reaction (fever, rash, myalgias), Stevens-Johnson syndrome
Didanosine	Lactic acidosis, pancreatitis, peripheral neuropathy
Emtricitabine	Lactic acidosis/hepatic steatosis (rare), skin hyperpigmentation/discoloration
Lamivudine	Lactic acidosis/hepatic steatosis (rare)
Stavudine	Lactic acidosis, pancreatitis, peripheral neuropathy, ascending muscle weakness, dyslipidemia
Tenofovir	Renal failure, pancreatitis, headache, diarrhea, nausea, vomiting
Zidovudine	Bone marrow suppression
<b>Non-nucleoside reverse transcriptase inhibitors</b>	
Delavirdine	Rash (blisters), transaminitis, headache
Efavirenz	Psychosis, depression, suicidal ideation
Nevirapine	Hepatic failure, Stevens-Johnson syndrome
<b>Protease inhibitors</b>	
Amprenavir	Toxicity from propylene glycol diluent
Atazanavir	Increased indirect bilirubin, prolonged PR interval
Darunavir	Nausea, diarrhea, headache, rash
Fosamprenavir	Rash, hyperlipidemia
Indinavir	Nephrotoxicity, urolithiasis, indirect hyperbilirubinemia
Nelfinavir	Secretory diarrhea
Ritonavir (with or without lopinavir)	Nausea, vomiting, hyperlipidemia, hyperglycemia
Saquinavir (always given with ritonavir)	Lipodystrophy, hyperglycemia
Tipranavir	Hepatotoxicity, intracerebral hemorrhage
<b>Entry and fusion inhibitors</b>	
Enfuvirtide	Injection site reaction, pneumonia
Maraviroc	Postural hypotension, abdominal pain
<b>Integrase inhibitors</b>	
Raltegravir	Nausea, headache, increased CPK

CPK, Creatine phosphokinase.

all other opportunistic infections have been reported to show exacerbations in the setting of immune reconstitution inflammatory syndrome as well, with manifestations generally being increased symptomatology associated with that pathogen. Noninfectious manifestations include aggravation of autoimmune illness. Risk factors associated with immune reconstitution inflammatory syndrome include being naive of antiretroviral medications at initiation of HAART, more recently having been diagnosed with an opportunistic infection, and a more rapid decrease in HIV ribonucleic acid levels on polymerase chain reaction.<sup>17</sup>

Immune reconstitution inflammatory syndrome, if it manifests, generally does so within the first 8 weeks after the initiation of HAART. Therapy is supportive, with anti-inflammatory medications and steroids, if the inciting opportunistic pathogen has an effective treatment agent, used for symptomatic relief. Discontinuation of HAART is rarely required.<sup>13,18</sup>

### Cardiovascular Disease in HIV-Infected Patients

As the HIV-positive population has seen an increase in life expectancy, the incidence of age-related illnesses, including cardiovascular disease, has increased. This increase has been attributed to the combination of aging and the resultant

increase in risk factors such as hypertension and diabetes, as well as HAART regimens that include stavudine or protease inhibitors. All medications in this latter class have a reported association with hyperlipidemia, hyperglycemia, and truncal obesity. However, there are differences in severity of this association within the protease inhibitor class, with ritonavir being most associated with dyslipidemia and atazanavir least associated.<sup>19</sup> Protease inhibitor use is associated with an increased risk of atherogenic lipoprotein dysfunction and resultant atherosclerosis as well.<sup>20</sup>

It has also been shown that increased time receiving HAART is associated with a 26% increased relative risk of myocardial infarction per year compared with HIV-infected patients not receiving HAART, though the absolute risk remained low.<sup>21</sup> A more recent study comparing HIV to non-HIV-infected patients showed that the increased relative risk for acute myocardial infarction in HIV-infected patients was 1.75 (95% confidence interval [CI] 1.51 to 2.02), after controlling for other risk factors.<sup>22</sup> Similarly, the relative rate of myocardial infarction per year of protease inhibitor exposure has been quantified as 1.16 (95% CI 1.10 to 1.23), though no association was found with non-nucleoside reverse transcriptase inhibitors.<sup>23</sup> For emergency physicians, HIV-infected patients receiving HAART, especially for prolonged periods and with

**Table 2.** Drug interactions with antiretroviral medications in emergency medicine.

Interacting Drug	Interacting Antiretroviral	Effect
Antiarrhythmics (amiodarone, flecainide)	All protease inhibitors	Increased concentration of antiarrhythmic (monitor for toxicity)
Anticonvulsants (phenytoin, carbamazepine, phenobarbital)	All protease and non-nucleoside reverse transcriptase inhibitors	Decreased concentration of antiretroviral medications; increased concentration anticonvulsants
Benzodiazepines		
Midazolam (single doses for procedural sedation can be given)	All protease inhibitors, efavirenz, and delavirdine	Increased concentration benzodiazepine (sedation, respiratory depression)
Alprazolam	Delavirdine	Increased concentration benzodiazepine (sedation, respiratory depression)
Digoxin	Ritonavir	Increased digoxin concentration (monitor levels)
Diltiazem	Atazanavir	Increased concentration diltiazem (decrease diltiazem dose by half)
HMG-CoA reductase Inhibitors (simvastatin/lovastatin contraindicated; atorvastatin can be used at lowest possible dose)	Protease inhibitors	Increased risk of rhabdomyolysis
Metoprolol	Protease inhibitors	Increased metoprolol concentration (monitor for toxicity)
Proton-pump inhibitors	Atazanavir	Decreased absorption of atazanavir. Concomitant use contraindicated
Rifampin	All protease inhibitors and non-nucleoside reverse transcriptase inhibitors (except efavirenz)	Decreased concentration antiretroviral medications
Warfarin	Delavirdine, protease inhibitors	Increased concentration of warfarin (monitor INR)

regimens that include protease inhibitors, should be considered at risk for acute coronary syndromes, often at younger ages than the general population. Careful evaluation and a low threshold for admission or observation for provocative testing are advised.

Infection with HIV is associated with dilated cardiomyopathy. In the pre-HAART era, the prevalence of symptomatic cardiomyopathy was as high as 8%.<sup>24</sup> However, HAART appears to decrease the risk of this complication. Patients will present with symptoms of congestive heart failure, including dyspnea, orthopnea, and peripheral edema. The differential diagnosis includes pulmonary hypertension, with echocardiography and cardiac catheterization required to differentiate between the 2. Zidovudine-based HAART regimens may predispose as well to the development of dilated cardiomyopathy, and discontinuation of this medication is recommended in the setting of this diagnosis.<sup>25</sup> Treatment and disposition in the ED are similar to that observed in patients with congestive heart failure who are not HIV positive.

### Pulmonary Illness in HIV-Infected Patients

Before the era of HAART, *Pneumocystis pneumonia* was the most common infection observed in HIV-infected patients with pulmonary complaints.<sup>10</sup> Although *P jiroveci* remains the most common opportunistic infection observed in AIDS patients, HAART has resulted in a marked decrease in its incidence. Currently, *Streptococcus pneumoniae* is the most commonly identified cause of pneumonia in HIV-infected patients. In HIV-infected patients with good response to HAART and resulting increased CD4 counts, presenting symptoms and

radiographic appearance of pneumonia will likely be similar to that of non-HIV-infected patients. HIV-infected patients who are receiving HAART and have bacterial pneumonia may be candidates for outpatient treatment, if they meet preexisting risk assessment criteria,<sup>26</sup> with standard antimicrobial regimens used in the non-HIV population in close consultation with their primary treating physicians.<sup>27</sup> Emergency physicians may also find that patients who are receiving HAART are not receiving typical anti-*Pneumocystis* prophylaxis (trimethoprim-sulfamethoxazole, dapsone), should they have a CD4 count greater than 200 cells/mL for at least 3 months.<sup>28,29</sup>

Recent evidence has found that HIV may be an independent risk factor for chronic obstructive pulmonary disease. After adjusting for other known risk factors, including age and smoking, HIV-positive individuals may be 50% to 60% more likely to develop chronic obstructive pulmonary disease.<sup>30</sup> Preliminary evidence suggests that HIV may cause nonspecific inflammatory changes in small airways and increase airway hyperresponsiveness.<sup>31</sup> In the ED, HIV-infected patients manifesting signs and symptoms of chronic obstructive pulmonary disease can receive standard inhaler and steroid therapy.

Pulmonary hypertension, which does not appear to correlate with CD4 count, is observed in 0.5% of HIV-infected patients receiving HAART, though no particular agent seems associated with this diagnosis. Patients will present to the ED with dyspnea on exertion, fatigue, lethargy, syncope with exertion, and chest pain. Less common symptoms associated with pulmonary hypertension include cough, hemoptysis, and hoarseness.

Physical examination may reveal typical signs of right-sided heart failure, including hepatomegaly, peripheral edema, and ascites. Treatment options are limited to prostaglandins, anticoagulation, and sildenafil, with prognosis being poor, regardless of HIV status. Survival at 3 years has been found to be as low as 47%.<sup>32</sup>

### Renal/Urological Disease in HIV-Infected Patients

Renal disease is an increasingly common entity in HIV-infected patients. In addition to acute renal failure from pre- and postrenal causes, kidney damage in HIV-infected patients is related to HIV-mediated viral or immunologic disease or to treatment-related toxicity. HIV nephropathy will present with proteinuria, normotension, and often an absence of peripheral edema and is an indication for the initiation of HAART.<sup>12,33</sup> The incidence of acute renal failure in HIV-infected patients has been documented as 5.9 cases per 100 patient-years. As in non-HIV-infected patients, there is a higher association of acute renal failure in the black HIV population.<sup>34</sup> Tenofovir has been associated in case reports with renal toxicity that can cause HIV-infected patients to present in acute renal failure, as well as manifesting Fanconi syndrome, with resultant polyuria, polydipsia, hypokalemia, and type-2 renal tubular acidosis.<sup>35</sup> However, the incidence of acute renal failure with tenofovir is as low as 0.3%.<sup>36</sup> The development of acute renal failure is a strong predictor of mortality in hospitalized patients, and kidney disease has emerged as a leading cause of death among HIV-infected patients in the HAART era.<sup>37</sup> Emergency management of acute renal failure in the HIV-infected patient is similar to that of patients not infected with HIV. Discontinuation of nephrotoxic drugs temporarily, as well as proper volume expansion and ultrasonographic imaging to look for postrenal causes, should be undertaken.

The protease inhibitor indinavir has a well-recognized association with urolithiasis. Presenting symptoms to the ED are typical for patients with kidney stones, including intractable flank pain and vomiting. Indinavir-induced calculi are radiolucent but serve as a nidus for calcium-oxalate/-phosphate calculi formations that are radioopaque.<sup>38</sup> Standard imaging with noncontrast computed tomography (CT) will reveal the cause of these patients' symptoms, and treatment is similar to that for the non-HIV population. Atazanavir is now one of the most commonly used protease inhibitors, and although significantly more rare than with indinavir, cases of urolithiasis with this agent have recently been reported.<sup>39</sup>

### Neurologic Complications in HIV-Infected Patients

In the pre-HAART era, central nervous system opportunistic infections (*Toxoplasma gondii* and *C. neoformans*, among others) represented the predominant neurologic diseases in HIV-infected patients. HAART has resulted in a marked decrease in the incidence of these complications.<sup>40</sup> Figure 1 summarizes the common neurologic complications observed currently in HIV-infected patients. In assessing for these central nervous system conditions in the ED, CT should be obtained before lumbar

#### Central Nervous System

AIDS dementia

Cerebrovascular disease: Ischemic and intracerebral hemorrhage

Lymphoma: Result of Epstein-Barr virus

Opportunistic infections: Result of *T. gondii*, *C. neoformans*, *Cytomegalovirus* (all decreased in incidence in HAART era) and *M. tuberculosis*

Progressive multifocal leukoencephalopathy: Due to JC polyoma virus

#### Peripheral Nervous System

Distal sensory neuropathies: HIV- and HAART- (didanosine and stavudine) related

Ascending muscle weakness syndrome: Stavudine related

Acute demyelinating polyneuropathy: Early HIV manifestation

Chronic relapsing demyelinating polyneuropathy: Late HIV manifestation

**Figure 1.** Neurologic complications of HIV in the HAART era.

puncture, especially in the setting of new seizure, disorientation, or changing or prolonged headache pattern.<sup>41</sup>

Progressive multifocal leukoencephalopathy caused by JC polyoma virus remains a cause of encephalitis and mortality despite HAART. The prevalence of progressive multifocal leukoencephalopathy, although decreased from the pre-HAART era, is approximately 1% to 2% of AIDS patients.<sup>13,42</sup> Patients with progressive multifocal leukoencephalopathy present with altered mental status, speech disturbances, visual deficits, gait difficulty, weakness, hemiparesis, and limb incoordination.<sup>43</sup> Magnetic resonance imaging (MRI) of these patients shows hypodense white matter lesions without edema, and the diagnosis is confirmed by polymerase chain reaction for JC polyoma virus from cerebrospinal fluid.<sup>44</sup> HAART remains the mainstay of therapy, though stabilization as opposed to cure is most likely. HAART can also result in the manifestation of progressive multifocal leukoencephalopathy through the immune reconstitution inflammatory syndrome, as discussed above.<sup>45</sup> In immune reconstitution inflammatory syndrome-mediated progressive multifocal leukoencephalopathy, MRI will reveal contrast-enhancing lesions.<sup>46</sup>

Central nervous system lymphoma has also decreased in incidence in the HAART era. One study found that the overall incidence of central nervous system lymphoma in the population younger than 60 years has decreased from 10.2 to 5.1 per million person-years,<sup>47</sup> whereas specifically in the HIV

population the incidence has decreased from 8 to 2.3 per 1,000 person-years.<sup>48</sup> This complication is most commonly seen in patients with markedly reduced CD4 counts (<50 cells/mL) and will present with symptoms ranging from confusion to seizures. MRI may reveal single or multiple ring-enhancing lesions, with differentiation from toxoplasmosis made often by failure to respond to toxoplasmosis therapy or by stereotactic biopsy.<sup>49</sup> Because treatment is long term, involving radiation therapy and corticosteroids, emergency physicians should recognize that this is a diagnosis of exclusion requiring verification on more extensive medical evaluation.

As with cardiovascular disease, the incidence of cerebrovascular disease has increased in the HIV population, likely because of a combination of the aging of this population and the use of HAART regimens with protease inhibitors that produce lipid profiles associated with accelerated atherosclerosis.<sup>50</sup> HIV itself also appears to be a risk factor for cerebrovascular disease, independent of HAART. One study indicated that the adjusted relative risk for ischemic stroke is 9.1 and for intracerebral hemorrhage is 12.7 in comparison to that of the non-HIV population.<sup>51</sup> Patients receiving tipranavir may also have an increased risk of intracerebral hemorrhage.<sup>52</sup> As a result, in HIV-infected patients with new focal neurologic findings, cerebrovascular disease should be in the differential diagnosis. A timely noncontrast head CT, with consideration for a contrast study as well to evaluate for other structural lesions, and emergency neurologic consultation are recommended.

Sensory neuropathies, either because of HIV itself or nucleoside-analog reverse transcriptase inhibitors (didanosine and stavudine), are common, with the incidence higher in patients with low CD4 counts.<sup>53,54</sup> Patients present with hypersensitivity to the distal extremities and, at times, absent ankle reflexes. Treatment involves discontinuation of the causative medication and symptomatic treatment with gabapentin and ibuprofen as first-line agents.<sup>55</sup> Stavudine has also been associated with an ascending muscle weakness syndrome that is characterized by sensory loss and motor weakness, most prominently in the lower extremities. Most patients will respond with discontinuation of the medication.<sup>56</sup> In contrast, HIV can cause an acute demyelinating polyneuropathy that manifests as ascending limb paralysis, shows cerebrospinal fluid findings similar to Guillain-Barré syndrome, and requires aggressive therapy with plasmapheresis.<sup>13</sup>

### Gastrointestinal and Hepatobiliary Disease in HIV-Infected Patients

Gastrointestinal ailments remain among the most common complaints in HIV-infected patients. With the advent of HAART, the incidence of opportunistic infection in the gastrointestinal tract has decreased, though medication-related adverse effects have increased. HAART has resulted in a decrease in incidence of *C albicans* esophagitis, with a resultant decrease in the use of antifungal medications by HIV-infected

patients, in one study from 18% in 1995 to 2% in 2004.<sup>57</sup> Diarrhea remains a common problem in HIV-infected patients. In the HAART era, as with HIV-negative patients, *Clostridium difficile* is the most likely bacterial pathogen. Up to 36% of HIV-infected patients with acute diarrhea requiring hospitalization likely have *C difficile*.<sup>58</sup> It is unclear whether this susceptibility is due to previous antibiotic use, HIV infection, or a combination of the 2.<sup>59</sup> For the emergency physician, the diagnostic and treatment algorithm for HIV-infected patients with acute diarrhea is similar to that of non-HIV-infected patients, with an emphasis on hydration/volume status, stool investigation studies, and, in the case of bacterial diarrhea, appropriate antibiotic treatment. In patients with advanced AIDS who are at risk for *Cryptosporidium parvum* and *Microsporidia* species, special stool studies are required for diagnosis (acid-fast stain for *Cryptosporidium parvum*, light microscopy for *Microsporidia* species).<sup>13</sup>

Coinfection with hepatitis B and C is the most serious hepatic complications observed in patients with HIV. HIV-infected patients who are coinfecting with either virus are at 2 to 3 times the risk of developing chronic liver disease than non-HIV-infected patients with hepatitis B or C.<sup>60,61</sup> In addition, coinfection with hepatitis C is associated with a worse response to HAART in HIV-infected patients. In one study, a shorter time to progression of AIDS-defining illness was found in coinfecting patients compared with that of patients with HIV infection alone, with a hazard ratio of 1.55.<sup>62</sup> As discussed above, nearly all medications in HAART have hepatic adverse effects, most prominently nevirapine, and coinfection with hepatitis B and C is associated with an increased incidence of hepatic toxicity.<sup>63</sup> Lamivudine, emtricitabine, and tenofovir are the only antiretroviral medications active against hepatitis B as well. If these HIV medications are stopped in a patient with coinfection with hepatitis B, severe acute exacerbations of hepatitis B can occur. Emergency physicians should have a heightened awareness of the potential complications related to HAART and coinfection with hepatitis viruses. Patients presenting with signs and symptoms compatible with hepatic disease should be questioned about their hepatitis status and medication history.

Atazanavir, along with indinavir, is associated with a benign, Gilbert's disease-like increase in unconjugated bilirubin in up to 49% of patients, which can cause an extensive hepatic evaluation in the ED if it is not recognized as a normal adverse effect. If the increase in bilirubin level is indirect and not direct bilirubin, generally no further evaluation is indicated for a patient receiving atazanavir. Figure 2 provides a differential diagnosis for hepatic disease in the HIV-infected patient based on liver function test and clinical findings.<sup>13,64</sup>

Didanosine, stavudine, and tenofovir are associated with pancreatitis, often in association with lactic acidosis.<sup>12</sup> In addition, hyperlipidemia associated with protease inhibitor use can put patients at risk for pancreatitis.<sup>13</sup> Management is similar to that for the non-HIV-infected patient.

**Increased Transaminase Levels**

Hepatitis A, B, and C: Either new infection or reactivation of dormant infection from resistance or discontinuation of antiviral and antiretroviral medication

HAART adverse effects

Nevirapine: Increased transaminases and clinical liver disease

Protease inhibitors/delavirdine/efavirenz: Increased transaminases, often without clinical liver disease

Didanosine/stavudine/zidovudine: in association with lactic acidosis

Abacavir hypersensitivity reaction

Alcohol Toxicity and Substance Abuse

Opportunistic infection: Result of *M avium* complex and *Cytomegalovirus* (decreased in incidence in HAART era)

Immune reconstitution inflammatory syndrome

**Asymptomatic Hyperbilirubinemia (Indirect)**

Atazanavir/indinavir adverse effect

**Increased Alkaline Phosphatase and Direct Hyperbilirubinemia**

Cholangiopathy: Due to *Cryptosporidium parvum* most commonly: Poor prognosis

**Clinical Liver Failure**

Hepatitis B and C related

Nevirapine toxicity

Cholangiopathy

**Figure 2.** Differential diagnosis of hepatic disease in HIV patients based on liver function test and clinical findings in the HAART era.

**Hematologic and Oncologic Ailments in HIV-Infected Patients**

Anemia caused by primary HIV disease and adverse effects of HAART, particularly zidovudine, is observed in more than 50% of HIV-infected patients.<sup>65</sup> Zidovudine classically causes a macrocytic anemia, whereas anemia caused by HIV or other infectious ailments such as parvovirus are usually normocytic.<sup>66</sup> In addition, adjuvant medications used commonly by HIV-infected patients, notably, ribavirin and trimethoprim-sulfamethoxazole, are associated with anemia as adverse effects. Ribavirin in association with zidovudine can cause a hemolytic anemia that is often clinically severe.<sup>67</sup> Symptomatic anemia requires blood transfusion and further inpatient investigation of cause.

Neutropenia and thrombocytopenia are also common in HIV-positive individuals, usually because of acute or progressive HIV disease as opposed to antiretroviral therapy. HAART will usually result in improvement in these characteristics.<sup>68</sup> HIV-infected patients have a 2- to 10-fold increased incidence of venous thromboembolic disease in comparison with the general population, though the cause is unclear.<sup>69</sup> Emergency physicians should have a high threshold for consideration of this diagnosis in HIV-infected patients who present with signs or symptoms suggestive of thromboembolic disease. As discussed in Table 2, warfarin use in HIV-infected patients requires careful management, given its interaction with most protease inhibitors and delavirdine. Finally, HIV has a clear association with thrombotic thrombocytopenic purpura, independent of whether the patient is receiving HAART, and the combination of hemolytic anemia and thrombocytopenia should trigger consideration of this diagnosis.<sup>70</sup>

Although HAART has resulted in the decreased incidence of Kaposi's sarcoma in the HIV population, HIV-positive individuals are still at markedly increased risk of certain malignancies relative to the general population. The incidence of Hodgkin's lymphoma, anal cancer, and lung cancers appear to be increasing, whether because of aging of the HIV population or as a long-term adverse effect of HIV itself and resultant immunosuppression. HAART has had little effect on the incidence of anal cancer caused by human papilloma virus.<sup>71,72</sup> Although cancer screening in HIV-infected patients is beyond the normal practice of emergency physicians, referral of patients with anal condylomata and consideration of malignancy in the differential diagnosis of ED HIV-infected patients is vital.

**Endocrine Disease in HIV-Infected Patients**

Protease inhibitors, as discussed above, have an association with hyperlipidemia and truncal obesity. As a result, patients with HIV who are receiving HAART regimens using this class of medications are at risk for insulin resistance, though rarely frank diabetes mellitus. One study did find that the risk of diabetes in patients receiving protease inhibitors is 4.7 per 100 person-years, 4 times the relative risk of HIV-negative patients.<sup>73</sup> Up to 70% of male HIV-infected patients show evidence of low testosterone levels that present with fatigue as the most common symptom. The threshold testosterone level at which this diagnosis is made is controversial, with age and symptoms playing a role in the decision to provide supplemental testosterone. HAART does not alleviate this condition.<sup>74-76</sup> Because fatigue is a nonspecific chief complaint and has a broad differential diagnosis, including anemia, renal insufficiency, and hypothyroidism, in addition to low testosterone levels, emergency physicians should consider low testosterone levels a diagnosis of exclusion that can best be diagnosed in the outpatient setting after other more emergency conditions have been excluded. Emergency physicians may also treat HIV-infected patients recently receiving HAART who develop Graves's disease and frank thyrotoxicosis in the context

of the immune reconstitution inflammatory syndrome, during which the restoration of immune function can induce autoimmune disease. Patients will present with tachycardia, hyperthermia, and at times, mental status change, with diagnosis made by standard thyroid function tests.<sup>77</sup>

### Psychiatric Illness in HIV-Infected Patients

Psychiatric ailments occur commonly in HIV-infected patients, regardless of stage of the disease. Demoralization and depression represent 40% of all psychiatric referrals in this patient population. Demoralization is an exaggerated sense of sadness or hopelessness, not associated with complete anhedonia, which distinguishes it from depression. It manifests both because of acute changes in life circumstances and the stressor of HIV itself. Unlike depression, demoralization does not respond to antidepressants and requires referral to psychiatric counseling, mostly on an outpatient basis. Depression is observed in up to 40% of patients with HIV. Although the treatment is similar to that for the non-HIV-positive patient population, it is vital for emergency physicians to refer these patients promptly for treatment because adherence to HAART is often impaired in patients who are depressed.<sup>78</sup>

AIDS mania is a late psychiatric manifestation of HIV disease. Patients will present in a manic state but with no history of manic or mood disorder. This condition is associated with cognitive impairment (AIDS dementia).<sup>79</sup> For the emergency physician, the differential diagnosis includes meningoencephalitis. An evaluation for other organic causes of mental status change should be performed, including CT of the brain and potentially a lumbar puncture. Haloperidol and risperidone can be used for acute management, whereas lithium and valproic acid have shown some effectiveness in long-term management.<sup>78</sup>

The non-nucleoside reverse transcriptase inhibitor efavirenz is well recognized to have neuropsychiatric adverse effects. Within the first 4 weeks of initiation of therapy, a psychotic state similar to that observed with the use of lysergic acid diethylamide can manifest, whereas milder earlier symptoms include nightmares and increased irritability. Psychosis necessitates termination of usage of the drug, in concurrence with the primary treating physician, but the other early adverse effects will usually resolve after 4 weeks with continuation of the medication. Depression can manifest as a late adverse effect and may require adjunctive antidepressant and counseling therapy.<sup>80</sup>

### Musculoskeletal/Rheumatologic Disease in HIV-Infected Patients

Before the introduction of HAART, HIV-positive individuals manifested multiple musculoskeletal and rheumatologic ailments, most commonly HIV-associated arthritis, polymyositis, and diffuse infiltrative lymphocytosis syndrome, in which lymphocyte infiltration causes salivary gland enlargement and dyspnea because of pulmonary infiltration that can mimic *Pneumocystis* pneumonia in appearance.<sup>81</sup> In contrast, recent studies that have examined

HIV-infected patients receiving HAART have found that a new spectrum of musculoskeletal/rheumatologic disease has become more common. Bacterial infectious complications (septic arthritis, osteomyelitis, and diskitis) are more likely to be diagnosed.<sup>82</sup> Staphylococcal pyomyositis can also be observed in HIV-infected patients, most commonly in the HAART era in patients with CD4 counts less than 50 cells/mL, with symptoms being indolent fever and gradually developing pain and swelling without accompanying leukocytosis. The thigh is the most common site of infection.<sup>83,84</sup> Patients with infectious complications will present similarly to the non-HIV population, and treatment can be started empirically according to the prevailing bacterial spectrum in that practice setting.

A new rheumatologic ailment caused by the immune reconstitution inflammatory syndrome has also manifested in the HAART era. This condition typically causes patients to develop sarcoidosis or autoimmune thyroiditis, with a mean onset of symptoms by 9 months after the initiation of HAART. HIV-infected patients with this condition will present to the ED with varied connective tissue disorder symptoms, including arthralgias, dyspnea (sarcoidosis), or hypo/hyperthyroidism.<sup>18,77,85</sup> This condition is self-limited, does not usually require discontinuation of HAART, and can be treated symptomatically with low-dose corticosteroids or nonsteroidal anti-inflammatory medications.<sup>13</sup>

The most common musculoskeletal disorders associated with HIV in the HAART era are osteoporosis and osteonecrosis, usually involving the hip. Osteoporosis has increased in prevalence with the initiation of HAART, but HIV-infected patients not receiving HAART have also shown an increased risk, suggesting that HIV itself, along with adverse effects of antiretroviral medications, is involved in osteoporotic pathogenesis.<sup>86</sup> HIV-infected patients are at increased risk of fractures of their lumbosacral spine and hip.<sup>87,88</sup> Osteonecrosis of the hip has been reported in HIV-infected patients since the pre-HAART era, though its incidence has increased with the advent of HAART. Case-controlled studies have not found an association with the use of protease inhibitors, as previously thought. It is now believed that this condition is associated directly with HIV, and the resultant aging of this population has caused osteonecrosis to become more prevalent.<sup>86</sup> Patients will present to the ED with chronic recurrent pain of the hip. Radiographic examination shows avascular necrosis of the femoral head and neck. Treatment in the ED is symptomatic, with surgical intervention required in the long term.

Didanosine and stavudine can cause lactic acidosis (Table 1), and as a result, patients may present with severe diffuse muscle pain.<sup>12</sup> Similarly, patients receiving protease inhibitors who have developed high cholesterol levels and are taking HMG-CoA reductase inhibitors can present with rhabdomyolysis (Table 2) caused by the interaction between these 2 classes of medications.<sup>89</sup> Treatment includes aggressive volume expansion

Bacterial folliculitis: <i>S aureus</i> related: Low CD4 counts (<250 cells/mL) or with immune reconstitution
Drug reactions:
Abacavir: Hypersensitivity reaction (macular/urticarial rash, fever, and hypotension)
Atazanavir: Stevens-Johnson syndrome
Delavirdine: Blisters, Stevens-Johnson syndrome
Indinavir: Associated with paronychia, ingrown toenails, curling of hair
Nevirapine: Stevens-Johnson syndrome
Herpes zoster: May require inpatient treatment if more than 1 dermatome or ophthalmic involvement
Kaposi's sarcoma: Decreased in incidence and prevalence in patients with positive response to HAART
<i>M contagiosum</i> : Associated with long-term HAART use
Photosensitivity reaction: Hyperpigmentation: associated with long-term HAART
Scabies
Seborrheic dermatitis: Treated with topical steroids (hydrocortisone)
Warts: Oral, genital, and anal: Increased incidence of human papilloma virus-related malignancy; requires urgent referral

**Figure 3.** Dermatologic conditions commonly observed in HIV patients in the HAART era.

with normal saline solution and careful monitoring of renal function.

### Dermatologic Disease in HIV-Infected Patients

Dermatologic conditions, either as adverse effects of HAART or as primary disease, are the most common clinical ailment in HIV-infected patients. Figure 3 provides an overview of the most commonly observed HIV-related dermatologic conditions in the HAART era. HIV-infected patients have a significantly higher incidence of drug-related skin reactions, and this often plays a role in HAART regimen noncompliance.<sup>90</sup> In the HAART era, folliculitis caused by *Staphylococcus aureus* has emerged as a common primary skin condition observed in HIV-infected patients. Usually observed in patients with CD4 counts below 250 cells/mL, folliculitis will present most commonly on the face and trunk, be pruritic, and require therapy with either topical or systemic antimicrobial agents, often covering for methicillin-resistant strains. Immune reconstitution can also cause folliculitis to become clinically apparent.<sup>13</sup> In one study, receiving HAART was associated with a decreased prevalence of folliculitis.<sup>91</sup> Patients who

are receiving HAART are also at increased risk for photosensitivity reactions and in one study showed an increased risk of *Molluscum contagiosum* virus infection.<sup>92</sup>

Abacavir can cause a severe hypersensitivity reaction in up to 5% of patients receiving this medication. It is more common in white patients,<sup>13</sup> and testing for the HLA-B 5701 allele, which is associated with abacavir hypersensitivity,<sup>93</sup> can be undertaken before use of this agent. The mean time of onset is 9 days after initiation of therapy, though this complication can occur many months after abacavir is started. Patients may present with various permutations of a macular or urticarial rash, fever, and hypotension. Laboratory evaluation may reveal increased creatine phosphokinase levels, increased liver function test results, and lymphopenia. Treatment is supportive, with admission to the hospital often required, along with discontinuation of the medication.<sup>13,94</sup> Patients who discontinue abacavir as a result of a hypersensitivity reaction should be instructed to never take this medication again because reintroduction can be fatal.

### Oropharyngeal and Ocular Complications in HIV-Infected Patients

Before the advent of HAART, 2 of the most commonly observed manifestations of HIV/AIDS were oral/esophageal candidiasis and *Cytomegalovirus* retinitis. HAART has resulted in a decreased incidence of both conditions, with candidiasis reduced by up to 50% in population-based observational studies<sup>95</sup> and *Cytomegalovirus* retinitis by up to 80%.<sup>96</sup> Emergency physicians will find that patients who have shown a positive response to HAART will no longer be taking prophylactic medication for candidiasis or *Cytomegalovirus*. However, patients receiving HAART are at increased risk of oral warts and continue to be at risk of HIV-related periodontal disease.<sup>95</sup> Similarly, the immune response generated by HAART places patients at risk for immune reconstitution vitritis and uveitis. Patients will present to the ED with visual loss and be found on slit-lamp and fundoscopic examination to have macular edema and epiretinal membranes. Treatment involves corticosteroids, under the concurrent care by ophthalmology, with most patients recovering lost vision.<sup>97</sup>

### CONCLUSION

The advent of HAART has provided enormous benefit to HIV-infected patients. These individuals now have a greatly increased life expectancy. However, the spectrum of illness that may bring HIV-infected patients to the ED has changed and broadened. Emergency physicians, in collaboration with primary care physicians and infectious disease specialists, will require an increased familiarity with the ways that HAART has modified the evaluation and treatment of HIV-infected patients in the ED.

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