INTRODUCTION

Human immunodeficiency virus (HIV)-infected patients require critical care for various reasons that may or may not be related to their underlying immunodeficiency. The evaluation of HIV-infected persons admitted to the intensive care unit (ICU) requires consideration of all processes that can occur in HIV-uninfected persons, as well as those particular to HIV infection, namely opportunistic infections (OIs), neoplasms, and HIV-associated comorbidities or toxicities associated with antiretroviral therapy (ART). Management of acute, life-threatening conditions requires institution of similar therapies in HIV-infected persons as in HIV-uninfected persons, with awareness of potential drug toxicities and drug interactions that can occur in those on ART.

This chapter reviews the critical care of HIV-infected patients, including causes of ICU admission and patient outcomes. Special emphasis is placed on the etiology and management of respiratory failure, particularly that due to *Pneumocystis jirovecii* pneumonia (PCP), which carries an especially high mortality risk. Other major indications for ICU admission and the potential impact of combination ART on mortality risk are discussed. The evaluation of HIV-infected persons admitted to the ICU requires consideration of all processes that can occur in HIV-uninfected persons, as well as those particular to HIV infection, namely opportunistic infections (OIs), neoplasms, and HIV-associated comorbidities or toxicities associated with antiretroviral therapy (ART). Management of acute, life-threatening conditions requires institution of similar therapies in HIV-infected persons as in HIV-uninfected persons, with awareness of potential drug toxicities and drug interactions that can occur in those on ART.

**EPIDEMIOLOGY OF HIV-INFECTED PATIENTS IN THE ICU**

**ICU Admission Rates and Outcomes**

The first cases of HIV/AIDS were reported in 1981. Since that time, there have been many developments in the treatment of HIV and its associated diseases, most notably the introduction of highly active, combination ART in 1996. Rates of ICU admission and mortality related to ICU admission for HIV-infected patients have shifted multiple times during the AIDS epidemic.

Overall, there has been a steady decline in ICU mortality after the introduction of ART, mirroring a general improvement in survival in critically ill HIV-uninfected populations. In studies from San Francisco General Hospital, ICU mortality decreased significantly from 37% in 1992–1995 to 29% in 1996–1999 and 11% in 2000–2004 (1–3). Is it possible to include the Nickas and Wachter reference here (Current reference number 6)? Please advise if this would require too many changes to keep the references in order of their first appearance. More contemporary multicenter cohorts from the Veterans Health Administration in the United States (U.S.) and from France have reported further improvements in ICU outcomes. Thirty-day mortality among HIV-infected patients from the Veterans Aging Cohort Study (VACS) admitted to the ICU between 2002 and 2010 was 19% (4). Similarly, the French Collège des Utilisateurs de Base de données en Réanimation (CUB-Réa) network, including ICU admissions between 1999 and 2010, reported ICU mortality of 17.6% (5). In recent studies, the average reported in-hospital mortality for HIV-infected patients admitted to the ICU ranged between 19% and 40%, with a median ICU length of stay of 2 to 11 days (2,4–13) (Table 91.1).

In HIV-infected patients on ART, overall survival has improved, resulting in an increase in the number of persons living and aging with HIV. Patients aging with HIV are developing non-AIDS-related medical comorbidities that account for a growing proportion of hospitalizations and ICU admissions (4,5,14,15). Improved survival and increasing prevalence of non-AIDS-related comorbidities likely influence medical decision making by patients and providers, contributing to pursuit of more aggressive life-supporting measures in the ICU for patients living with HIV (8,16).

Despite decreasing hospitalization rates for HIV-infected patients, ICU admission rates have not changed substantially in the ART era (2,7–9,16,17). Approximately 5% to 18% of hospital admissions for HIV-infected patients involve ICU care (8,12,15). While a significant proportion (range 17%–40%) of HIV-infected patients continue to be admitted to the ICU without prior known HIV infection (8,9,17), this may be less frequent in more contemporary cohorts with access to HIV testing and ART. In addition, approximately 30% to 50% of patients are not on ART at the time of admission (8,9,12,15), attributable to new diagnoses among patients not yet in care and barriers to treatment or compliance among patients with known HIV infection.

**Indications for ICU Admission**

Studies of critically ill HIV-infected patients indicate that the spectrum of diseases requiring ICU admission is changing in the setting of ART. Early in the epidemic, most patients were admitted with an AIDS-associated condition, most often PCP. Increasingly, patients with HIV infection are admitted with a non-AIDS-associated condition. Data from San Francisco General Hospital found a high proportion of patients (79%) admitted with non–AIDS-related conditions from 2000 through 2004 (3). Similarly, in VACS, approximately 80% of ICU admissions were for non–HIV-associated conditions (4). Likewise, in CUB-Rée, the proportion of admissions for main diagnosis of non–AIDS-defining conditions increased significantly from 74% to 83% between 1999–2001 and 2008–2010, respectively (5).

Acute respiratory failure is the most common indication for ICU care, accounting for approximately 21% to 59% of ICU admissions in HIV-infected patients (2–6,9–12,17–20). *Pneumocystis jirovecii* was the responsible pathogen in approximately 25% to 50% of these patients in earlier investigations (6,10,21). Although decreased in some studies (5,7,15), it remains a significant cause of respiratory failure in recent studies, accounting for 14% to nearly 50% of cases of respiratory
<table>
<thead>
<tr>
<th>Setting (reference)</th>
<th>ICU Patients (N)</th>
<th>Time Period</th>
<th>HIV Unknown at Admission</th>
<th>ART at Admission</th>
<th>HIV or AIDS-Related Illness</th>
<th>Overall ICU Mortality</th>
<th>Independent Predictors of ICU or In-Hospital Mortality(^a)</th>
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<tbody>
<tr>
<td>University hospital, Jacksonville, FL (11)</td>
<td>141</td>
<td>1995–1999</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>30(^b)</td>
<td>Transfer from another hospital ward, APACHE II score</td>
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<td>University hospital, Paris, France (9)</td>
<td>230</td>
<td>1997–1999</td>
<td>40%</td>
<td>28%</td>
<td>37%</td>
<td>20%</td>
<td>SAPS II score, mechanical ventilation, Omega score</td>
</tr>
<tr>
<td>University hospital, Paris, France (8)</td>
<td>236</td>
<td>1998–2000</td>
<td>28%</td>
<td>50%</td>
<td>50%</td>
<td>25%</td>
<td>PCP with pneumothorax; mechanical ventilation; Kaposi sarcoma; inotropic support; CD4+ count &lt;50 cells; SAPS II score</td>
</tr>
<tr>
<td>Urban hospital, New York, NY (12)</td>
<td>259</td>
<td>1997–1999</td>
<td>—</td>
<td>48%</td>
<td>60%</td>
<td>30%</td>
<td>Mechanical ventilation; admission with HIV-related illness</td>
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<tr>
<td>Urban hospital, New York, NY (7)</td>
<td>53</td>
<td>2001</td>
<td>—</td>
<td>52%</td>
<td>33%</td>
<td>29(^b)</td>
<td>No multivariate analysis provided; low albumin associated with increased mortality on univariate analysis</td>
</tr>
<tr>
<td>Urban hospital, San Francisco, CA (2)</td>
<td>295</td>
<td>1996–1999</td>
<td>7%</td>
<td>25%</td>
<td>37%</td>
<td>29(^b)</td>
<td>Mechanical ventilation; PCP; APACHE II scores &gt;13; albumin &lt;2.6 g/dL; AIDS-associated diagnosis</td>
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<td>Hospital Virgen de la Victoria, Malaga, Spain (22)</td>
<td>49</td>
<td>1997–2003</td>
<td>31%</td>
<td>31%</td>
<td>61%</td>
<td>57%</td>
<td>Not reported</td>
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<tr>
<td>Urban hospital, San Francisco, CA (3)</td>
<td>281 (311 admissions)</td>
<td>2000–2004</td>
<td>Not reported</td>
<td>33%</td>
<td>21%</td>
<td>31%</td>
<td>Mechanical ventilation; Albumin, per 1 g/dL decrease</td>
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<tr>
<td>University hospital, The Netherlands (13)</td>
<td>117 (127 admissions)</td>
<td>1990–2008</td>
<td>13%</td>
<td>23%</td>
<td>52%</td>
<td>37%</td>
<td>1-yr mortality: mechanical ventilation, APACHE II &gt;20, older age</td>
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<tr>
<td>VACS, 8 Department of Veterans Affairs medical ICUs (4)</td>
<td>539</td>
<td>2002–2010</td>
<td>Not reported</td>
<td>71%</td>
<td>19%</td>
<td>18% (30 days)</td>
<td>VACS Risk Index</td>
</tr>
<tr>
<td>CUB-Rea, Paris, France (5)</td>
<td>6,373</td>
<td>1999–2010</td>
<td>Not reported</td>
<td>Not reported</td>
<td>21.9% (main diagnosis)</td>
<td>17.6%</td>
<td>Malignancy, liver disease</td>
</tr>
</tbody>
</table>

\(^a\) In order of descending magnitude of association.
\(^b\) Data given as in-hospital rather than ICU mortality.

ICU, intensive care unit; HIV, human immunodeficiency virus; ART, antiretroviral therapy; AIDS, acquired immunodeficiency syndrome; APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score; PCP, Pneumocystis pneumonia; VACS, Veterans Aging Cohort Study.
failure, particularly in HIV-infected patients who are not on ART (2,3,5,7,12,22). Bacterial pneumonia (BP) is also a frequent cause of acute respiratory failure and in some studies is now as common (2) or more common (5,7,17,23) than PCP.

Sepsis is an increasingly frequent indication for ICU admission, accounting for 10% to 57% of all admissions for HIV-infected patients during recent years (3–5,9,24). Other commonly reported causes of ICU admission include CNS dysfunction (11%–27%), gastrointestinal (GI) and liver diseases (4%–15%), and cardiovascular disease (8%–18%) (2–6,9,10,19,21). Other reasons for ICU admission unrelated to immunodeficiency include trauma, routine postoperative care, noninfectious pulmonary diseases such as asthma and pulmonary embolism, renal failure, metabolic disturbances, and drug overdose. Given the frequent coinfection with hepatitis C among patients with HIV, liver disease may be increasing as a cause of death (4,24–26), and complications related to cirrhosis often require ICU admission. In addition, solid organ transplantation (liver, kidney) is currently being studied in HIV-infected patients; thus, these patients may also be encountered in the ICU setting.

Predictors of Mortality during ICU Admission

Mortality in the ICU has improved for HIV-infected patients but remains substantially higher than uninfected comparators, even after adjusting for diagnosis for ICU admission (4,24,27). The highest mortality rates for HIV-infected patients requiring ICU admission are associated with sepsis, respiratory failure, chronic liver disease, and malignancy (3–5,17). Mortality rates of approximately 50% (6,19) and as high as 68% have been reported for sepsis (27,28). Among HIV-infected patients coinfectected with hepatitis C admitted for severe sepsis, 30-day mortality can be as high as 82% (24). If respiratory failure is due to PCP, mortality remains nearly 50% (2,3,12) and is increased if complicated by PCP-associated pneumothorax (2,8). For AIDS patients admitted to the ICU for other HIV-related reasons, the reported mortality is generally lower. For example, the reported mortality for CNS dysfunction is 20% to 48% (6,10,11,19,29), whereas the mortality for GI disease is approximately 30% to 35% (6,10,11).

As ART use increases and HIV-infected patients are living longer, the impact of HIV-related versus non–HIV-related conditions on ICU mortality is changing. Although HIV-related conditions remain important predictors for mortality, they are becoming less common in areas with access to ART (3). Comorbidities such as chronic liver disease and cancer are increasingly important predictors of ICU mortality in HIV-infected patients (4,5,27).

Mortality during hospitalization is also related to the severity of the acute illness (Table 91.1). Predictors of increased hospital mortality include the need for mechanical ventilation and disease severity (as assessed by scoring systems such as the Simplified Acute Physiology Score II [SAPS II], the Acute Physiology and Chronic Health Evaluation II [APACHE II] score, and the VACS Index, a mortality prediction tool including biomarkers for HIV-specific and general organ dysfunction) (2,4–6,9,12,19,30). ICU mortality has also been related to the preadmission health status of the patient. Patients with a decreased serum albumin level or a history of weight loss may also have a higher mortality (2,3,6,19). The CD4+ T-cell count and the plasma HIV RNA level have generally not been independent predictors of short-term mortality during the ICU stay (2,6,7,11,12,21,30).

However, long-term mortality after ICU admission has been related to the underlying severity of HIV disease in most studies (6,19,21). Long-term survival following ICU discharge is improved compared with the pre-ART era (8,9,13).

Impact of Antiretroviral Therapy on ICU Mortality

The full impact of ART on outcomes of HIV patients in the ICU remains unclear, as prospective, randomized trials assessing the initiation of ART on outcomes in critically ill patients have not been completed. Two retrospective studies conducted at San Francisco General Hospital suggest that ART may improve outcomes in critically ill HIV patients. In a review of all HIV-infected patients admitted to the ICU between 1996 and 1999, patients receiving combination ART at the time of ICU admission were less likely to present with two conditions associated with decreased survival, an AIDS-associated diagnosis and decreased serum albumin, but ART itself was not independently associated with survival (2). In a study of all HIV-infected patients with PCP who were admitted to the ICU at San Francisco General Hospital between 1996 and mid-2001, patients who were on ART at the time of ICU admission or started ART during hospitalization had an improved survival compared to patients not receiving ART (31). However, in another study from New York City, ICU mortality was not different in patients admitted between 1997 and 1999 when comparing patients receiving ART versus those not on ART (12). Furthermore, the prior use of ART was not associated with differences in overall hospital mortality or length of stay (12). Another study found that although ICU mortality had improved in recent years, this improvement could not be attributed to ART because none of the patients received this therapy (32). Conclusions regarding the impact of ART on outcomes are limited by the nonrandomized nature of these retrospective studies and by the inability to measure potential bias in the selection of patients received ART. In addition, these studies do not address treatment failure, drug resistance, or medication nonadherence prior to or after ICU admission, all of which influence long-term outcome (12).

IMMEDIATE CONCERNS IN MANAGING CRITICALLY ILL HIV-INFECTED PATIENTS

The initial management of critically ill HIV-infected patients includes all the immediate concerns in HIV-uninfected patients such as securing a stable airway and ensuring adequate respiration and circulation. The immediate management of patients with respiratory failure depends on the underlying reason for respiratory compromise, but consideration of OIs is warranted early in the course of care to ensure prompt diagnostic evaluation and initiation of appropriate antibiotic therapy. Management of patients in shock consists of similar strategies as in HIV-uninfected patients and depends on the cause of shock, with use of volume resuscitation, vasopressors, and/or inotropic agents as appropriate to maintain adequate mean arterial pressures and systemic perfusion. For patients with septic shock, guideline-based therapy focusing on early identification, fluid resuscitation, appropriate antimicrobials, and other ICU support should be instituted (33,34). Given the
increased association of HIV with cardiovascular disease, cardiomyopathy (35), and adrenal insufficiency (36), providers should be alert to the possibility that these conditions may also cause shock in HIV-infected patients.

Certain aspects of the patient’s history are important for initiating early appropriate management. The degree of immunosuppression related to HIV infection, reflected by the CD4+ cell count, is a critical determinant of risk for OIs. In addition, use of and adherence to ART and prophylactic antibiotics, as well as intravenous drug use and exposures to endemic fungi and mycobacteria, are key components of the patient’s history. The evaluation and management of the most common indications for ICU admission among HIV-infected patients are discussed in detail below.

PULMONARY MANIFESTATIONS OF HIV

Spectrum of Respiratory Diseases and Approach to Diagnosis

Although the spectrum of diseases leading to respiratory failure has changed during the ART era, acute respiratory failure is still the most common cause of ICU admission for HIV-infected patients in studies throughout the world (2,4-6,9,11,12,20,37). Respiratory failure can occur from a multitude of causes including infections, neoplasms, drug overdose, and cardiac and neurologic conditions that may be both HIV- and non–HIV-related. Rapid diagnosis and initiation of appropriate therapy is crucial, particularly in patients with HIV-associated infections. Although these conditions have typical signs and symptoms, many of the presentations can overlap and patients may occasionally present with more than one etiology for their respiratory failure. Therefore, definitive diagnosis should be pursued whenever possible. It is important to remember that all the conditions leading to respiratory failure in the HIV-uninfected patient also occur in those with HIV infection. Diagnoses such as pulmonary embolism, asthma, chronic obstructive pulmonary disease, and cardiogenic pulmonary edema also present with respiratory failure, and appropriate testing should be performed.

Pneumocystis Pneumonia (PCP)

PCP has historically been the most common cause of respiratory failure in AIDS patients, but its frequency has declined (6,10,21,38). PCP is caused by the organism P. jirovecii, formerly Pneumocystis carinii. The number of patients admitted to the ICU with PCP has decreased since the introduction of ART, but it remains an important cause of morbidity and mortality in the HIV-infected ICU patient. In the 1980s, patients with PCP who were admitted to the ICU had a mortality rate as high as 81%, with mortality for those individuals requiring mechanical ventilation approaching 90% (39). The introduction of adjunctive corticosteroids for moderate to severe PCP in the mid-1980s led to an improvement in mortality to approximately 60% (40–42). Since that time, there has been little change in outcomes from severe PCP, with later studies still reporting a hospital mortality of approximately 60% (2,6). The primary critical care factors that determine mortality in patients with PCP are the need for mechanical ventilation and the development of a pneumothorax. Either of these factors portends a poor prognosis, and the occurrence of both concurrently is almost uniformly fatal (2,43). Other factors that have been reported to be associated with mortality in some studies include low serum albumin, admission to the ICU after 3 to 5 days of hospitalization, increased age, and elevated serum lactate dehydrogenase (LDH) (2,32,43–45).

Clinical Presentation. PCP is most frequent in patients with a CD4+ cell count below 200 cells/μL, with the risk of PCP increasing as the CD4+ count decreases below that level (46,47). Although use of PCP prophylaxis decreases the incidence of PCP, patients receiving prophylaxis may still develop PCP, especially if severely immunocompromised (48). However, many patients with PCP do not know that they are HIV-infected, and therefore never receive PCP prophylaxis. Published studies have reported that 28% to 57% of patients admitted to the ICU are diagnosed with PCP as their first manifestation of HIV; thus clinicians need to consider PCP in any patient with a consistent clinical picture if the patient’s HIV status is unknown (31,43). Additional risk factors for PCP other than a low CD4+ cell count include the presence of oropharyngeal candidiasis and prior PCP.

The symptoms of PCP can be nonspecific but include fever, tachypnea, dyspnea, and cough. The cough associated with PCP is most often nonproductive or productive of clear sputum. Patients with purulent sputum are more likely to have BP. The pace and duration of symptoms is also important in distinguishing PCP from BP. Unlike in the HIV-uninfected immunosuppressed population, HIV-infected patients with PCP generally report the subacute onset of symptoms progressing over several weeks, with the median duration of symptoms in one study being 28 days (49).

Many patients with PCP have an unremarkable lung examination, with inspiratory crackles being the most frequent abnormal finding. They will often manifest hypoxemia and an increased alveolar–arterial oxygen gradient. Laboratory tests can suggest the diagnosis but are often nonspecific. The white blood cell count can be normal, decreased, or increased. Serum LDH is often elevated in patients with PCP but a normal serum LDH does not rule out the diagnosis (50–52). Also, multiple pulmonary and nonpulmonary conditions can result in an elevated LDH, so an elevated LDH does not rule out the diagnosis. In general, the LDH is more useful as a prognostic rather than a diagnostic test. The degree of elevation correlates with outcome and response to therapy, and patients with a rising serum LDH in the face of treatment have a worse prognosis (52). The arterial blood gas in PCP demonstrates hypoxemia and a widened alveolar–arterial gradient (Paw–O2), which can be seen in any pulmonary disease but is useful in determining the need for adjunctive corticosteroids and ICU care. Finally, 1,3 β-D-Glucan, which is a component of fungal cell walls, is often elevated in PCP and other fungal infections.

The classic chest radiographic appearance of PCP is a diffuse interstitial, reticular, or granular infiltrate (Fig. 91.1); PCP can also result in focal airspace consolidation, although this presentation is less common. Infiltrates are occasionally unilateral or asymmetric and, in patients receiving aerosolized pentamidine for prophylaxis, there may be an upper lobe predominance. In general, the pattern (reticular or granular) is more suggestive of the diagnosis than the distribution. Severe PCP is similar to the acute respiratory distress syndrome (ARDS) in causing widespread capillary leak that results in
bilateral radiographic infiltrates, and these two entities may be indistinguishable radiographically. Single or multiple cysts or pneumatoceles occur in about 10% to 20% of patients, and these changes can be seen before, during, or after PCP treatment (53,54). Patients with PCP are at risk for developing spontaneous pneumothoraces, and PCP should be high in the differential for any HIV-infected patient presenting with a pneumothorax. Radiographic findings such as pleural effusions or lymphadenopathy are uncommon in PCP, and their presence should lead the clinician to consider alternate or concurrent diagnoses. High-resolution CT scans can be helpful in demonstrating diffuse ground glass opacities typical of PCP, but these findings are nonspecific.

**Diagnosis.** Although patients may present with typical signs and symptoms of PCP, a definitive diagnosis is preferred, particularly in patients in the ICU. Many HIV-associated respiratory diseases have overlapping or nonspecific presentations, which makes it difficult for even experienced clinicians to diagnose empirically. Definitive diagnosis allows for the timely administration of appropriate antibiotics and avoids exposure to unnecessary medications. We are currently unable to culture *Pneumocystis* and, thus, the diagnosis relies on microscopic visualization of the organism in a respiratory sample from a patient with a compatible clinical presentation.

PCP can be diagnosed either through examination of induced sputum or from samples obtained at bronchoscopy. Spontaneous sputum is generally not acceptable for diagnosis of PCP (55). In the ICU, bronchoscopy with bronchoalveolar lavage (BAL) is generally the primary means of diagnosis although endotracheal aspirates have also been used. For patients with HIV infection, BAL has a sensitivity of well over 90% for diagnosis of PCP and should be performed as early as possible in undiagnosed patients (56). Transbronchial biopsy does not add significantly to the yield for PCP in an HIV-infected individual and is technically challenging in an intubated patient on mechanical ventilation; however, it may be useful in diagnosing other pulmonary infections that are also in the differential (57). It is reasonable to perform transbronchial biopsy as part of the initial procedure when the probability of PCP is low or as a follow-up test when the initial BAL is nondiagnostic.

Traditional staining methods for PCP include Gomori methenamine silver, toluidine blue O stain, or a modified Wright–Giemsa stain. Immunofluorescent antibody staining can also be used to examine induced sputum or BAL and has a high sensitivity (58,59). Newer polymerase chain reaction (PCR)-based methods have been reported; PCR can also detect *Pneumocystis* DNA in persons without microscopic PCP who are considered to be colonized with the organism.

**Treatment and Corticosteroids.** The duration of PCP treatment is 21 days. First-line therapy for moderate to severe PCP is intravenous trimethoprim/sulfamethoxazole (TMP/SMX) (Table 91.2). TMP/SMX is curative in 60% to 86% of patients (60,61). The dosage of TMP/SMX is 15 to 20 mg/kg of trimethoprim and 75 to 100 mg/kg of sulfamethoxazole daily, divided every 6 to 8 hours. TMP/SMX is associated with a high rate of adverse reactions, particularly in those with HIV infection. Approximately one-fourth to one-half of patients will develop therapy-limiting toxicity (49,60,62–64). Adverse reactions to TMP/SMX include nausea, vomiting, integumentary rash, elevation of transaminases, hyponatremia, hyperkalemia, renal insufficiency, and bone marrow suppression.

Intravenous pentamidine isethionate is the preferred alternative treatment for patients who cannot tolerate TMP/SMX or who have failed treatment. Patients should receive 3 to 4 mg/kg/day of pentamidine. Some studies have found that the efficacy of pentamidine is similar to TMP/SMX, but others have reported a lower survival rate with pentamidine (61% vs. 86% for TMP/SMX) (60,61,65). Pentamidine has several serious adverse effects that can limit therapy and may be seen in as many as 50% of patients. Toxicity from pentamidine includes nausea, vomiting, hypotension, bone marrow suppression, hepatic transaminitis, and nephrotoxicity. Glucose levels should be monitored in patients receiving pentamidine because it is toxic to pancreatic islet cells and can result in initial hypoglycemia from a surge of insulin release, followed by hyperglycemia from inadequate insulin. Some patients can even progress to chronic diabetes mellitus. Pancreatitis also occurs with pentamidine and may be fatal (66,67). Other side effects that have been reported include myoglobinuria,

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
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<tbody>
<tr>
<td>Trimethoprim–sulfamethoxazole</td>
<td>15–20 mg/kg/day trimethoprim with 75–100 mg/kg/day sulfamethoxazole IV, divided every 6–8 hrs</td>
</tr>
<tr>
<td>Pentamidine isethionate</td>
<td>3–4 mg/kg/day IV, infused over &gt;60 min Start at 4 mg/kg but can reduce to 3 mg/kg if substantial clinical improvement (e.g., transfer out of ICU)</td>
</tr>
<tr>
<td>Clindamycin/primaquine</td>
<td>600 mg IV every 6 hrs or 900 mg IV every 8 hrs (clindamycin) 30 mg (base) PO daily (primaquine)</td>
</tr>
<tr>
<td>Adjunctive therapy: Prednisone if Po2 &lt;70 mmHg or A-a gradient ≥35 mmHg</td>
<td>40 mg PO every 12 hrs for 5 days, 40 mg PO daily for 5 days, 20 mg PO daily for 11 days</td>
</tr>
</tbody>
</table>

*Duration of PCP treatment is 21 days. PCP, Pneumocystis pneumonia; ICU, intensive care unit; IV, intravenously; PO, by mouth; Po2, arterial oxygen tension; A-a, alveolar–arterial.*
CHAPTER 91 Human Immunodeficiency Virus in the Intensive Care Unit

hyperkalemia, and increases in creatinine kinase. Pentamidine also has cardiac side effects, leading to bradycardia, prolonged Q-T intervals, and ventricular arrhythmias (68,69).

When TMP/SMX and pentamidine are either ineffective or toxic, it is possible to use clindamycin and primaquine as another salvage regimen option, but this use may be limited in the ICU because primaquine is administered orally and its absorption may be impaired. Clindamycin should be dosed from 600 to 900 mg every 6 to 8 hours intravenously, with primaquine given 15 to 30 mg orally daily. Patients should be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency before starting primaquine; side effects include rash, diarrhea, and methemoglobinemia.

Adjunctive corticosteroids have been shown to decrease mortality in those patients with moderate to severe PCP (41,42,70,71). A meta-analysis of all randomized trials of corticosteroids found that the administration of corticosteroids was associated with a risk ratio of 0.56 for mortality and 0.38 for requiring mechanical ventilation (72,73). Patients with a room air arterial oxygen pressure less than 70 mmHg or with an alveolar–arterial gradient 35 mmHg or greater should receive corticosteroids. Corticosteroid therapy should be started early in the ICU because primaquine is administered orally and its absorption may be impaired. Clindamycin should be dosed from 600 to 900 mg every 6 to 8 hours intravenously, with primaquine given 15 to 30 mg orally daily. Patients should be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency before starting primaquine; side effects include rash, diarrhea, and methemoglobinemia.

Treatment Failure. Due to the increased inflammatory response during the initial phase of treatment, clinical deterioration can frequently be seen in the first 3 to 5 days of PCP treatment. Patients may experience worsening hypoxemia and increasing respiratory distress, and radiographic infiltrates may progress. This worsening is likely due to an inflammatory response to dead or dying organisms that results in increased capillary permeability and formation of pulmonary edema. Assessment of treatment failure is challenging given this potential for initial worsening combined with the inability to culture Pneumocystis or to determine antibiotic sensitivities. In general, treatment should be continued for at least 5 to 7 days before diagnosing treatment failure and switching to another agent. It is important to remember that other processes present at baseline or processes that have developed since admission can explain the patient’s lack of improvement, and these diagnoses must be excluded before concluding that treatment failure is solely to blame. Other frequent diagnoses to consider include nosocomial, community-acquired, or other opportunistic pneumonia and cardiogenic or noncardiogenic pulmonary edema. Patients who worsen or fail to improve while receiving PCP treatment should undergo diagnostic procedures such as chest CT, sputum cultures, or echocardiography as clinically indicated. Repeat bronchoscopy is useful to identify pathogens other than PCP but is not useful to evaluate treatment failure because Pneumocystis can persist in the BAL, even in patients who are successfully treated (74).

It is unknown if treatment failure is more likely in patients with previous exposure to anti-Pneumocystis prophylaxis. Pneumocystis develops mutations at the dihydropteroate synthase (DHPS) locus with exposure to sulfonamides-containing medications such as TMP/SMX and dapsone (75–77). In other microorganisms, mutations at this locus have been shown to produce resistance to TMP/SMX, but the evidence for clinically important resistance in Pneumocystis is not clear-cut. Some authors have found an increased mortality and rate of treatment failure in patients with DHPS mutations (78–81), but others have not observed this association (76,82). In general, most patients with previous exposure to TMP/SMX or dapsone respond to treatment with TMP/SMX, and it should still be regarded as first-line therapy for these patients.

Ventilatory Support. Because the physiology of PCP is very similar to that of ARDS, principles of ventilatory management should be the same. Barotrauma (or volutrauma) is of particular concern in ventilated patients with PCP, as the development of a pneumothorax heralds a poor prognosis. Although patients with PCP were not included in the ARDSnet study published in 2000, these patients should probably be ventilated in a similar fashion—with tidal volumes of 6 mL/kg of ideal body weight and levels of positive end-expiratory pressure (PEEP) as needed to maintain oxygenation according to the ARDSnet guidelines (83). Noninvasive positive pressure ventilation (NIPPV) with continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) may be useful in patients with PCP. One study found that use of noninvasive ventilation decreased the rate of intubation, lowered the number of pneumothoraces, and improved survival (84). Thus, NIPPV may be tried as a first-line ventilation mode in patients with PCP who are awake, cooperative, and able to protect their airway. High-flow oxygen delivered through nasal cannula may improve outcome for patients with hypoxic respiratory failure, although its role in HIV-infected patients with PCP and other pulmonary conditions has not specifically been studied (85).

Bacterial Pneumonia

BP is significantly more frequent in HIV-infected compared to uninfected individuals, despite an overall decline in incidence (86,87). Earlier initiation and more widespread use of ART, as well as TMP/SMX for PCP prophylaxis in eligible individuals, have contributed to an overall decline in the numbers of cases of HIV-associated BP (29,88,89). Although absolute numbers of cases of BP have declined since the introduction of ART, BP now accounts for a greater percentage of ICU admissions for respiratory failure since the number of PCP cases has also declined (2,11). Similarly, nosocomial or hospital-acquired pneumonia (HAP) has also declined since the introduction of ART but remains common in mechanically ventilated patients (90). Risk factors for BP include injection drug use, cigarette smoking, older age, and lower CD4+ cell count, although BP can occur in patients at any CD4+ cell count and with increasing frequency as the CD4+ cell count declines (89,91–93).

BP can be associated with significant morbidity and with increased short- and long-term mortality in HIV-infected patients (94). CD4+ cell count below 100 cells/μL, shock, and radiographic progression have been associated with mortality from BP in HIV-infected patients (95). ICU mortality in HIV-infected patients admitted with BP has been reported between 17% and 24% (5,7).

Clinical Presentation. Clinical presentation of BP in the HIV-infected patient is similar to that in the HIV-uninfected population. Patients typically present with an acute onset of fever, cough,
shortness of breath, and purulent sputum. Chest radiographs frequently reveal lobar infiltrates that may progress to an ARDS-like picture in severe cases. The most common causes of BP in HIV include Streptococcus pneumoniae and Haemophilus influenzae. Pseudomonas aeruginosa and Staphylococcus aureus are also frequent causes of BP, particularly hospital-acquired cases, but can be community-acquired as well. Drug-resistant S. pneumoniae and S. aureus are common in HIV-infected patients, particularly in those on macrolide prophylaxis for Mycobacterium avium complex (MAC) and in injection drug users (96–98). Atypical pneumonia with Mycoplasma pneumoniae is reported in approximately 20% to 30% of HIV-infected patients with community-acquired pneumonia (CAP) but is less commonly a cause of ICU admission (99). HIV-infected patients are more likely to be bacteremic, particularly those with S. pneumoniae infection (100). Additionally, the incidence of bacteremia increases as the CD4+ lymphocyte count declines.

**Diagnosis and Treatment.** Diagnosis and treatment for both CAP and HAP should generally follow published guidelines, although these guidelines do not specifically address pneumonia in HIV-infected patients (101,102). Blood cultures should be obtained, and sputum should be sent for Gram stain and culture. Bronchoscopy should be considered, particularly in cases of ventilator-associated pneumonia or when the diagnosis is uncertain to assess for other OIs. Additional diagnostic evaluation such as pneumococcal and legionella urinary antigen testing may be useful. Treatment should include empiric coverage for the organisms above. Because of the higher incidence of pseudomonal and staphylococcal pneumonia in HIV-infected patients with severe pneumonia, it is important to initiate coverage for these organisms. As methicillin-resistant Staphylococcus aureus (MRSA) is common in HIV infection and is associated with decreased survival (90), empiric antibiotics effective against this pathogen are warranted particularly in injection drug users and in patients with other risk factors for multi-drug-resistant organisms pending results of cultures and antimicrobial sensitivities. Empirical monotherapy with a macrolide is not advised in organisms pending results of cultures and antimicrobial sensitivities. Empirical monotherapy with a macrolide is not advised in patients on macrolide prophylaxis for MAC because of increasing pneumococcal resistance rates (103). Patients on TMP/SMX prophylaxis may be more likely to have penicillin- and TMP/SMX-resistant S. pneumoniae. For patients with CD4+ lymphocyte counts less than 100 cells/µL, consideration should be given to including coverage against P. aeruginosa.

**Other Respiratory Diseases**

Other respiratory diseases that occur in HIV-infected ICU patients include Mycobacteria tuberculosis pneumonia; fungal pneumonias such as Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immitis, and Aspergillus fumigatus; cytomegalovirus (CMV) pneumonia; and Toxoplasma gondii pneumonitis. Malignancies such as Kaposi sarcoma and non-Hodgkin lymphoma can also lead to respiratory failure, but they are far less common than infections.

**IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME**

Immune reconstitution inflammatory syndrome (IRIS) encompasses a paradoxical worsening of clinical status in the setting of recovery of the immune system following immunosuppression, typically after the initiation of ART in HIV-infected patients. IRIS is thought to result from immune activation and dysregulated host inflammatory responses to previously recognized or subclinical infections, or in response to cancer or self-antigens (104–106). Immunopathogenesis of IRIS may be different depending upon the pathogen (105).

**Clinical Presentation**

IRIS can occur days to months after ART is started, with the majority of cases occurring within the first 1 to 3 months (106). Immune reconstitution is most often seen in infection with Mycobacterium tuberculosis, Cryptococcus, CMV, Pneumocystis, MAC, and endemic fungi (106–108). Cancers such as Kaposi sarcoma can also cause IRIS. Manifestations of IRIS that can result in the need for ICU care include meningitis, pneumoni-tis, hepatitis, and pericarditis. Cryptococcal meningitis has been associated with increased mortality. Respiratory failure secondary to IRIS is most common in tuberculosis and PCP (109,110). Paradoxical worsening in these cases presents with fever, hypoxemia, and new or increased radiographic infiltrates.

**Diagnosis and Treatment**

The diagnosis of IRIS is one of exclusion, as IRIS can be difficult to distinguish from acute OIs or other etiologies on the basis of clinical features alone. It is thus imperative that other causes of clinical deterioration, such as a new infection, drug resistance, or inadequate drug levels against a known infection, are sought and ruled out before assigning a diagnosis of IRIS.

Treatment is generally supportive, and ART should be continued whenever possible. Nonsteroidal anti-inflammatory agents can be used to decrease inflammation. Steroids are not routinely given, but may be indicated if the excessive inflammatory response is particularly harmful, such as in the setting of life-threatening complications including meningitis, central nervous system lesions, or airway involvement. In these cases, prednisone or methylprednisolone at approximately 1.5 mg/kg of body weight per day for 2 weeks followed by 0.75 mg/kg/day for an additional 2 weeks are recommended while monitoring clinical response (103).

**SEPSIS**

Sepsis is increasingly common among HIV-infected patients admitted to the ICU. In the ART era, more deaths in the HIV population have been attributed to sepsis and bacteremia (111–113). Amongst ICU patients, severe sepsis is associated with higher mortality compared to other indications for ICU admission (24,113). Furthermore, severe sepsis may be associated with greater mortality in HIV-infected patients compared to HIV-uninfected patients (24,27,112).

In-hospital mortality has been reported to be between 40% and 60% (9,28,30,112,114), with worse outcomes associated with higher severity of illness scores (30,113). Longer-term outcomes are also poor, with 6-month mortality reported at 60% (113). However, in published studies of HIV-infected critically ill patients, the majority of patients admitted with sepsis in these studies were severely immunocompromised with CD4+ cell counts below 200 cells/µL, and many were not
on ART (112,113). Prognosis and outcomes, particularly following hospitalization, should be considered in this context.

**Clinical Presentation**

Clinical presentation of sepsis, severe sepsis, and septic shock are the same in HIV-infected as in non–HIV-infected persons. Providers should consider a broad differential diagnosis, including bacterial as well as nonbacterial causes for infection, and ensure adequate source control in the case of invasive infections. Pneumonia is generally reported as the leading cause of sepsis in HIV-infected persons, with bloodstream and intra-abdominal infections common sources as well (24,27,112,113). Nosocomial infections are frequent in HIV-infected persons in studies from the United States and Europe, with gram negatives such as *P. aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter* species, and gram-positive organisms such as *S. aureus* and *S. pneumoniae*. By way of contrast, in other parts of the world, such as in studies from Uganda, sepsis is frequently due to bacteremia from *M. tuberculosis* (115,116).

**Diagnosis and Treatment**

Care of the HIV-infected patient with sepsis should follow current guidelines (34). Broad-spectrum antibiotics should be based on the patient’s CD4+ cell count, the presumed source as noted above, and previous use of prophylactic antibiotics that might predispose to resistant bacteria. Clinicians should consider empiric coverage and diagnostic evaluation for bacterial infections, PCP, mycobacterial diseases, endemic fungi, and other OIs as suggested by the patient’s presentation. Because HIV-infected patients may have an increased risk for adrenal insufficiency, steroids should be considered in patients who are persistently hypotensive despite adequate fluid resuscitation and vasopressors.

**NEUROLOGIC MANIFESTATIONS OF HIV**

The spectrum of neurologic disorders requiring critical care for patients with HIV infection includes all the causes commonly seen in the HIV-uninfected population in addition to particular OIs, neoplasms, and sequelae of HIV. As many as 80% of these conditions required mechanical ventilation among HIV-infected patients in an earlier series (117). Nonetheless, neurologic causes of ICU admission may be decreasing. Coma as the ICU admission diagnosis decreased from 29% in 1999–2001 to 15% in 2008–2010 in CUB-Réa (5). In the most recent reports from San Francisco General Hospital, neurologic diagnoses accounted for 16% of ICU admissions and delirium diagnosis was associated with approximately 75% survival (2,3). Another study found that CNS toxoplasmosis and progressive multifocal leukoencephalopathy (PML) had decreased, but the incidence of ischemic stroke, hemorrhagic stroke, and primary CNS lymphoma had increased (118).

CNS toxoplasmosis is one of the most frequent CNS infections seen, although the number of cases has fallen dramatically with the introduction of ART (119,120). Patients typically present with fever, headache, focal neurologic deficits, and a decreased level of consciousness; seizures can also occur. CT scan reveals characteristic ring-enhancing lesions (Fig. 91.2). Similar findings can also be seen with CNS lymphoma. Treatment for CNS toxoplasmosis is pyrimethamine given as a 200-mg loading dose, followed by 50 to 75 mg orally every 24 hours, with sulfadiazine at a dose of 1 to 1.5 g every 6 hours orally. Patients should also receive 10 to 20 mg of folic acid daily while receiving pyrimethamine. Other CNS infections that are seen in HIV infection include bacterial and *C. neoformans* meningitis. Diagnosis of *C. neoformans* is confirmed by visualization of encapsulated yeast on cerebrospinal fluid (CSF), a positive CSF culture, or a positive CSF cryptococcal antigen. Treatment should be initiated with liposomal amphotericin B (3–4 mg/kg/day intravenously) and flucytosine (100 mg/kg/day orally, divided into four doses). Repeated lumbar puncture is often required to normalize CSF pressure. Other CSF infections that occur in HIV include PML, which is a progressive demyelinating disease, CMV, and herpes simplex virus. Any of these diseases can worsen and present with a neurologic IRIS in the setting of introduction of ART (118).

**GASTROINTESTINAL MANIFESTATIONS OF HIV**

GI diseases, in particular liver diseases, have increased as a cause of death in HIV-infected patients (111). These diseases are either the primary cause or a complicating factor in the ICU admission of many HIV-infected patients. As in the HIV-uninfected population, significant GI bleeding often results...
in ICU admission. Upper GI bleeding is more common than lower GI bleeding, and approximately half of the cases are HIV-related (121). Common HIV-associated diagnoses include infectious esophagitis (e.g., CMV) and ulcers, Kaposi sarcoma, and AIDS-associated lymphoma (121). In cases of lower GI bleeding, approximately 70% are a result of HIV infection (121). CMV colitis and idiopathic colon ulcers are most common, but Kaposi sarcoma, AIDS-associated lymphoma, and infections such as MAC may also contribute (122). Hemorrhoids and anal fissures can also result in significant bleeding in HIV-infected patients with thrombocytopenia (123). Care of the HIV-infected patient with a GI bleed is the same as for the HIV-uninfected patient and should include immediate resuscitation, source identification, reversal of coagulation defects, and achievement of hemostasis.

Coinfection with HIV and hepatitis C is increasingly common and complicates the management of both diseases. Mortality from hepatitis C has increased in recent years (124–127), and infection in HIV-infected individuals seems to be more severe with a higher mortality and risk of cirrhosis (128–132). There is an increased risk of renal failure in hospitalized patients coinfected with HIV and hepatitis C (133,134). Hepatitis B is also common among HIV-infected patients.

Other GI conditions that are common in HIV-infected patients include peritonitis and bowel perforation. The most common cause of life-threatening abdominal pain is small bowel or colon peritonitis from CMV (135). Kaposi sarcoma, AIDS-associated lymphoma, and mycobacterial infection have also been associated with bowel perforation (122). Pancreatitis can also be seen, particularly with exposure to certain antiretroviral medications or pentamidine. AIDS cholangiopathy can result from various infectious and neoplastic processes and can be asymptomatic or present with fulminant biliary sepsis (122). In addition to the usual care of cholangitis with intravenous fluids and broad-spectrum antibiotics, endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy may be helpful in patients with common bile duct dilatation (135).

OTHER HIV-ASSOCIATED CONDITIONS

Cardiac Disease

Since the introduction of ART, there has been growing evidence that HIV-infected patients are developing premature atherosclerosis, and cardiovascular disease is a primary cause of non–HIV-related deaths in these patients (111,136). Although the literature has been conflicting, HIV-infected patients have an elevated risk of cardiovascular disease compared to uninfected patients in recent studies when controlling for other risk factors and confounders (137,138). Thus, HIV-infected patients may be commonly admitted to the ICU with acute coronary syndromes.

The increased risk for cardiovascular disease in HIV-infected patients is in part explained by a high prevalence of metabolic abnormalities, chronic inflammation, and other cardiac risk factors such as cigarette smoking. The development of metabolic abnormalities that contribute to atherosclerosis has been associated with the use of nonnucleoside reverse transcriptase inhibitors (NNRTIs) and/or protease inhibitors (PIs). Elevated triglycerides, hypercholesterolemia, decreased high-density lipoproteins, glucose intolerance, and frank diabetes have all been associated with various antiretrovirals (139–142). There may also be direct endothelial effects of PIs or HIV itself that play a role in the development of vascular complications. Chronic inflammation and immune activation associated with HIV infection have also been associated with risk for cardiovascular events (143).

Congestive heart failure may also be an indication for ICU admission. In the precombination ART era, HIV was associated with dilated cardiomyopathy that was often severe. In the ART era, however, systolic heart failure has decreased in prevalence, while diastolic dysfunction has increased, often in association with traditional cardiac risk factors (144). There are few data on treatment or outcomes of cardiac disease specifically in the HIV-infected population. In the absence of specific data, treatment of acute coronary syndromes should be the same as in the HIV-uninfected population. HIV-infected patients should be referred for cardiac surgery and coronary artery bypass grafting when appropriate. Heart failure should also be managed similarly as in HIV-uninfected patients.

Renal Disease

HIV-infected patients are at risk of acute and chronic renal failure that can either lead to ICU admission or complicate care in the ICU. Baseline renal function is abnormal in approximately 30% of HIV-infected patients. HIV-associated nephropathy has decreased with the use of ART but is still a common cause of end-stage renal disease (145–147). Renal dysfunction can occur from use of certain antiretroviral medications and other therapies such as pentamidine, TMP/SMX, and amphotericin B. Patients who are coinfected with hepatitis C also have an increased risk of renal failure (133,148). Other common comorbidities including hypertension and diabetes are emerging as major risk factors for end-stage renal disease in HIV-infected patients who achieve viral suppression (148).

Acute kidney injury is likely more common in HIV-infected patients, occurring in 66% of all HIV-infected patients admitted to the ICU with nearly one-third requiring renal replacement therapy (149). The diagnostic workup and treatment of renal dysfunction in HIV-infected patients is similar to that for the HIV-uninfected patient and should include renal ultrasound to rule out obstruction, examination of the urine, discontinuation of nephrotoxic medications, and renal biopsy if indicated. Dialysis should be offered to appropriate patients.

Metabolic Abnormalities

Metabolic abnormalities are common in the HIV-infected ICU patient. As described above, lipid and glucose abnormalities are often seen. Hyperglycemia secondary to drugs such as pentamidine also occurs in this population. It has been noted that hospitalized patients with HIV have high rates of hyponatremia (150–152). Causes of hyponatremia include hypovolemia, adrenal insufficiency, drugs, and the syndrome of inappropriate antidiuretic hormone (SIADH). A high incidence of adrenal abnormalities has been noted on autopsy of HIV-infected patients (153–155). Causes of adrenal pathology include infections such as CMV, tumors such as Kaposi sarcoma, and drugs such as ketoconazole and pentamidine (156). The clinical significance of the adrenal abnormalities...
is uncertain, but it seems that HIV-infected patients have a higher likelihood of adrenal dysfunction (36,137). Adrenal insufficiency can present with hyperkalemia, hyponatremia, and hypotension, and patients with these symptoms should be evaluated and treated appropriately. As with HIV-uninfected patients, adrenal insufficiency may be common in sepsis.

Lactic acidosis is another metabolic abnormality that can occur in HIV-infected patients receiving ART. This syndrome was first described in the 1990s and can occur with any nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) but is mostly commonly seen with didanosine and stavudine (158,159). Mitochondrial toxicity secondary to impaired synthesis of adenosine triphosphate (ATP)-generating enzymes is believed to be the cause of lactic acidosis (160–162). Patients particularly at risk of developing lactic acidosis from these drugs include those with a creatinine clearance less than 70 mL/min and a nadir CD4+ cell count below 250 cells/µL (163). Although some patients may have only an asymptomatic lactic acidosis, others present with life-threatening acidemia. These patients also commonly complain of abdominal pain, nausea, and vomiting. Hepatic steatosis and transaminases also occur, and patients can progress to respiratory failure and shock.

In any patient presenting with these symptoms, an arterial lactate level should be checked and all antiretroviral medications discontinued if the level is greater than 5 mmol/L. Supportive care should be administered with bicarbonate therapy and hemodialysis if necessary. Based on anecdotal data, riboflavin, thiamine, and L-carnitine may reverse toxicity (164–167). Riboflavin is administered at a dose of 50 mg daily with 50 mg/kg of L-carnitine, and 100 mg of thiamine. Although the exact length of treatment is unknown, it should be continued at least until acidosis resolves.

**Fever of Unknown Origin**

Fever is common in all ICU patients. The differential for fever is broad in the HIV-infected patient and includes infections, neoplasms, medications, and collagen vascular diseases. Several studies have examined the etiology of fevers of unknown origin in those with HIV infection. Most studies have found that infectious causes are responsible for most prolonged fevers in the HIV-infected patient, with mycobacterial diseases diagnosed most commonly. PCP, cryptococcus, histoplasma, CMV, and bacterial infections are also seen (168,169). The most common neoplastic cause of prolonged fever is lymphoma. Patients receiving ART are less likely to present with a fever of unknown origin than those not receiving ART (170).

Recurrent fever in an HIV-infected ICU patient should also prompt evaluation of those conditions commonly seen in HIV-uninfected ICU patients. Common infectious causes of fever in the ICU include HAP, catheter-related infections, sinusitis, and pseudomembranous colitis. Noninfectious causes include drug reactions, pancreatitis, venous thromboembolism, calcific cholecystitis, adrenal insufficiency, and thyroid storm. A thorough physical examination and imaging studies should be obtained, often including CT scan of the chest, abdomen, and pelvis. Diagnostic workup should include standard evaluation for infections such as blood, sputum, and urine cultures. Bronchoscopy with BAL should be performed in patients who demonstrate a new infiltrate on chest radiograph or have a worsening respiratory status. Testing should be performed for mycobacterial and fungal pathogens. Other diagnostic options include fluorodeoxyglucose (FDG)/positron emission tomography (PET), bone marrow biopsy and culture, and lymph node biopsy (171–174). Generally, workup should be performed as would be done in the HIV-uninfected population.

**ANTIRETROVIRAL THERAPY IN THE ICU**

**Treatment Strategies**

HIV-infected patients may be receiving ART at the time of ICU admission or may have ART initiated in the ICU. The use of ART in critically ill patients presents distinct issues related to patient involvement, drug delivery, drug dosing, drug interactions, and antiretroviral-associated toxicities. The success of ART in decreasing HIV-associated morbidity and mortality has raised questions regarding the ability of ART to improve outcomes in critically ill HIV-infected patients, the HIV patients with the highest short-term mortality, and it is important for the critical care physician to consider ART in every HIV-infected patient.

There are several factors related to using ART in the ICU that are important to consider. ART improves immune function. In chronic HIV infection, improving immune function with ART significantly reduces the risk of OIs and neoplasms. This could contribute to reductions in morbidity and mortality in critically ill HIV-infected patients by decreasing the risk of subsequent HIV-associated diseases. ART is also important in treating conditions such as PML that otherwise lack effective therapy. For patients already receiving ART, discontinuing therapy could result in the selection of drug-resistant virus that could limit future therapy. This is especially true if patients are receiving efavirenz or nevirapine, as these antiretrovirals have longer half-lives than other antiretroviral medications. As a result, levels of these medications may persist as the levels of the other antiretroviral medications decrease, resulting in functional monotherapy.

ART is also associated with several risks. Current ART guidelines recommend implementing a series of patient-based strategies and patient involvement to optimize adherence to ART, strategies that are often impossible in a critically ill ICU patient (173). Drug interactions and ART-associated toxicities can also complicate management. Pharmacokinetic interactions can occur during drug absorption, metabolism, and elimination of the antiretroviral(s) as well as the interacting drug. In addition, there are uncertainties surrounding dosing in acute and multiple organ system failures. These uncertainties could place patients at risk for subtherapeutic drug levels and drug resistance or, conversely, supratherapeutic levels and toxicity. IRIS could result in significant clinical worsening of an already critical disease. The potential threat of this syndrome may make physicians reluctant to initiate ART in the ICU.

There are now several randomized clinical trials to support the initiation of ART in acutely ill HIV-infected patients with OIs but no randomized clinical trials and no consensus guidelines to assist in decisions regarding ART use in the ICU, particularly amongst mechanically ventilated patients with respiratory failure, as these patients have not been represented in prior clinical trials. Only a few retrospective studies address some of the clinical issues that critical care clinicians face. Although decisions regarding ART use in the ICU require a
case-by-case basis review, Huang et al. (176) suggested the following general framework (Fig. 91.3). Patients receiving ART prior to ICU admission who have evidence of virologic suppression (plasma HIV RNA below the limit of detection) should continue ART, if possible. These patients should have no contraindications to continuing ART such as drug interac-
tions or ART-associated toxicities. Prompt placement of a feeding tube is especially critical in these patients. In patients whose plasma HIV RNA is detectable despite ART, the risks of continuing ART may outweigh the benefits of incomplete HIV viral suppression, especially if the CD4+ cell count response has been poor. In these individuals, switching to a new ART regimen may be preferable to continuing a potentially failing regimen. However, consultation with an expert in HIV medicine should be obtained prior to any decision to continue, switch, or discontinue ART.

Patients not receiving ART prior to ICU admission represent the largest proportion of HIV-infected patients admitted to the ICU in most published studies (2,7–9). Two studies from the ART era suggest that patients admitted with an AIDS-defining diagnosis, especially PCP, have the poorest prognosis and, thus, the greatest theoretical benefit from ART (2,31). Although one study found that patients receiving or started on ART during ICU admission for PCP had decreased mortality (25% vs. 63%), this study was retrospective and based on a limited number of patients.

Based on the limited available data, ART initiation should be deferred in HIV-infected patients admitted to the ICU with a non–AIDS-associated condition (see Fig. 91.3) (176). The immediate prognosis in these patients is generally better than for an AIDS-associated diagnosis, and the short-term outcome is most likely related to successful treatment of the underlying non-AIDS condition (2). As a result, the risks of ART initiation in the ICU outweigh the short-term benefits of this therapy. If, however, patients remain in the ICU for a prolonged period, ART (and OI prophylaxis) should be considered if the patients have a CD4+ cell count less than 200 cells/μL since the risk of OIs is increased below this CD4+ count.

In contrast, ART should be considered for HIV-infected patients admitted to the ICU with an AIDS-associated diagnosis. This is especially true for patients whose condition is worsening despite optimal ICU management and treatment for the AIDS-associated condition. In these individuals, the prognosis is dire, and aggressive measures are warranted. Patients who receive ART should be followed for development of IRIS, and consultation with an expert in HIV medicine should be obtained.

**Drug Delivery, Dosing, and Interactions**

All of the currently approved antiretroviral medications are dispensed orally, either as tablets or capsules, with the sole exception of enfuvirtide, a fusion inhibitor that is delivered subcutaneously. Several antiretrovirals are available in an oral solution, oral suspension, or in an oral powder, but only zidovudine has an intravenous formulation. If the medications
that are only available as tablets or capsules are to be continued or initiated in the ICU, then these medications need to be crushed and reconstituted for delivery via feeding tube. As an additional consideration, the administration of many antiretrovirals requires the interruption of enteral feedings that are usually delivered continuously, while other antiretrovirals should be taken with food to minimize adverse effects.

Critical illness may complicate the absorption of antiretroviral medications. Decreased gastric motility (177,178), continuous feeding (179), nasogastric suctioning, and gastric alkalinization recommended for stress ulcer prophylaxis (34) may contribute to variations in the absorption of enterally administered drugs. H₃ blockers and proton pump inhibitors, used for stress ulcer prophylaxis, are contraindicated with certain antiretroviral medications, necessitating the use of alternative prophylaxis agents or antiretroviral medications (Table 91.3) (175). Absorption of subcutaneously injected medications may also be altered (180,181). Furthermore, atypical drug volumes of distribution and compromise of elimination pathways due to acute organ failures may confound the achievement of appropriate drug levels (182).

The impact of acute and multiple organ system failures on the pharmacokinetics of antiretroviral medications, particularly when used in combination, have been largely unstudied. The presence of renal insufficiency or hepatic impairment will affect antiretroviral dosing. Renal insufficiency will reduce the clearance of all NRTIs except abacavir and will require dose adjustment of these NRTIs. Patients with renal insufficiency cannot use the fixed-dose NRTI combinations if each component has a different dose adjustment. Instead, each antiretroviral must be used individually and dosed accordingly. Liver impairment will reduce the clearance of all NNRTIs except efavirenz and will require dose adjustment of these NNRTIs. Patients with hepatic impairment will affect antiretroviral dosing. The presence of renal insufficiency or hepatic impairment will affect antiretroviral dosing. Renal insufficiency will reduce the clearance of all NRTIs except abacavir and will require dose adjustment of these NRTIs. Patients with renal insufficiency cannot use the fixed-dose NRTI combinations if each component has a different dose adjustment. Instead, each antiretroviral must be used individually and dosed accordingly. Liver impairment will reduce the clearance of all NNRTIs except efavirenz and will require dose adjustment of these NNRTIs. Patients with hepatic impairment will reduce the clearance of all NNRTIs except efavirenz and will require dose adjustment of these NNRTIs. Patients with hepatic impairment will reduce the clearance of all NNRTIs except efavirenz and will require dose adjustment of these NNRTIs. Patients with hepatic impairment will reduce the clearance of all NNRTIs except efavirenz and will require dose adjustment of these NNRTIs. Patients with hepatic impairment will reduce the clearance of all NNRTIs except efavirenz and will require dose adjustment of these NNRTIs. Patients with hepatic impairment will reduce the clearance of all NNRTIs except efavirenz and will require dose adjustment of these NNRTIs. Patients with hepatic impairment will reduce the clearance of all NNRTIs except efavirenz and will require dose adjustment of these NNRTIs. Patients with hepatic impairment will reduce the clearance of all NNRTIs except efavirenz and will require dose adjustment of these NNRTIs. Patients with hepatic impairment will reduce the clearance of all NNRTIs except efavirenz and will require dose adjustment of these NNRTIs. Patients with hepatic impairment will reduce the clearance of all NNRTIs except efavirenz and will require dose adjustment of these NNRTIs. Patients with hepatic impairment will reduce the clearance of all NNRTIs except efavirenz and will require dose adjustment of these NNRTIs. Patients with hepatic impairment will reduce the clearance of all NNRTIs except efavirenz and will require dose adjustment of these NNRTIs. Patients with hepatic impairment will reduce the clearance of all NNRTIs except efavirenz and will require dose adjustment of these NNRTIs. Patients with hepatic impairment will reduce the clearance of all NNRTIs except efavirenz and will require dose adjustment of these NNRTIs. Patients with hepatic impairment will reduce the clearance of all NNRTIs except efavirenz and will require dose adjustment of these NNRTIs. Patients with hepatic impairment will reduce the clearance of all NNRTIs except efavirenz and will require dose adjustment of these NNRTIs. Patients with hepatic impairment will reduce the clearance of all NNRTIs except efavirenz and will require dose adjustment of these NNRTIs. Patients with hepatic impairment will reduce the clearance of all NNRTIs except efavirenz and will require dose adjustment of these NNRTIs. Patients with hepatic impairment will reduce the clearance of all NNRTIs except efavirenz and will require dose adjustment of these NNRTIs. Patients with hepatic impairment will reduce the clearance of all NNRTIs except efavirenz and will require dose adjustment of these NNRTI...
medications, especially benzodiazepines. Midazolam, a benzodiazepine of choice in the ICU, should be avoided in nonventilated patients who are receiving efavirenz (an NNRTI) or PIs, as benzodiazepine drug levels may be markedly increased (175). For mechanically ventilated patients, any resulting increased sedation may be a relative, rather than an absolute, contraindication. However, excess sedation is a significant factor in patients weaning from a ventilator and nearing extubation. Other drug–drug interactions may require close monitoring, dose adjustment (increase or decrease), or avoidance of a specific antiretroviral medication and/or the other drug.

**Drug Toxicity**

In general, the newer antiretroviral medications possess better safety profiles compared to their predecessors. Nevertheless, several antiretrovirals are associated with potentially life-threatening and serious adverse effects (Table 91.4).

**TABLE 91.4 Potentially Life-Threatening and Serious Adverse Effects of Antiretroviral Agents**

<table>
<thead>
<tr>
<th>Life-threatening and Adverse Effect</th>
<th>Principal Antiretroviral Agent</th>
<th>Onset</th>
<th>Prevention/Monitoring and Management</th>
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<tr>
<td><strong>Dermatologic</strong></td>
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| Hypersensitivity reaction (HSR)—fever, diffuse rash; may progress to hypotension, respiratory distress, and vascular collapse | Abacavir (ABC) Check HLA-B*5701 status; patients who are HLA-B*5701-positive are at highest risk; ABC is contraindicated if HLA-B*5701-positive | Onset, 9 days (median); approximately 90% occur within first 6 wks; symptoms worsen with continuation of ABC | • Discontinue ABC and other ARVs  
• Rule out other causes of symptoms  
• Discontinue other potential agent(s)  
• Do not rechallenge patients with ABC after suspected HSR regardless of HLA-B*5701 status |
| Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) | Chiefly NNRTIs Nevirapine (NVP) more than other NNRTIs Reported cases with NRTIs, PIs, and raltegravir (RAL) | Onset within first few days to weeks | • NVP: 2-wk lead in period with 200 mg QD dosing, then increase to 200 mg BID or 400 mg QD (XR tablet)  
• Repeat 2-wk lead in period if therapy is discontinued for >7 days  
• Discontinue NNRTI and other ARVs  
• Rule out other causes of symptoms  
• Discontinue other potential agent(s)  
• Do not rechallenge patients with NNRTI |
| **Neurologic**                     |                                |       |                                      |
| CNS effects including somnolence, insomnia, abnormal dreams, hallucination, psychosis, depression, and suicidal ideation | Efavirenz (EFV) | Approximately 50% may have some symptoms Onset within first few days; most symptoms subside or diminish after 2–4 wks but symptoms may necessitate discontinuation in some | • Administer at bedtime or 2–3 hrs before bedtime for nonintubated, nonsedated patients  
• Take on an empty stomach to reduce CNS effects  
• Consider discontinuing EFV if symptoms persist and cause significant impairment or exacerbation of psychiatric illness |
| **Gastrointestinal**               |                                |       |                                      |
| Hepatotoxicity                     | All ARVs: nevirapine (NVP) > other NNRTIs, tipranavir (TPV)/ritonavir (RTV) > other PIs Tipranavir (TPV)/Ritonavir (RTV) is contraindicated in hepatic insufficiency (Child-Pugh B or C) | Frequency varies with ARV Onset (NRTIs), months to years; PIs generally weeks to months Risk of severe hepatotoxicity from NVP is increased in ARV-naive | • Monitor liver enzymes  
• For symptomatic patients, discontinue all ARVs  
• Rule out other causes of hepatotoxicity  
• Discontinue other potential agent(s) |
| Pancreatitis                       | Didanosine (ddI), also stavudine (d4T) | Onset usually weeks to months | • Avoid in patients with a history of pancreatitis  
• Monitoring of serum amylase/lipase in asymptomatic patients is generally not recommended  
• Discontinue offending ARV  
• Rule out other causes of pancreatitis  
• Discontinue other potential agent(s) |
| **Hematologic**                   |                                |       |                                      |
| Bone marrow suppression (macrocytic anemia and neutropenia) | Zidovudine (AZT, ZDV) | Onset, weeks to months | • Avoid use in patients at risk  
• Avoid other bone marrow suppressants if possible  
• Monitor CBC with differential  
• Switch to another NRTI if there is an alternative  
• Discontinue concomitant bone marrow suppressants if there are alternatives  
• Blood transfusion and other therapies as indicated |
Abacavir is associated with a hypersensitivity syndrome that, in rare cases, can lead to death if the patient is rechallenged. The rash associated with nevirapine can be severe, presenting with systemic symptoms and, in rare cases, progressing to Stevens–Johnson syndrome and toxic epidermal necrosis. Efavirenz is associated with mental status alterations that may be attributed erroneously to analgesics, sedatives, or the sleep-disrupted schedule in the ICU. These complications may be difficult to recognize as secondary to ART. If toxicities to antiretroviral agents are suspected, the offending agent should be discontinued promptly. Since antiretroviral drug resistance can develop within days of a partially suppressive regimen, all antiretroviral medications should be discontinued or a replacement drug should be substituted for the suspected agent. Consultation with an expert in HIV medicine is recommended for patients with suspected antiretroviral-associated toxicities.

**HIV TESTING IN THE ICU**

In the current era, 13% to 40% of patients are unaware of their HIV infection at the time of their ICU admission (2,7–9). For these patients, the first opportunity for HIV testing and diagnosis occurs in an ICU setting. Thus, critical care physicians need to consider evaluation for HIV risk factors and HIV testing in the ICU.

In general, HIV testing should be performed whenever HIV infection is suspected. Most states, per the Centers for Disease Control and Prevention (CDC) recommendations, do not require separate written consent for HIV testing, and instead, general informed consent for medical care includes HIV testing unless the patient declines screening. However, laws are not uniform across all states and local institutional policies may vary. HIV testing and disclosure requirements can present challenges to critical care physicians. If local requirements for testing cannot be obtained or HIV testing is refused, physicians must weigh the risks and benefits of diagnostic procedures and empiric therapy without a confirmed diagnosis; these decisions may harm patients with and without HIV infection.

**CONTROL OF HIV INFECTION IN THE ICU**

**Blood-borne Pathogen Precautions**

Risks for occupational transmission of HIV depend on the type and severity of exposure. Potentially infectious fluids include blood, any visibly bloody body fluid, semen, vaginal secretions, and cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluid. Transmission may occur via percutaneous injury or via contact with mucous membranes or nonintact skin with infectious material. The average risk for transmission of HIV following a percutaneous exposure to HIV-infected blood is estimated to be approximately 0.3%; transmission after mucous membrane exposure is estimated to be approximately 0.09% (183).

Primary preventive measures should be used to decrease the risk of exposure to HIV, as well as other infections including hepatitis B and C. Health care workers should use universal precautions for handling blood and body fluids for all patients, regardless of known HIV status. These precautions include the routine use of personal protective equipment such as gloves, face protection, and gown, depending on the nature of the patient's infection.
of the procedure, anticipated contact with blood or bodily fluids, and the potential for splashing or splattering of fluids. Additional components of a primary prevention strategy include work practice controls—for example, not recapping needles, announcing all sharps introduced onto or removed from the field, not leaving sharps on the field—and engineering controls—for example, self-retracting needles, needleless systems, and sharps disposal containers.

Management of Needle Sticks

In health care workers exposed to potentially infectious body fluids, secondary prevention measures should be used promptly. The first step in postexposure management is the immediate provision of first aid in the event of broken skin or other wound. Exposures should be reported promptly to the appropriate contact at each facility. If the HIV status of the source patient is unknown, evaluation of the risk factors and HIV testing following proper consent procedures should be performed.

In workers with a potential exposure to HIV, postexposure prophylaxis (PEP) should be offered urgently. PEP should begin within hours of exposure, as data suggest that PEP is likely to be more effective if started shortly after exposure (183,184). If a source patient’s HIV status is unknown, PEP should be started immediately rather than delayed, particularly if ascertainment of HIV status will be delayed by hours to days.

Preferred PEP regimens should consist of three (or more) antiretroviral drugs for 4 weeks (183,184). A recommended regimen by the US Public Health Service is a backbone of emtricitabine plus tenofovir (often dispensed as Truvada, a fixed-dose combination tablet) with raltegravir as the third drug (183). This regimen has the advantage of being potent, tolerable, conveniently administered, and has minimal drug interactions. Alternative recommendations are also available, depending upon HIV resistance patterns of the source patient and any comorbidities or use of concurrent medications in the health care worker. If three antiretroviral drugs cannot be used, two are acceptable (184). Expert consultation should be considered early, particularly in cases with exposure to documented HIV drug resistance. Substantial side effects are associated with PEP. Because of toxicity, PEP is not justified in exposures that have a negligible risk for transmission of HIV.

Health care workers with potential exposure to HIV should undergo serial HIV antibody testing. The CDC-recommended schedule is initial testing at the time of exposure, with repeat testing at 6 weeks, 12 weeks, and 6 months after exposure. HIV testing should be extended to 12 months in those patients with a pneumothorax while on mechanical ventilation. Many patients admitted with pneumonia (PCP) are not aware of their HIV status.

Diagnoses such as BP, sepsis, and non–AIDS-related conditions have increased in frequency since the introduction of highly active ART.

Intensive care survival of patients with HIV. Early bronchoscopy with BAL should be performed in patients with pneumonia who do not have an established microbiologic diagnosis.

PEP should be discontinued if HIV testing of the source patient is negative.

Respiratory Isolation

As with HIV-uninfected patients, HIV-infected patients with suspected airborne-spread infections should be placed in respiratory isolation. Airborne precautions in the hospital setting consist of the use of personal protective equipment in the form of respirators and engineering controls such as the use of negative pressure rooms (185). Diseases requiring airborne isolation precautions include tuberculosis, varicella (chickenpox and herpes zoster), measles, and the severe acute respiratory syndrome (SARS) (185). Because tuberculosis is common in the HIV-infected population and is often difficult to distinguish from other types of pneumonia, most HIV-infected patients with respiratory symptoms and chest radiographic abnormalities should be considered for respiratory isolation. The immune status of staff caring for the patient should also be considered, and limiting the number of staff exposed to the patient may be warranted. Patients with suspected airborne-transmitted diseases should wear a surgical mask during transport. Criteria for removing patients from respiratory isolation vary by disease. For example, patients with tuberculosis can be removed from respiratory isolation when the patient is on effective therapy, is clinically improving, and has three consecutive negative sputum smears for acid-fast bacilli on different days, or tuberculosis has been ruled out.

SUMMARY

The outcome for HIV-infected ICU patients has improved dramatically since the beginning of the AIDS epidemic. The spectrum of admitting diagnoses in the ICU has shifted to include more non–HIV-related conditions and diagnoses related to side effects of ART. Because many patients are admitted to the ICU as their first manifestation of HIV, clinicians also need to consider a diagnosis of HIV in any patient with a compatible clinical history. Issues regarding continuing or starting HIV therapy are complex, and although ART seems to have had some impact on the outcomes of critically ill HIV-infected patients, much remains to be discovered about its role in the ICU. Unfortunately, few data exist to guide clinicians in this difficult decision, and until future randomized, controlled studies examine this question, physicians must balance the risks and benefits for individual patients.

Key Points

- Intensive care survival of HIV-infected patients has improved over the course of the AIDS epidemic with survival rates that justify ICU care for most patients.
- Diagnoses such as BP, sepsis, and non-AIDS-related conditions have increased in frequency since the introduction of highly active ART.
- Definitive diagnosis of pneumonia is highly recommended in patients with HIV. Early bronchoscopy with BAL should be performed in patients with pneumonia who do not have an established microbiologic diagnosis.
- Despite decreasing numbers of cases of *Pneumocystis pneumonia* (PCP), PCP is still common in HIV-infected patients. It is associated with a high mortality, particularly in those patients with a pneumothorax while on mechanical ventilation. Many patients admitted with PCP are not aware of their HIV status.
- First-line treatment for PCP is intravenous trimethoprim/ sulfamethoxazole, although many patients develop side effects. Corticosteroids should be given to those meeting oxygenation criteria.
• IRIS can result in pneumonitis, meningitis, hepatitis, and pericarditis. Respiratory failure is most often from tuberculosis and PCP. The syndrome occurs after starting ART and needs to be distinguished from acute OIs.

• Patients can develop fatal lactic acidosis as a result of antiretroviral medications. Treatment consists of drug discontinuation. Administration of riboflavin, thiamine, and L-carnitine might be helpful but is unproven.

• Coinfection with HIV and hepatitis C is increasingly common and can complicate ICU care.

• Administration of ART in the ICU is challenging because of the multiple side effects and drug interactions, difficulty with administration of oral medications, and the possibility of inducing viral resistance; however, use of these medications may be beneficial in certain patients.

References


