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Critical Care of Persons Infected with the Human Immunodeficiency Virus

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INTRODUCTION

Individuals infected with the human immunodeficiency virus (HIV) who are admitted to the intensive care unit (ICU) can be grouped into 3 distinct populations. The first group includes individuals admitted to the ICU with an AIDS-related opportunistic infection (OI) such as *Pneumocystis jirovecii* pneumonia (PCP). Antiretroviral therapy (ART) has had a dramatic effect in reducing the incidence of OIs for those patients who have access to care and who are adherent to therapy. However, in the United States, only about 20% of patients are well controlled virologically.¹ The others are unaware of their HIV status, do not have access to care, or are not successfully controlled because of adherence challenges or other issues. Thus, many hospitals continue to see OIs, especially in the 12 US cities that are home to 50% of the total HIV population.² Intensivists must be well versed in the management of AIDS-related OIs. The second group is those who are immunologically reconstituted but receive care in the ICU for a non-HIV-related condition such as complications of elective surgery, trauma-related admissions, pancreatitis, and gastrointestinal bleeding. Unique challenges faced in this group relate to the management of ART in the ICU, which requires knowledge about how to administer ART to preserve antiretroviral efficacy, the recognition of ART-related toxicities, and a critical understanding of the potential for drug-drug interactions with ICU medications. The third group is those admitted to the ICU for noninfectious complications of HIV/AIDS that are related to the enhanced inflammatory condition observed in patients infected with HIV.³ Accelerated atherosclerotic cardiovascular and cerebrovascular disease and renal, hepatic, and neurocognitive disorders should be recognized as possibly HIV-related, as should solid tumors and hematologic malignant neoplastic diseases that were not traditionally linked to HIV/AIDS. In this review, recent advances in our understanding of immune reconstitution inflammatory syndrome

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(IRIS) are highlighted, management of some OIs is discussed, and the challenges of managing ART in the ICU are addressed.

THE STATE OF HIV INFECTION IN THE UNITED STATES

Although potent ART has been available since 1996, it is estimated that only 1 in 5 persons infected with HIV in the United States is receiving effective therapy and has an undetectable viral load.¹ In the United States, between 22% and 52% of individuals infected with HIV report ART use at ICU admission (Table 1).^{4–10} Hence, not unexpectedly, even in the current ART era, 21% to 44% of all ICU admissions are caused by an AIDS-related illness (see Table 1).^{5,8,9}

San Francisco General Hospital (SFGH) has carefully assessed their ICU admissions over the past 2 decades.^{8–11} At SFGH, admissions to the ICU have declined,⁹ and the spectrum of diseases that necessitate ICU admissions has shifted.^{8–10} More than 60% of the admissions in the current ART era are attributed to a non-AIDS-related diagnosis.^{8,9} Compared with the earliest ART era, in-hospital survival has significantly improved; although this finding could represent a shift in patient demographics, it more likely relates to the shift from AIDS-related to AIDS-unrelated diagnoses in a city in which HIV services are highly developed. However, in more recent years (2005–2009), in-hospital mortality seems to have plateaued.⁹

SURVIVAL

In the combination ART era in the United States, between 56% and 71% of patients infected with HIV survive their stay in the ICU and are discharged alive from the hospital.^{4–10} Similar rates (43%–80%) have been reported from Europe (see Table 1).^{12–20} Survival rates clearly reflect the patient population being served: hospitals serving patients infected with HIV who present with OIs have higher mortality. In Brazil, where a high fraction of ICU admissions are HIV/AIDS-related, only a third survived their hospitalization.²¹ Similarly, in other parts of the world where AIDS-related admissions predominate, mortality is higher.^{22,23}

In the United States and Great Britain, short-term outcomes for patients infected with HIV and uninfected patients admitted to the ICU seem similar.^{6,12,15} A 2007 British study reported similar survival rates among adult patients infected with HIV and uninfected adult patients admitted to a London ICU for a general medical condition of 65% and 68%, respectively.¹⁵ In a US study that examined patients with acute lung injury, survivors infected with HIV and uninfected survivors spent similar number of days in the ICU (median length of stay: 12 vs 15 days) and in the hospital (median length of stay: 29 vs 25 days). ICU and hospital mortality were also comparable between the 2 groups, with 56% of the individuals infected with HIV and 61% of uninfected individuals surviving their hospitalization.⁶

ART use seems to positively affect long-term survival.^{9,14,24} The effect of ART on short-term outcomes is mixed, with some studies showing improved outcomes with ART use, whereas others have failed to show a benefit.^{8,10,12} Table 1 and Fig. 1 detail overall survival rates and survival by ART use.

SPECTRUM OF DISEASES NECESSITATING ICU ADMISSION

Respiratory failure remains the most common reason for ICU admissions for patients infected with HIV, accounting for 30% to 40% of all ICU admissions.^{4,7,8,10,12,14,15,19} However, the proportion of ICU admissions related to respiratory failure has been

decreasing. In a series from San Francisco, ICU admissions related to respiratory distress declined from 52% in 2000 to 34% in 2004.⁸

The cause of respiratory failure varies according to ART use. Although overall rates of respiratory failure caused by PCP have declined, among untreated individuals, PCP remains the leading cause of respiratory failure.^{7,8,10,12} *Streptococcus pneumoniae* is also a common cause of pneumonia and respiratory failure.¹³ Tuberculosis (TB) and fungal diseases are not common causes in most parts of the United States, unless there is an unusual demographic. Some pathogens that can cause substantial pulmonary morbidity in other populations, such as cytomegalovirus (CMV), atypical mycobacteria, or herpes simplex virus (HSV), are uncommon causes of clinically significant pulmonary disease among individuals infected with HIV.¹³ Among ART-treated individuals, respiratory failure is often caused by complications associated with entities common in the general population, such as cardiogenic pulmonary edema, chronic obstructive pulmonary disease, community-acquired pneumonia, or adult respiratory distress syndrome caused by sepsis or trauma.^{8,13} Sepsis accounts for between 15% and 30% of all ICU admissions for persons infected with HIV.^{7,8,14,23} The causes of sepsis mirror the general population. Neurologic problems, such as AIDS-related cryptococcal meningitis (CM) and AIDS-unrelated events such as intracranial hemorrhage, account for 12% to 26% of all ICU admissions.^{4,8,10,12,14,19} About half of the ICU admissions are now non-AIDS-related.^{7-10,12,24} Non-AIDS admissions are varied in their cause and include admissions for gastrointestinal bleeding, cardiac disorders, metabolic complications, or those that follow elective surgery and trauma. The epidemiology and demographics of such patients mirror the HIV-uninfected populations.

RESPIRATORY DISTRESS

Intensivists need to clearly understand the relationship of recent CD4 count to the likely cause of respiratory disease. Although CD4 counts are not absolute indicators of susceptibility, in HIV disease they are extremely sensitive and specific markers for susceptibility to opportunistic pathogens. For example, PCP is more likely at a CD4 count less than 200 cells/ μ L compared with patients with higher CD4 counts.²⁵

Patients admitted to the ICU with severe respiratory failure and HIV/AIDS are often assumed to have an infectious cause and are treated accordingly, yet intensivists must be vigilant to recognize noninfectious causes, many of which are similar to the HIV-uninfected population.^{6,13} Patients infected with HIV are not any less susceptible than the general population to non-OIs such as influenza, respiratory syncytial virus, atypical pneumonias, exacerbations of chronic obstructive lung disease, asthma, ischemic cardiac disease, or to the occurrence of pulmonary emboli. Some noninfectious entities may occur more frequently in patients infected with HIV, such as congestive heart failure related to accelerated ischemic heart disease despite apparently adequate HIV viral suppression, or AIDS-related or ostensibly non-AIDS-related malignant neoplasms.^{26,27}

Pulmonary Kaposi sarcoma (KS) and lymphoma are well recognized to occur with enhanced frequency among patients infected with HIV and can be confused with infectious processes when they occur in the lungs. KS can present as diffuse infiltrates, and the disease is often more subacute than typical bacterial or viral pneumonias. Patients may not have apparent cutaneous lesions.²⁸ Classically, pulmonary KS has been associated with bloody pleural effusions, but many patients do not have these effusions. The diagnosis can be established by visualizing endobronchial lesions and ruling out concurrent infections. Pulmonary KS is generally treated with systemic chemotherapy such as liposomal doxorubicin. Pulmonary lymphoma is often but not invariably associated with mediastinal adenopathy and

extrapulmonary disease, but biopsy is required to establish this as the cause of pulmonary dysfunction, and concurrent infection must be ruled out.

Primary effusion cell lymphoma (PEL) is closely associated with HIV/AIDS. This unusual lymphoproliferative disorder is etiologically linked to human herpes virus 8.²⁹ Classic PEL originates in the serosal surface and can involve the pleura, pericardium, and peritoneum. Patients present with dyspnea, and radiographic imaging shows the presence of pleural/pericardial effusions usually without any accompanying parenchymal findings. The pleural fluid is exudative and shows the presence of malignant cells. Although a variety of approaches have been attempted, treatment of PEL is not highly effective.

When patients infected with HIV are admitted to the ICU with respiratory compromise or failure, the strategic management approach is not dramatically different from HIV-uninfected patients. In each population, there is an urgency to obtain a specific diagnosis so that therapy can be directed and not overly broad. If the patient seems to have an infectious process after blood cultures are obtained, and the patient can produce sputum, a conventional battery of stains, cultures, and molecular tests should be performed to assess the cause. If this strategy does not yield a pathogen, bronchoalveolar lavage usually suffices to identify the most likely bacterial, fungal, viral, and mycobacterial pathogens. Patients infected with HIV have a wider differential diagnosis such that additional tests for pathogens such as *Pneumocystis*, *Histoplasma*, and *Mycobacterium tuberculosis* must be added depending on the clinical presentation and the epidemiology of the patient.

When there is suspicion of a noninfectious process in patients with HIV/AIDS, the diagnostic approach needs to focus on modalities that detect the cardiac, neoplastic, embolic, or other processes that might be involved. Similarly, in terms of empiric therapy, the approaches should follow the options discussed in the accompanying article on evaluation of respiratory disease in HIV/AIDS elsewhere in this issue by Laurence Huang.

Intensivists need to be cognizant of the possibility that patients infected with HIV may need to be placed in respiratory isolation. TB is a consideration depending on patient demographics and exposures. Among patients infected with HIV residing in the United States without obvious exposure, TB is surprisingly rare. Most cases among patients infected with HIV occur in those coming from endemic areas who reactivate their TB in the United States.³⁰ However, the principle remains that respiratory isolation should be carefully considered for all patients with HIV/AIDS admitted to the ICU with apparent respiratory infection. For a more detailed review on specific pneumonias and respiratory disorders, the reader is referred to other articles elsewhere in this issue.

SEPSIS

When patients infected with HIV or uninfected patients present with distributive shock, sepsis is the most likely explanation. However, in approaching such patients, intensivists need to consider HIV-related syndromes that may masquerade as sepsis, such as IRIS.

In the combination ART era, sepsis-related admissions seem to be increasing.^{8,14} In a French study,¹⁴ the relative proportion of patients who had sepsis listed as the main indication for their ICU admission increased from 3% in the precombination ART era to 22.6% in the postcombination ART era. The cause, diagnosis, and management of sepsis in patients with HIV do not differ substantially from other patient populations with similar non-HIV-related risk factors. Patients infected with HIV who are intravenous drug abusers or who have indwelling intravascular catheters develop infections caused by *Staphylococcus epidermidis*, *Staphylococcus aureus*, or gram-negative bacillary sepsis just as HIV-uninfected patients do.⁵ Patients who are admitted to the ICU with non-HIV-related

problems such as pneumonia, urosepsis, biliary complications, or diverticulitis, for example, develop the complications expected by the anatomy and microbiology of their disease.

Patients infected with HIV are predisposed to some causes of bacterial sepsis. In the United States, the introduction of ART has resulted in declines in the rates of invasive pneumococcal disease; nevertheless, the risk of invasive pneumococcal infection remains substantially higher in individuals when compared with uninfected individuals.³¹ Although *Streptococcus pneumoniae* is most common in patients infected with HIV with CD4 counts less than 100 cells/ μ L, pneumococcal pneumonia and pneumococcal sepsis occur with enhanced frequency, and perhaps with enhanced severity, at every CD4 count stratum. Fungi are also occasional causes of sepsis in patients with HIV infection.⁵ *Cryptococcus* and histoplasma are important causes of fungemia, especially in patients with CD4 counts less than 100 cells/ μ L. Not all patients with cryptococcal sepsis have obvious clinical signs of meningitis. Histoplasma is especially common in certain geographic areas in the United States such as the midwest.³² Although mucosal disease caused by *Candida* is common in patients infected with HIV, invasive disease is unusual unless there is concurrent intravenous drug abuse or an indwelling intravenous catheter.

There are reported cases of distributive shock in patients infected with HIV caused by *Pneumocystis*, CMV, varicella zoster, HSV, *Bartonella*, *Rhodococcus*, acute HIV infection, and many other organisms.⁵ However, such causes of sepsis are unusual, and they are usually suggested by the presence of other typical manifestations such as skin lesions (*Bartonella*, zoster, or HSV), pneumonia (*Rhodococcus*), or specific end-organ damage (CMV).

The management of sepsis for patients with HIV infection should not differ from principles followed for HIV-uninfected patients. The use of fluids, pressors, and antibiotics should follow guidelines for surviving sepsis.³³ Whether patients with HIV infection are more likely to benefit from steroid supplementation than HIV-uninfected patients is unknown. Steroids seem to improve the responsiveness of HIV-uninfected patients to sepsis-related fluid resuscitation.³³ However, their use in the general population remains controversial, because their administration has not been shown to have survival benefit.³⁴

As described later, other entities specific to HIV/AIDS can present as shock, including distributive shock. These entities include: (1) abacavir hypersensitivity reactions, which present with fever and rash, and are rare in the era of HLA testing³⁵ (2) lactic acidosis/hepatic steatosis, which is also unusual in this era because the major offending drugs (ie, DDI, D4T, and DDC) are rarely used³⁶; (3) IRIS, which occurs in the days or months after initial ART is started (discussed in further detail later)³⁷; (4) multicentric Castleman disease, which is usually more subacute than bacterial or fungal sepsis.³⁸ but can present with a picture that resembles a systemic inflammatory response syndrome characterized by high fevers and cytopenias accompanied by lymphadenopathy, weight loss, and high circulating human herpesvirus 8 levels.³⁸

NEUROLOGIC COMPLICATIONS

Neurologic issues are often cited as the primary reason for an ICU admission in individuals infected with HIV.^{8,10,14,19} Neurologic complications can result from OIs such as toxoplasma encephalitis (TE), CM, or IRIS, or may be related to conditions that are unrelated to the underlying HIV status such as seizures related to alcohol withdrawal, community-acquired bacterial meningitis, viral encephalitis, or trauma.³⁹

For HIV-related OIs, the most common presenting syndromes are meningitis, space-occupying lesions with or without seizures, and nonfocal cognitive decline. For each

syndrome, knowledge of the most recent CD4 count, recent exposures, and concurrent medications (especially those recently started) help considerably in narrowing the differential diagnosis. The evaluation of stroke syndromes does not differ between patients infected with HIV and uninfected patients. However, clinicians should be aware that patients infected with HIV on ART, even if well controlled, seem to develop accelerated atherosclerosis.^{40,41} Thus, relatively young patients not usually considered to be stroke candidates may present with thrombotic or embolic strokes.^{40,41} Focal neurologic defects are often caused by mass lesions that are easily apparent on contrast-enhanced computed tomography scan or magnetic resonance imaging (MRI). In patients with CD4 counts less than 100 cells/ μ L, the major differential diagnosis is toxoplasmosis versus lymphoma.⁴² The radiologic image does not definitively distinguish one from the other, although certain features such as the presence of multiple ring enhancing lesions favor TE.⁴³ Patients who are seronegative for toxoplasma are unlikely to have central nervous system (CNS) toxoplasmosis, although commercial laboratories may use relatively insensitive enzyme-linked immunosorbent assay tests that give false-negative results in patients who have low titers.^{42,44} Those receiving and adhering to PCP prophylaxis are also unlikely to have TE.⁴⁵ If there is no contraindication to lumbar puncture (LP), a cerebrospinal fluid (CSF) analysis can be helpful. A positive CSF Epstein-Barr virus (EBV) polymerase chain reaction (PCR) test or CSF toxoplasma PCR is suggestive of a diagnosis of primary CNS lymphoma and TE, respectively.⁴⁶ However, there is considerable variability in how these tests are performed, and neither the EBV nor the toxoplasma PCR in CSF should be considered a 100% sensitive or specific test.^{47,48}

For patients with CD4 counts less than 100 cells and space-occupying lesions, most experts empirically treat for 2 weeks with 1 of the recommended antitoxoplasma regimens (sulfadiazine-pyrimethamine, clindamycin-pyrimethamine, or sulfamethoxazole-trimethoprim). If there is a clinical and radiologic response at 2 weeks, a full course of therapy is completed and the diagnosis is presumed to be toxoplasmosis. If there is no convincing response by both radiologic and clinical parameters, a brain biopsy is indicated. For patients who present with a CD4 count greater than 100 cells, the likelihood of toxoplasmosis is remote. Thus, such patients usually proceed directly to biopsy, unless some other test is considered definitive, such as a serum cryptococcal antigen titer. Interpretation of such tests is not straightforward. The advice of an expert should be sought in these cases. Other entities can present as mass lesions, but are less common. TB is always a consideration, although it is uncommon in native-born residents of the United States who have not had an identified exposure. Fungal infections (*Cryptococcus*, *Histoplasma*, *Coccidioides*) should also be considered in the appropriate epidemiologic setting. Non-HIV-related processes such as bacterial brain abscesses and primary and metastatic tumors should also be included in the diagnostic possibilities.

Patients with HIV/AIDS can develop meningitis caused by common community-acquired pathogens such as *Streptococcus pneumoniae*. However, for patients infected with HIV with CD4 counts less than 100 cells/ μ L, CM is a more likely cause. CM is an indolent disease and often presents with fever and headache, but patients can become progressively obtunded over days or weeks as the disease progresses. This subacute process differs in tempo of presentation from the acute presentation of common bacterial and viral pathogens. Patients with CM may have an antecedent pneumonia or skin lesions that are suggestive of disseminated disease.

If there are no contraindications a LP should be performed on all patients with suspected CM. Approximately 20% of patients with CM have a normal CSF formula (ie, normal CSF cell count, protein, and glucose).⁴⁹ Thus, CM cannot be ruled out in patients with normal CSF chemistries and cell counts. The diagnosis is generally established by a positive CSF

cryptococcal antigen test, which is highly sensitive and specific. Because the burden of organisms is high in patients with HIV infection, the India ink test, serum cryptococcal antigen tests, and blood cultures are also positive in a high percentage of patients.⁵⁰

The treatment of choice for CM is amphotericin B with or without flucytosine.⁵¹ Lipid formulations of amphotericin B are efficacious and should be used in preference to conventional amphotericin B, especially in patients at risk for renal insufficiency. Fluconazole is used for therapy in many parts of the world, but is inferior to liposomal amphotericin in terms of efficacy and should not be the drug of first choice in the United States.⁵²

Increased intracranial pressure should be managed aggressively. If the opening pressure is greater than 250 mm H₂O, CSF drainage is indicated until the pressure is less than 200 mm H₂O, or to 50% of the initial opening pressure.⁵¹ LPs should be performed daily if CSF pressures are increased and until they normalize.⁵¹ There is no indication to treat patients with CM with corticosteroids.

When patients present with progressive cognitive decline, 3 entities should receive primary consideration: progressive multifocal leucoencephalopathy (PML), HIV encephalopathy, and CMV encephalitis. PML is an OI caused by the polyoma virus (JC virus). PML manifests with focal neurologic signs and symptoms. The symptoms are often insidious in onset, with symptoms progressing over weeks. The neuroradiologic features of PML are distinct and help differentiate this condition from other conditions such as TE and CNS lymphoma.^{53,54} The white matter lesions are usually hyperintense on T2-weighted imaging and hypointense on T1-weighted imaging. In the precombination ART era, the CSF PCR was often positive for JC virus DNA, but the predictive value of the CSF PCR has been reported to be lower in the postcombination ART era.^{55,56} The only effective treatment of PML is ART.⁵⁰ HIV encephalopathy presents with progressive cognitive impairment over weeks or months, without the focal motor and sensory defects seen in PML. CNS imaging shows no enhancing lesions, but enlarged ventricles and cortical atrophy. The only effective therapy is ART, which may stabilize the progression or be associated with modest improvement in cognitive function. CMV encephalitis presents more acutely than HIV encephalopathy and is more likely to present with delirium, confusion, and focal neurologic signs and symptoms.⁵⁷ CNS imaging is characterized by periventricular enhancement without significant cortical atrophy.⁵⁸ The CSF may show lymphocyte or neutrophil predominance. The CSF PCR for CMV should be positive.⁵⁹ Therapy is not highly effective. Whether combination therapy with ganciclovir plus foscarnet is better than either ganciclovir or foscarnet alone is uncertain.⁵⁰

RENAL INJURY

Compared with HIV-uninfected hospitalized patients, acute kidney injury (AKI) was documented in a significantly greater proportion of hospitalized patients infected with HIV, in the era before widespread use of effective ART, and also more recently (2.9% vs 1% in 1995 and 6% vs 2.7% in 2003).⁶⁰ Between 2000 and 2002, 1 center reported that acute renal disease occurred in 9.4% of ambulatory patients with HIV.⁶¹ Both short-term and long-term mortality is higher among patients infected with HIV who develop AKI.⁶²

Many of the causes of AKI in this patient population are no different from HIV-uninfected patients. Although prerenal causes (infections and sepsis, hypovolemia, cirrhosis) and acute tubular necrosis (ischemic or drug-induced) account for many of these cases,⁶¹ intensivists should be aware of the following specific associations: (1) tenofovir, one of the most commonly used antiretroviral agents, can cause acute renal failure with or without associated Fanconi syndrome.⁶³ (2) crystalluria (both indinavir [rarely used any more] and

atazanavir can cause renal crystals and acute renal failure⁶⁴) (interstitial nephritis caused by indinavir has also been reported); (3) HIV-associated microangiopathy can cause acute or chronic renal dysfunction (this condition is uncommonly seen in patients on effective ART); (4) several drugs used to treat HIV-associated complications are associated with acute renal injury, such as amphotericin B, foscarnet, cidofovir, pentamidine, high-dose trimethoprim-sulfamethoxazole, and acyclovir.⁶¹

ART dosing may need to be modified in patients with AKI. Whereas protease inhibitors (PI), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and integrase inhibitors do not need dose modifications in AKI, all nucleoside and nucleotide reverse transcriptase inhibitors (NRTI) except abacavir need their doses adjusted. Tenofovir should not be used in patients with an estimated glomerular filtration rate (GFR) less than 50 mL/min. DDI and D4T, although uncommonly used nowadays, should also be discontinued. AZT (zidovudine) should be discontinued in patients with an estimated GFR less than 10 mL/min. Because most fixed-dose combinations include tenofovir, they cannot be used in patients with estimated GFR less than 50 mL/min.

Hepatic Failure

Liver disease is the leading cause of death in some recent series of patients infected with HIV.^{65,66} Chronic viral hepatitis is a common coinfection in patients, and is an important cause of liver-related morbidity and mortality in this patient population.^{65,67} Alcohol use is frequent in this population and also contributes to liver-related mortality.⁶⁷ Although previous studies suggest that the prolonged exposure to antiretrovirals increases the risk of liver-related deaths, a 2012 report suggests that liver-related death caused by ART-related toxicities in HIV-monoinfected patients is rare.^{65,68} Intensivists should recognize some unique associations with HIV that may result in increases of liver-related enzymes. For patients who are not on ART, and who have relatively low CD4 counts, OIs of the liver are not common, but do occur. Disseminated fungal disease (*Cryptococcus*, *Histoplasma*, other yeasts and molds), toxoplasma, and mycobacteria can involve the liver. OIs in the gastrointestinal lumen, such as cryptosporidia and microsporidia, can gain access to the biliary and pancreatic ducts, causing cholecystitis, cholangitis, and pancreatitis. CMV can also cause either hepatitis or cholangiopathies. Neoplastic processes such as lymphoma and KS can occasionally invade the liver as well.

Drugs are a common cause of acute liver injury. Common offenders for patients with HIV are isoniazid, fluconazole, and trimethoprim-sulfamethoxazole. None of the antiretrovirals in common use has high rates of hepatotoxicity. The hepatic steatosis and lactic acidosis seen with DDI, DDC, and D4T are now rare, because these drugs are used so uncommonly.⁶⁹ Nevirapine-induced immune-mediated liver injury can be averted by avoiding nevirapine in women with a CD4 count greater than 250 cells/ μ L or in men with CD4 counts greater than 400 cells/ μ L.⁷⁰ Intensivists should also be aware that patients starting ART who are hepatitis B antigen-positive or PCR-positive may develop a severe flare of their hepatitis. This reactivation of hepatitis B is likely caused by the suddenly enhanced immunologic function induced by ART. Discontinuation of drugs with activity against hepatitis B virus (HBV) such as tenofovir or lamivudine or emtricitabine can lead to flares in the underlying hepatitis B and severe liver failure.⁷¹ Hence, discontinuation of ART with anti-HBV activity should be avoided in hepatitis B coinfecting individuals.

ADMINISTRATION OF ART IN THE ICU

Continuation of ART for Admitted Patients Who Have Been on Stable Regimen

The administration of ART in the ICU is not easy to accomplish. Almost all antiretroviral drugs are available only in oral formulations (only zidovudine and enfuvirtide are available

for parenteral administration). Patients in the ICU often have disrupted gastrointestinal motility. Administration of antiretroviral drugs to patients with uncertain gastrointestinal absorption may lead to suboptimal drug serum levels, which can lead to drug resistance and complicate future options. Drug levels may also be altered by drug interactions related to the urgent administration of drugs in the ICU. Stopping drugs safely to minimize the effects on ART efficacy requires sophisticated knowledge of drug pharmacokinetics. Although it may be safer to stop ART in the ICU, there are immunologic disadvantages related to HIV management to stopping drugs even for a short period. Moreover, for certain subpopulations of patients, such as those with hepatitis B infection, stopping antiretroviral drugs that are also active against HBV can lead to life-threatening flares of previously suppressed infection.⁷¹ The decision to continue or discontinue ART depends on why the patient was admitted to the ICU, the severity of the acute illness, and multiple other factors that must be individualized for each patient.

Initiating ART in the ICU

ART is infrequently initiated in the ICU setting. For ART to be effective, patients need to be committed to adhering to lifelong therapy, a decision that is difficult to arrive at in the setting of an acute illness. The regimen must be appropriate for the patient's individual health status, and renal and hepatic function, which may also be difficult to predict in the ICU. Drug interactions must also be carefully considered, and it is often unclear what medical regimen the patient will receive on hospital discharge. Thus, initiating therapy in the ICU is fraught with hazards. For patients who are admitted to the ICU with a non-AIDS-related illness, there is no urgency to start ART in terms of days or even a few weeks.

For patients in the non-ICU setting receiving care for HIV/AIDS-related OIs, there is a growing body of literature⁷² suggesting that early initiation of ART (ie, within 2 weeks of initiating OI therapy) is preferable to late initiation of ART. Numerous studies (conducted in both resource-rich and resource-constrained environments) have reported a survival benefit among patients initiating ART early.^{73–76} The greatest benefits were observed in those with CD4 counts less than 50 cells/ μ L, the same group with the greatest risk of IRIS.^{73,75} Exceptions seem to be patients undergoing treatment of Cryptococcal and TB meningitis; in these patients, the data do not support early initiation of ART, and early initiation of ART seems to be harmful in patients with CM.^{77,78}

Several features of these studies reduce their generalizability to an ICU population. These studies generally excluded patients who were critically ill, and none included patients who required mechanical ventilation. Thus, the relevance of study conclusions for patients in the ICU is suspect. Given these challenges, the decision to initiate or discontinue ART in a critically ill patient should not be taken lightly and expert consultation with an infectious diseases specialist should be sought when initiating ART in a critically ill patient.

CHALLENGES ASSOCIATED WITH THE CONTINUATION/INITIATION OF ART

Drug Interactions

Whereas drug interactions are infrequent with NRTI, they occur commonly with NNRTIs and with PIs. Neither maraviroc (a C-C chemokine receptor type 5 inhibitor) nor raltegravir (an integrase inhibitor) significantly affects the levels of other drugs. Table 2 summarizes some commonly observed drug-drug interactions.

IRIS

In about 10% to 40% of individuals infected with HIV, the introduction of ART is associated with paradoxical worsening of signs and symptoms. This phenomenon can be life-threatening, and is referred to as IRIS. IRIS represents an exaggerated inflammatory response commonly to an infectious agent and is caused by the recovery of pathogen-specific T-cell responses. This syndrome occurs most often in the first few days or weeks after initial ART is started, and most typically occurs in patients with very low CD4 counts (<100 cells/ μ L) and high HIV viral burdens.^{37,79} Manifestations may include fever, myalgias, and other nonspecific signs of inflammation. Patients may also present, although more infrequently, with life-threatening pulmonary dysfunction, vision-threatening retinitis, meningitis, or distributive shock, depending on which opportunistic pathogens are latent or subclinically active. There is no clinical or laboratory test that distinguishes IRIS from an infectious or neoplastic process, or from a drug toxicity. IRIS is a diagnosis of exclusion, and thus most patients must be managed as if they have an acute infectious process until appropriate tests and clinical monitoring make such diagnoses unlikely.

The overall mortality associated with any type of IRIS is estimated to be 5% but varies according to the patient's baseline immunologic and virologic status and the specific opportunistic pathogen involved.⁸⁰ Whereas nearly 21% of those with CM-associated IRIS died, the risk of death in patients diagnosed with TB IRIS was significantly lower, at about 3.5%.⁸⁰ IRIS that is not severe should be managed symptomatically with nonsteroidal antiinflammatory agents while continuing ART. Severe IRIS symptoms can be treated with prednisone or methylprednisone at a dose of 1 mg/kg, with a gradual taper after 1 to 2 weeks.

Life-Threatening ART-Related Toxicities

Life-threatening ART-related toxicities include hypersensitivity reactions, lactic acidosis, severe hepatitis, and acute renal failure. These toxicities and the offending drugs are summarized in Table 3.

SUMMARY

Critical care of the patient infected with HIV is not dissimilar from HIV-uninfected patients. The differential diagnosis must take into account the patient's immune status (ie, CD4 counts). At CD4 counts less than 200 cells/ μ L, OI, AIDS-defining malignancies should be considered, and at higher CD4 counts, the differential is similar to that in an uninfected patient. IRIS, unique ART-related toxicities, such as abacavir-induced hypersensitivity reaction, should be considered in the differential. In general, the use of ART in the ICU requires a nuanced approach, and whenever possible ART should be initiated in consultation with an HIV specialist.

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KEY POINTS

- In the current antiretroviral therapy (ART) era, the spectrum of illnesses that necessitate admissions to an intensive care unit (ICU) in persons infected with the human immunodeficiency virus (HIV) has shifted; non-AIDS events account for more than half of all ICU admissions in the United States. AIDS-related opportunistic infections remain an important cause of admissions in newly diagnosed individuals and those not on ART.
- Noninfectious complications of HIV/AIDS, such as accelerated atherosclerotic cardiovascular disease and malignancies, must be retained in the differential while evaluating the critically ill patient infected with HIV.
- Immune reconstitution inflammatory syndrome associated with ART initiation and ART-related toxicities may necessitate ICU admission and should be recognized.
- ART should rarely be initiated in the ICU. For patients who are receiving ART, therapy should be continued in most patients who are likely to absorb oral medications, but such decisions and strategies should be developed with an expert.

Fig. 1.

ICU/in-hospital survival rates in critically ill ART-treated and ART-untreated individuals. ^a Significant differences were observed by ART use.

Table 1
Outcomes and characteristics of critically ill persons infected with HIV admitted to the ICU

Reference	Year Studied	Sample Size	Overall ICU/ Hospital Survival (%)	Survival in ART Treated (%)	Survival in ART Untreated (%)	AIDS-Related Admission (%)	Newly Diagnosed HIV Infection at Hospitalization (%)	% on ART at ICU/ Hospital Admission
United States								
Morris et al, 2002 ¹⁰	1996–1999	295	71 ^a	80 ^a	69 ^{a,b}	37	5.6	25
Khouli et al, 2005 ⁴	1997–1999	259	70/61	51/56	49/44	60	NA	48
Narasimhan et al, 2004 ^{7, c}	2001	53	71 ^a	71 ^a	49 ^{a,b,d}	33	NA	52
Powell et al, 2009 ^{8, e}	2000–2004	281	69 ^a	70 ^a	67 ^a	21	NA	33
Mendez-Tellez et al, 2010 ^{6, f}	2004–2007	66	59/56	60 ^a	54 ^a	NA	9	38
Greenberg et al, 2012 ^{5, e,g}	2006–2009	120	58 ^a	64 ^a	55 ^a	44	11	22
Yoon et al, 2011 ⁹	2005–2009	219	68 ^a	NA	NA	24.8	NA	51
Europe								
Casalino et al, 2004 ¹⁴	1995–1996	196	77 ^e	80 ^{d,e}	73 ^{d,e}	58	42	3
	1997–1999	230				37	40	28
Vincent et al, 2004 ¹⁸	1995–1996	189	74 ^e	75 ^{d,e}	73 ^{d,e}	55	20	3
	1998–2000	236				50	28	50
Palacios et al, 2006 ¹⁷	1990–1996	17	33 ^a	60 ^a	40 ^a	47 ^h	35	NA
	1997–2003	49	43 ^a			61 ^h	31	31
Dickson et al, 2007 ¹⁵	1999–2005	102	76/66	78/67	75/66	67 ^h	27	37
Barbier et al, 2009 ^{13, f}	1996–2006	147	88/80	70 ^a	85 ^a	50	29	29
Van Lelyveld et al, 2011 ²⁰	1990–1996	47	53/40	65/45	71/61	55	16	0

Reference	Year Studied	Sample Size	Overall ICU/ Hospital Survival (%)	Survival in ART Treated (%)	Survival in ART Untreated (%)	AIDS-Related Admission (%)	Newly Diagnosed HIV Infection at Hospitalization (%)	% on ART at ICU/ Hospital Admission
	1996–2002	42	59/45			52	8	26
	2003–2008	38	79/66			47	15	47
Morquin et al, 2012 ¹⁹	1997–2008	98	63/47	61 ^e	63 ^e	26	8	45
Adlakha et al, 2011 ¹²	1999–2005	102	79/72	87/80 ^b	75/67 ^b	67 ^h	27	37
	2006–2009	90				34 ^h	10	60
Asia and South America								
Vargaz-Infante et al, 2007 ²²	1986–1993	16	13 ^e	Not applicable	13 ^e	94	25	0
	1993–1996	22	29 ^e	Not applicable	29 ^e	76	48	0
	1996–2006	53	57 ^e	NA	NA	77	26	28
Croda et al, 2009 ²¹	1996–2006	278	45/33	47 ^e	42 ^e	81	38	45
Chiang et al, 2011 ²³	2001–2010	135	63/51	NA	NA	NA	44	36

Abbreviation: NA, data not available.

^aSurvival to hospital discharge.

^bP value significant.

^cCompared precombination and postcombination ART patients: compared 65 admissions between 1991 and 1992 with 63 admissions in the combination ART era (2001).

^dPrecombination and postcombination ART eras were compared.

^eICU survival.

^fAll admissions in this series were for acute lung injury.

^gAll admissions in this series were for a diagnosis of sepsis.

^hHIV-related but not necessarily AIDS-related admissions.

Table 2

Common drug-drug interactions observed in the ICU setting

Drug-Drug Interactions of Commonly Used PIs and NNRTIs ^a	Notes
Proton-pump inhibitors (PPI) Both atazanavir (ATV) and rilpivirine require a low gastric pH for their absorption. Concomitant use of PPI reduces levels of both drugs	Rilpivirine: should not be used with PPI Unboosted ATV: should not be used with PPI Boosted ATV: boosted ATV and a PPI should be used only in PI-naïve patients. PPIs should be avoided in PI-experienced patients who are receiving boosted ATV. The PPI dose should not exceed the equivalent of 20 mg omeprazole, and the 2 drugs should be administered at least 12 h apart
Warfarin ATV ± r: warfarin possible LPV/r: warfarin possible DRV/r: , warfarin Efavirenz: / , levels of warfarin Etravirine: warfarin possible Rilpivirine: no interactions identified	Monitor international normalized ratio closely when stopping or starting these drugs, and adjust warfarin dose accordingly
Anticonvulsants Carbamazepine ATZ/r, LPV/r: may PI levels substantially DRV/r: carbamazepine area under curve 45%; DRV: no significant change Efavirenz: carbamazepine and efavirenz levels when used concomitantly Etravirine: carbamazepine and etravirine possible Rilpivirine: rilpivirine possible	Consider alternative anticonvulsants when used with ATZ/r or LPV/r; if they are used together, anticonvulsant levels should be monitored When used with DRV/r, monitor anticonvulsant levels and adjust dose accordingly When using efavirenz, monitor anticonvulsant levels and use alternative anticonvulsants if possible Do not coadminister etravirine or rilpivirine with carbamazepine
Phenobarbital May all PI levels substantially	Consider alternative anticonvulsants with all PIs and efavirenz or monitor levels of both drugs and assess virologic response Do not coadminister with the NNRTIs etravirine and rilpivirine
Phenytoin ATV/r, LPV/r, DRV/r: phenytoin possible PI possible Efavirenz: efavirenz and phenytoin possible Etravirine: phenytoin and etravirine possible Rilpivirine: rilpivirine possible	Consider alternative anticonvulsants with all PIs and efavirenz. If used together monitor anticonvulsant levels and assess virologic response Do not coadminister with etravirine and rilpivirine
Dexamethasone PI levels possible Efavirenz: efavirenz Etravirine: etravirine Rilpivirine: significant	Systemic dexamethasone should be used with caution with all PIs, efavirenz, and etravirine and an alternative corticosteroid should be considered for long-term use More than a single dose of dexamethasone should not be administered to patients on rilpivirine
Fluticasone fluticasone levels with all ritonavir-boosted PIs and decreases in cortisol levels	Coadministration can result in adrenal insufficiency and Cushing syndrome. Do not coadminister unless the benefits outweigh the risks
Benzodiazepines levels of alprazolam, diazepam, triazolam, and midazolam with PIs. These drugs should not be coadministered with PIs Efavirenz: should not be coadministered with oral midazolam, triazolam	Consider use of oxazepam, temazepam, and lorazepam; these benzodiazepines are metabolized through non-CYP450 pathways and there is less potential for interaction
Salmeterol salmeterol levels possible with all PIs	Do not coadminister with all PIs because of potential increased risk of salmeterol-associated cardiovascular events, including QT prolongation, palpitations, and sinus tachycardia

Abbreviations: ATV, atazanavir; DRV, darunavir; LPV, lopinavir; PPI, proton pump inhibitor; r, ritonavir.

^aThe following boosted PIs are discussed: atazanavir, darunavir, lopinavir. NNRTIs discussed include rilpivirine, efavirenz, and etravirine.

Adapted from Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at: <http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf>. Accessed September 9, 2012.

Table 3

Life-threatening ART toxicities

Life-Threatening Toxicity	Drugs	Comment
Hypersensitivity syndrome	Abacavir and nevirapine have been primarily associated with this syndrome Rare cases have been reported in patients using raltegravir	Abacavir hypersensitivity syndrome often presents with fever and rash. The syndrome can mimic sepsis. The syndrome usually occurs within the first 6 weeks of initiating abacavir in individuals who are HLAB5701 positive. Screening for the presence of HLAB5701 is recommended in all patients initiating abacavir. Abacavir should be avoided in HLAB5701-positive individuals Nevirapine hypersensitivity presents with rash and hepatotoxicity. Risk is greater in women and highest in the first few months of starting treatment. Nevirapine should be avoided in ART-naïve women with a CD4 count greater than 250 cells/μL or in men with a CD4 count greater than 400 cells/μL
Rapidly ascending paralysis	Stavudine	Mimics Guillain-Barré syndrome
Lactic acidosis	All nucleoside reverse transcriptase inhibitors; D4T>DDI>AZT>tenofovir and abacavir	Lactic acidosis has been reported with all NRTIs, especially with D4T, DDI, and AZT. Usually presents with lactate levels >5 mmol/L. The syndrome is often insidious, presenting with nonspecific signs and symptoms. Modest increases in liver function tests (<10 times the upper limit of normal) often accompany this condition. Rapidly progressive forms of the disease can occur and present with respiratory distress. The offending ART should be discontinued
AKI	Tenofovir, atazanavir, indinavir	Atazanavir and indinavir are associated with urolithiasis, whereas tenofovir-related AKI is often accompanied by evidence of tubular injury
Fanconi syndrome	Tenofovir	Fanconi syndrome is characterized by proximal tubular proteinuria, aminoaciduria, phosphaturia, and glycosuria. It is often reversible with discontinuation of tenofovir
Rhabdomyolysis and creatinine phosphokinase increase	Raltegravir and AZT	5%–13% of patients who are on a raltegravir-based regimen have increased creatinine phosphokinase levels, although clinically significant myopathy and rhabdomyolysis are rare. Cardiomyopathy has not been reported with raltegravir use AZT use has been associated with rare cases of cardiomyopathy
Stevens-Johnson syndrome and toxic epidermal necrolysis	NNRTI: highest incidence with nevirapine PI: darunavir, fosamprenavir, atazanavir	Darunavir and fosamprenavir have a sulfonamide moiety and should be used with caution in patients with known sulfonamide allergies
Hepatotoxicity	Primarily reported with the following agents PI: tipranavir NRTI: DDI, D4T, ZDV NNRTI: nevirapine	DDI and D4T especially when used in combination are associated with hepatic steatosis Long-term DDI use has been linked to noncirrhotic portal hypertension
Pancreatitis	DDI, D4T	Especially in patients receiving a combination of DDI and D4T

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