

REVIEW ARTICLE

CURRENT CONCEPTS

Intensive Care of Patients with HIV Infection

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ANTIRETROVIRAL THERAPY HAS INCREASED THE LIFE EXPECTANCY OF patients who are infected with the human immunodeficiency virus (HIV) and has reduced the incidence of illnesses associated with the acquired immunodeficiency syndrome (AIDS). However, the frequency of pulmonary, cardiac, gastrointestinal, and renal diseases that are often not directly related to underlying HIV disease has increased.¹⁻⁴ Although the guiding principles of management in the intensive care unit (ICU) pertain to critically ill patients with HIV infection, antiretroviral therapy and unresolved questions regarding its use in the ICU add an additional level of complexity to already complicated cases. This review focuses on some of the important clinical problems related to the use of antiretroviral therapy in critically ill patients with HIV infection and on the challenging issues associated with the intensive care of such patients, including legal statutes concerning HIV testing and disclosure, the administration of antiretroviral medications, important potential drug interactions with medications commonly used in the ICU, and controversies surrounding the use of antiretroviral therapy in the ICU.

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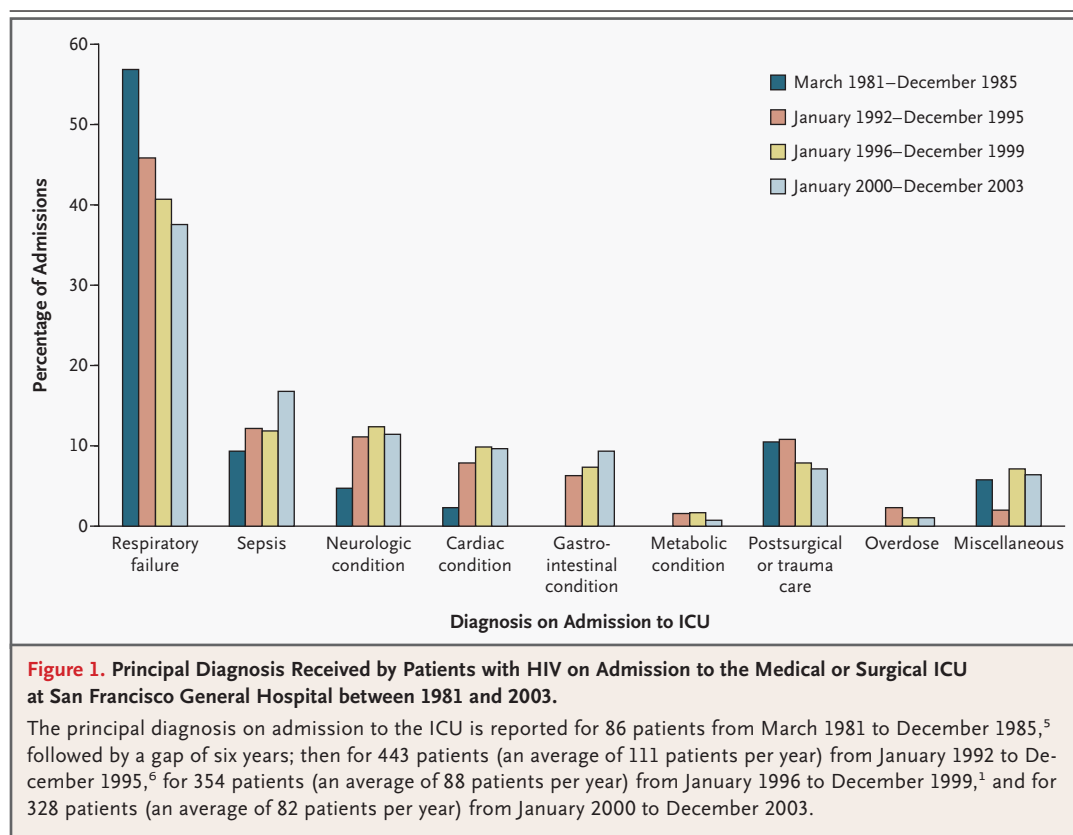
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COMPLICATIONS ASSOCIATED WITH HIV INFECTION

PULMONARY DISEASE

Since the beginning of the AIDS epidemic, respiratory failure has been the most common indication for ICU admission among patients with HIV infection.^{1,3,5,6} However, the proportion of ICU admissions caused by respiratory failure has declined (Fig. 1). Pneumocystis pneumonia, bacterial pneumonia (including that due to methicillin-resistant *Staphylococcus aureus* [MRSA]), and tuberculosis remain important infectious causes of respiratory failure, but non-HIV causes, such as asthma and emphysema, are increasingly common, since patients with HIV infection are living longer.¹⁻⁴ Respiratory failure can also result from immune reconstitution syndromes to pneumocystis pneumonia, tuberculosis, or other mycobacterial disease after the initiation of antiretroviral therapy.⁷⁻⁹ The immune reconstitution syndrome for these pathogens is manifested as paradoxical worsening of the underlying respiratory disease. The syndrome occurs days to weeks after the initiation of antiretroviral therapy and is caused by an exuberant inflammatory response to pneumocystis or mycobacterial antigens. The diagnosis of the immune reconstitution syndrome requires the exclusion of other causes of respiratory decompensation. Treatment includes corticosteroids; even patients with severe cases of the syndrome are able to continue antiretroviral therapy.¹⁰

Patients with HIV infection who also have the acute respiratory distress syndrome (ARDS) requiring mechanical ventilation should receive such therapy according to the ARDS Network guidelines with the use of low tidal volumes and plateau pressures.¹¹ The application of these guidelines is especially crucial in



patients with pneumocystis pneumonia because of the frequent presence of pneumatoceles associated with the infection¹² and the resulting increased risk of pneumothorax during mechanical ventilation.¹³ *Pseudomonas aeruginosa* and *S. aureus* are the predominant causes of nosocomial bacterial pneumonias in patients with HIV infection,^{14,15} just as they are for patients without HIV infection in the ICU. Therefore, the management strategy for hospital-acquired and ventilator-associated pneumonia (including the prevention, diagnosis, and treatment of the condition) is similar to that for patients without HIV infection.¹⁶ The presence of MRSA is an independent risk factor for death in patients with HIV infection and nosocomial pneumonia,¹⁵ which should be considered in the formulation of initial empirical antibiotic regimens.

CARDIAC DISEASE

Antiretroviral therapy is associated with a host of atherogenic metabolic complications, including dyslipidemias, insulin resistance, and diabetes.¹⁷ These therapies may have contributed to the increasing rate of cardiovascular disease among pa-

tients with HIV infection, although traditional risk factors remain the dominant factors.^{18,19} The management of acute coronary syndromes in patients with HIV infection includes coronary-artery bypass grafting and cardiac transplantation in appropriate patients.²⁰ However, restenosis is more likely to develop in patients with HIV infection and acute coronary syndromes who undergo percutaneous coronary intervention than in patients without HIV infection.²¹ Although the precise reasons for the increased rate of restenosis are unclear, consideration of the use of newer, drug-eluting stents, which are associated with a reduced incidence of restenosis, may be practical.

LIVER DISEASE

End-stage liver disease secondary to viral hepatitis has emerged as a frequent cause of morbidity and mortality, and decisions about antiretroviral therapy are intertwined with those regarding hepatitis therapy.^{22,23} Three antiretroviral medications — lamivudine, emtricitabine, and tenofovir — are also active against hepatitis B virus (HBV).²⁴ Owing to high rates of HBV resistance to monotherapy with lamivudine or emtricitabine, clini-

cians should consider combining either of these drugs with tenofovir to reduce the likelihood that resistant HBV will develop. If antiretroviral therapy is initiated in a patient with untreated HIV and HBV infections, clinicians can cotreat HBV by selecting tenofovir and either emtricitabine or lamivudine as two components of the antiretroviral regimen.²⁴ Patients receiving concurrent HIV and HBV therapy who are admitted to the ICU should have these therapies continued if possible, since severe flares of underlying hepatitis B have been reported after the discontinuation of therapy.²⁴

The toxic effects and drug interactions that are associated with pegylated interferon and ribavirin (e.g., severe neutropenia, thrombocytopenia, and dose-related anemia) often preclude treatment in critically ill patients with liver failure associated with hepatitis C infection. Patients who are already receiving therapy for hepatitis C infection should continue to receive therapy, if possible. Patients with HIV infection and end-stage liver disease may be candidates for orthotopic liver transplantation, and referral to a specialty center should be considered.²⁵

The nucleoside reverse-transcriptase inhibitors (NRTIs), especially stavudine, have been associated with the development of lactic acidosis, hepatic steatosis, and in rare cases, acute liver failure.²⁴ In such cases, the mortality rate approaches 50 percent, and antiretroviral therapy should be discontinued immediately if one of these complications arises.

RENAL DISEASE

End-stage renal disease secondary to HIV-associated nephropathy, hepatitis B or C coinfection, diabetes, or hypertension is a frequent cause of morbidity and mortality.²⁶ The management of end-stage renal disease in patients with HIV infection includes dialysis and renal transplantation in appropriate patients.²⁵ Because HIV infection appears to be the cause of HIV-associated nephropathy, patients with this condition should be treated with antiretroviral therapy, which may slow the progression of the disease.²⁶ Corticosteroids may be required in refractory cases.²⁶

HIV TESTING AND DISCLOSURE IN THE ICU

In the current era, up to 40 percent of patients with HIV infection are unaware of their status at

the time of ICU admission.¹⁻⁴ HIV testing and disclosure requirements may present legal barriers that discourage, or even prevent, this testing when patients cannot provide their own consent. Thus, the intensivist may be forced to defer HIV testing until the patient recovers. However, knowledge of a patient's HIV status may influence the differential diagnosis and affect diagnostic and treatment decisions, including the use of antiretroviral therapy. The availability of a rapid HIV test that can provide results within hours has increased the potential usefulness of HIV diagnosis in the treatment of patients.²⁷

All states and the District of Columbia have specific legislation regarding HIV testing, which requires informed consent.²⁸ If a patient is incapacitated, some states permit a surrogate to consent on the patient's behalf. In states without explicit legislation regarding surrogate consent, the hospital's ethics committee or legal representatives should be consulted for guidance. If HIV testing cannot be performed, physicians need to weigh the risks and benefits of diagnostic procedures and empirical therapy without a confirmed diagnosis. These decisions may harm patients with and those without HIV infection. In cases in which HIV testing cannot be performed, well-intentioned physicians may order plasma HIV RNA assays or CD4 cell counts to infer HIV status. This practice is ill advised and may be in violation of legal statutes in some states. Although a normal CD4 cell count argues against the presence of an opportunistic infection such as pneumocystis pneumonia, low CD4 counts, which are characteristic of advanced HIV disease, are often seen in critically ill patients without HIV.^{29,30}

The disclosure of a patient's HIV status requires the consent and participation of the patient. States also have specific (and differing types of) legislation regarding HIV disclosure. In general, physicians may disclose a patient's HIV diagnosis under certain circumstances to a spouse and to the legally designated surrogate. However, it is unclear whether such disclosure is permitted if the patient does not authorize it before becoming incapacitated, particularly if such information is unrelated to decisions by surrogates regarding care. Clinicians cannot disclose a patient's HIV diagnosis to family and friends, unless such persons are the legally designated decision makers. This restriction can result in awkward interactions between ICU staff and patients' loved ones.

HIV-testing requirements pose an additional risk to health care personnel after an occupational exposure. Some states explicitly allow HIV testing after an occupational exposure, whereas others, including New York, prohibit HIV testing without consent. In high-risk cases, exposed workers should receive postexposure prophylaxis. However, the requirement of consent from patients or their surrogates for HIV testing may delay the determination of the patient's HIV status, which can expose workers to the toxic effects of antiretroviral therapy and delay testing for resistance to HIV drugs that might assist in refining therapy.

ANTIRETROVIRAL THERAPY IN THE ICU

The use of antiretroviral therapy in critically ill patients presents distinct challenges related to drug delivery, doses, drug interactions, and antiretroviral-associated toxic effects. Some issues are unique to critically ill patients with HIV infection; others pertain to all patients with HIV infection but are especially important in the ICU.

DRUG DELIVERY, ABSORPTION, AND DOSES

All of the approved antiretroviral medications are dispensed as capsules or tablets, except for enfuvirtide.²⁴ Several drugs are also available as an oral solution, but only zidovudine has an intravenous formulation (Table 1). For medications without an oral solution, capsules can be opened and tablets can be crushed and reconstituted for delivery through a feeding tube, although it remains unclear whether adequate plasma levels are achieved with this approach.³¹ Extended-release and enteric coated formulations should never be crushed, since such action will destroy the enteric coating and will most likely result in decreased plasma levels of the antiretroviral medication.

Critical illness may complicate the absorption of antiretroviral medications, which have been studied primarily in the ambulatory setting. Decreased gastric motility,^{32,33} continuous feeding,³⁴ nasogastric suctioning, and gastric alkalinization for stress-ulcer prophylaxis³⁵ can contribute to variations in the absorption of enteral medications. For example, some antiretroviral medications require the interruption of continuous enteral feeding for optimal absorption, whereas other antiretroviral medications should be taken

with food to minimize adverse effects.²⁴ In addition, histamine₂ blockers and proton-pump inhibitors, which are used for stress-ulcer prophylaxis, are contraindicated with certain antiretroviral medications (Table 1).

The presence of renal or hepatic impairment will affect the dose that is selected for antiretroviral drugs.²⁴ Renal insufficiency will reduce the clearance of all NRTIs except abacavir and will require dose adjustment (Table 1). Patients with renal insufficiency cannot use most of the fixed-dose NRTI combinations. Instead, each medication must be used individually and administered accordingly. Hepatic impairment will reduce the metabolism of many protease inhibitors and nonnucleoside reverse-transcriptase inhibitors (NNRTIs) and may require dose adjustment (Table 1). Finally, the dose of these medications must be readjusted as the patient's renal and hepatic functions change.

DRUG INTERACTIONS AND TOXICITY

Antiretroviral medications, especially NNRTIs and ritonavir-boosted regimens of protease inhibitors, have several important drug interactions with other medications.²⁴ Such interactions involve other HIV-associated medications and common ICU medications (Table 1). For example, the administration of midazolam requires close monitoring in patients who are not dependent on a ventilator and who are receiving NNRTIs or protease inhibitors, since benzodiazepine levels may be markedly increased.

The safety profile of the newer antiretroviral medications is substantially better than that of their predecessors, but the side effects of these agents still pose diagnostic and management challenges in patients in the ICU (Table 2). Although antiretroviral therapy has reduced the incidence of AIDS-related illnesses, it has also resulted in rare but potentially life-threatening toxic effects, such as hypersensitivity reactions, the Stevens-Johnson syndrome, hepatic necrosis, pancreatitis, and lactic acidosis.²⁴ For example, abacavir is associated with a hypersensitivity syndrome that in rare cases can lead to death if the patient is rechallenged with this medication (Table 2). Such a systemic hypersensitivity reaction occurs in approximately 8 percent of patients who receive abacavir; in such cases, symptoms usually develop within six weeks and can include high fever, diffuse rash, nausea, headache, and less

Table 1. Important Characteristics of Antiretroviral Medications.***Oral solution**

NRTIs: abacavir (Ziagen), didanosine (Videx), emtricitabine (Emtriva), lamivudine (EpiVir), stavudine (Zerit), and zidovudine (Retrovir)

Nonnucleoside reverse-transcriptase inhibitors NNRTIs: nevirapine (Viramun)

Protease inhibitors: lopinavir and ritonavir (Kaletra), nelfinavir (Viracept), and ritonavir (Norvir)

Intravenous formulation

Zidovudine (Retrovir)

Drugs requiring dose adjustment in patients with renal insufficiency†

All NRTIs except for abacavir (Ziagen)

Drugs requiring dose adjustment in patients with hepatic impairment‡

Atazanavir (Reyataz), fosamprenavir (Lexiva), and indinavir (Crixivan)

Common ICU drugs contraindicated with NNRTIs

Midazolam§ and triazolam (both with efavirenz)

Common ICU drugs contraindicated with protease inhibitors

Midazolam,§ triazolam, amiodarone (with indinavir, ritonavir, or tipranavir), bepridil (with atazanavir, fosamprenavir, ritonavir, or tipranavir), proton-pump inhibitors (with atazanavir), histamine₂ blockers (if doses are administered twice daily with atazanavir), propafenone (with lopinavir and ritonavir, ritonavir monotherapy, or tipranavir), and quinidine (with ritonavir or tipranavir)

* Data are from guidelines listed on the AIDSinfo Web site.²⁴ NRTIs denotes nucleoside reverse-transcriptase inhibitors, and NNRTIs nonnucleoside reverse-transcriptase inhibitors.

† Patients receiving antiretroviral therapy that includes two or more antiretroviral drugs coformulated into a single tablet (e.g., combivir, consisting of zidovudine and lamivudine) should receive each antiretroviral medication in separate doses.

‡ Tipranavir is contraindicated in patients with moderate-to-severe hepatic impairment. All NNRTIs and protease inhibitors should be used with caution in patients with hepatic impairment. Data are not yet available regarding dose adjustment in this setting for NNRTIs and protease inhibitors that are not listed in the table.

§ Alternatives to midazolam include lorazepam (oral and intravenous), oxazepam (oral), and temazepam (oral). Midazolam can be used with caution as a single-dose agent and be given in a monitored situation for procedural sedation.

commonly, dyspnea. Most symptoms resolve within 48 hours after the discontinuation of abacavir, but continued use may result in progression to respiratory distress and hypotension. If toxic effects of antiretroviral agents are suspected, the offending agent should be discontinued promptly.

TREATMENT STRATEGIES

The lifesaving role of antiretroviral therapy has led to questions concerning the potential treatment of patients with HIV infection in the ICU. Can antiretroviral therapy improve the outcome among critically ill patients? Do the risks associated with these medications outweigh the possible benefits? Should patients who are already receiving antiretroviral therapy continue to receive treatment in the ICU? At the conclusion of the first decade of the era of combination antiretroviral therapy, such important questions remain unanswered. Fueling the debate are compelling ar-

guments for and against the use of antiretroviral therapy in the ICU.

Antiretroviral therapy improves immune function. On the basis of studies conducted in ICUs,¹⁻⁴ the short-term effect of the CD4 cell count and the plasma HIV RNA level on mortality is unclear, although the use of antiretroviral therapy to improve immune function could be beneficial. In chronic HIV infection, improvement of immune function with antiretroviral therapy reduces the risk of opportunistic infections and cancers and is important in the treatment of conditions such as progressive multifocal leukoencephalopathy that otherwise lack effective therapy. This treatment could contribute to a reduction in complications and death in critically ill patients with HIV infection. The decreased toxicity that is associated with the newer antiretroviral medications and combinations further strengthens the argument for the use of such drugs in the ICU. For patients already receiving antiretroviral therapy, the discontinuation of therapy could

Table 2. Potentially Life-Threatening and Serious Adverse Effects of Antiretroviral Agents.*

Life-Threatening or Adverse Effect	Principal Antiretroviral Agent
Systemic hypersensitivity reaction	Abacavir
Stevens–Johnson syndrome or toxic epidermal necrosis	Nevirapine
Hepatotoxicity	All antiretroviral agents, especially nevirapine
Pancreatitis	Didanosine and stavudine
Lactic acidosis syndrome, hepatotoxicity, and hepatic steatosis	NRTIs, especially stavudine, didanosine, and zidovudine
Nephrotoxicity and acute renal failure	Indinavir and tenofovir

* Data are from guidelines listed on the AIDSinfo Web site.²⁴ This table lists only potential life-threatening and serious adverse effects with an onset starting from the initial dose up to months after the initiation of therapy. However, there are several important adverse effects — including cardiovascular effects, hyperlipidemia, insulin resistance or diabetes mellitus, and osteonecrosis — that may result from antiretroviral therapy.

result in the selection of drug-resistant virus, which would render the patients' current regimens ineffective in the future. This is especially true if patients are receiving efavirenz or nevirapine, since these antiretroviral agents have exceptionally long half-lives that may result in functional monotherapy as the levels of other antiretroviral drugs decrease.

Many clinicians argue against the use of antiretroviral therapy in the ICU. Immune reconstitution syndromes could result in a clinical worsening of an already critical disease, and the threat of this syndrome may make physicians reluctant to initiate antiretroviral therapy in the ICU. Drug interactions and toxic effects that are associated with antiretroviral medications can complicate the management of life-threatening conditions. In addition to issues regarding the delivery and absorption of antiretroviral drugs, there are uncertainties surrounding the administration of such medications in patients with acute and multi-organ-system failure. Altered pharmacokinetics caused by malabsorption, organ failure, and drug interactions could place patients at risk for subtherapeutic drug levels and drug resistance or, conversely, suprathreshold levels and adverse effects.

There are no randomized clinical trials and no consensus guidelines to assist in decisions regarding the use of antiretroviral therapy in the ICU. Only a few retrospective studies address some of the clinical issues that practitioners face.

Although we acknowledge that decisions regarding the use of antiretroviral therapy require a case-by-case review, we suggest the following framework (Fig. 2). Patients who are receiving antiretroviral therapy with evidence of virologic suppression (plasma HIV RNA below the limit of detection) before admission to the ICU should continue their antiretroviral regimen, if possible. The patients who continue to receive treatment should have no contraindications to the continuation of treatment, such as interactions between drugs used in the ICU and antiretroviral therapy. In contrast, the benefits of continued antiretroviral therapy in the ICU are less clear for patients with detectable plasma HIV RNA. For these patients, practitioners should consult with an HIV expert.

Patients who did not receive antiretroviral therapy before ICU admission are the largest subgroup of patients with HIV infection admitted to the ICU.¹⁻⁴ Two studies conducted within the past four years suggest that patients who are admitted with an AIDS-defining diagnosis (especially pneumocystis pneumonia) have the poorest prognosis and, theoretically, will receive the greatest benefit from antiretroviral therapy.^{1,41} The only study to date evaluating the effect of combination antiretroviral therapy on an AIDS-related illness in the ICU is a retrospective review of 58 patients with HIV infection who were admitted to the San Francisco General Hospital's ICU with confirmed pneumocystis pneumonia.⁴¹ In this study, the mortality rate was significantly lower among patients receiving antiretroviral therapy than among those not receiving such therapy (25 percent vs. 63 percent, $P=0.03$).

On the basis of limited available data, we suggest the following management principles. Initiation of antiretroviral therapy should be deferred among patients admitted to the ICU with a condition that is not associated with AIDS. Among these patients, the immediate prognosis is generally better than among those with an AIDS-associated diagnosis, and the short-term outcome is most likely related to successful treatment of the underlying non-AIDS condition.¹ However, antiretroviral therapy should be considered if the CD4 cell count is below 200 cells per cubic millimeter and there is a prolonged course in the ICU, since the risk of opportunistic infection is increased among patients whose levels are below this CD4 count. For patients with

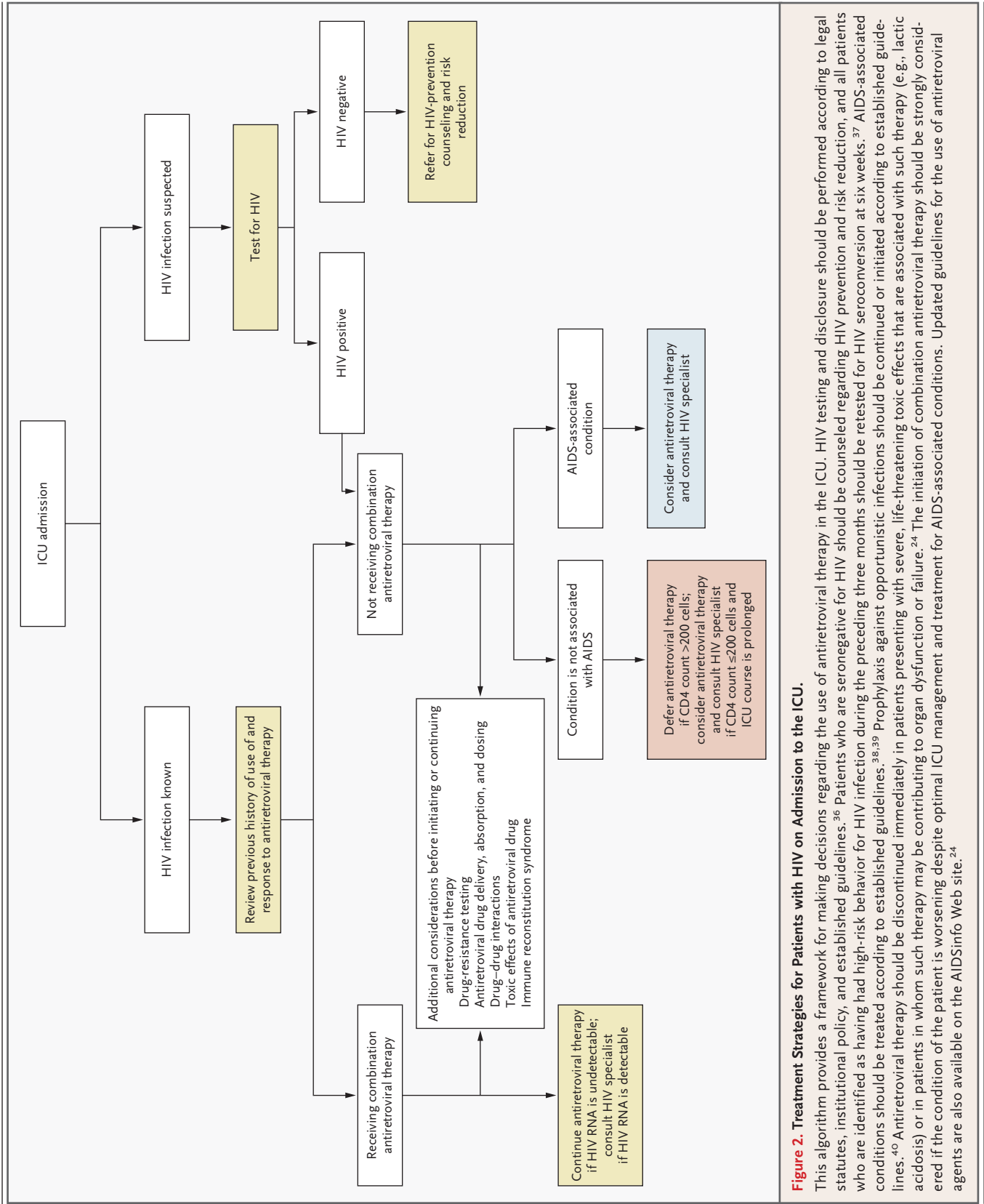


Figure 2. Treatment Strategies for Patients with HIV on Admission to the ICU.

This algorithm provides a framework for making decisions regarding the use of antiretroviral therapy in the ICU. HIV testing and disclosure should be performed according to legal statutes, institutional policy, and established guidelines.³⁶ Patients who are seronegative for HIV should be counseled regarding HIV prevention and risk reduction, and all patients who are identified as having had high-risk behavior for HIV infection during the preceding three months should be retested for HIV seroconversion at six weeks.³⁷ AIDS-associated conditions should be treated according to established guidelines.^{38,39} Prophylaxis against opportunistic infections should be continued or initiated according to established guidelines.⁴⁰ Antiretroviral therapy should be discontinued immediately in patients presenting with severe, life-threatening toxic effects that are associated with such therapy (e.g., lactic acidosis) or in patients in whom such therapy may be contributing to organ dysfunction or failure.²⁴ The initiation of combination antiretroviral therapy should be strongly considered if the condition of the patient is worsening despite optimal ICU management and treatment for AIDS-associated conditions. Updated guidelines for the use of antiretroviral agents are also available on the AIDSinfo Web site.²⁴

a CD4 cell count below 200 cells per cubic millimeter, prophylaxis against opportunistic infections should also be prescribed (e.g., trimethoprim-sulfamethoxazole for pneumocystis pneumonia), as recommended in current guidelines.⁴⁰

In contrast, antiretroviral therapy should be considered for patients who are admitted to the ICU with an AIDS-associated diagnosis. This recommendation especially applies to patients whose physiological condition is worsening despite optimal ICU management and treatment for the AIDS-associated condition. However, there are several important factors to consider before the initiation of antiretroviral therapy, including testing for HIV-drug resistance, antiretroviral pharmacokinetics, drug interactions, and toxic effects. Patients who receive antiretroviral therapy should be followed for the development of the immune reconstitution syndrome.

CONCLUSIONS

Antiretroviral therapy has changed the long-term prognosis and the clinical spectrum of diseases in patients with HIV infection who are admitted to the ICU, and it also presents the potential to influence the outcome in the ICU. However, the optimal approach to patients with HIV infection

in the ICU requires awareness of the complex management issues on the part of both ICU and HIV specialists. Continued progress will occur through the revision of policies surrounding HIV testing and disclosure and addressing unresolved questions regarding the use of antiretroviral therapy in the ICU.

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