17 HIV in ICU

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17.1 Introduction

With the advent of highly active antiretroviral treatment (HAART), screening for opportunistic infections and appropriate treatment for the same, there has been a trend to increased chronicity of HIV infection. Thus, there is an increased exposure of patients to intensive care units (ICU) due to prolonged survival. In the modern era of highly active antiretroviral therapy, clinicians must be aware of traditional opportunistic infections, as well as newer syndromes such as immune reconstitution inflammatory syndrome (IRIS), multicentric Castleman’s disease, and primary body cavity lymphoma. They must recognize the drug toxicities and drug interactions. This chapter aims to address the above issues with a glimpse of the road ahead.

17.2 Epidemiology

As per estimates, 37.9 million people are living with HIV in 2018. Approximately two-thirds are living in Africa and 10% each in Americas and South-East Asia. Estimates of new infections reported was 1.7 million in 2018 with maximum contribution again from Africa. The number of deaths attributed to HIV/AIDS was 0.77 million. It is noteworthy that the majority of patients, new infections and deaths are all reported from resource-limited settings.

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Two major classification systems on HIV diseases are currently in use: the U.S. Centers for Disease Control and Prevention (CDC) (Centers for Disease Control and Prevention 1992) classification system, which assesses the severity of HIV disease by CD4 cell counts and by the presence of specific HIV-related conditions. The definition of AIDS includes all HIV-infected individuals with CD4 counts of <200 cells/μL (or CD4 percentage <14%) as well as those with certain HIV-related conditions and symptoms. The alternate classification being the World Health Organization (WHO) Clinical Staging and Disease Classification System (World Health Organization 2007), which is based on clinical manifestations that can be recognized and treated by clinicians in diverse settings, including resource-constrained settings without access to CD4 cell count measurements or other diagnostic and laboratory testing methods.

Since the introduction of more potent antiretroviral agents in the mid-1990s, it has been apparent to all clinicians that the frequency of opportunistic infections has declined, and patient survival has increased (Palella et al. 1998). The decline in opportunistic infections has been uniform but, some neoplastic complications have not been affected in the same manner (Clifford et al. 2005; Cooksley et al. 1999; Grulich et al. 1999; Mocroft et al. 2004; Parkert et al. 1998; Scadden 2003). Although Kaposi’s sarcoma and primary central nervous system (CNS) lymphoma have declined in incidence, the incidence of non-primary CNS B-cell lymphoma has been stable, and may be increasing in terms of lifetime risk as patients live longer. In addition, it is becoming apparent that unusual tumors linked to human herpes virus 8 (HHV-8) are increasing, such as multicentric Castleman’s disease and primary effusion cell lymphoma (Aaron et al. 2002; Boulander et al. 2005; Lim et al. 2005; Oksenhendler et al. 1996; Simonelli et al. 2003). Solid tumors may also be increasing, such as bronchogenic carcinoma, melanoma, and renal cell carcinoma, although more data are needed to confirm these initial observations (Bower et al. 2003; Herida et al. 2003).

As opportunistic infections have declined, the causes for hospitalization have changed. The proportion of hospitalizations due to respiratory diseases is still considerable, but has been falling (Grubb et al. 2006). The proportion of hospitalizations due to hepatic disease (especially sequelae of hepatitis C), renal disease (consequences of HIV nephropathy and other disorders), and cardiovascular disease has increased. Among pulmonary complications, the incidence of pneumocystis pneumonia (PCP) has declined, and the fraction of PCP cases that require hospitalization, or admission to the ICU, is falling. Thus, the face of HIV infection in the hospital and in the ICU has changed over the past decade.

We must recognize that there are two distinct populations of patients (Fig. 17.1). First, there are patients with access to care and to the full armamentarium of HIV-related drugs. For these patients, survival is longer and opportunistic complications are fewer, as noted above. These patients are more likely to be admitted to the ICU for non-HIV-related problems, or for complications of their HIV drugs. These patients may eventually lose their responsiveness to antiretroviral therapy (ART), but with opportunistic infection prophylaxis, and perhaps with continuation of ART, they appear to have fewer infectious complications.
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**Etiology and Spread**

The HIV epidemic in India is driven by heterosexual sex, which accounted for 87% of new infections. Sex workers, men who have sex with men, people who inject drugs, and transgenders—all four of these groups have been prioritized in the Indian national AIDS response since its inception in 1992.

The epidemiologic profile of patients with HIV infections is shifting. There are a substantial number of homosexual males who are infected in large urban areas, but there is a growing proportion of infected patients who are female, who reside in smaller cities or rural areas, and who have acquired their infection heterosexually or via intravenous drug abuse. The population of HIV-infected patients is also getting older: patients with HIV infection benefit from improved management, and live longer. Individuals without HIV infection are also living longer, and are sexually active longer, extending the period of risk for acquiring HIV infection.

It has been seen that the spectrum of diseases requiring ICU admission is changing in the setting of HAART. Besides, in the HAART era, hospitalization of HIV-infected patients has significantly decreased, but the rate of ICU admissions has not. (Table 17.1).

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**Table 17.1** Table summarizing reasons for increased ICU admissions in HIV patients

| Reasons for increased ICU admissions in ICU despite HAART era |  |
|---------------------------------------------------------------|--|
| 1. About 25–40% of HIV-infected patients were not known to be positive at the time of ICU admission |  |
| 2. Around 50% of patients usually were not found to be on effective HAART during admission |  |
| 3. Number of persons living with HIV has increased as overall survival improved because of effective HAART. So more number of patients living with HIV, is likely to get admitted in ICU |  |
| 4. Many patients are being admitted to ICU for medical and surgical causes unrelated to their HIV infections such as trauma, post-operative care, asthma, renal failure, liver diseases, and surgical causes |  |
HIV patients may be admitted to ICU for many reasons. Acute respiratory failure as a result of opportunistic infections accounts for approximately half (Sarkar and Rasheed 2013) of ICU admissions which itself can have a myriad of etiologies (Fig. 17.2). Other common indications for ICU admission are sepsis and central nervous system (CNS) dysfunction and complications due to Cryptococcal and Candida meningitis, sub acute encephalitis, herpes simplex encephalitis, multifocal leukoencephalopathy (Casalino et al. 2004; Narasimhan et al. 2004).

Health care professionals should recognize that these patients also become hospitalized for the same reasons that HIV-uninfected patients are admitted (i.e., for HIV-unrelated issues, such as trauma, acute infections, chronic pulmonary disease, chronic coronary artery disease, etc.). These patients need the same management strategies as HIV-uninfected patients with a few exceptions.

There are however, some differences in management (Table 17.2) for HIV-infected patients. First, if they are receiving antiretroviral agents, a decision must be made whether to continue the drugs in the hospital (see below) or whether to discontinue them. Second, certain antiretroviral drugs have profound drug–drug interactions that must be considered when prescribing other agents whose pharmacokinetics might be substantially affected. Third, health care providers need to be cognizant that there is nosocomial exposure to percutaneous or mucosal fluids that might be HIV infected; they must take appropriate preventive steps to reduce the likelihood of occupational HIV transmission.
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17.5 **Level of Immunosuppression**

When a patient with HIV infection presents to a health care provider, it is important to recognize that the patient may or may not have an HIV-related problem. Clinicians often assume that such patients have an opportunistic infection, neoplastic problem, or metabolic disorder that is related to HIV infection, yet such patients are also at risk for common processes. Even if the patient is infected, the infectious process may be caused by a common community-acquired pathogen, and not by an opportunistic pathogen.

CD4 T-lymphocyte counts continue to be excellent indicators of the susceptibility of patients to HIV-related opportunistic infections. The key parameter is the current CD4 T-lymphocyte count, not the nadir count from the past. There are subtle differences in immunologic function based on nadir count that can be dissected by laboratory evaluations, but it is not clear that these differences have major clinical implications (Miller et al. 1999).

### Table 17.2

| HIV in ICU—special focus areas |
|--------------------------------|
| 1. Decision to start/continue/stop HAART |
| 2. Drug–drug interactions |
| 3. Opportunistic infections/malignancies |
| 4. Nosocomial spread to doctor/other patients |

17.6 **ART in the ICU**

When HIV-infected patients are admitted to the ICU, a major issue is whether to continue their ART or stop the drugs. Intensivists need to be aware of several important principles.

1. Antiretroviral agents are only available as oral tablets and suspensions, for the most part. Zidovudine and enfuvirtide are the only agents available in parenteral form. Thus, the pharmacokinetics of ART will be unpredictable in severely ill patients, with uncertain gastrointestinal absorption and potential drug interactions.

2. Protease inhibitors and non-nucleoside reverse transcriptase inhibitors are metabolized by the cytochrome p-450 enzyme system. They alter the metabolism of other drugs metabolized by this system, and they themselves will have their pharmacokinetics altered (Boffito et al. 2005; Flexner and Piscitelli 2003). This may lead to drug toxicity or reduced efficacy.

3. For ART, even a few days of suboptimal levels due to poor absorption or pharmacokinetic interactions can have disastrous results (i.e., irreversible drug resistance can occur).

4. Drug toxicities are often difficult to attribute to a specific drug. Thus, when ART is added to a regimen and potential toxicities such as rash, liver function test abnormalities, or elevated amylase level occur, it is difficult to assess whether it is related to the toxicity of ART or to another drug or disease process. Thus,
discontinuing ART simplifies management of clinical issues that could potentially be due to ART.

5. The initiation of ART for patients in the ICU can cause immune reconstitution syndromes (IRS). These can be life threatening and difficult to distinguish from other clinical syndromes, as described below.

17.6.1 Bacterial Infections

Clinicians should recognize that *Streptococcus pneumoniae* continues to be the most common cause of upper and lower respiratory disease in this patient population. Patients have an increased incidence of bacterial respiratory infections at all CD4 T-cell strata, although the incidence does increase as the CD4 T-cell count declines (Wallace et al. 1997).

A single centered Indian study showed that poly-microbial infection was present in around 20% of the cases (Mane et al. 2018). Studies also show that the incidence of MDR Pneumococcal pneumonia has not changed in pre-HAART and post-HAART era, while there is substantial reduction in MDR Pseudomonas infection. Also MDR Pseudomonas infection correlates with CD4 reduction while higher CD4 counts are related to drug susceptible Pseudomonas infections. Significantly high mortality is seen with MDR Staphylococcal, Pseudomonas, and Klebsiella infections (Allen et al. 2003).

*Haemophilus influenzae*, both the encapsulated and nonencapsulated types, is also common. There is a growing literature about the occurrence of pneumonia due to *Staphylococcus aureus*, especially oxacillin-resistant strains, and about *Pseudomonas aeruginosa*, especially among patients with low CD4 T-cell counts (Allen et al. 2003; Mathews et al. 2005). The clinical presentation, diagnosis, and therapy for bacterial pneumonia do not differ substantially for HIV-infected patients compared with HIV-uninfected patients. Bacteremia and extrapulmonary disease appear to be more common, at least for *S. pneumoniae*.

17.6.2 Mycobacterial Infections

In most parts of the world, *Mycobacterium tuberculosis* is a major cause of pulmonary and extrapulmonary disease in patients with HIV infection (Kirk et al. 2000; Lawn et al. 2005). Tuberculosis must be a consideration for every patient who presents with pulmonary disease both to facilitate appropriate therapy and to prevent transmission to health care workers, patients, and visitors.

The recognition and management of tuberculosis is a complex process that, unlike the other bacterial diseases above, has many differences in recognition and management in HIV-uninfected patients. Tuberculosis presents in many typical and atypical forms both for pulmonary and extrapulmonary manifestations. The likelihood of disease is estimated to be 10% per year, as opposed to 10% per lifetime for HIV-uninfected individuals.
Treatment of tuberculosis is complicated by the drug interactions of ART agents and antituberculous agents (Gordin 2003; Dean et al. 2002a). Rifampin, in particular, has complex interactions with the protease inhibitors and non-nucleoside reverse transcriptase inhibitors. ART agents and antituberculous drugs also have overlapping toxicities, especially liver adverse events. There are guidelines recommending the appropriate dose and drug adjustments to be made to standard regimens (Panel on Antiretroviral Guidelines for Adults and Adolescents 2019). Treatment of tuberculosis is also complicated by the occurrence of IRIS (Breen et al. 2004; Michailidis et al. 2005; Navas et al. 2002; Shelburne et al. 2002; Shelburne et al. 2005) which is discussed below. Such syndromes associated with recent tuberculosis can be clinically severe and can make initiation of ART a much more complicated endeavor in regions where tuberculosis is common.

*M. avium* complex clearly causes considerable morbidity in this patient population when patients have CD4 T-cell counts below 50–75 cells/µL. The disease almost always manifests as mycobacteremia, lymphadenitis, or enteritis. Although the lung may be colonized with *M. avium* (i.e., *M. avium* may be readily found in pulmonary secretions), this organism is almost never the cause of pulmonary dysfunction. There are a few documented cases, but in most instances, tissue is needed to be certain that another process is not causing the pulmonary dysfunction. Other mycobacteria occasionally cause pulmonary disease in patients with HIV infection.

### 17.6.3 Pneumocystis jiroveci

*Pneumocystis jiroveci* (abbreviated PCP to indicate pneumocystis pneumonia) continues to be a common cause of pulmonary disease in developing countries. As indicated above, the outcome of patients with PCP has improved over the past decade. Clinicians are more aware of this entity at CD4 T-cell counts below 200 cells/µL, and diagnosis has improved with the more widespread availability of induced sputum examination and immunofluorescent antibody staining to supplement bronchoalveolar lavage and transbronchial lung biopsy stained with methenamine silver or Giemsa. Clinicians need to be cognizant; however, that about 10–15% of cases of PCP occur at CD4 T-cell counts higher than 200 cells/µL (Chu et al. 1995). Thus, when patients present with pulmonary processes at CD4 T-cell counts greater than 200 cells/µL, PCP should usually not be the first diagnosis considered, but it should not be excluded from the differential diagnosis.

In one study the outcome of HIV negative patients were worse than positive patients. It was proposed that the course of HIV-associated PCP is indolent, leading to better tolerance, unlike in non-HIV patients. But the proportion of patients who fail on NIV was significantly high in HIV-positive patients. Hence a low threshold for intubation is required in patients with HIV. Also the role of corticosteroids is proven when administered in the first 72 h. No evidence is supportive for delayed use of corticosteroids as salvage therapy (Monnet et al. 2008).

PCP usually presents as a subacute illness over several weeks, and the chest radiograph typically demonstrates bilateral, symmetric interstitial infiltrates (Thomas Jr and Limper 2004). However, atypical presentations are not uncommon:
PCP has been documented to produce lobar infiltrates, nodules, cavities, and effusions. Thus, empiric diagnoses on the basis of clinical presentation are less desirable than specific diagnoses on the basis of direct microscopy, culture, or some type of antigen or nucleic acid detection to be certain that the correct pathogen is being treated, and that toxicities of unnecessary drugs are avoided.

Extra pulmonary PCP also occurs in patients with HIV infection. Lesions in the liver and spleen are probably most common. However, lesions in the kidneys, brain, eye, and lymph nodes have also been seen.

The therapy of choice for PCP continues to be trimethoprim–sulfamethoxazole (TMP-SMX); prednisone should be added to patients who present with room air Po2 of less than 70 mm Hg.

For patients who cannot tolerate TMP-SMX or who fail this drug, the most effective alternative is intravenous pentamidine. This drug is well known for its toxicities, which include renal impairment, dysglycemias, and pancreatitis. Dapsone–trimethoprim is effective, but this combination is only available in oral form, and dapsone cross-reacts with sulfamethoxazole in approximately 50% of patients. Thus, this combination offers only modest breadth to the anti-PCP armamentarium. Clindamycin plus primaquine, atovaquone, and trimetrexate are other options. Of these, only trimetrexate can be administered parenterally.

17.6.4 Fungal Pneumonia

Fungal pneumonias (other than PCP) occur in patients with HIV infection, but they are not common in most geographic areas. Cryptococcus, histoplasma, and coccidioides are all recognized to cause focal or diffuse pulmonary disease. In general, diffuse disease is more frequent among patients with CD4 T-lymphocyte counts lower than 200 cells/μL.

Diagnosis and therapy of these pneumonias do not differ substantially from that for disease in other immunosuppressed patients. When these pneumonias occur in patients with low CD4 T-lymphocyte counts, they are difficult to distinguish clinically from PCP. This reinforces the desirability of establishing a specific diagnosis when patients with HIV infection present with pulmonary pathology. For patients with disease and CD4 T-cell counts less than 200 cells/mm³, therapy must usually be continued throughout life unless immunity is reconstituted by ART.

Aspergillus has been reported as a cause of tracheobronchial or pulmonary disease with increasing frequency (Mylonakis et al. 1998). Patients typically have either a low CD4 T-cell count or neutropenia. The diagnosis may be established by smear- and culture-positive for aspergillus.

The occurrence of candidal infection in HIV patients is high not only in terms of muco-cutaneous infections but also involving invasive infections like candidemia. Studies show that the incidence of candidemia is directly proportional to the level of immunosuppression and extent of muco-cutaneous involvement. Patient who received fluconazole both for treatment and as prophylaxis has high chances of azole resistant candidemia, both albicans and non-albicans. It is also shown that the
removal of central lines along with pharmacological treatment also resulted in complete eradication of the organism when appropriate (Anwar et al. 2012).

17.6.5 Viral Pneumonia

Interestingly, the herpes viruses have not been common cause of pulmonary dysfunction in patients with HIV. CMV is often found in respiratory secretions when patients have low CD4 T-lymphocyte counts, but CMV is rarely the cause of pulmonary dysfunction. Studies have shown, for instance, that the prevalence of CMV in respiratory secretions correlates inversely with the CD4 T-lymphocyte count. It has also been shown that when CMV was present in the lung biopsies of patients with PCP, patients did as well with anti-PCP therapy alone as did patients who had no such inclusions. Thus, to document CMV as the cause of pulmonary dysfunction in this patient population requires tissue demonstrating multiple inclusion bodies and the absence of another likely pathogen.

Herpes simplex virus and varicella-zoster virus have been described as causing pulmonary disease in this patient population. However, this is usually in the setting of disseminated disease when lesions in the skin are apparent. Some cases of herpes simplex virus pneumonia appear to be extensions from the oropharynx, but such cases are unusual in this patient population.

Influenza, respiratory syncytial virus, adenovirus, and coronavirus all cause pulmonary disease in this patient population. However, they are not considered to be HIV-associated opportunistic infections.

17.6.6 IRIS

When ART is initiated in patients with HIV infection, immune function improves as the viral load is reduced and the CD4 T-cell count increases. This improved immunologic responsiveness often manifests as organ dysfunction in response to latent or apparent antigens that can range from mild and clinically unimportant to severe and life threatening. Definition and risk factors are summarized in Table 17.3.

IRIS have been described in case series. Its incidence has been described as varying between 10% and 30% (Dean et al. 2002b; Fishman et al. 2000; Narita et al. 1998; Phillips et al. 2005; Wislez et al. 2001). There are few well-constructed studies defining the immunologic correlates, or the factors that predict their occurrence. From the observational studies published to date, it would appear that the syndrome is most likely to occur in patients who started ART when their CD4 T-cell count is low, typically less than 100 cells/μL, and when their viral load is high, typically greater than 100,000 copies/mL.

The immunopathogenesis of the syndrome is unclear and appears to be result of unbalanced reconstitution of effector and regulatory T cells, leading to exuberant inflammatory response in patients receiving ART. Biomarkers, including interferon-γ
(INF-γ), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), and interleukin (IL)-2, 6, and 7, are subject of intense investigation at present.

The IRS occurs within weeks or months of starting ART: some syndromes can occur within days, and others, as described below, may not manifest for many months or several years. Because immune function improves qualitatively as soon as the viral load falls, some patients with IRS may not manifest a higher CD4 T-lymphocyte count at the time of the IRS. Alternatively, some patients with organisms in a sequestered focus, such as bone, are more likely to have the late manifestations.

These IRS appear to be most common in areas where tuberculosis or cryptococcosis is common. The relationship of IRS to specific pathogens is being defined. Some experts report, for instance, that IRS rarely occurs due to latent *M. tuberculosis*, but commonly occurs due to latent *M. avium* complex. IRS commonly occurs after active tuberculosis is diagnosed. For CMV retinitis, IRS can occur weeks, months, or years after the CMV retinitis is stabilized by drug therapy if ART is belatedly initiated.

There is no consensus case definition of IRS, and thus the literature includes reports that categorize clinical manifestations differently. It is extremely difficult when a patient presents with a new clinical syndrome after starting IRS to determine if the manifestation is an immunologic reaction that needs no specific intervention, or whether the process represents an active opportunistic infection in need of therapy. Some series include patients with fungemia or mycobacteremia as examples of IRS. Other series would include such patients as cases of active or new opportunistic infections in need of specific therapy. These uncertainties leave the clinician with a dilemma about how aggressive to be diagnostically or therapeutically.

### Table 17.3  IRIS-Definitions, Risk factors, Categories and Mechanism

| IRIS definition                      | RISK factors                                      |
|--------------------------------------|---------------------------------------------------|
| Samuel generic criteria              | • ART naïve                                       |
| 1. HIV positive                      | • Short interval of start of ART                  |
| 2. On HAART with decrease in HIV-1 RNA or increase in CD4 count(which may lag) | • Dramatic fall of HIV RNA                        |
| 3. Clinical symptoms consistent with inflammatory process | • Young age                                       |
| 4. Clinical course not consistent with previous OI/New OI/Drug toxicity | • Lower CD4 count at start of treatment           |
| 5. Genetic susceptibility            |                                                   |
| French criteria—2 major or          | Categories of IRIS                                |
| 1 major + 2 minor for diagnosis     | • Unmasking OI                                    |
| 1. Major-                           | • Paradoxical OI                                  |
| • atypical OI/tumor responding to ART | • Auto-immune                                    |
| • HIV RNA fall by 1 log 10 copies/mL | • Malignancy                                      |
| 2. Minor-                           | • Grave disease, etc.                             |
| • Increase in cd4                   |                                                   |
| • Increase in immune response       |                                                   |
| • Spontaneous resolution            |                                                   |
| NACO, India                         | Underlying mechanism of IRIS                      |
| Occurrence of new OI in 6 weeks–6 months of starting ART, associated with increase in CD4 count | Mechanism                                          |
|                                      | Shift from Th2 to Th1 response                    |

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Some syndromes have been managed without therapy. Some syndromes that were clinically more severe have been treated with antiinflammatory agents, including prednisone. Other syndromes have been treated with long courses of specific antiinfective therapy.

Studies show that it is prudent to start ART after 2 weeks of initiation of ATT but no later than 8 weeks. But no much clarity exists for other opportunistic infections. In general, it appears prudent that ART should be initiated before the onset of severe immunodeficiency and after the treatment of opportunistic infection. But the benefit of delaying ART initiation should not unnecessarily curb the treatment of HIV in case of severe disease. Regardless of presence of absence of infection, it is advisable to start ART with CD4 count less than 50 (Sharma and Soneja 2011).

All the above mentioned infections and IRIS can present with respiratory failure requiring ICU admission. Besides altered senosium due to CNS—tuberculosis, cryptococcosis, toxoplamosis, PMLE, HIV encephalopathy, etc. can also be a cause for intensive care.

Mild IRIS can be treated with NSAIDS. Life threatening or those with organ dysfunction need steroid use. It should be clear that using steroid in presence of inappropriate dosage of treatment of OI may inadvertently worsen the same. Hence treatment optimization for OI is needed, taking into consideration of all possible drug interactions (Sharma and Soneja 2011).

17.7  Neoplastic Disease

Kaposi’s sarcoma and lymphoma are well-recognized causes of pulmonary disease in patients with HIV infection. The incidence of Kaposi’s sarcoma has declined as the epidemic has moved into heterosexual individuals and women, groups that do not characteristically have a high incidence of Kaposi’s sarcoma. In addition, ART use has been associated with a decline in this tumor, which is linked to HHV-8 infection.

When Kaposi’s sarcoma does occur in the lung, it presents as patchy bronchial lesions (Aboulafia 2000; Cadranel et al. 1994; Hartman et al. 1994; Huang et al. 1996; Tirelli et al. 2000). Often, there is an associated pleural effusion that is bloody when thoracentesis is performed.

The diagnosis is often anticipated by concurrent skin lesions and the presence of prominent lesions in the tracheobronchial tree, which are easily recognized by bronchoscopy. The diagnosis is not easy to establish definitively.

Transbronchial biopsies of the bronchus or lung parenchyma reveal crush artifact that is hard to distinguish from Kaposi’s sarcoma. On cytology, there is no diagnostic feature. Thus, either tissue must be obtained on open lung biopsy or video-assisted thoracoscopy, or a presumptive diagnosis must be made when Kaposi’s sarcoma in seen in the tracheobronchial tree and bronchoalveolar lavage reveals no other likely pathogens.

Pulmonary Kaposi’s sarcoma can respond well to chemotherapy (Dupin et al. 1999; Holkova et al. 2001; Lichterfeld et al. 2005; Martin-Carbonero et al. 2004).
The use of ART and opportunistic infection prophylaxis has contributed to the success rates of management strategies.

Lymphoma continues to be a cause of pulmonary disease (Bazot et al. 1999; Eisner et al. 1996). Although primary CNS lymphomas have greatly diminished in frequency in patients treated with ART, primary B-cell lymphomas elsewhere continue to occur. Patchy pulmonary infiltrates have been well described. Biopsy or cytology is needed to establish a diagnosis.

Combination chemotherapy for HIV-associated lymphoma has become impressively more successful when ART is continued with opportunistic infection prophylaxis (Little et al. 2003; Ratner et al. 2001; Re et al. 2003). Some regimens provide a brief drug holiday while the patients is actively receiving chemotherapy to avoid problems with drug absorption or drug interactions. However, it would appear that active ART and opportunistic infection prophylaxis are important elements contributing to improved survival. Stem cell transplantation has also been used successfully (Krishnan et al. 2005; Serrano et al. 2005).

As life expectancy in HIV is increasing and the literature is evolving, other pulmonary neoplastic processes have been recognized that clinicians should be aware of. Primary effusion cell lymphoma can present in the pleural, pericardial, or abdominal cavities, and presents as effusions. Primary effusion lymphomas are always associated with human herpes virus 8 (HHV8), and sometimes with Ebstein barr virus (EBV) also. They are often diagnosed by cytopathology and resistant to conventional chemotherapy. Treatment guidelines invariably include continuing HAART with chemotherapy and prognosis remains poor. It is not clear how effective chemotherapy is for this tumor.

A multi-centric European study showed that the degree of disease progression is directly proportional to the nadir CD4 values more than the proximal CD4 values. The presence of opportunistic infection, for which the patient is admitted, will influence the level of CD4 count; hence CD4 count of the current admission may not be reliable. It was also noted that the viral load was significantly higher in patients who were not receiving ART, but with high CD4 count than those with relatively low CD4 count, in spite of being on ART. Arguments were raised that those patients with high CD4 count would not have taken ART as they would have been asymptomatic, and hence their viral load tends to be higher. But this does not hold good in today’s scenario, since all diagnosed HIV-positive patient should be started on ART. It should also be remembered that the level of immunosuppression is interplay of CD4 counts, both proximal and nadir, viral load, duration, and compliance with ART, level of disease progression before the current admission. No single parameter should be used to conclude the level of immunosuppression (Miller et al. 1999).

Multicentric Castleman’s disease is another unusual neoplastic process that is associated with HIV infection (Hillier et al. 2004). This HHV-8 process can present with pulmonary infiltrates, as well as fever, lethargy, adenopathy, and cytopenias. Diagnosis usually requires a combination of HHV-8 titers and bone marrow or lymph node tissue, plus flow cytometry (Oksenhendler et al. 2000). Patients often develop lymphoma and/or Kaposi’s sarcoma subsequently. It is unclear how effective any therapy is for this disease.
Several large databases have suggested that certain solid tumors can be overrepresented in this patient population (Braun et al. 1990; Tenholder and Jackson 1993). Bronchogenic carcinoma as well as melanoma, colon cancer, and breast cancer appear to occur with increased frequency even when other risk factors are considered.

### 17.8 Drug Toxicities

Several antiretroviral agents have toxicities that can present with pulmonary or respiratory manifestations.

When patients receive ART regimens that contain abacavir, they can develop a hypersensitivity syndrome that is difficult to distinguish from nonspecific febrile respiratory illnesses (Tenholder and Jackson 1993; Escaut et al. 1999; Hewitt 2002; Keiser et al. 2003; Walensky et al. 1999). However, because abacavir hypersensitivity reactions can be fatal, this syndrome must be recognized. Patients present during the initial 4–8 weeks of abacavir therapy with fever, rash, fatigue, nausea, or vomiting. About 20% of patients will have cough; some of these patients have been described to have pulmonary infiltrates.

The syndrome usually persists unless the drug is discontinued. A feature that clinicians must be aware of is the danger of “rechallenge.” Patients with this syndrome may stop taking their drugs due to their systemic illness, or their nausea and vomiting. Cases of distributive shock, some fatal, have occurred on rechallenge. Thus, most experts would recommend that if a potential syndrome occurs, and the drug is discontinued, rechallenge should not be permitted. There is a link between abacavir hypersensitivity syndrome and HLA B27, but it is not clear yet whether screening patients for this genotype would be cost-effective.

Another drug toxicity that can present with dyspnea occurs when patients have been receiving nucleoside antiretroviral agents for long periods of time (Gerard et al. 2000). Any of the nucleosides (zidovudine, stavudine, didanosine, lamivudine, abacavir, emtricitabine) can probably cause this syndrome, although it is best described with didanosine and stavudine. This syndrome is a reflection of mitochondrial toxicity. Patients with this syndrome are often female and obese. Hepatic steatosis is frequently associated with the disease. Patients present with weakness and fatigue, and eventually develop lactic acidosis. Serum lactate levels are typically considerably above 5 mmol/L. These patients may appear to be septic, although they are not usually febrile. The only effective therapy is to stop the drug; other interventions, such as carnitine or riboflavin, have no documented benefit. Whether patients can subsequently be safely rechallenged with other nucleosides has not been well studied, although abacavir, lamivudine, and FTC seem to impart very little risk.

### 17.9 Precautions: The Key to Prevention

The use of universal precautions in the ICU cannot be over-emphasized for the safety of everyone—hospital staff, other patients, and the HIV patients’ relatives. These should be pasted in ICU to ensure strict compliance.
1. Personal protective equipment.
   (a) Wear gloves when handling infectious material or where there is a possibility of exposure to blood or other body fluids.
   (b) Discard gloves whenever they are thought to have become contaminated wash your hands and put on new gloves.
   (c) Do not touch your eyes, nose, or other exposed membranes or skin with gloved hands.
   (d) Do not leave the workplace or walk around the laboratory wearing gloves.
   (e) Wash your hands with soap and water immediately after any contamination and after work is completed. If gloves are worn, wash your hands with soap and water after removing gloves.
   (f) Wear a laboratory gown, overall, or uniform when in the laboratory. Wrap-around gowns are preferable. Remove this protective clothing before leaving the laboratory. Eye-covers and masks should also be worn.
   (g) Keep the ICU clean, neat, and free from extraneous material and equipment.

2. Disinfection
   (a) Disinfect work surfaces when procedures are completed and at the end of each working day. An effective all-purpose disinfectant is a hypochlorite solution with a concentration of 0.1% available chlorine (1 g/L, 1000 ppm).
   (b) Spills of infected or potentially infected material should first be covered with paper towelling or other absorbent material. A disinfectant should be poured around the spill area and then over the absorbent material and left for 10 min. The standard disinfectant recommended for cleaning contaminated surfaces is a hypochlorite solution with a concentration of 0.5% available chlorine (5 g/L, 5000 ppm). However, for laboratories working with HIV cultures and virus preparations, a higher concentration of available chlorine (1.0%) is recommended.
   (c) Needle-stick or other puncture wounds, cuts, and skin contaminated spills or splashes of specimen material should be thoroughly washed with soap and water. Bleeding from any wound should be encouraged.
   (d) All spills, accidents, and overt or potential exposure to infectious material should be reported immediately to the laboratory supervisor. A written record should be kept of all such incidents. Appropriate medical evaluation, surveillance, treatment and, if necessary, counselling should be provided.
   (e) Handwashing using all steps should be strictly followed before and after any exposure/procedure/patient handling.

3. Sharps handling
   (a) Whenever possible, avoid using needles and other sharp instruments. Place used needles, syringes, and other sharp instruments and objects in a puncture-resistant container. Do not recap used needles and do not remove needles from syringes.
17.10 Conclusions

The clinical features of patients with HIV infection who present to ICUs have changed over the past 25 years. As patients with HIV infection live longer, more are being seen in ICUs for issues unrelated to their HIV infection. When they are admitted to the ICU, for whatever reasons, intensivists need to be knowledgeable about the complex issues related to efficacy and toxicities of ART. New manifestations, such as IRS and premature atherosclerosis, are emerging. HIV-infected patients in the ICU are clearly a population that requires special expertise for optimal management.

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