CRITICAL CARE

REVIEW

Clinical review: Respiratory failure in HIV-infected patients - a changing picture

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Abstract

Respiratory failure in HIV-infected patients is a relatively common presentation to ICU. The debate on ICU treatment of HIV-infected patients goes on despite an overall decline in mortality amongst these patients since the AIDS epidemic. Many intensive care physicians feel that ICU treatment of critically ill HIV patients is likely to be futile. This is mainly due to the unfavourable outcome of HIV patients with *Pneumocystis jirovecii* pneumonia who need mechanical ventilation. However, the changing spectrum of respiratory illness in HIV-infected patients and improved outcome from critical illness remain under-recognised. Also, the awareness of certain factors that can affect their outcome remains low. As there are important ethical and practical implications for intensive care clinicians while making decisions to provide ICU support to HIV-infected patients, a review of literature was undertaken. It is notable that the respiratory illnesses that are not directly related to underlying HIV disease are now commonly encountered in the highly active antiretroviral therapy (HAART) era. The overall incidence of *P. jirovecii* as a cause of respiratory failure has declined since the AIDS epidemic and sepsis including bacterial pneumonia has emerged as a frequent cause of hospital and ICU admission amongst HIV patients. The improved overall outcome of HIV patients needing ICU admission is related to advancement in general ICU care, including adoption of improved ventilation strategies. An awareness of respiratory illnesses in HIV-infected patients along with an appropriate diagnostic and treatment strategy may obviate the need for invasive ventilation and improve outcome further. HIV-infected patients presenting with respiratory failure will benefit from early admission to critical care for treatment and support. There is evidence to suggest that continuing or starting HAART in critically ill HIV patients is beneficial and hence should be considered after multidisciplinary discussion. As a very high percentage (up to 40%) of HIV patients are not known to be HIV infected at the time of ICU admission, the clinicians should keep a low threshold for requesting HIV testing for patients with recurrent pneumonia.

Introduction

During the HIV epidemic in the early 1980s, critical illness in HIV infected patients was associated with poor prognosis with very high mortality and morbidity. Since then there has been debate on the role of the ICU in the management of HIV patients. Use of such resources for HIV patients has often raised ethical and economical questions. Respiratory failure needing invasive mechanical ventilation in HIV-infected patients remains an indicator for poor outcome and often poses a challenge to intensive care physicians making decisions about aggressive ICU support. Most ICUs are reluctant to

provide multiple organ support to critically ill HIV patients.

As the controversy on ICU care of HIV patients goes on, a review of the published literature (identified by searching Medline, Uptodate, Pubmed, EMBASE and CINAHL) was undertaken with particular attention given to respiratory complications in this group of patients. The main aim of this review is to provide an overview of changing outcome and disease patterns in HIV patients presenting with respiratory failure. We believe this review will update ICU physicians with factors related to ICU outcomes in HIV patients at the current time and provide guidance to make appropriate decisions while approaching such cases.

Reasons for ICU admission of HIV patients

HIV-infected patients might be admitted to ICU for many reasons (Table 1). Acute respiratory failure has remained the most common cause for ICU admission in

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Table 1. Reasons for ICU admission of HIV-infected patients in the HAART era[a]

Respiratory failure	25-50%
Sepsis	33-50%
Central nervous system dysfunction	11-27%
Gastrointestinal problems	6-15%
Cardiovascular	8-13%
Immune reconstitution inflammatory syndrome[b]	20-25%

[a]There may be significant overlap of these conditions during acute presentation.
[b]In HIV patients with tuberculosis/cryptococcus infection on highly active antiretroviral therapy (HAART).

HIV patients. It is the presenting symptom in 25 to 50% of HIV cases, pneumonia being the most common ICU admission diagnosis [1-10]. Sepsis is emerging as an increasingly common cause for ICU admission in HIV patients, shown to range from 33 to 50% of cases in recent studies. Admission diagnosis of sepsis in HIV patients is independently associated with hospital mortality [10,11,12].

HIV patients may still present to ICU with severe *Pneumocystis jirovecii* pneumonia despite decreased incidence of such infection after introduction of *Pneumocystis* prophylaxis in 1989 and highly active antiretroviral therapy (HAART) in 1996. The percentage of AIDS cases having *P. jirovecii* infection declined from 53% in 1989 to 42% in 1992 (Centers for Disease Control and Prevention, AIDS Surveillance Summaries, 1989 to 1992). The later use of HAART further reduced the rates of *P. jirovecii* among adults by 3.4% per year [13]. Overall, opportunistic infections and AIDS-related illness are responsible for a smaller proportion of ICU admissions and are most commonly seen in patients with a new HIV diagnosis [4,6,14-16].

Other causes of ICU admission include central nervous system dysfunction in 11 to 27%, gastrointestinal bleeding in 6 to 15%, cardiovascular dysfunction in 8 to 13%, and other causes [1-2,5-8]. The immune reconstitution inflammatory syndrome (IRIS) and complications of HAART therapy may also indicate ICU admission. Initiation of HAART results in paradoxical tuberculosis (TB)-IRIS in approximately 20 to 25% of HIV patients being treated for TB or cryptococcal meningitis [17-19]. This is due to exaggerated inflammatory response against concurrent opportunistic infection.

Although the rate of hospitalization has decreased significantly amongst HIV-infected patients, the ICU admission rate has remained constant or has increased [7,20,21]. Approximately 5 to 12% of HIV-infected patients admitted to hospitals require intensive care. This seems to be associated with either a new diagnosis of HIV on admission or not being on HAART [7,20-23].

With the advent of HAART in 1996, HIV has now become a chronic disease. These patients are living longer and more likely to present to hospitals with co-morbid conditions and non-AIDS related illnesses. In studies from the HAART era, nearly half of ICU admissions in HIV patients were for non-HIV related critical illness [2,4,5,10,11,22].

It is notable that approximately 25 to 40% of critically ill HIV-infected patients were not known to be HIV infected at the time of ICU admission in recent studies [7,14,22]. Also, many HIV-infected patients (up to 50%) are not on HAART at the time of ICU admission [11,14,22,24].

Changing outcome of HIV-infected patients

The outcome of HIV-infected patients needing ICU support has improved since the AIDS epidemic. Studies in the pre-HAART era showed poor outcomes for such patients from critical illness, with the mortality rate ranging between 70% and 91%. The worst outcomes were seen in ventilated patients [25,26]. In the era of HAART, the reported in-hospital mortality for HIV/AIDS patients admitted to ICU is approximately 25 to 40%, with a median critical care length of stay of 5 to 11 days [4-7].

It is clear that ICU mortality is related to the reason for ICU admission in HIV patients. The highest mortality rates are associated with respiratory failure and sepsis. In these patients, mortality rates remained as high as 50 to 68% [2,5,27,28]. For patients admitted to the ICU for other HIV-related illnesses, the reported mortality is generally lower.

Overall hospital mortality from *P. jirovecii*-related respiratory failure seems to be gradually decreasing over time. Studies after the mid-1990s reported an in-hospital survival rate of up to 50% [1-4,6] and up to 75% in one series [8]. One study confirmed nearly 40% hospital survival in HIV patients with *P. jirovecii* infection requiring mechanical ventilation [29]. Improved survival of 75% versus 37% has been reported in HIV patients with severe *P. jirovecii* on HAART compared with those not on HAART, respectively [30]. In addition, other factors are likely to contribute to better outcomes, including low tidal volume ventilation for acute lung injury, early treatment for sepsis, and other general improvements in delivery of ICU care over the past decade [31,32].

Recent studies reported good short and long-term outcome of HIV-infected patients which is comparable to that of non-HIV ICU patients [9,16,24,33-37]. One study found no difference in crude hospital mortality (44% versus 46%) between HIV and non-HIV patients with lung injury [38]. Predictors of 1-year mortality for HIV-infected patients admitted to the ICU in the HAART era were non-HIV-related.

The on-going ICU dilemma

Despite improvement in ICU outcome in the HAART era, there is wide variation in the approach of ICU

physicians towards patients with HIV or AIDS. A survey of Italian ICUs has shown that the admission of patients with HIV or AIDS is perceived as appropriate in only 30.4 and 14.3% of ICUs, respectively [39]. A US study showed that HIV-infected patients with sepsis were less likely to be admitted to the ICU (37% versus 56%; $P < 0.0001$) than those without HIV [40]. Patients with severe sepsis without HIV/AIDS were universally more likely to be admitted to the intensive care unit, even when they had comorbid illnesses with equal or worse expected in-hospital mortality (for example, metastatic cancer).

The reluctance to admit HIV-infected patients to ICU may be because studies persistently reported need for mechanical ventilation as the main predictor of mortality in these patients [2,5,8,15,16,23,30,31,33,35,37]. Also, this group of patients demonstrates significantly higher rates of developing ventilator-associated pneumonia compared to non-HIV patients needing mechanical ventilation [41]. However, admission to ICU was recently shown to be independently associated with increased survival in HIV-infected patients [22]. Intensive care physicians need to be aware of improving outcomes in this group of patients while making decisions on ICU support.

Respiratory complications in HIV-infected patients

HIV patients are at high risk of developing lung disease of infectious and non-infectious etiology, which is the main cause of morbidity and mortality in this group [2-11,23,42,43]. The spectrum of respiratory disorders associated with HIV infection has changed over the past decade with bacterial pneumonia, sepsis or non-infective respiratory complications emerging as frequent causes of critical illness [9-11]. A recent US study reported that chronic obstructive pulmonary disease and bacterial pneumonia were the most common lung diseases seen in patients with HIV and the incidence was much higher than in non-HIV patients [44].

Differential diagnosis of respiratory complications in HIV patients

Respiratory illnesses in HIV-infected patients include both infectious and non-infections conditions (Table 2). Each of these infections or neoplasms has a characteristic clinical and radiographic presentation. However, there may be considerable overlap of these conditions during acute illness.

Respiratory failure due to infective causes
Pneumocystis jirovecii pneumonia

P. jirovecii was a common and rapid cause of death in persons living with AIDS in the early years of the HIV epidemic [45]. It still remains a cause for life threatening opportunistic infection [46,47] and a real concern in patients without adequate access to optimal medical care.

Table 2. Differential diagnosis of respiratory complications in HIV patients

Infectious conditions	Non-infectious conditions
Bacterial[a]	Chronic obstructive pulmonary disease, emphysema
Streptococcus pneumoniae	
Staphylococcus aureus	Acute or chronic bronchitis
Haemophilus influenzae	Bronchiectasis
Pseudomonas aeruginosa	Pulmonary arterial hypertension
Klebsiella pneumoniae	Asthma
Fungal[b]	Lymphocytic interstitial pneumonitis[c]
Pneumocystis jiroveci[b]	
Cryptococcus neoformans[b]	Non-specific interstitial pneumonia
Histoplasma capsulatum[b]	Illicit drug-induced lung disease
Coccidioides immitis[b]	Medication-induced lung disease
Aspergillus	Immune reconstitution inflammatory syndrome
Mycobacterial	
Mycobacterium tuberculosis[b]	Bronchiolitis obliterans with organizing pneumonia
Mycobacterium kansasii[b]	
Mycobacterium avium complex[b]	Sarcoidosis
Virus	Foreign body granulomatosis
Cytomegalovirus[b]	
Herpes simplex virus	**HIV-related neoplasms**
	Kaposi sarcoma[b]
Parasites	Non-Hodgkin lymphoma[b]
Toxoplasma gondii[b]	Primary effusion lymphoma[b]
	Lung cancer[b]

[a]AIDS defining if patient with HIV has two or more episodes of bacterial pneumonia within 12 months. [b]AIDS defining conditions. [c]AIDS defining in children aged <13 years and not applicable to adults.

Even now about 200 new cases a year are diagnosed in the UK and it can still be fatal, particularly in people who have their HIV diagnosed very late. Before the widespread use of prophylaxis, it was estimated that up to 80% of people with AIDS would eventually develop *P. jirovecii* infection [48]. Use of prophylaxis against *P. jirovecii* and HAART have dramatically reduced the incidence of this infection [13,49]. The current rate of pneumocystis infection in the HIV-infected population in the developed world is about 10 to 20%.

P. jirovecii is distributed worldwide [50]. A high exposure to the organism has been noticed and more than 75% of children are found to be seropositive by the age of 4 years. This makes asymptomatic pneumocystis infection extremely common. A post-mortem study conducted in Chile of 96 persons who died of unrelated causes found 68% of them had *P. jirovecii* in their lungs [51]. It is believed that the organism is transmitted early in life by the aerosol route and remains in a latent state unless the patient becomes immunocompromised [52]. However, this theory of latency has come under question. While carriers may be agents for airborne transmission of the organism, re-infection with different genotypes probably occurs with as much regularity as reactivation of endogenous organisms [53]. It only occurs in an immuno-compromised host and, in the absence of any other reason for being immunocompromised, *P. jirovecii* may be the first clue to a new AIDS diagnosis [54].

Before the HAART era started, the incidence of *P. jirovecii* in HIV-infected patients increased as CD4 count decreased. Generally, it did not occur until the CD4 count dropped below 200 cells/mm³ [55-58]. However, the incidence of *P. jirovecii* in developed countries has greatly decreased since approximately 1988. This appears to have resulted from both recommendations for primary prophylaxis against the infection in patients with CD4 cell counts <200/μl and widespread adoption of HAART [13,55,59-62]. In populations that do not have access to preventive treatment, *P. jirovecii* continues to be a major cause of death in HIV-infected patients.

P. jirovecii pneumonia is generally gradual in onset and characterized by fever, cough and progressive dyspnea [63]. Other symptoms include fatigue, chills, chest pain, and weight loss. In up to 25% of these patients chest radiographs are initially normal. The most common radiographic abnormalities are diffuse, bilateral, interstitial, or alveolar infiltrates [64]. Less common presentations include pneumothorax, lobar or segmental infiltrates, cysts, nodules and pleural effusions [63,65].

The two most common abnormal laboratory values associated with *P. jirovecii* infection in HIV patients are a CD4 count below 200 cells/mm³ and an elevated lactate dehydrogenase level (LDH) [58,66,67]. LDH levels appear to reflect the degree of lung injury and are usually elevated above 220 U/L in about 90% of such patients. This test has a high sensitivity (78 to 100%) but a much lower specificity. However, consistently elevated LDH levels during treatment may indicate therapy failure and a worse prognosis [46,48,50,66,67].

When possible, a definite diagnosis of *P. jirovecii* should be made by documentation of the organism in respiratory specimens. The most simple, rapid and least invasive method of diagnosing pneumocystis is by analysis of induced sputum. While the specificity of this method approaches 100%, the sensitivity ranges from 55 to 92% [68,69]. A high diagnostic sensitivity can be achieved with induced sputum with a good technique and bronchoscopy may need to be done less frequently. However, the limitations of induced sputum include the need for a skilled team, the experience of the centre and the laboratory methods employed [69,70]. Endotracheal aspirates from intubated and ventilated patients appear to have a high sensitivity for the detection of *P. jirovecii* [71].

Bronchoalveolar lavage (BAL) is a common procedure used in the ICU to diagnose *P. jirovecii*, having a diagnostic yield that exceeds 90% [72]. However, it has been suggested that the diagnostic sensitivity of BAL in patients using aerosolized pentamidine prophylaxis may be as low as 62% [73]. In these patients, trans-bronchial biopsy, which has a diagnostic yield of up to 100%, can be added, but this method is associated with complications. Site-directed lavage, which involves sampling the most heavily involved lobes on chest radiograph, can also increase the yield in patients with focal infiltrate [74]. Since the prevalence of pneumocystis infection has decreased and infection with other organisms is common, we feel BAL should be considered as a diagnostic procedure in suspected HIV patients with respiratory complications, particularly if induced sputum is negative.

Pneumocystis colonization is widespread and is well documented [50-54,75,76]. Hence, distinguishing colonization from infection is not easy. Studies looking at the utility of PCR in diagnosing *P. jirovecii* from sputum and BAL specimens have yielded sensitivities ranging from 81 to 100% and specificities of 86 to 100% [77-79]. Various studies over the past decade have documented limited specificity of positive PCR in respiratory specimens and discrepancies between positive PCR and negative staining results have been reported. The false positive PCR was mostly due to *P. jirovecii* colonization [80-85]. A meta-analysis documented that 31.8% of the patients with false-positive PCR results had prior or later *P. jirovecii* pneumonia, suggesting these false-positive results should be regarded as true-positive results [86]. Quantitative PCR, as against conventional PCR, demonstrates potential for distinguishing colonization from infection, but clinical validation is required [82,87-89].

High resolution computed tomography (HRCT) has a high sensitivity and specificity for diagnosing pneumocystis infection, particularly when the presence of patchy or nodular ground-glass attenuation was used to indicate this [90-92]. HRCT is useful in patients with suspected *P. jirovecii* who have a normal, equivocal, or non-specific chest X-ray finding. A negative HRCT may allow exclusion of *P. jirovecii* pneumonia in such patients.

Arterial blood gas analysis is a useful test, particularly in symptomatic HIV patients who have normal chest X-ray. The presence of *P. jirovecii* pneumonia is highly unlikely if the response to exercise is normal, that is, a decrease in the alveolar-arterial oxygen gradient or an increase in oxygen saturation with exercise [93]. This test is useful for screening for *P. jirovecii*.

Bacterial pneumonia

Bacterial pneumonia is a common cause of acute illness in HIV patients and is among the most common causes of respiratory failure resulting in ICU admission [2,6,14,20,21,37,94-96]. Centres for Disease Control and Prevention (CDC) added recurrent bacterial pneumonia (two or more episodes in a 12-month period) as AIDS defining [96].

Data on the incidence of bacterial pneumonia in HIV patients are mixed [30,37,94-96]. The annual incidence ranges from 5.5 to 29 per 100 person-years, compared with 0.7 to 10 per 100 person-years in non-HIV patients [20,21,97].

Risk factors for bacterial pneumonia include advanced immunosuppression, interruption of antiretroviral therapy, smoking, intravenous drug use and pre-existing lung disease. Bacterial pneumonia can occur at any stage of HIV infection but tends to occur frequently in individuals with advanced immunosuppression, particularly when the CD4 count drops below 200 cells/μl [21,98,99]. HIV patients that smoke have a two- to five-fold increased risk of developing bacterial pneumonia compared to non-smoker HIV patients [21,100]. The incidence of bacterial pneumonia has decreased significantly in the HAART era [95,101] and interruption in HAART is associated with an increased incidence [100]. The traditional risk factors that may be associated with pneumonia include pre-existing lung disease, neutropenia, steroid therapy, or malnutrition [102].

The most common pathogens causing community-acquired pneumonia in HIV patients are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus*, with *S. pneumoniae* accounting for the majority of cases in which a bacterial pathogen is isolated [98,103]. The incidence of recurrent and invasive pneumococcal disease is higher in HIV patients than in the general population [21,95,96,104,105]. This may be partially explained by a predisposition for pneumococcal naso-pharyngeal colonization in such patients [106,107]. *Legionella* infection, although uncommon, occurs approximately 40 times more frequently in HIV patients than in the general population. Although relatively rare, rapidly progressing necrotizing pneumonia can be caused by community-onset methicillin-resistant *S. aureus*, usually harbouring the PVL (Panton-Valentine leukocidin) virulence factor [108,109]. These cases are associated with high rates of morbidity and mortality. Nosocomial pneumonia in HIV-infected patients is most commonly caused by *S. aureus* and Gram-negative organisms.

The occurrence of bacterial pneumonia in HIV-infected patients is associated with a permanent decline in pulmonary function and a two- to five-fold increase in long-term mortality compared with non-HIV patients [21,104,110]. It has been reported that bacterial pneumonia was associated with permanent reduction in FEV1, FVC, FEV1/FVC, and the diffusing capacity of carbon monoxide [104]. This study concluded that both *Pneumocystis carinii* pneumonia and bacterial pneumonia result in expiratory airflow reductions that persist after the acute infection resolves. These changes contribute to chronic lung disease (for example, chronic obstructive pulmonary disease) in HIV-infected patients [44].

Tuberculosis, cytomegalovirus and other infections in HIV patients

Millions of people worldwide are infected with both HIV and TB, especially in developing countries. The World Health Organization reported in 2010 that there were 8.8 million new cases of TB, of which 1.1 million were among people living with HIV. About 24% of all TB deaths were associated with HIV [111]. In the United States, HIV-associated TB is most common among intravenous drug users and in Africa it is the most common pulmonary complication of HIV [112,113].

In addition, infection caused by endemic fungi, parasites and viral pathogens contribute substantially to the morbidity and mortality of this population worldwide. *Cryptococcus*, *Histoplasma* and *Aspergillus*, cytomegalovirus (CMV) and *Toxoplasma gondii* have all been associated with acute respiratory failure in HIV patients, although the risk and predictors of acute respiratory failure for these pathogens are unknown.

The clinical and pathogenic significance of CMV infection has been questioned, although autopsy findings of many HIV patients that died of respiratory failure had evidence for CMV pneumonitis [114-116]. CMV is not commonly found as the sole pathogen in respiratory specimens and it occurs as a concomitant infection with *P. jirovecii*. Positive culture or PCR for CMV in a respiratory specimen does not correlate with clinical or radiological abnormalities, or with acute morbidity due to pulmonary disease [117,118]. Many such patients with *P. jirovecii* and CMV infection get better with proper treatment of pneumocystis without specific anti-CMV treatment. However, the presence of concomitant CMV infection with *P. jirovecii* may indicate poor prognosis for long-term survival [119].

Non-infective causes of respiratory failure

Non-infectious pulmonary diseases, including lung cancer and emphysema, are important causes of morbidity and mortality in HIV patients. The incidence of Kaposi sarcoma and AIDS-related lymphoma has decreased in the HAART era, but compared with the general population, the risk of these malignancies and pulmonary hypertension is still very high in HIV patients [43]. In addition, organizing pneumonia, sarcoidosis, drug hypersensitivity, primary effusion lymphoma, foreign body granulomatosis, and other forms of lung disease can occasionally develop in HIV-infected patients.

The immune reconstitution syndrome can affect the lung and mimic other conditions such as infections and even lung cancer [120]. Lymphocytic interstitial pneumonitis, a rare interstitial lung disease in the general population, is seen with increased frequency in HIV-infected individuals, particularly children. Use of HAART is associated with reduction in some non-infectious pulmonary complications, most likely as a result of immune reconstitution [121].

Factors affecting ICU and hospital outcome

Intensive care clinicians need to be aware of the factors affecting outcome in HIV-infected patients. Mechanically

ventilated HIV patients are twice as likely to die in the ICU compared to non-HIV patients [41]. The need for invasive mechanical ventilation and duration of ventilation remains a predictor of ICU and hospital mortality in this group [2,5,8,15,16,31,33-35,37]. A US study in the 1990s observed that 81% of patients who had *P. jirovecii* pneumonia and needed mechanical ventilation died [122].

The rate of ventilator-associated pneumonia is significantly higher among HIV patients than the non-HIV population [41]. It has been reported that the majority of HIV patients who received non-invasive positive pressure ventilation (NIV) avoided intubation and had lower rates of pneumothorax [123]. Hence, early intervention with NIV or continuous positive airway pressure (CPAP) seems useful and appropriate in patients with *P. jirovecii* pneumonia. Outcome for HIV patients without any known AIDS-defining condition needing either NIV or invasive mechanical ventilation is reported to be good [124]. Corticosteroid therapy instituted within 24 to 72 hours of *P. jirovecii* therapy has been shown to prevent the initial deterioration often seen in patients with *P. jirovecii* and to reduce the rate of respiratory failure and death [125].

Delayed ICU admission, for example, a time interval from hospital admission to ICU admission of more than 24 hours, is associated with increased mortality in critically ill HIV patients [10,34,37]. Admission of such patients to ICU was recently found to be independently associated with increased survival [22].

Other factors independently associated with poor outcome are the presence of sepsis [10-12,27,28], increasing age and severity of illness [12,28,33,35] and vasopressor use [24,37,126]. Evidence of hypoalbuminaemia, weight loss and decreased functional status are associated with high mortality risk in HIV patients needing ICU care [5,6,10,22,33,127]. Low CD4 count (<200/mm^3) and high viral load may not be associated with short-term ICU mortality but are associated with in-hospital and long-term mortality at 1 year [8,24,35,41].

Presence of pneumothorax is thought to be an ominous sign and is associated with poor outcome in these patients. Pneumothorax occurs in 1 to 2% of hospitalized HIV patients and is associated with 30 to 34% mortality [4,128-131]. Several investigators reported that extensive tissue invasion within the alveolar interstitium is common in severe *P. jirovecii* infection, and is an important factor in causing necrosis and subsequent pneumothorax [132,133]. The administration of aerosolized pentamidine has also been implicated in the pathogenesis of cavitation and pneumothorax [130]. Pleural effusion is seen in 7 to 27% of hospitalized patients with HIV infection; the three leading causes are parapneumonic effusions, TB and Kaposi sarcoma. The prognosis of patients with pleural

Kaposi sarcoma and non-Hodgkin lymphoma in AIDS remains poor, and the major goal of treatment is palliation [128].

Use of HAART in HIV patients admitted to ICU

Clinical trials and meta-analysis have definitely shown that HAART improves survival and reduces AIDS-related complications in patients with advanced disease even when they present with acute opportunistic infections [134,135]. In addition, there is growing interest in understanding how HAART may decrease immune activation and positively impact other comorbidities, such as cardiovascular, kidney and liver disease. Consequently, many guidelines from around the world now recommend routine initiation of HAART when CD4 count decreases below 350 cells/mm^3 [136].

Initiation of HAART within 14 days of starting treatment for the opportunistic infection has been shown to reduce progression of AIDS and death when compared with delayed initiation of HAART [137]. Mortality was also significantly lower among those started on HAART during treatment for TB rather than delaying HAART until treatment was complete [138]. However, these studies did not include critically ill HIV patients.

Starting HAART in critically ill HIV patients admitted to ICU is debatable. Recent studies reported that up to 50% of HIV patients are not on HAART at the time of ICU admission [11,14,22,24]. The lifesaving role of HAART has led to questions concerning the potential treatment of patients with HIV infection in the ICU with HAART. At the moment there are no randomized clinical trials evaluating the safety, efficacy, and timing of starting HAART in the ICU setting and there is no consensus guideline to help make such decisions.

Some valid concerns persist regarding administration of antiretroviral therapy in HIV patients in the ICU, such as the possibility of unpredictable medication absorption, variable drug levels, and the potential for medication toxicities and drug interactions [139]. Paradoxical worsening of the underlying respiratory failure can also result from IRIS to pneumocystis pneumonia, TB, or other mycobacterial disease after the initiation of anti-retroviral therapy. Manifestations of IRIS that can result in critical illness include pneumonitis, acute respiratory distress syndrome, meningitis, hepatitis, pancreatitis, pericarditis and lactic acidosis [17-19,139-146]. In addition, some studies observed that ICU mortality was not different when comparing patients receiving effective HAART with those not on HAART [15,16,36,37].

However, findings of some recent studies suggest that use of HAART in the ICU may be associated with better outcome and stopping HAART in ICU is not beneficial [126,147,148]. HAART use at ICU admission has been associated with higher CD4 cell counts, lower plasma

HIV RNA levels, higher serum albumin, and lower proportions with AIDS-associated ICU admission [16]. HAART was also associated with a decreased risk of bacterial pneumonia [21]. A French study observed that introducing or continuing HAART in the ICU was protective and was associated with better long-term outcome [24]. Any potential toxic side effects like IRIS can be treated with corticosteroids and in most cases HAART can be continued. Deferral of the initiation of HAART to the first 4 weeks of the continuation phase of TB therapy can reduce the risks of adverse effects of HAART without increasing the risk of death [17].

Conclusion

Respiratory failure is a relatively common presentation in HIV-infected patients, often requiring admission to critical care. Outcomes for such patients have significantly improved since the AIDS epidemic and currently is comparable to that of non-HIV patients. Improving ICU outcome of HIV patients reflects general advancement in management of critical illness in such cases rather than improvements in the management of HIV-related illnesses. Hence, we feel that HIV patients with respiratory failure will benefit from early admission to critical care.

Patients with severe AIDS-defined disease are less likely to benefit from invasive mechanical ventilation and NIV/CPAP should be the primary consideration. HIV patients with less severe AIDS-related illness and the ones without any known AIDS defining condition should be considered for either NIV or invasive mechanical ventilation, because the outcomes are good in this population. To avoid complications of barotrauma, a lung protective ventilation strategy with low tidal volume and low inspiratory plateau pressures should be adopted similar to patients with acute respiratory distress syndrome.

Whenever possible, samples of induced sputum should be sent for culture, cytology and acid fast bacilli. BAL needs to be considered if the sputum results are inconclusive for organisms. Clinicians should be aware of limited specificity of PCR in respiratory specimens for detection of *P. jirovecii* due to widespread colonisation. HRCT is to be considered if chest X-ray is normal or shows non-specific changes. Serum protein, CD4 T-cell count, HIV RNA viral load and serum LDH should be requested.

In view of the frequent occurrence of bacterial pneumonia and sepsis in HIV patients, prompt administration of broad-spectrum antibiotics should be considered in the initial treatment regime while awaiting results of sputum culture, BAL or PCR. Empirical treatment for *P. jirovecii* with trimethoprim sulpha-methoxazole and steroid should be considered if clinical suspicion of *P. jirovecii* is high. Possibility of active TB, in particular multi-resistant TB, should be ruled out prior to initiation of steroid therapy. Evidence of concomitant CMV infection may be clinically irrelevant and does not need anti-CMV treatment if the patient is getting better with treatment for pneumocystis and other infections.

In patients who have been on HAART prior to admission to ICU, this treatment should be continued if possible, provided absorption from the gut seems appropriate. HIV patients that are not on HAART on ICU admission should be considered for this after multi-disciplinary discussion and after treating other acute illnesses for 2 weeks. HAART should be deferred for 4 weeks if a patient with HIV has TB and is on anti-TB treatment. However, HAART should be considered as soon as patient starts to tolerate anti-TB treatment (WHO recommendations 2010). Doses of antiretroviral drugs should be adjusted according to renal and liver functions. In the event of a patient developing IRIS due to HAART, corticosteroids should be considered and HAART may be continued.

Intensive care clinicians should keep in mind that a high percentage of HIV patients (up to 40%) are not known to have HIV prior to admission to critical care. As recurrent bacterial pneumonia is associated with HIV, clinicians should request a HIV test in such patients.

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