Critical illness due to infection in people living with HIV

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Summary

People living with HIV comprise a substantial number of the patients admitted to intensive care. This number varies according to geography, but all areas of the world are affected. In lower-income and middle-income countries, the majority of intensive care unit (ICU) admissions relate to infections, whereas in high-income countries, they often involve HIV-associated non-communicable diseases diagnoses. Management of infections potentially resulting in admission to the ICU in people living with HIV include sepsis, respiratory infections, COVID-19, cytomegalovirus infection, and CNS infections, both opportunistic and non-opportunistic. It is crucial to know which antiretroviral therapy (ART) is appropriate, when is the correct time to administer it, and to be aware of any safety concerns and potential drug interactions with ART. Although ART is necessary for controlling HIV infections, it can also cause difficulties relevant to the ICU such as immune reconstitution inflammatory syndrome, and issues associated with ART administration in patients with gastrointestinal dysfunction on mechanical ventilation. Managing infection in people with HIV in the ICU is complex, requiring collaboration from a multidisciplinary team knowledgeable in both the management of the specific infection and the use of ART. This team should include intensivists, infectious disease specialists, pharmacists, and microbiologists to ensure optimal outcomes for patients.

Introduction

Despite a reduction in HIV incidence and mortality the number of people living with HIV remains globally high.[1] In 2022, 39 million (IQR 33·1–45·7) people were living with HIV and 1·3 million (IQR 1–1·7) people with newly acquired HIV. [1]At the same time, 29·8

million people have access to antiretroviral therapy (ART) and, even though mortality has declined substantially (by 69% since the peak in 2004 and 51% since 2010), in 2022, about 630 000 (IQR 480 000–880 000) people died from AIDS-defining illnesses worldwide.[1]

The reduction in intensive care unit (ICU) admissions and mortality can largely be attributed to earlier diagnosis of HIV with improved access to ART. Although these reductions do represent improved short-term mortality, whether these improvements can be applied to long-term mortality remains unclear. [2,3] Previous studies indicate that 5–10% of hospitalised people living with HIV are admitted to the ICU if resources are available, with up to 40% of these patients diagnosed with HIV on admission to the ICU.[4] Although the reasons for hospital admission are largely due to HIV-related comorbidity, the HIV diagnosis can be an incidental finding. Criteria for ICU admission of people living with HIV can differ markedly between different facilities and among high-income and lower-income and middle-income countries, depending on multiple factors. These factors include predicted mortality, often assessed using the APACHE II or SOFA scores, as well as resource constraints such as bed capacity or availability, access to medications, and staff availability. These are important considerations, especially in lower-income and middle-income countries that still bear the brunt of the HIV pandemic. For example, of 903 patients admitted to a South African ICU in 2017, 204 (23%) were living with HIV. The main reasons for admission were sepsis-related (n=95 [47%]), postoperative care (n=69 [34%]), and non-sepsis-related illnesses (n=40 [20%]).[5] Bacterial pneumonia was the most common infectious disease, followed by tuberculosis, *Pneumocystis jirovecii* pneumonia (PJP), malaria, bacterial meningitis, and acute gastroenteritis. This contrasts

with the situation in Europe, where a multicentre trial evaluated the shifting epidemiology from 1997 to 2020.[6] Overall, 24 298 admissions were registered with 630 (3%) of these admissions in people living with HIV. As expected, the mean age, the number of comorbidities (diabetes, renal, respiratory, solid organ neoplasia) and the number of people on ART increased over this period, whereas the proportion diagnosed with HIV on admission decreased significantly. The admission diagnoses overall were acute respiratory distress 223 (35%), shock 117 (19%), and coma 109 (17%), with infection, mostly pneumonia, diagnosed in 342 (54%). Of those with HIV, 38% were related to an AIDS-classifying condition, and 11% to an HIV associated non-AIDS condition—with 51% having conditions not directly related to HIV.[6]

Worse outcomes in people living with HIV are associated with many different factors, including the acuity of illness, low albumin levels, need for vasopressor or inotropic support, requirement for mechanical ventilation, and the presence of PJP or other AIDS-related illnesses.[5,7] Although controversial, it has been noted that HIV viral load and CD4 cell count are not always predictive of ICU mortality. Furthermore, a multicentre, prospective cohort study of people living with HIV receiving ICU care concluded that delayed ICU admission and severity of critical illness determined short-term and medium-term mortality rates rather than factors associated with HIV infection. [8]Outcomes for people living with HIV admitted to critical care in high-income countries are largely similar to those of people living without HIV when matched for disease severity, with mortality rates similar for unselected patients..[3]

If a patient is found to be living with HIV, several management considerations follow, including whether the person is on or adherent to ART, whether the individual is

virally suppressed, which specific therapeutic regimen they are on, and whether they would be able to continue that therapy while in hospital.

Careful consideration for HIV testing without explicit consent, especially in patients too ill to provide consent, is a difficult area and best undertaken following recovery with appropriate counselling and consultation with physicians experienced in this matter.

This Review examines common HIV-associated infections that require ICU admission, including treatment, outcomes, and recommendations regarding ART.

Sepsis

Any type of infection can cause sepsis which is an all-encompassing term indicating the severity of the underlying condition and its clinical impact. The Third International Consensus Definitions for Sepsis and Septic Shock defined sepsis as “life-threatening organ dysfunction caused by a dysregulated host response to infection”.[9] As early as 2013, sepsis was the primary cause of ICU admission and death in hospitalised patients with HIV and has remained so in both high-income countries and low-income and middle-income countries.[10,11] In a small study from Africa, patients with sepsis were evaluated according to HIV status and viral load.[12] Of 148 patients, 96 patients with sepsis were HIV-positive and 39 were not on ART. Disease-specific mortality was two of eight for *Streptococcus pneumoniae* ; five of 14 for cryptococcal disease; seven of 22 for tuberculosis; and three of five and three of nine for bacteraemic patients with Gram-positive and Gram-negative infections, respectively.[12] In a systematic review of patients with sepsis from high-income countries and low-income and middle-income countries (n=82 905), mortality was 28% higher in people living with HIV (95% CI 1·13–1·46;

p<0·01) and was higher in low-income and high-income countries (relative risk [RR] 1·43 [1·15–1·77]; p=0·0010 *vs* RR 1·29 [1·10 1·53]; p=0·0020).[13]

In a study from the USA, out of 1095 patients with sepsis, 15% were people living with HIV with only 22% of these patients on ART. Using multivariable analysis and correcting for confounders, HIV infection (odds ratio 1·78; p=0·0050) was an independent predictor of mortality.[14] Despite this, a prospective study of patients with sepsis demonstrated that people living with HIV and those without HIV were similar in terms of disease severity, plasma concentrations of host response biomarkers, and survival. [15]

Respiratory Infections

Community-acquired pneumonia (CAP)

Bacterial respiratory diseases, including CAP, are among the most common infectious complications in PLWH, occurring at all levels of CD4 cell count, but with increasing frequency the greater the degree of immunosuppression.[16]

Despite ART, CAP remains twenty-five times more common in PLWH, both in LMIC and HIC because of incomplete immune reconstitution and ongoing immune activation.[16–18] Other factors that predispose to CAP in PLWH are chronic viral hepatitis, alcohol use, smoking, chronic obstructive pulmonary disease, malignancy, chronic kidney disease and heart failure. Many of these are as a consequence of patients on ART living longer and being afflicted with diseases associated with aging. A recent study from South Africa indicated that despite a stable prevalence of HIV and increased roll-out of ART, the burden of invasive pneumococcal disease (IPD) in adults has not decreased.[19] Even in

HIC the incidence of CAP and IPD remains high even if virally suppressed and with high CD4 cell counts.[20]

The most common pathogens causing CAP are *Streptococcus pneumoniae* and *Haemophilus influenzae*; however, in LMIC, *Mycobacterium tuberculosis* (Mtb) may be the predominant pathogen in up to or even exceeding 20% of patients.[16,18,21–23] In Europe, the German CAPNETZ-Cohort included *Staphylococcus aureus* as a potential pathogen and determined there was no difference in the frequency of pathogens in patients with and without HIV.[24,25] Both monomicrobial and polymicrobial infections occur, and the risk of bacteraemia is greater in PLWH, [23,25] particularly with pneumococcal infections.[16]

Although atypical bacterial pathogens are uncommon, organisms such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* occur more frequently in PLWH than in patients without HIV and viral infections are also important, particularly influenza A and B.[22] Opportunistic pathogens including PJP and *Cryptococcus neoformans,* also cause pneumonic illnesses in those with advanced immunosuppression. In very immunocompromised patients with CD4 cell counts < 200/cells/mm^3, infections with *Mycobacterium avium* complex, *Nocardia* spp., *Rhodococcus equi*, and *Aspergillus* spp., should also be considered.[3]

Severity of illness scores such as the pneumonia severity index (PSI), Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guideline, or the CURB-65 may be valid for use in patients with HIV when combined with the CD4 cell count.[16] Where the PSI did not predict increased mortality risk, a CD4 count < 200 cells mm^3 was predictive,[26] and these patients should be hospitalised and considered for ICU.[16] Both the modified ATS criteria and the Pittsburgh bacteraemia score (PBS) best identify patients

who might benefit most from intensive care whether living with HIV or not.[16] In a setting of high HIV prevalence, an increasing, or persistently elevated procalcitonin > 10ng/ml in the first 48 hours after ICU admission also predicted higher mortality than if it had remained unchanged or decreased.[27] While some studies suggest CAP is associated with increased mortality in PLWH others do not.[16,28] In the CAPNETZ study, independent predictors of increased mortality included CD4 count < 100 cells/mm^3, radiographic progression of disease, and septic shock.[24]

A previous study from South Africa of people living with HIV admitted to ICU indicated that respiratory illness, mainly community-acquired pneumonia, was responsible for 30·7% of admissions, and the ICU and hospital mortality were 25·3% and 34·7%, respectively.[29] Predictors of mortality in this study were an APACHE-II score of more than 13 and need for renal replacement therapy and inotropes, whereas use of ART, CD4 cell count, detectable HIV viral load, and HIV diagnosis on ICU admission were not considered predictors.

Diagnostic testing is in general similar for hospitalised patients without HIV, but additional testing is recommended for immunocompromised patients. This involves sputum specimens, blood cultures, urine antigen testing (*L pneumophilia, S pneumoniae*), thoracentesis, and if possible, bronchoscopy and lavage along with appropriate imaging.[16]

Antibiotic therapy for pneumonia in people living with HIV is similar to that for those without HIV (table 1)..[16,18,22,30–35] Empiric therapy is directed at the likely organism, with consideration given to the possibility of Pseudomonal or Staphylococcal infection.[16,18,22] Patients with severe bacterial CAP should be treated with combination therapy, a β-

Table 1: Treatment of common infections in PLWH in the ICU

Condition	Typical CD4 Strata	Causative organism(s)	Therapy	Additional considerations
Sepsis	Any CD4 cell count	Common: *Escherichia coli, Klebsiella pneumoniae, Streptococcus pneumoniae Staphylococcus aureus, Mycobacterium tuberculosis,* Other: *Salmonella* spp., *Cryptococcus* spp., *Pneumocystis jirovecii, Candida* spp.	Directed at the specific pathogen	
Respiratory infections				
Community-acquired pneumonia	Any CD4 cell count	Common: *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Mycobacterium* tuberculosis. Other: *Pseudomonas aeruginosa*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Cryptococcus* spp., *Nocardia* spp. *Aspergillus* spp., *Mycobacterium avium* complex, *Rhodococcus equi*.	Therapy, in general, is similar to that for HIV-negative individuals, with a higher incidence of atypical organisms in PLWH with CD4<200 cells/mm^3. **Empiric therapy:** β-lactam antibiotic plus macrolide or fluoroquinolone (guided by patient-specific risk factors, local epidemiology and sensitivity).[16,18,22] **Definitive therapy:** Directed at the specific pathogen	The role of corticosteroids as adjunctive therapy in CAP in PLWH has not been studied and the current ATS/IDSA guideline does not recommend routine use except with refractory shock and possibly severe disease.[30]
Pneumocystis jirovecii pneumonia (PJP)	CD4 <200 cells/mm^3	*Pneumocystis jirovecii*	**1st line:** Trimethoprim-sulfamethoxazole (TMP-SMX) (15-20mg/kg/day of the trimethoprim component) q6hrly or q8hrly for 21 days.[31] **2nd line** (intolerance or treatment failure on 1st line): Clindamycin 600mg IVI q8hrly PLUS Primaquine (base 15-30mg po q24hrly) for 21 days.[31]	ART should be initiated ***within two weeks*** of initiating therapy for PJP Following 21 days of anti-PJP therapy, PJP prophylaxis should be given until CD4 count>200 cells/mm^3 for at least 3 months[31]

			Adjunctive therapy: corticosteroids 15-30mins before commencing anti-PJP therapy (prednisone Day 1-5: 40mg q12hly, Days 6-10: 40mg q24hrly, Days 11-21: 20mg q24hrly; or equivalent).[31]	
Pulmonary tuberculosis	Any CD4 cell count*	*Mycobacterium tuberculosis*	Therapy, in general, is similar to that for HIV-negative individuals **Drug-susceptible tuberculosis:** standard four-drug therapy for an Intensive Phase of two months: Rifampicin (10mg/kg/day) Isoniazid (5mg/kg/day) Ethambutol (15mg/kg/day) Pyrazinamide (25mg/kg/day) Followed by rifampicin and isoniazid for a Continuation Phase of at least 4 months. **Parenteral therapy:** Where the enteral route of administration is compromised, intravenous therapy options may include a combination of at least three of the following: Rifampicin (10mg/kg/day)[#] Linezolid 600mg/day Fluoroquinolones (levofloxacin 750-1000mg/day and moxifloxacin 400mg/day) Amikacin 15mg/kg/day.[32]	In order to reduce the environmental risk of *Mycobacterium tuberculosis* exposure to hospital staff, mechanical ventilators should be fitted with heat moisture exchangers and have filters on the exhalation ports. Intubation should involve the use of N95 masks and patients should preferably be nursed and managed in a negative pressure environment
COVID-19	Any CD4 cell count	SARS-CoV-2	Therapy, in general, is similar to that for HIV-negative individuals	

Cytomegalovirus pneumonitis	CD4 <50 cells/mm^3	Cytomegalovirus	**Option 1:** Ganciclovir 5 mg/kg IV q12h for 14–21 days then Ganciclovir 5 mg/kg IV daily, or valganciclovir 900 mg PO daily.[33] **Option 2:** Valganciclovir 900 mg PO q12h for 14–21 days, then 900 mg once daily.[33]	Cytomegalovirus may also cause colitis, encephalitis or disseminated disease.
Central nervous system infections				
Bacterial meningitis	Any CD4 cell count	Common: *Streptococcus pneumoniae, Neisseria meningitidis* Other: *Haemophilus influenzae, Staphylococcus aureus, Listeria monocytogenes Salmonella* spp., *Escherichia coli*.	Therapy, in general, is similar to that for HIV-negative individuals and guided by patient-specific risk factors, local epidemiology and sensitivities	
Cryptococcal meningitis	CD4 <100 cells/mm^3	Common: *Cryptococcus neoformans*. Other: *Cryptococcus gatii*	**Induction therapy:** Single high-dose (10mg/kg) of liposomal amphotericin B with 14 days of flucytosine (25mg/kg/day q6hrly) and fluconazole (1200mg q24hrly).[34] Alternative regimens: Amphotericin B deoxycholate (1mg/kg q24hrly) or liposomal amphotericin B (3mg/kg q24hrly) and flucytosine (25mg/kg q6hrly) for 7 days followed by fluconazole (1200mg q24hrly) for 7 days. [34] **Consolidation therapy:** Fluconazole (800mg q24hrly) for 8 weeks.[34] **Maintenance therapy:** Fluconazole (200mg q24hrly) for at least 1 year, and	ART should be initiated ***4-6 weeks*** after initiating therapy for CCM

			until immune reconstitution (CD4>200 cells/mm^3) and viral load suppressed.[34]	
Tuberculous meningitis	Any CD4 cell count*	*Mycobacterium tuberculosis*	Standard 4-drug TB therapy is recommended for at least 9-12 months See doses above	ART should be initiated ***4-8 weeks*** after initiating therapy for TBM The role of corticosteroids in the treatment of TBM in PLWH is unclear and guided by expert opinion
Toxoplasma encephalitis	CD4 <100 cells/mm^3	*Toxoplasma gondii*	**Option 1:** Sulfadiazine (1000-1500mg q6hrly) AND pyrimethamine (200mg loading dose followed by 50-75mg q24hrly) AND folinic acid (10-25mg 24hrly) for 6 weeks.[35] **Option 2**: Trimethoprim-sulfamethoxazole (TMP-SMX) (5mg/kg of the trimethoprim component q12hrly) for 6 weeks.[35]	ART should be initiated ***within two weeks*** of initiating therapy for toxoplasmosis

* Risk increases with decreasing CD4 cell count
# IV formulation is not widely available in LMIC

lactam antibiotic plus macrolide or fluoroquinolone (Table 1). The role of corticosteroids in patients with severe community-acquired pneumonia has not been studied in people living with HIV[16] and the most recent American Thoracic Society/Infectious Diseases Society of America guidelines do not recommend routine use of corticosteroids.[30]

Pneumocystis jirovecii Pneumonia

Although ART has resulted in a decline in the incidence of PJP, it still occurs regularly in those unaware of their diagnosis or those who have their treatment interrupted. In 29 studies reporting on HIV-associated PJP from January, 2000, to December, 2022, the pooled prevalence was 35·4% (95% CI 23·8–47·9)[36]

Severe disease usually presents with respiratory failure, and a retrospective cohort study of PLWH admitted with severe pneumonia requiring high- or intensive care, found PJP to be the aetiological agent in 21.4% (25/117).[37] The mortality in this cohort was high (40.1%) but there was no significant survival difference between those with PJP or without. Need for ICU admission, requirement for MV, and CMV viremia were however all associated with increased mortality.

Induced sputum or bronchoalveolar lavage fluid (BALF) can be used to make a definitive diagnosis with by staining the cell wall of the cyst.[38] Overall, because the sensitivity of these stains performed on BALF is variable, they are performed less often in HIC. [38] Similarly immunofluorescent stains are used less frequently with a significant range in specificities and sensitivities depending on where the test is performed.[38] Newer techniques have become available and are inclusive of; molecular methods of detection such as the polymerase chain reaction (PCR), (pooled sensitivity 98%, 99%, and 97%

and pooled specificity 91%, 90%, and 94%) from BALF samples, and loop-mediated isothermal amplification (LAMP) which has sensitivity and specificity similar to PCR.[38] β-d-glucan testing performed on blood has a high sensitivity but relatively low specificity at approximately 95% and 75% to 86% respectively.[38]

Treatment usually consists of trimethoprim -sulfamethoxazole (TMP-SMX) and corticosteroids although alternatives exist for treatment failure or where toxicity limits use of TMP-SMX.[31] (Table 1) Recently echinocandins have also been suggested as alternative or add-on therapy in severe cases but more evidence for efficacy is required.[39]

Even with early and appropriate therapy and the best standard of care, those with severe disease (defined as hypoxaemic respiratory failure requiring high flow nasal oxygenation (HFNO) with a fraction of inspired oxygen of ≥0.5, non-invasive ventilation (NIV) or MV) have a mortality of 50%.[40] For this reason, and given that availability of mechanical ventilators is frequently limited, other less invasive and costly interventions, such as high flow nasal oxygen (HFNO) and NIV are options. In a study of 120 patients (56 HFNO and 57 NIV after exclusions), 94.7% of whom had PJP with respiratory failure, there was no significant difference in day 28 intubation rate between the two modalities (28.6% vs. 35.1%, p = 0.457).[41] HFNO was better tolerated and required fewer airway care interventions.[41] The mortality of patients who fail these modalities and require MV is high, in the region of 50-60%.[42] Recently, multiple case reports describing the management of PJP utilising venovenous (VV)-extracorporeal membrane oxygenation (ECMO) in both PLWH and people without HIV have been published, however, there are as yet no randomised controlled trials.

Tuberculosis

Tuberculous infection requiring ICU support has a high mortality, which is significantly and adversely impacted by HIV coinfection.[43] Most studies of HIV and TB co-infection are from LMIC given the increased incidence of both, relative to HIC. In a South African study of 84 patients with TB admitted to the ICU, 44 (53%) were co-infected with HIV. Of these, the mortality was 40.9%.[44] In a study of 120 patients in the ICU from Brazil with HIV and tuberculosis co-infection, 86% of whom were classified as having acute respiratory distress syndrome, the mortality was even higher at 78%, although there were many comorbidities in these patients that could have contributed to this outcome.[45]

Patients with CD4 counts < 200 cells/mm^3 are more likely to develop TB bacteraemia, have mycobacterial infections other than TB complicating the choice of appropriate therapy, and are also more likely to have multidrug-resistant mycobacterial infections on presentation.[46,47] Common risk factors for mortality in PLWH include low CD4 cell count, need for MV, disseminated or miliary TB, delay in initiation of appropriate treatment, and high severity of illness scores.[48] In the Brazilian study described above, the factors independently associated with mortality were requirement for MV ($p = 0.002$), hypoalbuminaemia ($p = 0.013$), and CD4 count < 200 cells/mm^3 ($p = 0.002$).[45]

Diagnostic difficulty often delays therapy; however, submission of sputum or other fluids such as BALF for nucleic acid amplification testing (NAAT) such as the GeneXpert® MTB/RIF-Ultra has simplified diagnosis. PLWH with pulmonary and extrapulmonary TB are often sputum-scarce and, although limited in the presence of anuria/oliguria, the urine lipoarabinomannan (U-LAM) lateral flow assay can be useful for diagnosis with a sensitivity and specificity in all settings of 42% (31–55%) and 91% (85–95%)

respectively.[49] Interferon-gamma release assays (IGRA) have poor sensitivity and specificity in critically ill patients and are estimated to range from 75% to 88% (95% CI 46% - 99%), and 35% to 51% (95% CI 30% - 54%) respectively, with both dependent on the country or study population.[50,51]

Treatment remains the same as that for patients not in the ICU and will require evaluation of the resistance profile of the organism. Shorter course therapies such as the combination of bedaquiline, pretomanid, linezolid (BPaL) and moxifloxacin for drug-resistant TB have dramatically improved outcomes in that setting.[52]

Treatment may however be complicated by a dysfunctional gastrointestinal tract (GIT) or involvement of the GIT by TB, and agents such as levofloxacin, linezolid, rifampicin and amikacin amongst others, can be administered parenterally as a temporary measure until the GIT is functional.(Table 1)[32] The presence of acute kidney injury and acute hepatic dysfunction in the critically ill patient also needs to be considered, along with the significant potential for drug interactions with ART (Table 2) which may also cause hepatic injury. The use of corticosteroids for respiratory failure is controversial in pulmonary TB and may actually increase mortality.[53,54]

An additional consideration is the environmental risk to hospital staff, an issue that is relevant for all communicable infectious diseases.[55] Mechanical ventilators should be fitted with heat moisture exchangers and have filters on the exhalation ports. Intubation should involve the use of N95 masks and patients should preferably be nursed and managed in a negative pressure environment. There is also a potential for spread in patients that require nebulisation.

Table 2. Drug interactions of commonly used drugs in the intensive care unit

	Antiretroviral therapy interactions	Mechanism
Antimicrobials		
β-lactams	Avoid lenacapavir and cabotegravir with flucloxacillin	Flucloxacillin is a moderate inducer of CYP3A4
Tuberculosis drugs *	Avoid lenacapavir, fostemsavir, cabotegravir, bictegravir, rilpivirine, cobicistat, dolutegravir, doravirine, and protease inhibitors with rifampicin, rifapentine, or rifabutin; if coadministration needed, increase antiretroviral dose; avoid pretomanid with efavirenz and etravirine	Induction of CYP3A4 resulting in decreased antiretroviral exposure; efavirenz and etravirine are moderate inducers of CYP3A4 and decrease pretomanid exposure
Isavuconazole	Avoid with elvitegravir, cobicistat, atazanavir, or darunavir; also avoid with efavirenz and etravirine	Isavuconazole is metabolised by CYP3A4/5 and uridine 5′-diphospho-glucuronosyltransferase, decreases elvitegravir, atazanavir, and darunavir exposure and increases isavuconazole concentrations; efavirenz and etravirine induce CYP3A4 and decrease isavuconazole exposure
Ketoconazole	Avoid with efavirenz	Efavirenz and ketoconazole prolong QT interval
Ribavirin	Monitor haemoglobin concentrations closely if administered with atazanavir	Anaemia exacerbation
Corticosteroids		
Dexamethasone	Avoid high doses for prolonged periods with rilpivirine and lenacapavir	Dexamethasone is a dose-dependent inducer of CYP3A4 and becomes a moderate CYP3A4 inducer at doses higher than 16 mg, decreasing rilpivirine and lenacapavir exposure
Gastrointestinal medications		
Proton pump inhibitors	Avoid with rilpivirine or protease inhibitors; if proton pump inhibitors are essential administer 12 h after or before atazanavir with cobicistat or atazanavir with ritonavir	Significant decreases in rilpivirine exposure might occur due to gastric pH increases
Bismuth and antacids	Avoid with bictegravir, cabotegravir, or dolutegravir	Chelation by high concentrations of trivalent bismuth cations might result in reduced bictegravir, cabotegravir, or dolutegravir exposure; bismuth should be administered at least 2 h before or 4 h after taking these antiretrovirals
Sucralfate	Avoid with raltegravir or dolutegravir	Decreases raltegravir concentrations by chelation with polyvalent cations
Domperidone	Avoid with lenacapavir, cobicistat, efavirenz, and protease inhibitors	Domperidone metabolised by CYP3A4
Anticoagulation		

Direct oral anticoagulants	Avoid with protease inhibitors or cobicistat-boosted antiretrovirals (if essential, dabigatran is safest)	Possible increased clinical effect as a result of inhibition of CYP3A4 metabolism and P-glycoprotein
Clopidogrel	Avoid with lenacapavir, lopinavir, darunavir, cobicistat, ritonavir, and atazanavir	Clopidogrel is a prodrug, active metabolite via CYPs 3A4, 2B6, 2C19, and 1A2; ritonavir and cobicistat decrease levels of active metabolite of clopidogrel reducing its efficacy
Ticagrelor	Avoid with atazanavir, cobicistat, lopinavir, and ritonavir	Possible increased risk of bleeding through inhibition of metabolism through CYP3A4 and inhibition of P-glycoprotein efflux
Analgesia		
Pethidine	Potential interaction with efavirenz, etravirine, lenacapavir, and protease inhibitors	Decreases pethidine concentrations and increases toxic metabolite concentrations; increases seizure risk
Morphine, fentanyl, hydromorphone, dimorphine	Potential interaction with protease inhibitors, lenacapavir, nevirapine, and efavirenz	Protease inhibitors inhibit CYP3A4 resulting in increased opioid concentrations
Oxycodone	Potential interaction with protease inhibitors, efavirenz, and etravirine, as well as with lenacapavir	CYP2D6 or CYP3A inhibition by protease inhibitors and lenacapavir results in increased oxycodone concentrations, so consider decreasing oxycodone dose; efavirenz and etravirine induce CYP3A4 which can decrease concentration of oxycodone
Methadone	Potential interaction with efavirenz	Decreases concentration of methadone due to induction of CYP3A4, watch for opioid withdrawal; increases QT interval
Anti-inflammatories	Watch for increases in nephrotoxicity with tenofovir disoproxil fumarate and tenofovir alafenamide (nephrotoxicity of tenofovir disoproxil fumarate combined with anti-inflammatory drugs is greater than that of tenofovir alafenamide combined with anti-inflammatory drugs); potential interaction of diclofenac and ibuprofen with etravirine	Dual nephrotoxicity
Piroxicam	Avoid using with ritonavir	Increases concentrations of piroxicam and increases risk of serious respiratory depression or haematological abnormalities
Sedation		
Midazolam, triazolam	Avoid with lopinavir, darunavir, atazanavir, ritonavir, or cobicistat	Midazolam is extensively metabolised by CYP3A4; coadministration with lopinavir, darunavir, atazanavir, ritonavir, or cobicistat increases midazolam concentrations
Haloperidol	Avoid with atazanavir, ritonavir, and lopinavir	Lopinavir, atazanavir, and ritonavir increase haloperidol concentrations and increase risk of QT prolongation
Antiarrhythmics		

Amiodarone	Avoid with atazanavir, ritonavir, cobicistat, darunavir, elvitegravir, and lenacapavir	Amiodarone is metabolised by CYP3A4 and concentrations might be increased due to inhibition of CYP3A4 by atazanavir, ritonavir, cobicistat, darunavir, elvitegravir, and lenacapavir
Antiepileptics		
Carbamazepine, cenobamate, oxcarbazepine, phenobarbital, primidone, phenytoin, eslicarbazepine	Avoid with fostemsavir; avoid with lenacapavir, dolutegravir, rilpivirine, ritonavir, doravirine, efavirenz, etravirine, and protease inhibitors	Fostemsavir is a prodrug and is hydrolysed to the active compound temsavir in the small intestine; temsavir is mainly metabolised by esterase-mediated hydrolysis with a small contribution of CYP3A4; antiepileptics result in CYP3A4 induction and hence lower fostemsavir exposure; carbamazepine, cenobamate, oxcarbazepine, phenobarbital, phenytoin, and primidone are strong inducers of CYP3A4 and hence result in lower lenacapavir, dolutegravir, rilpivirine, ritonavir, doravirine, etravirine, efavirenz, and protease inhibitor exposure

* Drug interactions, especially between rifamycin and pretomanid, are extensive and complex; guidelines should be consulted for guidance. Further drug–drug information can be found on the HIV Drug Interactions website.

COVID-19

Among people with COVID-19, the global prevalence of HIV is estimated to be 2% and as high as 11% in Africa.[56] There is controversy as to whether HIV seropositivity increases mortality. Initial multinational case-control studies showed no difference in cumulative outcomes in PLWH versus those without HIV, which was contradicted by subsequent larger analyses which indicated that PLWH are more vulnerable to severe disease, hospitalisation and death.[57–60]

Cytomegalovirus (CMV)

CMV causes disease in PLWH with CD4 counts < 50 cells/mm^3. The most common presentations in those requiring ICU are pneumonitis and neurological disorders.[61] These conditions are relatively rare particularly in the ART era. In a large epidemiological study of AIDS-defining opportunistic infections in 18,733 PLWH diagnosed from 1993 to 2008, only 0.6% had documented CMV infection and there were no cases of CMV pneumonia.[62]

In all critically ill patients, CMV reactivation is associated with prolonged ICU stay, increased risk for infection, prolonged MV, and markedly increased mortality.[63] This is, likely to be a marker rather than a cause of severe illness. Prophylactic treatment of critically ill CMV seropositive patients has shown mixed results. In one study that compared valganciclovir, valaciclovir or no treatment, the first two groups suppressed viral reactivation but, while not powered for mortality, the valacyclovir arm was stopped early due to a higher mortality rate than the placebo arm.[64] Other studies have shown no benefit.[65] Overall CMV-associated end organ disease is best prevented by prompt initiation of ART, although antivirals are necessary in CMV neurological disease where if

untreated, mortality occurs rapidly, and it may also be of benefit in CMV pneumonia although data in this setting is limited.[33] Therapeutic agents consist of ganciclovir initially intravenously (IV) followed by valganciclovir orally or alternatively valganciclovir can be given orally from initiation of therapy (Table 1).[33]

Central Nervous system (CNS) Infections

HIV infection in the ART era is associated with an 8-fold increased risk of meningitis, mostly caused by typical bacterial pathogens.[66] In the US, the most common cause of meningitis is *Cryptococcus neoformans* with cryptococcal meningitis (CCM) accounting for 30% of cases, bacteria accounting for 12% (of which *S. pneumoniae* is the most common), and 43% without a documented cause.[67] This can be compared to LMIC where CCM is followed by tuberculous meningitis (TBM) as the most common causes.[68] Mortality is high, particularly from TBM and CCM where it may exceed 50%.[69] As mentioned below, deferral of initiation of ART is warranted to avoid the potentially devastating effects of the immune reconstitution inflammatory syndrome (IRIS) with these infections.

People living with HIV may also be affected by *Toxoplasma* gondii, and viruses such as Herpes simplex and CMV, presenting with altered level of consciousness, localizing signs or convulsions.[70]

Lumbar puncture (LP) should be performed whenever meningitis is suspected with awareness of, and caution taken, for the possibility of obstructive hydrocephalus. Besides the standard assessment of cerebrospinal fluid (CSF), the WHO recommends automated NAATs be used for the initial diagnosis of TBM. This has a sensitivity and specificity in

CSF of 70% and 97% respectively for diagnosis, and 87% and 88% respectively for detection of rifampicin resistance when compared to microbiological reference standards.[52]

The preferred method for diagnosis of CCM is CSF cryptococcal antigen detection, which has advantages over microscopy and culture; better sensitivity and specificity (99.3% and 99.1% respectively),[71] ease of use, and short turnaround time (rapid diagnosis is essential to reduce mortality). Commercial NAATs are available for the rapid detection of bacterial and viral pathogens and next-generation sequencing (NGS) and matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) have potential for accurate, rapid diagnosis.[72]

Definitive diagnosis of toxoplasmosis can be achieved by biopsy of lesions or PCR on CSF which has a high specificity (96%–100%), but low sensitivity (50%), especially once therapy has been initiated The diagnosis is also suggested by typical findings on CT and MRI scanning.[73]

Therapy for HIV-associated meningitis is similar to that of people without HIV; however, standard 4-drug TB therapy is recommended for 9-12 months for TBM (Table 1). To date, studies of intensified TB therapy with additional, high dose or intravenous antibiotics, although generally safe, have not proven to be more effective.[74,75] Trials investigating the benefits of adding drugs such as linezolid or fluoroquinolones, aspirin, and cytokines or using very high-dose rifampicin, have shown variable results or are still awaited .[76–78] The BPaL or BPaL-moxifloxacin regimens are not currently recommended for the treatment of rifampicin- or multidrug-resistant TBM although they might be considered if a resistant strain is identified.[79]

First-line therapy for CCM is a combination of either liposomal amphotericin B (LAmB)/amphotericin B deoxycholate with flucytosine and fluconazole (Table 1). Recent evidence with respect to efficacy, toxicity and cost-effectiveness, supports the use of one high dose of LAmB followed by two weeks of flucytosine and fluconazole (Table 1).[34] The cost is similar to an amphotericin B deoxycholate- based regimen and the toxicity lower with grade 3 or 4 adverse events occurring in (50% [210 of 420] with LAmB versus 62% [263 of 422], (P = 0.0003) with the deoxycholate, and life-threatening (grade 4) events in (22% [91 of 420] versus 30% [127 of 422] in controls. There were similar benefits in terms of anaemia and requirement for transfusions (7.6% versus 18.0%).[80]

Therapy of toxoplasmosis consists of pyrimethamine plus sulfadiazine and folinic acid for a minimum of 6 weeks, although where not available, TMP-SMX appears equivalent for the same duration (Table 1).[35]

Corticosteroids are recommended as adjunctive therapy for *S. pneumoniae* meningitis but have not been associated with improved outcomes in adults with other bacterial meningitides.[81] In fact, dexamethasone with amphotericin B and fluconazole is associated with worse neurological outcomes in patients with CCM and the recently published ACT HIV trial of adjunctive dexamethasone for TBM in advanced HIV disease, failed to show mortality benefit over 12 months versus placebo.[82] This study is in contrast to an earlier study that did not consider PLWH alone.[83] Agents directed against pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6 have been used for the treatment of refractory inflammatory complications of TBM however the evidence is limited and mostly confined to case reports.[84]

Raised intracranial pressure (ICP) occurs in both TBM and CCM but in up to 80% of patients with CCM. Opening pressure should be measured at initial LP and thereafter if pressure remains high, it should be repeated, especially with persistently altered mental state. Measures to decrease ICP in CCM include drainage of 20–30 mL of CSF to halve the opening pressure or to a pressure of <20 mmHg, repeated daily until symptoms and signs improve. Ventricular or lumbar shunts should be considered if LP drainage fails to relieve symptoms.[85]

Rarely CMV, and syphilis may involve the CNS and should be considered in the diagnosis if other results are negative.[3]

The use of antiretrovirals in the ICU

The choice of ART drugs has been simplified in the past decade with the advent of potent second-generation integrase inhibitors with minimal side-effects, almost always used in combination with nucleoside reverse transcriptase inhibitors. The benefits of immune restoration far outweigh the side-effects, such that most people living with HIV are initiated on ART immediately after diagnosis. However, rapid initiation has not been adequately explored in ICU settings. Although a systematic review suggested benefit,[86,87] major global recommendations for HIV care currently provide no direction regarding ART selection or timing.[88,89] For patients newly diagnosed with HIV admitted to ICU, ART initiation should not be delayed unnecessarily if hospitalisation is anticipated to be prolonged. Deferral, however, should be considered in unstable patients, where management could be complicated by the potential development of IRIS, ART-induced side effects, or drug interaction(s) (Table 2). Deferral

is specifically recommended in PLWH with newly diagnosed CCM or TBM, where clinical trials have demonstrated increased mortality with early ART (see above).[90]

Choice of ART should be guided by admission diagnosis, with avoidance of tenofovir prodrugs (tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF)) in patients with acute renal dysfunction. Genotype resistance testing to direct therapy when newly initiating ART is recommended in high-resource settings and may be indicated in viraemic patients on established ART entering ICU.[88,89]

For those on ART at admission, the role of specific side effects should be considered as possibly being directly related to the admission or as an exacerbating factor. The safety of currently used drug combinations is excellent, so side effects are unusual and largely a diagnosis of exclusion. Older agents such as abacavir (potentially life-threatening hypersensitivity reactions) and efavirenz (hepatotoxicity and encephalopathy) are used less frequently. The widely used TAF/TDF may exacerbate other causes of acute renal failure but may occasionally be the primary cause, and cause variants of Fanconi's syndrome. Zidovudine (AZT), still occasionally used as a second-line agent, may cause lactic acidosis, anaemia and neutropenia. Lamivudine (3TC) and emtricitabine (FTC), utilised in almost all ART combinations, are rare causes of red cell aplasia, usually within the first year of treatment. All classes of ART may cause or exacerbate hepatic dysfunction, and the protease inhibitors may cause hepatocellular, cholestatic, or mixed pattern disease. Integrase inhibitor/NRTI combinations rarely cause liver dysfunction, and where they do, it has a gradual onset and is easily monitored[91] and similarly, the onset of metabolic abnormalities is slow and relatively rare.

Discontinuation of treatment in the ICU should generally be avoided if possible, in patients on established ART, as resurgent viraemia may clinically manifest in acute antiretroviral syndromes, further complicating the clinical picture, and leading to unnecessary immunological deterioration.

Potential drug-drug interactions should be carefully considered and assessed. (Table 2) Integrase inhibitors and NRTI combinations have limited interactions, except with divalent cations that may supplement enteral feeding regimens, and as such careful attention needs to be paid to timing of administration if used and possibly to stop feeds for a short period before and after administration.[92] The less frequently used protease inhibitors and non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens have significant and often complex drug interactions (Table 2).[93]

There is little pharmacokinetic data to support any specific approach in the complex ICU environment. Assessment of any current regimen's potency or patient compliance can be monitored by HIVVL or drug levels if available. Although rarely necessary, therapeutic drug monitoring is an option even in resource limited settings by means of high performance liquid chromatography with ultraviolet detection, to ensure drug levels are adequate, particularly if the GIT is non- or partially functional.[94] In newly initiated patients, HIVVL decay depends on starting levels, but it is rapid and usually undetectable within weeks.

In general, it is recommended that ART be administered enterally in those on MV, as most formulations are only available in oral (tablet or syrup) form. Where there is GIT dysfunction, intramuscular cabotegravir/rilpivirine is an option for those on ART noting that access is currently very limited in most countries, and that drug-drug interactions are

significant. Additionally, lenacapavir (subcutaneous), ibalizumab (injectable), enfuvirtide (subcutaneous) and zidovudine (infusion) may be used, but access is also very limited. A useful review of administration options for each drug can be found in a paper by San et al.[95] An excellent prescribing resource, is available at www.hiv-druginteractions.org.

Immune reconstitution inflammatory syndrome (IRIS)

IRIS may complicate effective therapy for pre-existing infectious processes in the ICU following the initiation of ART. IRIS is an inflammatory disorder caused by reconstitution of pathogen-specific immunity in response to effective HIV viral suppression, characterised by paradoxical worsening of known and treated (paradoxical IRIS), or as yet undiagnosed (unmasking IRIS), infectious diseases.[96]

The most common pathogens associated with IRIS are mycobacterial (TB and *Mycobacterium avium* complex), viral (CMV, herpes simplex, varicella-zoster, hepatitis B and human herpes 8 viruses) and fungal (*Cryptococcus neoformans* and *Pneumocystis jirovecii*).[97] Rarely, bacteria (*Bartonella henselae*) and parasites (*Schistosomiasis* spp.) have been associated with IRIS.[98,99]

IRIS can develop between 1 week and several months following initiation of ART but typically within 90 days.[97] The incidence, depends on the particular infection and geographic setting, with rates between 7 and 18% and the consequences may be severe requiring ICU admission.[97,100] Although there is no consensus definition for the diagnosis, common features include; a low pre-treatment CD4 cell count and high HIVVL, a temporal association between ART initiation and onset or worsening of clinical features of illness,

clinical features of an inflammatory condition, and evidence of immune restoration and virological suppression.[101] Risk factors include a high infective antigenic burden or disseminated disease, low CD4 count (typically <100 cells/mm^3), high HIVVL, short interval between treatment of the underlying opportunistic infection and initiation of ART, and an increased rate of rise of the CD4 count and rapid decrease in HIVVL.[97,101] It does not seem that any specific antiretroviral agent is more likely to be associated with IRIS, rather it is a function of the efficacy of treatment.

Common nonspecific symptoms include fever and tachycardia and for respiratory diseases such as pulmonary TB or PJP, and there may be worsening of respiratory symptoms, hypoxaemia and radiographic abnormalities.[102] Patients with extra-pulmonary TB may develop lymphadenitis, new pleural effusions, expansion of tuberculomas and hepatitis. Intracranial tuberculomas, TBM or CCM may manifest with new neurological deficits, worsening headache, nuchal rigidity, and photophobia. Overall, the mortality associated with IRIS has been estimated at 4.5%[103] but in CCM-IRIS this approaches 20%.[103]

Despite the risk of IRIS, initiation of ART is recommended as soon as possible or within two weeks for most opportunistic infections. Exceptions exist for those with CNS-TB and CCM where adverse events outweigh benefits as described above.[89] If IRIS develops, ART should be continued unless it is life-threatening. Adjunctive corticosteroids or NSAID therapy may be needed for patients with severe disease plus appropriate therapy targeted to the causative infection.[104] Corticosteroids reduce the risk of IRIS in patients known to have TB who are initiating ART but should be avoided for IRIS associated with Kaposi sarcoma.

Conclusion

People living with HIV are still regularly admitted to the ICU with infectious diseases. They pose a unique set of diagnostic and management challenges and ideally, should be managed by physicians experienced in caring for PLWH with complex infections. These carers should consist of a skilled multidisciplinary team including amongst others, intensivists, infectious diseases specialists and pharmacists well versed in HIV drug-interactions and the pharmacokinetic properties of antiretroviral therapies.

Declaration of interests

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Health Sciences, University of the Witwatersrand performs evaluations of diagnostic devices for multiple biotech companies. Individually, WDFV receives honoraria for educational talks and advisory board membership for Gilead, ViiV Healthcare, Mylan/Viatris, Merck, Adcock-Ingram, Aspen, Abbott, Roche, J&J, Sanofi, and Virology Education. CF acts on the speaker's bureaus for AstraZeneca, Aurogen, MSD, and Pfizer, and on the advisory boards of MSD, and Pfizer. All other authors declare no competing interests.

Search Strategies

Search strategy and selection criteria for references for this review were identified through searches of PubMed with the search terms “HIV”, “ICU/Intensive Care”, “Infections”, “community acquired pneumonia”, “Tuberculosis”, “*Pneumocystis jirovecii* Pneumonia”, “Cytomegalovirus”, “CNS infections (Tuberculosis, cryptococcus, bacterial meningitis, toxoplasmosis)”, “Anti- retroviral therapy”, “Immune reconstitution syndrome (IRIS)”, from July 2000 until Dec 2023. Articles were also identified through searches of the authors’ own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the scope of this review".

Contributions

GAR prepared the introduction, the section on sepsis, and wrote and edited the manuscript. JZ prepared and wrote the section on COVID-19 and assisted with the referencing. IK prepared and wrote the section on tuberculosis in the respiratory infection section. AL contributed and prepared sections on admission of and outcomes in people

living with HIV. LWM prepared and wrote the section on immune reconstitution inflammatory syndrome and prepared the table on therapy. EJS prepared and wrote the section on *Pneumocystis jirovecii* and cytomegalovirus and prepared the table on drug interactions. SS prepared and wrote the section on cerebral infections. WDFV prepared and wrote the section on antiretrovirals and assisted with preparation of the table on drug interactions. CF prepared and wrote the section on community-acquired pneumonia and assisted with editing of the manuscript. All authors accept responsibility for the decision to submit for publication.

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