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Critical illness due to infection in people living with HIV

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Lancet HIV 2024; 11: e406–18

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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.[5] 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

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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

Bacterial respiratory diseases, including community-acquired pneumonia, are among the most common infectious complications in people living with HIV, occurring at all levels of CD4 cell count, but with increasing frequency under conditions of increased immunosuppression.[16]

Despite ART, community-acquired pneumonia remains 25 times more common in people living with HIV than those negative for HIV, both in low-income and middle-income countries and high-income countries because of incomplete immune reconstitution and ongoing immune activation.[16–18] Other factors that predispose to community-acquired pneumonia in people living with HIV are chronic viral hepatitis, alcohol use, smoking, chronic obstructive pulmonary disease, malignancy, chronic kidney disease, and heart failure. Many of these are a consequence of patients on ART living longer and becoming afflicted with diseases associated with ageing. 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 in adults has not decreased.[19] In high-income countries, the incidences of community-acquired pneumonia and invasive pneumococcal disease still remain high, and with high CD4 cell counts, even if virally suppressed.[20]

The most common pathogens causing community-acquired pneumonia are *S pneumoniae* and *Haemophilus influenzae*; however, in low-income and middle-income countries, *Mycobacterium tuberculosis* could 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 people living with HIV,[23,25] and particularly in those with pneumococcal infections.[16]

Although atypical bacterial pathogens are uncommon, organisms such as *Pseudomonas aeruginosa* and *S aureus* occur more frequently in people living with HIV than in patients without HIV and viral infections are also important to consider as potential pathogens, 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 of less than 200 cells per µL, infections with *Mycobacterium avium* complex, *Nocardia* spp, *Rhodococcus equi*, and *Aspergillus* spp, should also be considered.[3]

The severity of illness scores such as the pneumonia severity index, Infectious Diseases Society of America/American Thoracic Society guideline, or the CURB-65 might be valid for use in patients with HIV when combined with the CD4 cell count.[16] For cases in which the pneumonia severity index did not predict increased mortality risk, a CD4 count of less than 200 cells mm³ was predictive,[26] and these patients should be admitted to hospital and considered for the ICU.[16] Both the modified

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American Thoracic Society criteria and the Pittsburgh bacteraemia score 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 concentration (>10 ng/ml) in the first 48 h after ICU admission also predicted higher mortality than if it had remained unchanged or decreased.[27] Although some studies suggest that community-acquired pneumonia is associated with increased mortality in people living with HIV, others do not.[16,28] In the CAPNETZ study, independent predictors of increased mortality included CD4 count of less than 100 cells per µL, 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 for pneumonia is similar to that for hospitalised patients without HIV, but additional testing is recommended for immunocompromised patients. This involves sputum specimens, blood cultures, urine antigen testing (*Legionella pneumophilia, S pneumoniae*), thoracentesis, and if possible, bronchoscopy and bronchoalveolar 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 community-acquired pneumonia should be treated with combination therapy, a β-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. A retrospective cohort study of people living with HIV admitted with severe pneumonia requiring a high level of care or intensive care found PJP to be the cause in 21% (25 of 117) of cases.[37] The mortality in this cohort was high (40%) but there was no significant survival difference between those with or without PJP. The need for ICU admission, requirement for mechanical ventilation, and cytomegalovirus viraemia were all associated with increased mortality.

Induced sputum or bronchoalveolar lavage fluid can be used to make a definitive diagnosis by staining the cell wall of the cyst.[38] Overall, because the sensitivity of these stains performed on bronchoalveolar lavage fluid is variable, they are performed less often in high-income countries.[38] Similarly, immunofluorescent stains are used less frequently with a substantial 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 PCR (pooled sensitivity 98%, 99%, and 97% and pooled specificity 91%, 90%, and 94%) from bronchoalveolar lavage fluid samples, and loop-mediated isothermal amplification, 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 75–86%, respectively.[38]

Treatment usually consists of trimethoprim–sulfamethoxazole and corticosteroids, although alternatives exist for treatment failure or for cases in which toxicity limits the use of trimethoprim–sulfamethoxazole (table 1).[31] 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 with a fraction of inspired oxygen of ≥0·5, non-invasive ventilation, or mechanical ventilation) 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 oxygen and non-invasive ventilation are options. In a study of 120 patients (56 receiving high-flow nasal oxygen and 57 receiving non-invasive ventilation after exclusions), 95% 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] High-flow nasal oxygen was better tolerated and required fewer airway care interventions than non-invasive ventilation.[41] The mortality of patients who are unable to benefit from these modalities and require mechanical ventilation is high, in the range of 50–60%.[42] Recently, multiple case reports describing the management of PJP utilising venovenous-extracorporeal membrane oxygenation in both people living with HIV and people without HIV have been published; however, there are yet no published randomised controlled trials.

Tuberculosis

Tuberculous infection requiring ICU support has a high mortality, which is substantially and adversely affected by

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	Typical CD4 strata	Causative organisms	Therapy	Additional considerations
Systemic infections				
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	NA
Respiratory infections				
Community-acquired pneumonia	Any CD4 cell count	Common: *S pneumoniae, Haemophilus influenzae, S aureus, Mycobacterium tuberculosis;* other: *Pseudomonas aeruginosa, Legionella pneumophila, Mycoplasma pneumoniae, Cryptococcus* spp, *Nocardia* spp. *Aspergillus* spp, *Mycobacterium avium* complex, *Rhodococcus equi*	Therapy is similar to that for HIV-negative individuals, with a higher incidence of atypical organisms in people living with HIV with CD4 counts of less than 200 cells per µL; 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 community-acquired pneumonia in people living with HIV has not been studied and the current ATS/IDSA guideline does not recommend routine use except with refractory shock and possibly severe disease[30]
PJP	CD4 count of less than 200 cells per µL	*Pneumocystis jirovecii*	First line: trimethoprim–sulfamethoxazole (15–20 mg/kg per day of the trimethoprim component) every 6 h or 8 h for 21 days;[31] second line (intolerance or treatment failure on first line): clindamycin 600 mg intravenous infusion every 8 h plus primaquine (base 15–30 mg orally every 24 h) for 21 days;[31] adjunctive therapy: corticosteroids 15–30 mins before commencing anti-PJP therapy (prednisone days 1–5 at 40 mg every 12 h, days 6–10 at 40 mg every 24 h, days 11–21 at 20 mg every 24 h, or equivalent)[31]	ART should be initiated within 2 weeks of initiating therapy for PJP; following 21 days of anti-PJP therapy, PJP prophylaxis should be given until CD4 count is more than 200 cells per µL for at least 3 months[31]
Pulmonary tuberculosis	Any CD4 cell count*	*Mycobacterium tuberculosis*	Therapy is similar to that for HIV-negative individuals; drug-susceptible tuberculosis: standard four-drug therapy for an intensive phase of 2 months consisting of rifampicin (10mg/kg per day), isoniazid (5mg/kg per day), ethambutol (15mg/kg per day), and pyrazinamide (25mg/kg per day),followed by rifampicin and isoniazid for a continuation phase of at least 4 months ; parenteral therapy: for cases in which the enteral route of administration is compromised, intravenous therapy options might include a combination of at least three of the following which are rifampicin (10mg/kg per day),† linezolid (600 mg/day), fluoroquinolones (levofloxacin 750–1000 mg/day and moxifloxacin 400 mg/day), and, amikacin (15 mg/kg per day)[32]	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 is similar to that for HIV-negative individuals	NA
Cytomegalovirus pneumonitis	CD4 <50 cells per µL	Cytomegalovirus	Option 1: ganciclovir 5 mg/kg intravenously every 12 h for 14–21 days then ganciclovir 5 mg/kg intravenously daily, or valganciclovir 900 mg orally daily;[33] option 2: valganciclovir 900 mg orally every 12 h for 14–21 days, then 900 mg once daily[33]	Cytomegalovirus might also cause colitis, encephalitis, or disseminated disease

(Table 1 continues on next page)

HIV co-infection.[43] Most studies of HIV and tuberculosis co-infection are from low-income and middle-income countries, given the increased incidence of both, compared with high-income countries. In a South African study of 83 patients with tuberculosis admitted to the ICU, 44 (53%) were co-infected with HIV. Of these, the mortality was 41%.[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 of less than 200 cells per µL are more likely to develop tuberculosis bacteraemia, have mycobacterial infections other than tuberculosis 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 people living with HIV include low CD4 cell count, need for mechanical ventilation, disseminated or miliary tuberculosis, delay in initiation of appropriate treatment, and high severity of illness scores.[48] In the aforementioned Brazilian study, the factors independently associated with mortality were requirement for mechanical ventilation (p=0·0020), hypo-albuminaemia (p=0·013), and CD4 count of less than 200 cells per µL (p=0·0020).[45]

Diagnostic difficulty often delays therapy; however, submission of sputum or other fluids such as bronchoalveolar lavage fluid for nucleic acid amplification testing such as the GeneXpert MTB/RIF-Ultra has simplified diagnosis. People living with HIV with

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	Typical CD4 strata	Causative organisms	Therapy	Additional considerations
(Continued from previous page)				
CNS infections				
Bacterial meningitis	Any CD4 cell count	Common: *S pneumoniae, Neisseria meningitidis;* other: *Haemophilus influenzae, S aureus, Listeria monocytogenes, Salmonella* spp, *Escherichia coli*.	Therapy is similar to that for HIV-negative individuals and guided by patient-specific risk factors, local epidemiology, and sensitivities	NA
Cryptococcal meningitis	CD4 <100 cells per μL	Common: *Cryptococcus neoformans*; other: *Cryptococcus gatii*	Induction therapy: Single high dose (10 mg/kg) of liposomal amphotericin B with 14 days of flucytosine (25 mg/kg per day every 6 h) and fluconazole (1200 mg every 24 h);[34] alternative regimens: amphotericin B deoxycholate (1 mg/kg every 24 h) or liposomal amphotericin B (3mg/kg every 24 h) and flucytosine (25 mg/kg every 6 h) for 7 days followed by fluconazole (1200 mg every 24 h) for 7 days;[34] consolidation therapy: fluconazole (800 mg every 24 h) for 8 weeks;[34] maintenance therapy: fluconazole (200 mg every 24 h) for at least 1 year, and until immune reconstitution (CD4 >200 cells per μL) and viral load suppressed[34]	ART should be initiated 4–6 weeks after initiating therapy for cryptococcal meningitis
Tuberculous meningitis	Any CD4 cell count*	*Mycobacterium tuberculosis*	Standard four-drug tuberculosis therapy is recommended for at least 9–12 months	ART should be initiated 4–8 weeks after initiating therapy for tuberculous meningitis; the role of corticosteroids in the treatment of tuberculous meningitis in people living with HIV is unclear and guided by expert opinion
Toxoplasma encephalitis	CD4 <100 cells per μL	*Toxoplasma gondii*	Option 1: Sulfadiazine (1000–1500 mg every 6 h) and pyrimethamine (200 mg loading dose followed by 50–75 mg every 24 h) and folinic acid (10–25 mg every 24 hours) for 6 weeks;[35] option 2: trimethoprim–sulfamethoxazole (5 mg/kg of the trimethoprim component every 12 h) for 6 weeks[35]	ART should be initiated within 2 weeks of initiating therapy for toxoplasmosis

NA=not available. ATS/IDSA=American Thoracic Society/Infectious Diseases Society of America. PJP=*Pneumocystis jirovecii* pneumonia. ART=antiretroviral therapy. *Risk increases with decreasing CD4 cell count. †Intravenous formulation is not widely available in low-income and middle-income countries.

Table 1: **Treatment of common infections in people living with HIV in the intensive care unit**

pulmonary and extrapulmonary tuberculosis are often sputum-scarce and, although limited in the presence of anuria or oliguria, the urine lipoarabinomannan lateral flow assay can be useful for diagnosis with a positive predictive value estimated at 63% (95% CI 43–82%) in patients suspected of tuberculosis but unable to produce a sputum sample.[49] Interferon-γ release assays have poor sensitivity and specificity in critically ill patients and are estimated to range from 75% to 88% (95% CI 46–99) in sensitivity and from 35% to 51% (30–54) for specificity, 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, and moxifloxacin for drug-resistant tuberculosis have markedly improved outcomes in that setting.[52] However, treatment might be complicated by a dysfunctional gastrointestinal tract or involvement of the gastrointestinal tract tuberculosis, and agents such as levofloxacin, linezolid, rifampicin, and amikacin, among others, can be administered parenterally as a temporary measure until the gastrointestinal tract is functional (table 1).[32] The presence of acute kidney injury and acute hepatic dysfunction in critically ill patient also needs to be considered, along with the potential for drug interactions with ART, which might also cause hepatic injury (table 2). The use of corticosteroids for respiratory failure is controversial in pulmonary tuberculosis and might 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 the possibility of spread in patients that require nebulisation.

COVID-19

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

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	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

(Table 2 continues on next page)

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	Antiretroviral therapy interactions	Mechanism
(Continued from previous page)		
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.

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

For more on **HIV drug interactions** see https://www.hiv-druginteractions.org/

vulnerable to severe disease, hospital admission, and death.[57–60]

Cytomegalovirus

Cytomegalovirus causes disease in people living with HIV with CD4 counts of less than 50 cells per mm³. The most common presentations in those requiring ICU admission 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 18733 people living with HIV diagnosed from 1993 to 2008, only 0·6% had documented cytomegalovirus infection and there were no cases of cytomegalovirus pneumonia.[62]

In all critically ill patients, cytomegalovirus reactivation is associated with prolonged ICU stay, increased risk for infection, prolonged mechanical ventilation, and markedly increased mortality.[63] Cytomegalovirus positivity is likely to be a marker rather than a cause of severe illness. Prophylactic treatment of critically ill cytomegalovirus-seropositive patients has shown mixed results. In one study comparing valganciclovir, valaciclovir, or no treatment, the first two groups suppressed viral reactivation. Although this study was not powered to assess mortality, the valaciclovir group was stopped early due to a higher mortality rate than the placebo group.[64] Other studies have shown no benefit.[65] Overall, cytomegalovirus end-organ disease is best prevented by prompt initiation of ART. However, in cases of cytomegalovirus-associated neurological disease, where mortality can occur rapidly if untreated, antivirals are necessary. Additionally, antiviral therapy might also be beneficial in cytomegalovirus-associated pneumonia, although data in this setting are scarce.[33] Therapeutic agents include intravenous ganciclovir followed by oral valganciclovir (table 1).[33]

CNS infections

HIV infection in the ART era is associated with an overall 8-times higher risk of meningitis in people living with HIV, despite the availability of ART, mostly caused by typical bacterial pathogens.[66] In the USA, the most common cause of meningitis is *C neoformans* with cryptococcal meningitis, which accounts for 30% of cases; bacteria, which accounts for 12% of cases (of which *S pneumoniae* is the most common); and 43% of cases do not have a documented cause.[67] This can be compared with low-income and middle-income countries where cryptococcal meningitis is followed by tuberculous meningitis as the most common causes of meningitis.[68] Mortality is high and might exceed 50%, particularly from tuberculous meningitis and cryptococcal meningitis.[69] Deferral of initiation of ART is warranted to avoid the potentially devastating effects of immune reconstitution inflammatory syndrome (IRIS) with these infections.

People living with HIV might also be affected by *Toxoplasma gondii* and viruses such as herpes simplex virus and cytomegalovirus, presenting with altered levels of consciousness, and localising signs or convulsions.[70]

Lumbar puncture should be performed whenever meningitis is suspected, with careful consideration given

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to the possibility of obstructive hydrocephalus. Besides the standard assessment of cerebrospinal fluid, WHO recommends the use of automated nucleic acid amplification testing for the initial diagnosis of tuberculous meningitis. This test has a sensitivity of 70% and a specificity of 97% in cerebrospinal fluid for diagnosis, and 87% sensitivity and 88% specificity for detecting rifampicin resistance when compared with microbiological reference standards.[52]

The preferred method for diagnosis of cryptococcal meningitis is cryptococcal antigen detection in cerebrospinal fluid, offering advantages over microscopy and culture with better sensitivity (99·3%) and specificity (99·1%).[71] This method also offers ease of use and a short turnaround, essential for rapid diagnosis to reduce mortality. Commercial nucleic acid amplification testing is available for the rapid detection of bacterial and viral pathogens. Additionally, next-generation sequencing and matrix-assisted laser desorption ionisation-time of flight mass spectrometry have the potential for accurate and rapid diagnosis.[72]

Definitive diagnosis of toxoplasmosis can be achieved by biopsy of lesions or PCR on cerebrospinal fluid 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 received by people without HIV. However, standard four-drug tuberculosis therapy is recommended for 9–12 months for tuberculous meningitis (table 1). To date, studies of intensified tuberculosis therapy with additional high-dose or intravenous antibiotics, although generally safe, have not proven to be more effective than standard therapy.[74,75] Trials investigating the benefits of adding drugs such as linezolid or fluoroquinolones, aspirin, cytokines, or using very high-dose rifampicin, have shown variable results.[76–78] The bedaquiline, pretomanid, linezolid regime alone or in combination with moxifloxacin are not currently recommended for the treatment of rifampicin-resistant or multidrug-resistant tuberculous meningitis, although they might be considered if a resistant strain is identified.[79]

First-line therapy for cryptococcal meningitis is a combination of either liposomal amphotericin B or amphotericin B deoxycholate with flucytosine and fluconazole (table 1). Recent evidence assessing efficacy, toxicity, and cost-effectiveness, supports the use of one high dose of liposomal amphotericin B followed by 2 weeks of flucytosine and fluconazole (table 1).[34] The cost is similar to an amphotericin B deoxycholate-based regimen, with fewer reported adverse effects due to toxicity. Grade 3 or 4 adverse events occurred in 50% (210 of 420) of participants on liposomal amphotericin B, compared to 62% (263 of 422) of participants on deoxycholate (p=0·0003), with life-threatening (grade 4) events reported in 22% (91 of 420) versus 30% (127 of 422) in those on deoxycholate. There were similar benefits in terms of anaemia requiring transfusions (7·6% *vs* 18·0%).[80]

Therapy of toxoplasmosis consists of pyrimethamine plus sulfadiazine and folinic acid for a minimum of 6 weeks. However, where unavailable, trimethoprim–sulfamethoxazole treatment for the same duration appears to be an equivalent alternative (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] Dexamethasone in combination with amphotericin B and fluconazole is associated with worse neurological outcomes in patients with cryptococcal meningitis. The recently published ACT HIV trial of adjunctive dexamethasone for tuberculous meningitis in advanced HIV disease did not demonstrate mortality benefit over 12 months compared with placebo.[82] This study is in contrast to an earlier study that did not consider people living with HIV alone in which adjunctive treatment with dexamethasone improved survival in patients older than 14 years with tuberculous meningitis.[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 tuberculous meningitis; however, the evidence is mostly confined to case reports.[84]

Raised intracranial pressure occurs in both tuberculous meningitis and cryptococcal meningitis, but can occur in up to 80% of patients with cryptococcal meningitis irrespective of HIV status. Opening pressure should be measured at initial lumbar puncture and if pressure remains high, should be repeated, especially under conditions of a persistently altered mental state. Measures to decrease intracranial pressure in patients with cryptococcal meningitis include drainage of 20–30 mL of cerebrospinal fluid to halve the opening pressure or to a pressure of less than 20 mm Hg, repeated daily until symptoms and signs improve. Ventricular or lumbar shunts should be considered if lumbar puncture drainage fails to relieve symptoms.[85]

Rarely, cytomegalovirus and syphilis might 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

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direction regarding ART selection or timing.[88,89] For patients newly diagnosed with HIV admitted to the ICU, ART initiation should not be delayed unnecessarily if hospital admission is anticipated to be prolonged. Deferral, however, should be considered in unstable patients, for whom management could be complicated by the potential development of IRIS, ART-induced side-effects, or drug interactions (table 2). Deferral is specifically recommended in people living with HIV with newly diagnosed cryptococcal meningitis or tuberculous meningitis, for which clinical trials have demonstrated increased mortality with early ART.[90]

The choice of ART should be guided by admission diagnosis, with avoidance of tenofovir prodrugs (tenofovir alafenamide or tenofovir disoproxil fumarate) in patients with acute renal dysfunction. Genotype resistance testing to direct therapy when newly initiating ART is recommended in high-resource settings and might be indicated in viraemic patients on established ART entering the 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 tenofovir alafenamide or tenofovir disoproxil fumarate might exacerbate other causes of acute renal failure but might occasionally be the primary cause and cause variants of Fanconi's syndrome. Zidovudine, still occasionally used as a second-line agent, might cause lactic acidosis, anaemia, and neutropenia. Lamivudine and emtricitabine, utilised in almost all ART combinations, are rare causes of red cell aplasia, usually within the first year of treatment. All classes of ART can cause or exacerbate hepatic dysfunction, and the protease inhibitors might cause hepatocellular, cholestatic, or mixed pattern disease. Integrase inhibitor plus nucleoside reverse transcriptase inhibitor combinations rarely cause liver dysfunction, and when they do, it has a gradual onset and is easily monitored.[91] 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 might 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 nucleoside reverse transcriptase inhibitor combinations have limited interactions, except with divalent cations that can 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-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 efficacy or patient compliance can be monitored by HIV viral load or drug concentrations, if available. Although rarely necessary, therapeutic drug monitoring is an option even in resource-limited settings. This can be achieved using high-performance liquid chromatography with ultraviolet detection to ensure drug concentrations are adequate, particularly if the gastrointestinal tract is non-functional or partially functional.[94] In newly initiated patients, HIV viral load decay depends on starting concentrations, but is rapid and usually undetectable within weeks.

In general, it is recommended that ART be administered enterally in those on mechanical ventilation, as most formulations are only available in oral (tablet or syrup) form. Where there is gastrointestinal dysfunction, intramuscular cabotegravir or rilpivirine is an option for those on ART noting that access is currently very limited in most countries, and that drug–drug interactions are common and potentially serious. Additionally, lenacapavir (subcutaneous), ibalizumab (injectable), enfuvirtide (subcutaneous), and zidovudine (infusion) can be used, but access is also very limited.[95]

Immune reconstitution inflammatory syndrome

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

The most common pathogens associated with IRIS are mycobacterial (tuberculosis and *M avium* complex), viral (cytomegalovirus, herpes simplex, varicella-zoster, hepatitis B, and human herpes 8 viruses) and fungal (*C neoformans* and *P jirovecii*).[97] Rarely, bacteria (*Bartonella henselae*) or 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 develops within 90 days.[97] The incidence depends on the particular infection and geographical setting, with rates between 7% and 18% and the consequences can be severe and require ICU admission.[97,100] Although there is no consensus definition for the diagnosis, common features include low pre-treatment CD4 cell count and high HIV

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Search strategy and selection criteria

Selection criteria for references for this Review were identified through searches of Google Scholar and 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", and "Immune reconstitution syndrome (IRIS)", from July 1, 2000 to Dec 31, 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 currency, originality, and relevance to the scope of this Review.

viral load, 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 per mm³), high HIV viral load, a short interval between treatment of the underlying opportunistic infection and initiation of ART, and an increased rate of rise of the CD4 count with rapid decrease in HIV viral load.[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 non-specific symptoms include fever and tachycardia, and for respiratory diseases such as pulmonary tuberculosis or PJP, there might be worsening of respiratory symptoms, hypoxaemia, and radiographic abnormalities.[102] Patients with extra-pulmonary tuberculosis might develop lymphadenitis, new pleural effusions, expansion of tuberculomas, and hepatitis. Intracranial tuberculomas, tuberculous meningitis, or cryptococcal meningitis can manifest with new neurological deficits, worsening headache, nuchal rigidity, and photophobia. Overall, the mortality associated with IRIS has been estimated at 4·5%, but in cryptococcal meningitis-IRIS this approaches 20%.[103]

Despite the risk of IRIS, initiation of ART is recommended as soon as possible or within 2 weeks for most opportunistic infections. Exceptions exist for those with CNS-tuberculosis and cryptococcal meningitis, for which adverse events outweigh benefits.[89] If IRIS develops, ART should be continued unless it is life-threatening. Adjunctive corticosteroids or non-steroidal anti-inflammatory drug therapy might 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 tuberculosis who are starting 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 people living with HIV with complex infections. These carers should consist of a skilled multidisciplinary team including, among others, intensivists, infectious diseases specialists, and pharmacists well versed in HIV drug interactions and the pharmacokinetic properties of antiretroviral therapies.

Contributors

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

Declaration of interests

GAR reports honoraria from MSD, AstraZeneca, Boehringer, Fresenius, Acino, Baxter, Sandoz, Pfizer, Astellas, and Novartis and consulting fees from Cipla and Ampath laboratories and Mediclinic Hospital Group. EJS reports a grant award from AstraZeneca and honoraria from Sandoz and Organon. SS reports a grant award from AstraZeneca and honoraria from Novartis. WDFV's unit (Wits Ezintsha, Faculty of Health Sciences, University of the Witwatersrand) receives funding from the Bill & Melinda Gates Foundation, SA Medical Research Council, National Institutes for Health, Unitaid, Foundation for Innovative New Diagnostics, Merck, and the Children's Investment Fund Foundation; has previously received funding from USAID, and receives drug donations from ViiV Healthcare, Merck, J&J, and Gilead Sciences for investigator-led clinical studies. Wits Ezintsha, Faculty of Health Sciences, University of the Witwatersrand does investigator-led studies with Merck, J&J, and ViiV Healthcare who provide financial support and are doing commercial drug studies for Merck. Wits Ezintsha, Faculty of 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.

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