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HIV-associated lung disease

Ioannis Konstantinidis[1], **Kristina Crothers**[2], **Ken M. Kunisaki**[3], **M. Bradley Drummond**[4], **Thomas Benfield**[5], **Heather J. Zar**[6,7], **Laurence Huang**[8,9], **Alison Morris**[1,✉]

[1]Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Department of Medicine, University of Pittsburgh, Pittsburgh, PA, USA.

[2]Veterans Affairs Puget Sound Healthcare System and Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, University of Washington, Seattle, WA, USA.

[3]Section of Pulmonary, Allergy, Critical Care and Sleep Medicine, Department of Medicine, Minneapolis Veterans Affairs Health Care System, Minneapolis, MN, USA.

[4]Division of Pulmonary Diseases and Critical Care Medicine, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.

[5]Department of Infectious Diseases, Copenhagen University Hospital, Amager and Hvidovre, Hvidovre, Denmark.

[6]Department of Paediatrics & Child Health, Red Cross War Memorial Children's Hospital, Cape Town, South Africa.

[7]SA-MRC Unit on Child & Adolescent Health, University of Cape Town, Cape Town, South Africa.

[8]Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of California San Francisco, San Francisco, CA, USA.

[9]Division of HIV, Infectious Diseases, and Global Medicine, Department of Medicine, University of California San Francisco, San Francisco, CA, USA.

Abstract

Lung disease encompasses acute, infectious processes and chronic, non-infectious processes such as chronic obstructive pulmonary disease, asthma and lung cancer. People living with HIV

✉ morrisa@upmc.edu .

Author contributions

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are at increased risk of both acute and chronic lung diseases. Although the use of effective antiretroviral therapy has diminished the burden of infectious lung disease, people living with HIV experience growing morbidity and mortality from chronic lung diseases. A key risk factor for HIV-associated lung disease is cigarette smoking, which is more prevalent in people living with HIV than in uninfected people. Other risk factors include older age, history of bacterial pneumonia, *Pneumocystis* pneumonia, pulmonary tuberculosis and immunosuppression. Mechanistic investigations support roles for aberrant innate and adaptive immunity, local and systemic inflammation, oxidative stress, altered lung and gut microbiota, and environmental exposures such as biomass fuel burning in the development of HIV-associated lung disease. Assessment, prevention and treatment strategies are largely extrapolated from data from HIV-uninfected people. Smoking cessation is essential. Data on the long-term consequences of HIV-associated lung disease are limited. Efforts to continue quantifying the effects of HIV infection on the lung, especially in low-income and middle-income countries, are essential to advance our knowledge and optimize respiratory care in people living with HIV.

Introduction

The lung has historically been one of the organs most impacted by the immune deficits caused by infection with the human immunodeficiency virus (HIV). The first reports of an unusual pneumonia caused by the fungus *Pneumocystis jirovecii* reported among gay men heralded the start of the AIDS epidemic, and opportunistic pneumonias and malignancies quickly became a leading cause of morbidity and mortality in HIV infection[1]. With the development of effective antiretroviral therapy (ART), the incidence of lung infections and malignancies declined dramatically[2]. For example, the incidence of *P. jirovecii* pneumonia (PCP) decreased from 4.9 cases per 100 person-years to 0.3 cases per 100 person-years in the EuroSIDA cohort and from 3.1 cases per 100 person-years to 0.3 cases per 100-person years in the Multicenter AIDS Cohort Study following the widespread use of ART[3,4]. However, lung disease still remains a considerable problem in people living with HIV. Individuals who do not have access to ART, are unaware of their HIV infection or are not able to successfully take ART remain at high risk of pulmonary complications. In addition, despite ART, people living with HIV remain at elevated risk of certain chronic and acute lung conditions.

HIV is associated with both infectious and non-infectious pulmonary diseases. Opportunistic infections include PCP and mycobacterial pneumonia, and AIDS-associated malignancies include Kaposi sarcoma, lymphoma and primary lung cancer. Individuals with viral suppression on ART remain at elevated risk of bacterial pneumonia and tuberculosis (TB) and certain malignancies including lung cancer[5]. HIV infection also seems to be a risk factor for more severe COVID-19 pneumonia[6]. People living with HIV are at elevated risk of chronic obstructive pulmonary disease (COPD)[7]. Asthma, a common obstructive lung disease in the non-HIV population, is also seen in people living with HIV, and whether it has a different presentation and severity has been debated[8,9]. These diseases continue to have a considerable effect on the quality of life of people living with HIV, but few therapies have been studied in this population and the specific impacts of immunodeficiency, environmental

exposures, direct viral effects, other aspects of chronic infection and ART remain under investigation.

In this Primer, we first review the current epidemiology of and risk factors for HIV-associated lung disease. We then explore the mechanisms underlying lung disease in HIV, including the impact of HIV on specific lung and immune cell populations, the role of oxidative stress, interactions with exposures such as cigarette smoke or environmental pollutants, and the interplay of HIV, the microbiota and lung disease. We also provide an overview of the current state of screening, diagnosis, prevention and management of common lung diseases in adults and children living with HIV, including pneumonia, COPD, asthma and lung cancer. Finally, we highlight gaps in knowledge and future areas for research.

Epidemiology

An estimated 38 million people currently live with HIV worldwide, over two-thirds of whom are in Africa[10]. HIV infection is associated with increased risks of pneumonia from bacteria (including mycobacteria), viruses, fungi and parasites, at all $CD4^+$ T cell counts, although the risks increase with decreasing $CD4^+$ T cell count[4,11] (Fig. 1). For example, the risk of PCP in people living with HIV who have a $CD4^+$ T cell count <200/μl is fivefold to eightfold higher than in people living with HIV who have a $CD4^+$ T cell count >200/μl[12,13]. *Mycobacterium tuberculosis* and other bacteria are frequent causes of pneumonia across all levels of immunosuppression. The estimated annual risk of reactivating TB is up to 10% in people living with HIV compared with a lifetime risk of 5–10% for HIV-uninfected people[14–18]. Risks are mitigated by ART initiation with subsequent viral suppression (that is, undetectable HIV viral load) and immune recovery and with antimicrobial prophylaxis, but remain higher among people living with HIV than among HIV-uninfected people. Bacterial pneumonia is the most common pulmonary infection among people living with HIV in high-income countries (HICs), followed by PCP and TB. In people living with HIV, TB is the predominant pulmonary infection in low-income and middle-income countries (LMICs) and a leading cause of death globally[19]. Importantly, the range of pathogens causing pulmonary infections varies geographically, reflecting local factors and specific pathogen endemicity, which is particularly important in LMIC settings where pathogen identification can be challenging owing to limited resources. For example, melioidosis (caused by the bacterium *Burkholderia pseudomallei*) and talaromycosis (caused by the fungus *Talaromyces marneffei*) should be considered as aetiologies of pneumonia in Asia, whereas histoplasmosis (caused by the fungus *Histoplasma capsulatum*) should be considered an aetiology of pneumonia in temperate regions in Central, South and North America, Africa and Asia. Common risk factors for bacterial pneumonia, PCP and TB include decreased $CD4^+$ T cell count[11,20–29], detectable HIV viral load[11,22,23,29] and lack of ART[11,21,24,28–32]. Injection of illicit drugs[11,22,24], smoking[21–23,25,33], and extremes of age and comorbidities are additional risk factors for bacterial pneumonia (Box 1).

Smoking is more prevalent among people living with HIV than in uninfected people in HICs and LMICs, although rates vary depending on the specific characteristics of the population and the years being studied[34–40]. For example, the prevalence of current smoking has

previously been estimated as 40% in adults living with HIV compared with 21% in the general population, using nationally representative cross-sectional surveys in the USA[34]. Nevertheless, HIV infection is associated with COPD even after adjusting for smoking[41]. COPD prevalence among people living with HIV is in the range 3–38% in HICs[42–52], compared with 3–22% in LMICs[53–58]. Key risk factors for COPD in people living with HIV include smoking[43,44,46,52,59–65], older age[45,46,52,59–61,63–66], lower BMI[45,46,56,59,64,67,68] and history of pulmonary TB[55,56,67,68]. Lower nadir $CD4^+$ T cell count and greater HIV viral load have also been identified as unique COPD risk factors in people living with HIV[48,59,66,69] (Fig. 1). Additional non-tobacco-related risk factors for COPD in both the general population and in people living with HIV include socioeconomic disadvantage[70,71], biomass fuel burning[72] and chronic exposure to airborne particulate matter[73] (Box 1). There is conflicting evidence regarding the association between HIV infection and incident COPD[4,11,74], although data show that HIV is associated with more rapid lung function decline[75,76]. People living with HIV are at higher risk of COPD exacerbations (which are defined as episodes of acutely worsened respiratory symptoms requiring additional therapy) compared with HIV-uninfected people[77,78]. Among people living with HIV, prevalent and incident COPD is an independent risk factor for increased mortality[79–81].

Variability in asthma definition in epidemiological studies — including definitions based on self-report, the presence of variable airflow obstruction, and the combination of spirometry and symptoms — limits robust conclusions about the association between HIV infection and asthma. Asthma prevalence does not differ by HIV status in most studies and is in the range 5−38% in HICs[9,42,44,82–84], compared with 1–16% in LMICs[53,55,85–88]. There is conflicting evidence regarding the association between female sex, older age, smoking, higher BMI and HIV-related characteristics (such as nadir $CD4^+$ T cell count, HIV viral load and ART use) and asthma prevalence[8,9,62,84,89,90] (Fig. 1 and Box 1), and the association between asthma and symptom burden and respiratory health status[9,91]. HIV infection is associated with worse respiratory symptom burden among men with asthma but not among women with asthma[9]. Limited data suggest that asthma is not associated with increased mortality risk in people living with HIV[79].

Lung cancer is a leading non-AIDS-defining malignancy[92–95] (cancers that are more likely to occur in people infected with HIV than in those who are not infected) and the most frequent cause of mortality from cancer in people living with HIV[95–97]. HIV infection is independently associated with lung cancer[94,97–105]. Although higher smoking prevalence among people living with HIV is the greatest contributor to lung cancer risk[104–106], data support an association of older age[98,105,107], pneumonia[105,108], low $CD4^+$ T cell count and HIV viral load with lung cancer risk[98–100,102,107] (Fig. 1 and Box 1). Lung cancer is typically diagnosed at a similar stage[109–111] but at a younger age in people living with HIV than in uninfected persons[101,111]. HIV infection is associated with poorer survival in patients with lung cancer after adjusting for stage[99,104,109–112]. Data on the association between HIV infection and lung cancer incidence outside North America and Europe are limited[113,114].

Pulmonary diseases are also common in HIV-infected children, encompassing acute infection and chronic disease[115] (Fig. 1). Furthermore, HIV-exposed but uninfected infants, who are HIV-uninfected but born to an HIV-infected mother, have an increased risk

of respiratory illness compared with unexposed infants, a finding that may be at least partly explained by in utero and postnatal exposures leading to immune dysfunction[106]. Early diagnosis and use of ART have reduced the burden and severity of acute illness in HIV-infected children. With improved survival of perinatally infected children into adulthood, chronic respiratory disease contributes to morbidity[116]. Although the incidence and severity of pneumonia have decreased considerably with ART and improved preventive strategies including pneumococcal conjugate vaccine (PCV), vaccination against *Haemophilus influenzae* type b, and co-trimoxazole prophylaxis, pneumonia remains common[115]. Bacterial, viral or fungal pathogens can occur, with co-infections in severe AIDS. Bacterial pneumonia and TB are the most frequent respiratory infections in both ART-naive and ART-exposed children infected with HIV. In the Pneumonia Etiology Research for Child Health (PERCH) study, the most common pathogens in HIV-infected children hospitalized with severe or very severe pneumonia were *Staphylococcus aureus*, *Streptococcus pneumoniae* and *M. tuberculosis*[117,118]. HIV-infected children on ART have a higher risk of TB than HIV-uninfected children[119]. *Bordetella pertussis* may cause pneumonia in young HIV-infected or HIV-exposed infants, particularly if these children are incompletely immunized[117]. Viruses (especially respiratory syncytial virus) are increasingly reported as a cause of pneumonia in the context of high immunization coverage with PCV and *H. influenzae* type b vaccine[120]. In children undiagnosed with HIV or those not on ART, opportunistic infections such as PCP or cytomegalovirus (CMV) can cause severe pneumonia. *P. jirovecii* accounted for 23–25% of radiologically confirmed cases of pneumonia in HIV-infected African children in the PERCH study in South Africa and Zambia, although ART coverage was low[117,118]. HIV-exposed but uninfected infants are at higher risk of pneumonia than HIV-unexposed children, and have worse outcomes[121].

Mechanisms/pathophysiology

HIV

HIV is a member of the *Lentivirus* genus of the Retroviridae family[122]. HIV is a single-stranded, positive-sense, enveloped RNA virus. There are two species, HIV-1 and HIV-2. HIV-1 is more virulent and infectious than HIV-2 and by far the more common species. HIV-1 has given rise to the global epidemic of HIV/AIDS, with an estimated 38 million infected individuals living today, whereas HIV-2 is rare outside West Africa[123,124].

The HIV viral envelope trimeric glycoprotein (gp160 spike) binds to the CD4 receptor and either CC-chemokine receptor 5 (CCR5) or CXC-chemokine receptor 4 (CXCR4) of $CD4^+$ T cells, macrophages, microglia and dendritic cells. On binding, the HIV virion uncoats and fuses with the cell membrane. The viral RNA is injected into the cytoplasm together with several viral enzymes that are required for completion of the virus life cycle intracellularly. One enzyme, reverse transcriptase, reverse transcribes viral RNA into complementary DNA. Two complementary DNAs form a double-stranded viral DNA that translocates to the nucleus and integrates into the host genome by the action of the integrase enzyme, where it can lie dormant for years or immediately be transcribed to viral mRNA, transported to the cytoplasm, translated to an HIV polypeptide that is cleaved by a virally encoded serine protease, assembled, and released as progeny viral particles. These virions may infect other

cells and restart the replication cycle. Virion fusion with the target cell, co-receptor binding, reverse transcription, integration and protease cleavage are the main targets of antiretroviral treatment. HIV is highly genetically varied owing to its fast replication cycle (leading to the daily generation of 10^{10} virions), its high mutation rate (3×10^{-5} mutations per nucleotide base per cycle of replication), and its recombination ability. These properties give rise to immune escape and antiretroviral drug resistance. The development of novel antiretroviral drugs has largely diverted the issues of drug resistance, while viral integration, dormancy and immune escape are the largest obstacles to a cure and the development of vaccines.

Structural damage — cilia, epithelial cells

The surface of the airways interfaces with the environment through a continuous epithelial sheet containing distinct morphological characteristics based on location in the airway. In the proximal airway, the columnar epithelium includes mucus-secreting goblet cells along with ciliated epithelium responsible for mucus transport. Progressing from the distal airways to the alveolar epithelium is associated with a transition from columnar and ciliated epithelium to type I and type II alveolar epithelial cells. Data exist for specific impacts of HIV viral infection along the course of the human airway (Figs. 2 and 3). E-cadherin is an adhesion molecule produced by airway epithelial cells that plays a vital part in maintaining the intercellular epithelial barrier[125]. Disruption of this barrier can lead to increased epithelial permeability to harmful inhalants as well as altered mucosal immunity, both of which are mechanisms associated with chronic lung disease. Infection of human airway epithelial cells with HIV in vitro leads to decreased expression of E-cadherin and increased intercellular permeability[126]. Disruption of mucosal immunity can lead to alterations in the level and function of antimicrobial peptides. Reduced blood levels of the antimicrobial peptide cathelicidin are correlated with reduced lung function among people living with HIV[127]. It remains unclear whether HIV infection directly alters lung cathelicidin levels or function. Impairments in mucociliary clearance are a hallmark of chronic bronchitis and predispose individuals to recurrent respiratory symptoms and infections. HIV infection impairs mucociliary clearance through multiple mechanisms. Specifically, exposure of the bronchial epithelium in vitro to HIV Tat impairs airway cellular differentiation, cystic fibrosis transmembrane conductance regulator (CFTR) function and ciliogenesis[128]. The mechanisms for such alterations might involve HIV infection-related induction of transforming growth factor-β1 (TGFβ1) expression[129], which is implicated as a putative mechanism for COPD development in the general population[130].

Immune deficits

The lungs are constantly exposed to inhaled pathogens (for example, bacteria, viruses and *Pneumocystis*), allergens (for example, pollen, dust mites and animal dander) and toxins (for example, tobacco, illicit drugs and air pollutants) (Fig. 2). The innate and adaptive immune systems in the lungs respond to these stimuli. HIV infection affects both the innate and adaptive immune systems at multiple key points (Fig. 3). The resultant impaired or dysregulated responses result in opportunistic infections and chronic lung diseases such as COPD[131].

Similar to other mucosal surfaces (such as the skin and gastrointestinal tract), the epithelial surface of the lungs presents a barrier to pathogen entry. However, HIV can infect bronchial epithelial cells, as they express CD4, CCR5 and CXCR4. HIV infection can alter the function of bronchial epithelial cells through impaired cell–cell adhesion and increased expression of inflammatory mediators[126] as well as suppressed tracheobronchial mucociliary clearance[128]. Cigarette smoking can potentiate HIV infection of bronchial epithelial cells through upregulation of CD4 and CCR5 expression. HIV and cigarette smoking additively suppress CFTR mRNA transcription and function[132]. HIV can also infect alveolar macrophages — the primary innate immune cells in the lung — through contact of these cells with infected $CD4^+$ T cells[133], disrupting alveolar macrophage phagocytosis and altering their release of cytokines[134–137]. Alveolar macrophages also represent a potential HIV reservoir[138]. Finally, HIV can infect dendritic cells, the main antigen-presenting cells in the lung. Dendritic cells exposed to HIV and suppressive T cells develop a more tolerogenic phenotype and express multiple co-inhibitory molecules that can result in suppressed immune responses[139]. Although surfactant proteins D and A can inhibit the ability of HIV to infect $CD4^+$ T cells, they can also stimulate HIV transfer from dendritic cells to $CD4^+$ T cells[140,141].

During acute HIV infection, there is systemic depletion of $CD4^+$ T cells from the gut mucosa and release of pro-inflammatory cytokines[142]. Subsequently, the systemic immune activation from chronic HIV infection leads to progressive depletion of $CD4^+$ T cells, including in the lungs. HIV causes an influx of $CD8^+$ T cells into the lungs, with a resulting lymphocytic alveolitis. These $CD8^+$ T cells target HIV-infected cells and opportunistic pathogens such as CMV and *P. jirovecii*. HIV-1-specific $CD4^+$ T cells and $CD8^+$ T cells in bronchoalveolar lavage fluid (BALF) demonstrate decreased proliferative capacity and increased expression of the immune checkpoint protein PD1 (ref. 143). HIV infection is also associated with B cell dysfunction, including polyclonal B cell activation, hypergammaglobulinaemia, impaired antibody response and loss of memory B cells[144].

Oxidative stress

HIV infection exacerbates oxidative stress within the alveolar space, thereby contributing to increased susceptibility to pulmonary infections and chronic pulmonary diseases (Figs. 2 and 3). People living with HIV have decreased systemic and pulmonary total antioxidant capacity and elevated serum levels of lipid peroxidation products[145,146]. Greater oxidative stress can persist despite ART[147], although ART and the concomitant increase in $CD4^+$ T cell count are beneficial, as higher levels of oxidative stress correlate with lower $CD4^+$ T cell counts[146]. For example, healthy people living with HIV who are not on ART have decreased glutathione levels in BALF compared with people living with HIV who are on ART[148]. Furthermore, healthy people living with HIV who are on ART have altered critical mediators of alveolar macrophage oxidative stress and phagocytic function, with abnormalities including increased hydrogen peroxide in BALF, decreased peroxisome proliferator-activated receptor-γ and increased NADPH oxidase isoforms NOX1, NOX2 and NOX4, and TGFβ1, contributing to immune dysfunction that increases the risk of pulmonary infection[149].

HIV also increases oxidative stress through the effects of HIV proteins, resulting in impaired alveolar macrophage function and alveolar epithelial barrier cell function. In HIV transgenic rats, chronic expression of gp120 and Tat is associated with considerable oxidative stress and glutathione depletion in the lung[150]. gp120 and Tat inhibit nuclear factor erythroid 2-related factor 2 (NF2L2), the master transcription factor that regulates antioxidant defences within alveolar macrophages, and alveolar epithelial cell barrier function via increased expression of microRNA-144 in the alveolar epithelium[151,152].

The increased oxidative stress in people living with HIV can place them at greater risk of lung injury from other factors that also cause oxidative stress. The HIV proteins Nef, Tat and gp120 are implicated in oxidative stress-mediated apoptosis of endothelial cells[153,154], and HIV acts synergistically with other exposures, such as cocaine and opioids, to increase oxidative stress and augment remodelling of pulmonary microvascular endothelial cells, including medial hypertrophy, intimal proliferation and complex lesion formation, in non-human primate models[155]. Susceptibility to lung injury in the setting of infection can also be enhanced by increased oxidative stress. For example, endotoxin administration in an HIV transgenic mouse model resulted in significantly greater lung oxidative and nitrosative stress, with elevated nitric oxide metabolites and decreased glutathione levels in BALF[156].

Other oxidative stressors include cigarette smoke exposure, hypoxia and air pollution. Cigarette smoking is more common among people living with HIV than in uninfected populations across different regions of the world and country income categories[34–40] and is a major risk factor for pulmonary infections and chronic pulmonary diseases. Plasma glutathione levels are significantly lower in people living with HIV who are smokers than in those who are non-smokers[157], and over time, glutathione levels in BALF decrease to a greater extent in people living with HIV who are smokers than in those who are non-smokers[158]. Taken together, these effects of chronic HIV infection that result in increased oxidative stress contribute to the pathogenesis of acute and chronic pulmonary diseases in people living with HIV.

Microbiota

The effects of HIV have been studied primarily in the gut microbiota, but given the immune defects caused by HIV, alterations in the lung microbiota in people living with HIV are possible (Fig. 2). In healthy individuals, the lung microbiota typically has a very low biomass, and most detectable bacteria originate primarily from the oral cavity[159,160]. Lung bacteria in healthy people living with HIV are essentially indistinguishable from those of HIV-uninfected people[161,162]. People with advanced HIV not on ART have decreased α diversity (within sample diversity) and increased β diversity (between sample diversity) in BALF, with differential abundance of several bacterial taxa, including increased *Streptococcus*[161]. Differences between people living with HIV and HIV-uninfected people decrease after ART initiation but do not completely resolve[161]. *Tropheryma whipplei* (the causative agent of Whipple disease) has been detected in the lungs of people living with HIV and in non-human primate models of HIV-like immunodeficiency, but its significance is unknown[163,164]. The fungal microbiome has also been investigated in people living with HIV, with differences identified in fungal communities between people living with HIV and

HIV-uninfected people[162]. In particular, *P. jirovecii* is disproportionately found in people living with HIV regardless of $CD4^+$ T cell count.

Alterations in the microbiota of various body sites might play a direct or indirect part in the pathogenesis of COPD in HIV. A study in people with advanced HIV found a correlation of certain bacterial taxa with lung function and inflammation[165], but other studies in people living with HIV on ART did not find differences in the lung bacterial communities despite lung function differences[161,162]. By contrast, oral bacterial communities are altered in people living with HIV and COPD. A study of the oral microbiota in people living with HIV found a relationship between alterations in the oral microbiome and airway obstruction, impaired diffusing capacity and systemic inflammation, suggesting that aspiration of oral microbial communities may contribute to COPD[166]. In addition, detection of *P. jirovecii* in the lung is associated with COPD in people living with HIV and in non-human primate models[162,164].

The gut microbiota might also influence lung disease via production of metabolic products and/or influencing systemic immune response. HIV is linked to disruptions in the translocation of bacterial or fungal organisms or products, which might result in an aberrant immune response and inflammation. The microbiota can gain access to the circulation through an impaired epithelial barrier in people living with HIV, leading to systemic inflammation and immune activation even in those on ART[167–169]. Several lines of evidence show that HIV increases gut epithelial permeability through direct disruption of tight junctions, inflammatory damage to the epithelium and loss of lymphoid-associated tissue[167–169]. While investigations have generally focused on bacterial translocation from the gut, translocation of fungal organisms or parts of the fungal cell wall occurs in people living with HIV and COPD. Serum levels of β-d-glucan (BDG) are used as a marker of clinical fungal infection but can also indicate fungal translocation in people without active infection[170]. People living with HIV have detectable BDG in the peripheral blood that is associated with systemic inflammation and COPD[171]; however, detection of BDG as a marker of translocation is not clinically applicable currently.

CMV seropositivity is also associated with worse lung function in adolescents living with HIV[172], raising questions about the role of viral co-infections and the virome on lung health in people living with HIV. CMV seropositivity has been associated with higher COPD mortality[173] and more rapid lung function decline in adults without HIV[174], but data in adults living with HIV are currently lacking.

Smoking and interactions with HIV

Cigarette smoking is common among people living with HIV, and might serve as a ‘second hit’ with HIV to enhance susceptibility to lung diseases (Fig. 2). Smoking has multiple harmful consequences including immunosuppression, inflammation, oxidative stress and tissue injury. Smoking is associated with greater systemic levels of inflammatory and endothelial biomarkers in people living with HIV[175]. In a study of Nepalese people living with HIV, longer duration and greater intensity of smoking, as measured by pack-years or number of daily cigarettes, correlated with higher levels of C-reactive protein (defined as >3 mg/l)[176].

Smoking also causes perturbations within the alveolar space that might be unique in people living with HIV. HIV infection together with cigarette smoking favour a pro-inflammatory macrophage phenotype and increased expression of inflammatory mediators[177]. Cigarette smoking is associated with decreased $CD8^+$ T cells in BALF of both people living with HIV and HIV-uninfected people, but with increased mucosal $CD8^+$ T cells in people living with HIV who smoke[178]. Greater numbers of mucosal $CD8^+$ T cells are inversely correlated with mean lung aeration on chest CT scan, suggesting that mucosal $CD8^+$ T cells might be associated with lung inflammation and remodelling. Cigarette smoke exposure also increases the concentration of matrix metalloproteinase 9 in the alveolar space, but this response is greater in the presence of HIV proteins, demonstrating the synergy between HIV and cigarette smoke in promoting lung disease[179].

People living with HIV who smoke are at risk of accelerated progression of HIV[180] and impaired response to ART[181–185]. Although some of these associations may be due to persistent residual confounding, current smoking and intensity of smoking correlate with higher HIV DNA and cell-associated RNA levels in peripheral blood mononuclear cells in people living with HIV on long-term ART and virally suppressed for over 2 years[186].

Within the lungs, smoking is associated with increased detection of HIV in BALF and might enhance HIV viral entry and replication[187]. Exposure to smoke results in upregulation of CCR5 expression on bronchial epithelial cells via a TGFβ pathway as well as suppression of the expression and function of CFTR, resulting in enhanced HIV viral entry and viral replication[132]. In laboratory-based studies, benzo(a) pyrene, a carcinogenic component of cigarettes, enhances HIV replication in alveolar macrophages through a cytochrome p450 pathway[188]. The increase in HIV viral replication may contribute to a feedback loop, further driving lung inflammation and tissue injury.

Diagnosis, screening and prevention

Adults

Infections.—Signs and symptoms of bacterial pneumonia, PCP and pulmonary TB may be useful to distinguish PCP from the other infections, while signs and symptoms of bacterial pneumonia and pulmonary TB overlap. The symptoms of PCP in people living with HIV typically develop over weeks and include shortness of breath, a non-productive cough, fever, fatigue and weight loss. Oral thrush caused by candidiasis is often present, and is indicative of immunodeficiency. Bacterial pneumonia characteristically develops over days, leading to acute onset of symptoms that include a cough (often productive but may be dry), shortness of breath, fever and chest pain. Symptoms of pulmonary TB are typically more prolonged than those of bacterial pneumonia and develop over weeks, with a cough (usually productive and may contain blood in more advanced stages), fever, night sweats, difficulty breathing, weight loss and fatigue. Chest radiographs are often non-specific due to overlapping findings. However, PCP is characterized by diffuse bilateral infiltrates, bacterial pneumonia by lobar infiltrates, and pulmonary TB by upper lobe infiltrates and cavitation, although such TB findings are less likely with more severe immunodeficiency (Fig. 4). Plasma lactate dehydrogenase levels are often elevated with PCP, while plasma C-reactive protein typically is elevated with bacterial pneumonia.

The diagnosis of *Pneumocystis* is ideally made by visualizing cysts of trophozoites by microscopy after immunostaining of BALF, but is more often guided by either molecular detection of PCP DNA in an airway specimen or by detection of BDG in serum. Bacterial pneumonia and pulmonary TB are diagnosed by microscopy and culture of a specimen from the lower respiratory tract. While bacterial infections rarely are diagnosed by molecular methods, the diagnosis of pulmonary TB increasingly relies on rapid molecular detection, which is also able to detect rifampin resistance. Testing of urine for lipoarabinomannan might be useful to diagnose TB in severely immunocompromised individuals. CMV pneumonia remains a diagnostic challenge. Demonstration of CMV inclusion bodies in a lung tissue specimen is highly suggestive, while detection of CMV in serum, sputum or BALF by culture, PCR, immunohistochemistry or in situ hybridization might be suggestive in severely immunocompromised individuals. Respiratory viruses can be detected by molecular (DNA or RNA) or immunological testing (antigen) of either a nasopharyngeal or an oropharyngeal swab specimen. Broad diagnostic work-up is often indicated, as the presence of more than one pathogen is more common in immunosuppressed individuals.

The cornerstone of prevention of pneumonia is ART-induced immune recovery followed by smoking cessation and immunization against *S. pneumoniae*, influenza and SARS-CoV-2. Prophylaxis against PCP is indicated in individuals with a $CD4^+$ T cell count <200/μl, a $CD4^+$ T cell percentage <14% of total lymphocyte count, and a $CD4^+$ T cell count in the range 200–300/μl if ART initiation is delayed and $CD4^+$ T cell count monitoring is unfeasible, or following an episode of PCP. Prophylaxis continues until the $CD4^+$ T cell count is >200/μl for at least 3 months while on ART[18]. Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended prophylactic drug. In individuals who cannot tolerate TMP-SMX, alternative regimens include dapsone, dapsone plus pyrimethamine plus leucovorin, aerosolized pentamidine, and atovaquone[18]. Individuals with latent TB can be treated with 12 weeks of once-weekly rifapentine plus isoniazid plus pyridoxine or daily rifampin plus isoniazid plus pyridoxine. Daily isoniazid plus pyridoxine for 6–9 months is an alternative regimen when drug–drug interactions between rifamycins and specific ART drugs limit the use of rifamycin-based regimens for latent TB[18]. Globally, the provision of TB-preventive treatment to people living with HIV has been a remarkable success, exceeding 2.5 million treatments annually[19].

COPD.—The most common symptoms of COPD are dyspnoea (shortness of breath) on exertion and chronic bronchitis (classically defined as having cough and mucus production on most days for at least 3 months per year and for at least 2 years in a row). COPD symptoms in people living with HIV are similar to those in seronegative individuals, although the symptom burden in people living with HIV may be higher for the same degree of impairment in lung function[48].

The high prevalence of COPD in people living with HIV has raised questions about optimal COPD screening and case-finding approaches in HIV clinics. The current diagnostic approach to COPD is the same in people with and without HIV (Fig. 4). The gold standard test for COPD diagnosis is spirometry, which is recommended in people with COPD symptoms and risk factors (such as tobacco smoking, biomass fuel burning exposure, history of TB, and HIV)[189]. However, screening for COPD with spirometry in adults at

high risk who are asymptomatic is not recommended by organizations such as the US Preventive Services Task Force (USPSTF) and the Global Initiative for Chronic Obstructive Lung Disease[189,190]. Studies of COPD case-finding in people living with HIV have found very low spirometry completion rates of 30–50% in HICs[191]. In LMICs, where access to spirometry can be constrained, completion rates might be even lower, although we are unaware of COPD case-finding studies in this setting. Alternative COPD case-finding methods such as hand-held micro-spirometers are available and could be combined with newer COPD screening questionnaires, but these approaches require further study and validation before wide implementation[192].

Prevention strategies in people living with HIV who smoke should focus on smoking cessation. Data demonstrate that people living with HIV who smoke are at higher risk for COPD[74] and lose lung function faster than people living with HIV who do not smoke[193]. Among people living with HIV who do not smoke, COPD prevention measures should focus on optimizing indoor air quality and mitigating exposures to outdoor air pollution sources. In TB-endemic settings, public health efforts at TB control would also be expected to reduce the burden of COPD, given data that prior TB is associated with increased risk of COPD[194]. Further research is needed to identify effective HIV-specific COPD prevention strategies, targeting proposed mechanisms of COPD pathogenesis in people living with HIV, such as heightened inflammation, immune dysregulation and microbial dysbiosis.

Asthma.—Asthma is defined as a chronic disorder of the airways involving a complex interaction of variable and recurring respiratory symptoms, airflow obstruction, airway hyper-responsiveness and underlying inflammation[195]. The common symptoms of asthma include wheezing, dyspnoea, chest tightness and cough. These symptoms vary over time and in intensity. The physiological signs of asthma include variable expiratory airflow limitation, bronchodilator reversibility and airways hyper-responsiveness measured through spirometry testing. The diagnosis of asthma requires a history of asthma symptoms together with variable expiratory airflow limitation[195]. The diagnostic approach to asthma in people living with HIV is similar to that in the general population[195].

Because the penetrance of symptoms and airflow abnormalities are variable in asthma, multiple definitions of asthma have been used in clinical studies[196]. Self-reported asthma has good agreement with physician diagnosis in reports from the general population, with 92% agreement and 94% specificity[197]. Studies of asthma and HIV typically define asthma using self-reported data, but incorporating respiratory symptoms, lung function and treatment for asthma is likely to provide a more robust approach to diagnosing asthma among people living with HIV. In the most recent analysis of the MACS/WIHS Combined Cohort Study, asthma prevalence was found to be twofold to threefold higher when using self-report than when using robust criteria[9]. While HIV was not associated with increased asthma prevalence, regardless of the definition used, there was increased respiratory burden among men with HIV and asthma than among seronegative men with asthma.

Lung cancer.—The presentation, radiographic findings and diagnosis of lung cancer are similar in people living with HIV to those in HIV-uninfected people (Fig. 4). Adenocarcinoma is the most frequent cancer type, followed by squamous cell

carcinoma[98,105]. Lung cancer tends to be diagnosed at a younger age in people living with HIV than in the general population[198,199]. Considering demographic differences and access to care, stage of lung cancer at presentation is generally similar by HIV status, with approximately 70% of all patients diagnosed at stage III or stage IV in the absence of screening[105,198,200]. Bronchoscopic biopsy, lymph node sampling with endobronchial ultrasonography, and transthoracic needle aspiration or sampling of extra-pulmonary sites that may represent metastatic disease should be pursued to obtain a tissue diagnosis when feasible; genetic sequencing should be performed to identify targetable mutations that will affect the treatment regimen.

Smoking cessation is of primary importance in decreasing the risk of lung cancer among people living with HIV, although sustained smoking cessation is difficult to achieve despite investigations combining behavioural and pharmacological cessation therapies. Although less than optimal, harm reduction may also be a beneficial goal[201]. In the context of smoking cessation, harm reduction is defined as decreasing the negative effects of smoking without complete cessation. In people living with HIV, this can be most safely achieved by reducing the daily number of cigarettes smoked, as the safety and efficacy of substituting alternative forms of tobacco and nicotine products, including smokeless tobacco and electronic cigarettes, respectively, for harm reduction has not been extensively studied in this population.

Eligible people living with HIV should be offered lung cancer screening. In the National Lung Cancer Screening Trial, individuals with well-controlled HIV derived a similar mortality benefit from lung cancer screening as older, HIV-uninfected people with a heavy smoking history[202,203]. There are no lung cancer screening recommendations tailored for people living with HIV despite their high risk of lung cancer. In general, the USPSTF recommends screening for lung cancer annually with low-dose CT in adults at high risk (that is, smokers) aged 50–80 years who have a smoking history of ≥20 pack-years and currently smoke or formerly smoked but quit within the past 15 years[204]. An analysis of MACS/WIHS Combined Cohort Study data that investigated the application of the 2021 USPSTF screening recommendations to people living with HIV found that these lung cancer screening criteria would have detected lung cancer in only 44% of women with HIV and 63% of men with HIV[205]. These findings also suggest that decreasing the age and pack-year history eligibility requirements would increase the sensitivity and detect additional lung cancer cases in women; further work is needed to understand how to tailor lung cancer screening eligibility for people living with HIV to maximize benefits and minimize harms.

Children

Infections.—PCP in infants and children is usually acute with rapidly progressive hypoxia, in contrast to its more subacute and indolent course in adults. Compared with adults, the signs and symptoms of bacterial and viral pneumonia in infants and children can be more acute, and cough is frequently non-productive. Key signs are age-specific tachypnoea (rapid breathing) and lower chest indrawing. Pneumonia, especially severe disease, is frequently due to mixed infections, and clinical signs are unreliable for distinguishing bacterial from viral illness. TB in children may similarly present with acute illness (Fig. 4). In infants and

young children, a sample from the lower respiratory tract can be obtained using sputum induction. Molecular testing or culture methods are similar to those used in adults.

Effective specific preventive options include immunization with PCV and *H. influenzae* type b according to national immunization schedules. Current WHO recommendations are to provide a booster PCV dose in the second year in HIV-infected children who received their three-dose primary PCV series in infancy[206]. The use of effective ART is crucial to prevent opportunistic infections and optimize health. Long-term prophylaxis with co-trimoxazole (a combination of trimethoprim and sulfamethoxazole) is recommended in settings with a high burden of malaria or bacterial infections[206]. Prophylaxis can be stopped in children older than 5 years who are clinically stable, established on ART and virally suppressed in other settings[206]. Primary isoniazid prophylaxis in areas of high TB prevalence might reduce mortality and TB incidence[207] and WHO recommends its use in these areas in children older than 1 year for up to 3 years[208]. The Bacillus Calmette–Guérin (BCG) vaccine should be given to neonates born to women of unknown HIV status and to neonates with unknown HIV status born to HIV-infected women if they have no suggestion of HIV infection, as the benefits of BCG vaccination outweigh the risks[208]. In neonates with confirmed HIV infection, BCG should be delayed until ART has been instituted and the infant is clinically and immunologically stable[208].

Chronic lung disease.—Chronic respiratory disease is also common among children and adolescents living with HIV. Symptoms include chronic cough, dyspnoea, reduced exercise tolerance, increased work of breathing and impaired lung function. The spectrum of chronic lung disease includes bronchiolitis obliterans and bronchiectasis, chronic infection, lymphocytic interstitial pneumonitis (LIP), asthma, immune reconstitution inflammatory syndrome (IRIS) and malignancy[115] (Fig. 4). Before the widespread use of ART, chronic lung disease was dominated by LIP and chronic or recurrent infections with bronchiectasis. In children stable on ART, high-resolution CT scans indicate that bronchiolitis obliterans or bronchiectasis predominate[183,185]; these conditions are associated with prior TB or pneumonia.

Impairment in lung function has been found in children living with HIV, especially in those with delayed access to ART[116]. However, in a study of perinatally HIV-infected South African adolescents diagnosed in early childhood and stable on ART for several years, mild lung function impairment occurred in approximately 25%[209]. Lung function abnormalities included reductions in spirometry that were not bronchodilator-responsive, greater respiratory system resistance, and decreased compliance and alveolar gas diffusion compared with lung function in healthy age-matched controls[209]. Lung function impairment was associated with previous severe lower respiratory tract illness or pulmonary TB. Reassuringly, a small study found that if ART was initiated in infancy, most children had normal spirometry by school age[200].

Management

Adults

Infections.—The treatment of choice for PCP is trimethoprim plus sulfamethoxazole[210]. Alternative regimens include pentamidine and the combination of clindamycin and primaquine. Adjunctive corticosteroid therapy improves outcomes in severe PCP. Treatment of community-acquired pneumonia and TB follows general recommendations. For community-acquired pneumonia, recommendations for empiric treatment depend on the severity of illness and usually include a β-lactam antimicrobial plus a macrolide or doxycycline, or a fluoroquinolone. It is recommended that antimicrobials are narrowed according to the causative pathogen and antimicrobial susceptibility pattern, if these data are available[18]. Treatment of drug-susceptible pulmonary TB is with a four-drug regimen using a rifamycin (rifampin, rifabutin or rifapentine) and isoniazid for 6–9 months together with pyrazinamide plus ethambutol for the first 2 months[18,211]. A trial found that a 4-month regimen of isoniazid, rifapentine, ethambutol and moxifloxacin was non-inferior to a standard 6-month regimen[212]. Drug–drug interactions between rifamycins and specific ART drugs should be considered in selection and dosing (Box 2). Influenza is treated with oseltamivir or baloxavir. People living with HIV with COVID-19 might be considered at risk of progression to severe COVID-19, particularly if they are unvaccinated or older. Treatment strategies to reduce this risk include nirmatrelvir and ritonavir, remdesivir and molnupiravir. Treatment for severe COVID-19 consists of remdesivir and dexamethasone with the addition of anti-IL-6 monoclonal antibodies and baricitinib, depending on disease severity. Overall, treatment of COVID-19 in people living with HIV is the same as in the general population, with awareness of drug–drug interactions and overlapping toxicities between COVID-19 treatments and ART drugs[210].

COPD.—The goals of therapy for stable COPD are to improve survival, reduce symptoms, improve quality of life and functional status, and reduce the frequency and severity of exacerbations. The cornerstones of management are: smoking cessation; influenza, pneumococcal and SARS-CoV-2 vaccinations; pharmacotherapies; oxygen supplementation and non-invasive positive pressure ventilation in appropriately selected patients; and pulmonary rehabilitation[189]. Compared with HIV-uninfected smokers, people living with HIV who smoke are just as likely or more likely than HIV-uninfected people to initiate cessation interventions[213]. However, people living with HIV have low smoking quit rates with the usual behavioural and pharmacological interventions employed in HIV-uninfected people[214]. Promising smoking cessation strategies in people living with HIV include mobile health approaches[215] and clinic-level interventions rather than only provider-level or patient-level interventions[216].

Pharmacological therapies for COPD consist of inhaled bronchodilators (short-acting β2 agonists (SABAs), long-acting β2 agonists (LABAs), short-acting muscarinic antagonists (SAMAs) and long-acting muscarinic antagonists (LAMAs)), inhaled corticosteroids (ICSs), and combinations of these therapies (SABA/SAMA, LABA/LAMA, LABA/ICS, LABA/LAMA/ICS). Changes in the most recent COPD guidelines focus on the use of long-acting bronchodilators, with minimization of ICS use unless patients have asthma

features or peripheral eosinophilia, which are predictors of more favourable responses to ICSs[189,217,218]. ICS use in COPD is associated with an increased risk of pneumonia of approximately 40%[219] and possibly an increased risk of TB[220]. Given the underlying impact of HIV infection on pneumonia and TB risk, preventing further increases in pneumonia and TB risk from unnecessary ICS use in people living with HIV with COPD is clinically important (Box 2). ICSs also have well-described interactions with ART regimens that contain CYP3A4 inhibitors (such as ritonavir and cobicistat) that can lead to hypercortisolism. Due to the narrow indications for ICS use in COPD and the special risks of ICS use in people living with HIV with COPD, providers are encouraged to only prescribe ICSs in people living with HIV with COPD with asthma features or peripheral eosinophilia and to consider ICS de-escalation when these individuals do not meet these criteria and are clinically stable[221,222]. In people living with HIV who require both ICSs and CYP3A4 inhibitors, inhaled beclomethasone dipropionate is the preferred ICS due to minimal interactions with CYP3A4 inhibitors[223].

Asthma.—The management of asthma among people living with HIV aligns with the published guidelines for the general population[195], although specific considerations are necessary (Box 2). The main-stay of therapy consists of step-up treatment starting with either as-needed low-dose ICS and formoterol or as-needed ICS and SABA. With inadequate symptom control, treatment should be increased to regular ICS combined with a LABA. For severe disease, the addition of a LAMA and referral to a specialist are appropriate. Given the potential effect of HIV on atopy, obtaining serological testing for IgE and environmental sensitivities might be informative in individuals with uncontrolled asthma. Potential drug–drug interactions should be considered as described above. Current HIV treatment guidelines recommend against co-administration of the ICSs budesonide, ciclesonide, fluticasone, mometasone, betamethasone, and budesonide in individuals receiving protease inhibitors[224]. Beclomethasone can be used as an alternative ICS in this situation. The effects of the LABA salmeterol may be potentiated in people living with HIV who are on regimens that include a protease inhibitor or elvitegravir/cobicistat, raising concerns for QTc prolongation; no clinically significant drug–drug interactions have been reported for other LABAs. There are no reports of interactions between HIV-specific therapies and LAMAs.

Lung cancer.—Treatment of lung cancer in people living with HIV is generally similar to that in HIV-uninfected people. The risk of poor short-term outcomes following lung cancer surgery is similar in people living with HIV and in uninfected people, with pneumonia being the most common complication in both groups[225]. People living with HIV and malignancy have an increased risk of opportunistic infections, although the risk is similar in those with a $CD4^+$ T cell count >200/μl and suppressed HIV viral load to that in uninfected people[226] (Box 2). In terms of immunotherapies, large-scale studies on the safety and efficacy of immune checkpoint inhibitors (ICIs) among people living with HIV are limited. However, initial data suggest benefits and acceptable adverse effect profiles[227]. People living with HIV who are treated with ICIs might be more likely to have an increase in HIV viral load in the year after treatment, so close monitoring is warranted[228]. The effect of HIV infection on survival in patients with lung cancer is inconsistent, with some studies showing increased mortality in people living with HIV and others demonstrating similar outcomes[198,200].

Among people living with HIV, additional risk factors, such as a history of AIDS-defining illness at or before lung cancer diagnosis, can decrease survival[229].

Children

Infections.—Case management guidelines for pneumonia, as described in the WHO Integrated Management of Childhood Illness programme, are associated with decreased pneumonia and all-cause mortality[230] but should be adapted in areas with high HIV prevalence[231]. These management guidelines include ampicillin and gentamicin or ceftriaxone as first-line therapy for severe pneumonia; co-trimoxazole should be added in infants. Empiric therapy for TB traditionally included four drugs (isoniazid, rifampin or rifabutin, pyrazinamide and ethambutol) daily for 2 months followed by a minimum of 4 months of daily isoniazid and rifampin (or rifabutin), but the SHINE trial found that for non-severe TB, 4 months of treatment was non-inferior to 6 months[232]. Revised WHO guidelines now recommend 4 months of treatment for non-severe TB, depending on the degree of immunosuppression and ART status, and provided that there is no suspicion or evidence of multidrug-resistant or rifampin-resistant TB[208]. Adjunctive corticosteroids can be used for bronchial obstruction. Adjustment of ART and TB therapy might be needed to provide optimal therapy and minimize toxicity and drug interactions (Box 2). If TB is diagnosed in a child who has not yet started ART, TB treatment should be started first, followed by ART within 2 weeks to reduce the risk of IRIS. Co-trimoxazole is the treatment of choice for PCP. In severe PCP, corticosteroids might be beneficial[224]. Ganciclovir should be used for treatment of CMV pneumonia, with a switch to oral valganciclovir with clinical improvement (or in older children or those with mild illness)[224]. According to WHO recommendations, TB preventive treatment should be given to all children and adolescents who are household contacts of people with bacteriologically confirmed pulmonary TB and after TB disease has been excluded[208]. Options include 6 or 9 months of daily isoniazid, 3 months of weekly rifapentine plus isoniazid, 3 months of daily rifampin plus isoniazid, 1 month of daily rifapentine plus isoniazid, or 4 months of daily rifampin[208]. Children aged ≥12 months living with HIV who are unlikely to have TB disease should be offered TB preventive treatment as part of a comprehensive package of HIV prevention and care if they live in a setting with high TB transmission, regardless of contact with TB[208]. In high TB transmission settings, adolescents living with HIV who have an unknown or a positive TB infection test and are unlikely to have TB disease should receive at least 36 months of daily isoniazid preventive therapy, regardless of ART status and degree of immunosuppression[208].

Chronic lung disease.—Management includes ART, optimizing nutrition, vaccination against respiratory pathogens (including PCV and influenza), avoidance of exposure to tobacco smoke and air pollution, regular screening and prophylaxis for TB in endemic areas, and airway clearance techniques. Intercurrent infective exacerbations should be treated early. Azithromycin given weekly decreases acute respiratory exacerbations in adolescents with HIV-associated chronic lung disease but does not improve lung function[233]. Treatment of LIP includes ART, inhaled bronchodilators and oxygen for hypoxaemia. Although treatment of LIP with oral corticosteroids might improve hypoxaemia[234], there are no controlled clinical trials. To minimize the risk of IRIS, children should be carefully screened for TB and CMV before ART initiation. TB treatment should be initiated first followed by ART as

soon as possible and within 2 weeks. Oral corticosteroids might be beneficial in ameliorating IRIS, but there are no controlled trials in children[233]. Asthma should be treated with inhaled bronchodilators and ICSs, as for HIV-uninfected children, depending on phenotype and severity, with the same considerations for potential drug–drug interactions as described above. However, bronchodilator responsiveness should be evaluated, as wheezing may be due to bronchiolitis obliterans, endobronchial obstruction due to TB, or HIV-associated airway inflammation, none of which may be responsive to bronchodilators.

Quality of life

Respiratory-related quality of life is frequently suboptimal in people living with HIV, with many studies investigating respiratory symptoms such as cough and breathlessness. The presence of respiratory symptoms in people living with HIV is associated with more depressive symptoms and worse quality of life scores[235], highlighting the clinical relevance of these symptoms. A systematic review and meta-analysis of 24 publications found that, compared with HIV-uninfected controls, people living with HIV were more likely to report cough and breathlessness, in both resource-limited and resource-rich settings[236]. The difference in symptom burden seemed larger in people living with HIV who did not have access to ART compared with those with ART access, suggesting that ART might improve respiratory symptoms in people living with HIV. Potential benefits of ART on respiratory symptoms are also suggested by data showing that lower nadir $CD4^+$ T cell counts are associated with worse self-reported respiratory health status[91], along with results from the pulmonary substudy of the randomized START trial in which immediate ART initiation in early HIV was found to result in better respiratory symptoms than deferred ART initiation, but only in current smokers[237]. However, an analysis of men living with HIV showed that protease inhibitor use was associated with worse dyspnoea than the use of other classes of ART[238]. Ultimately, the effect of ART and specific ART regimens on respiratory symptoms currently remains unclear and requires further study.

In addition to self-reported symptoms, another method to assess respiratory health is functional testing such as the 6-min walk distance (6MWD) test. Two studies that measured 6MWD in both people living with HIV and in HIV-uninfected people found worse 6MWD in people living with HIV than in controls[239,240]. Both studies found no relationship between 6MWD and HIV variables such as $CD4^+$ T cell count, HIV viral load or ART use, suggesting that other non-viral mechanisms might be responsible for the impaired physical function seen in people living with HIV. Factors that have been associated with worse 6MWD in people living with HIV include respiratory disease markers such as impaired lung function[240,241] and increased radiographic emphysema[242], as well as non-respiratory factors such as older age, higher BMI and cigarette smoking[239,241]. 6MWD can also be affected by heart diseases such as heart failure, which is more common in people living with HIV than in HIV-uninfected people[243], but studies are lacking more comprehensive and concurrent assessments of 6MWD with measures of lung function, heart function and other factors that can affect 6MWD, such as sarcopenia, peripheral vascular disease and metabolic derangements.

Outlook

Unless an effective vaccine against HIV is developed and until there is a cure for people already infected with HIV, the estimated 38 million people living with HIV and those who will become HIV infected worldwide will continue to experience substantial morbidity and mortality from lung diseases. The tremendous success of ART in reducing new HIV transmission, HIV-associated opportunistic infections and malignancies, and AIDS-associated mortality has altered the epidemiology of AIDS and led to an ageing population of people living with HIV and the dominance of age-associated and non-communicable pulmonary conditions such as COPD. Similarly, the prevalence of chronic lung disease has increased in children and adolescents living with HIV. The long-term consequences of childhood respiratory infections, HIV-associated opportunistic pneumonias and chronic lung disease in these individuals as they transition into adulthood and especially late adulthood remain unknown. The ongoing scourges of inhaled tobacco products, illicit drug use, and air pollution, both indoor and outdoor, will continue to pose multiple threats to lung health worldwide. Thus, redoubled multifaceted efforts at tobacco and drug use cessation and improved air quality are crucial to mitigate additional morbidity and mortality. Given the impact of these scourges on cardiovascular disease and health in general, these efforts will have benefits beyond enhanced respiratory health. In addition, new dangers from pathogens both recent (for example, SARS-CoV-2) and centuries-old (for example, *M. tuberculosis*) and from emerging perils from global climate change will add to these enduring threats in unpredictable but ominous ways. Humanitarian crises from global pandemics, climate change and human conflict bring with them the potential to overwhelm our public health and medical systems and divert attention and essential resources away from vulnerable populations such as those living with HIV. As such, continued investigation into the effects of HIV on the lung is essential to expand our knowledge base and to ensure continued provision of the best clinical care to these millions of individuals (Box 3).

As detailed above, there have been considerable advances in our understanding of the often synergistic and deleterious effects of HIV infection and tobacco use on the lung. However, the chronic effects of the inhalation from electronic cigarettes (e-cigarettes) on the lungs of people living with HIV are unknown. In addition, although a wide range of acute pulmonary complications of illicit drugs that are injected or inhaled has been described previously[244], comparatively less is known about the long-term complications from chronic use of illicit drugs. With the longer life expectancy among people living with HIV, studying the chronic pulmonary complications of illicit drugs is needed. However, as the specific drugs that are used will undoubtedly change over time, flexibility to pivot and study new illicit drugs of choice will also be required.

Substantial advances have been made in the diagnosis of HIV-associated opportunistic pneumonias, especially pneumonia associated with *M. tuberculosis*, the major pulmonary pathogen in people living with HIV worldwide. Currently, the WHO recommends rapid molecular tests as the initial diagnostic test for suspected TB, supplanting smear microscopy from expectorated sputum. However, the requirement for an adequate sputum sample remains an important challenge to TB diagnosis in young children and infants and the continued study of alternative, non-sputum samples for diagnosis of TB is critical. Although

molecular tests have been developed for respiratory viral and bacterial pathogens, current guidelines from the American Thoracic Society and the Infectious Diseases Society of America continue to recommend sputum Gram stain and culture and blood cultures as the initial diagnostic tests for inpatients hospitalized with suspected community-acquired pneumonia[245]. These TB and community-acquired pneumonia guidelines also apply to people living with HIV[224]. The development, validation and widespread clinical application of rapid, point-of-care tests that can accurately detect a panel of the most frequent HIV-associated opportunistic pathogens, using readily collected samples and deployed in a range of clinical settings throughout the world, remains an aspirational goal as it would be a game-changing addition to our clinical toolbox.

Compared to advances in the diagnosis of the major HIV-associated opportunistic pneumonias (especially TB), diagnosis of the major HIV-associated non-communicable lung diseases, including but not limited to COPD and asthma, urgently needs similar advances. Spirometry is used to diagnose these obstructive lung diseases; this lung function test can be performed in medical (that is, hospital and clinic) settings, and portable equipment allows its clinical application in community settings, including in LMIC and resource-limited settings where the majority of people living with HIV reside. However, the most frequent lung function abnormality in people living with HIV is a reduction in the diffusing capacity of the lungs for carbon monoxide (DLCO). This test requires specialized equipment and a source of 0.3% carbon monoxide, and therefore is unavailable in community settings and is largely unavailable in LMIC settings. The presence of abnormal DLCO with normal spirometry ("iso↓DLCO") is a particularly novel, HIV-specific lung function phenotype[246]. Until these equipment and gas mixture limitations can be overcome, further advances in our understanding of this important, potentially HIV-specific lung function abnormality and its prevalence worldwide will be hampered. In addition, improved diagnosis and treatment of TB has led to an increasing appreciation for the substantial burden of post-TB lung disease and its impact in people living with HIV.

As noted, there are no HIV-specific guidelines for screening for non-communicable lung diseases, such as COPD and lung cancer, which are seen at increased frequency in people living with HIV. For COPD, alternative case-finding approaches and screening questionnaires described above require further study and validation. Moreover, given the results of two large randomized clinical trials that demonstrated that screening with low-dose chest CT reduces lung cancer mortality in high-risk patients[202,247], lung cancer screening should be undertaken in people living with HIV who meet USPSTF guideline criteria, particularly those with well-controlled HIV; additional guidance is needed to determine whether screening regimens or eligibility criteria should be tailored further for people living with HIV.

With the exception of PCP, there are limited data from large randomized controlled trials to guide the treatment of the major HIV-associated opportunistic pneumonias. Given the decreased incidence of these opportunistic pneumonias, it is unlikely that there will ever be such an evidence base from randomized controlled trials. There is an even greater paucity of data to guide management of COPD and asthma in people living with HIV. Instead, the findings of studies in people without HIV have been extrapolated to those living with

HIV, in general successfully. The development of additional, potent ICSs — for use either as single medications or in combination with long-acting bronchodilators — which can be co-administered with current antiretroviral medications would be an important addition to the medical management of people with these obstructive lung diseases who benefit from this therapy.

Tremendous advances have been made in our understanding of HIV's effects on the lung and in the diagnosis, screening and prevention, and the treatment and management of lung diseases in people living with HIV over the past >40 years, but major gaps remain. The magnitude of HIV/AIDS worldwide and the current absence of a vaccine against HIV and a cure for those already infected with HIV demands continued clinical focus and research in order to ensure provision of the best clinical care.

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Box 1

Risk factors for acute and chronic lung diseases in people living with HIV

Infection (bacterial, viral, fungal or parasitic)

Older age, infancy, cigarette smoking, low $CD4^+$ T cell count, neutropenia, high HIV viral load, history of AIDS-defining illness, history of bacterial pneumonia, co-infection with hepatitis C, lack of antiretroviral therapy, lack of appropriate *Pneumocystis jirovecii* pneumonia prophylaxis, lack of pneumococcal and influenza vaccinations, injection of illicit drugs, alcohol abuse, malnutrition, comorbidities.

Chronic obstructive pulmonary disease

Older age, cigarette smoking and more pack-years smoking, low BMI, low socioeconomic status, biomass fuel burning, injection of illicit drugs, low $CD4^+$ T cell count, low nadir $CD4^+$ T cell count, high HIV viral load, history of bacterial pneumonia, history of *P. jirovecii* pneumonia, history of pulmonary tuberculosis, co-infection with hepatitis C, antiretroviral therapy use[a], alcohol abuse[a].

Asthma

Parental history of asthma, obesity, history of bacterial pneumonia, female sex[a], older age[a], high BMI[a], $CD4^+$ T cell count[a], high HIV viral load[a].

Lung cancer

Older age, cigarette smoking and more pack-years smoking, low $CD4^+$ T cell count, high HIV viral load, history of chronic obstructive pulmonary disease, history of bacterial pneumonia, history of *P. jirovecii* pneumonia, oncogenicity of HIV itself[a], injection of drugs[a].

[a]Inconsistent or conflicting evidence regarding the association between these putative risk factors and corresponding lung disease.

Box 2

Special considerations for management of HIV-associated lung diseases

Infections

- Be aware of potential increased risk of progression to severe COVID-19 pneumonia
- Consider drug–drug interactions and overlapping toxicities between COVID-19 and TB treatments and ART

COPD

- Employ more intensive smoking cessation interventions given low quit rates among people living with HIV
- Consider risk of ICS use given potential for bacterial pneumonia and TB risk among people living with HIV
- Monitor for hypercortisolism with co-administration of ICSs and CYP3A4 inhibitors (for example, ritonavir and cobicistat)

Asthma

- Use beclomethasone as preferred ICS among people living with HIV using protease inhibitors
- Avoid budesonide, ciclesonide, fluticasone, mometasone, betamethasone, and budesonide in individuals receiving protease inhibitors
- Avoid salmeterol in individuals receiving protease inhibitors or elvitegravir/cobicistat
- Consider total IgE and testing for environmental sensitivities among people living with HIV

Lung cancer

- Be aware of increased risk of opportunistic infections in people living with HIV with lung cancer
- Monitor for increased HIV viral load with use of immune checkpoint inhibitors
- Follow lung cancer screening guidelines for the general population

Children

- Start TB treatment before ART initiation 2 weeks later in ART-naive children living with HIV and TB
- Consider weekly azithromycin in adolescents with HIV-associated chronic lung disease
- Screen children for TB and CMV before ART initiation given the risk of IRIS

- Consider alternative diagnosis to asthma in children living with HIV (for example, bronchiolitis obliterans, endobronchial obstruction due to TB, or HIV-associated airway inflammation)

ART, antiretroviral therapy; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; CYP34A, cytochrome P450 3A4; ICS, inhaled corticosteroid; IRIS, immune reconstitution inflammatory syndrome; TB, tuberculosis.

Box 3

Future directions for research in HIV-associated lung disease

- Elucidate the mechanistic role of perturbed innate and adaptive immunity, local and systemic inflammation, imbalance of lung proteases and antiproteases, endothelial activation, oxidative stress and accelerated cell senescence in the pathogenesis of HIV-associated lung disease
- Examine the impact of air pollution, electronic cigarettes, and inhaled illicit drugs on the development of chronic lung disease
- Assess the longitudinal disease course of HIV-associated chronic lung diseases
- Expand the evidence basis regarding prevalence of HIV-associated chronic lung diseases in low-income and middle-income countries
- Develop and deploy rapid, point-of-care tests to accurately detect HIV-associated respiratory pathogens
- Improve diagnostics for obstructive lung diseases that can be readily deployed in low-income and middle-income countries
- Develop HIV-specific screening strategies for chronic lung diseases
- Test interventions to prevent and treat chronic lung disease in people living with HIV at the patient, provider and systems levels
- Examine the impact of HIV infection on functional outcomes, exacerbations and mortality of chronic lung disease
- Evaluate biomarkers to predict lung disease development and outcomes in people living with HIV

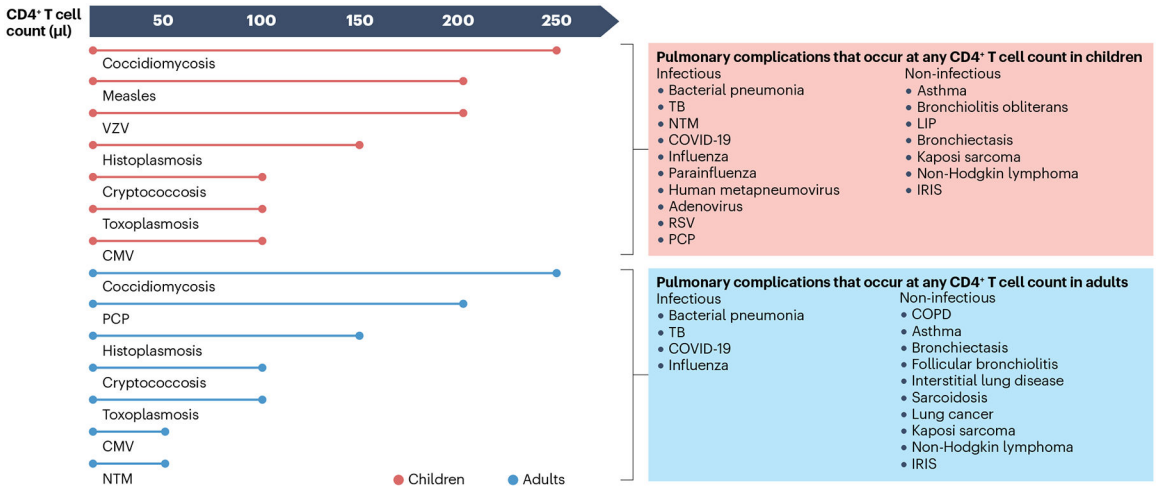

Fig. 1 |. Risk of HIV-associated lung diseases.

The risk of infectious and non-infectious pulmonary complications of HIV may vary between children and adults and by $CD4^+$ T cell count. For several infectious lung diseases, specific $CD4^+$ T cell count thresholds exist below which the risk is substantially increased (for example, the risk of *Pneumocystis jirovecii* pneumonia (PCP) is significantly increased in individuals with $CD4^+$ T cell counts <200/μl). By contrast, no specific thresholds exist for infections such as bacterial pneumonia, tuberculosis (TB), and COVID-19, and non-infectious complications, such as Kaposi sarcoma, non-Hodgkin lymphoma and immune reconstitution inflammatory syndrome (IRIS), although the risk generally increases with lower $CD4^+$ T cell count. CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; LIP, lymphocytic interstitial pneumonitis; NTM, non-tuberculous mycobacteria; RSV, respiratory syncytial virus; VZV, varicella zoster virus. Adapted from figure courtesy of S. Pipavath.

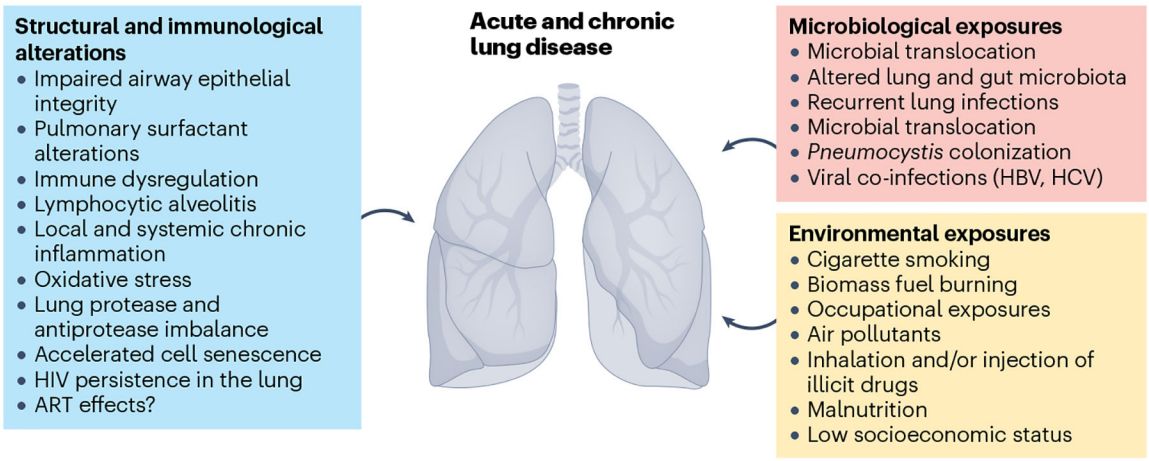

Fig. 2 |. Factors implicated in the pathogenesis of acute and chronic lung disease in people living with HIV.

There is a complex interplay between structural and immunological alterations and environmental and microbiological exposures. The degree to which these mechanisms are unique to HIV infection or whether their effect is modified by HIV infection is unknown. ART, antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus.

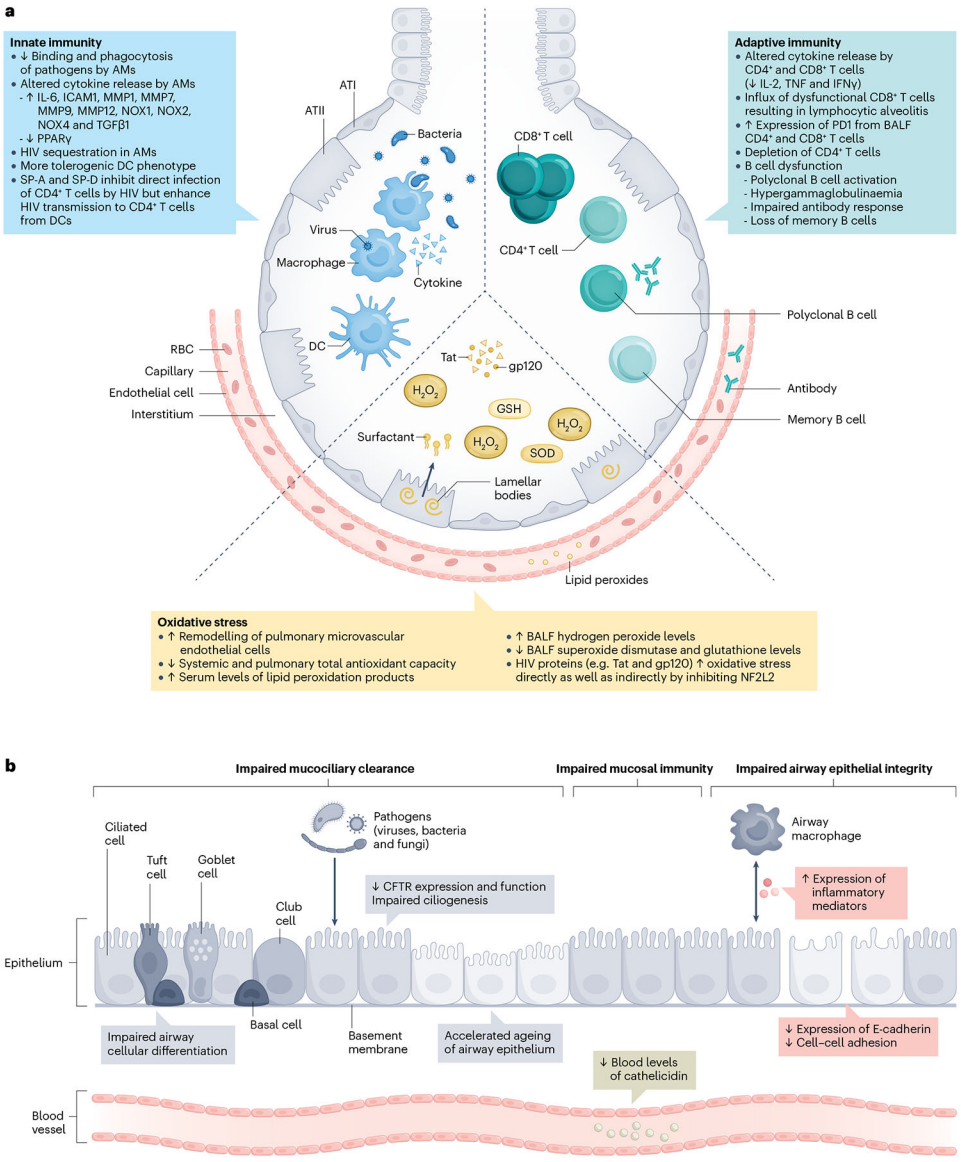

Fig. 3 |. Effects of HIV on the structure and function of alveoli and the airway epithelium.

a, Innate immune effects of HIV include impaired alveolar macrophage (AM) binding and phagocytosis of pathogens[134,135,151] and altered cytokine release[149,175,177], as well as sequestration of HIV[138]. Dendritic cells (DCs) display a more tolerogenic phenotype[139], and surfactant protein A (SP-A) and SP-D inhibit direct infection of $CD4^+$ T cells by HIV but enhance transmission of HIV from DCs to $CD4^+$ T cells[140,141]. Adaptive immunity effects include depletion of $CD4^+$ T cells[142], altered cytokine release by $CD4^+$ and $CD8^+$ T cells[136,137], influx of dysfunctional $CD8^+$ T cells (resulting in lymphocytic alveolitis[143]) and increased expression of PD1 by bronchoalveolar lavage fluid (BALF) $CD4^+$ T cells and $CD8^+$ T cells[143]. Furthermore, polyclonal B cell activation, hypergammaglobulinaemia, an impaired antibody response and loss of memory B cells result in B cell dysfunction[144]. HIV also increases oxidative stress by decreasing systemic and pulmonary total antioxidant capacity[147,151,157], decreasing superoxide dismutase (SOD)

and glutathione (GSH) levels[145,148,156,158] and increasing hydrogen peroxide levels[156] in BALF, and increasing serum levels of lipid peroxidation products[146]. HIV proteins (such as Tat and gp120) directly and indirectly inhibit nuclear factor erythroid 2-related factor 2 (NF2L2)[150]. HIV also increases remodelling of pulmonary microvascular endothelial cells[153–155]. **b**, HIV infection impairs airway epithelial integrity[126,150] by decreasing E-cadherin expression, increasing inflammatory mediator expression, and reducing cell–cell adhesion. Mucociliary clearance is also impaired[128,132] owing to impaired ciliogenesis and airway cellular differentiation, accelerated airway epithelium ageing, and decreased cystic fibrosis transmembrane conductance regulator (CFTR) expression and function. Mucosal immunity is disrupted by reduced levels of cathelicidin in blood[127]. ATI, alveolar epithelial type I cell; ATII, alveolar epithelial type II cell; RBC, red blood cell; TGFβ1, transforming growth factor-β1. Part **a** adapted from ref. 248, Springer Nature Limited. Part **b** adapted from ref. 249, Springer Nature Limited.

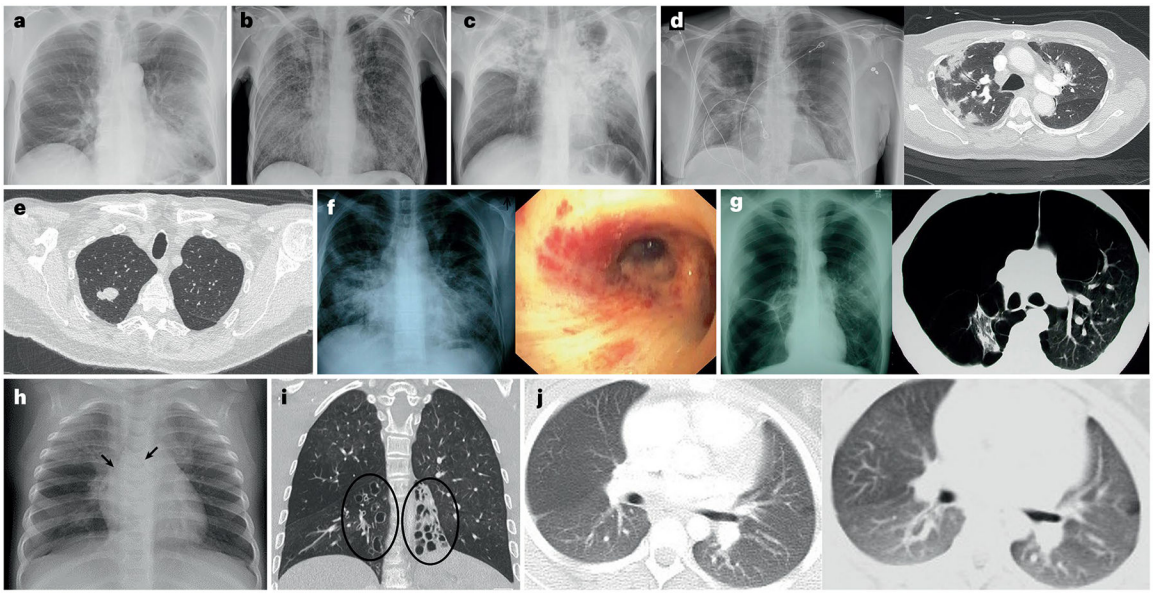

Fig. 4 |. Manifestations of HIV-associated lung disease.
In adults, different manifestations include bacterial pneumonia (part **a**; caused by *Streptococcus pneumoniae*), *Pneumocystis jirovecii* pneumonia (part **b**), pulmonary tuberculosis (part **c**), COVID-19 pneumonia (part **d**), primary lung cancer (part **e**), Kaposi sarcoma (part **f**) and emphysema (part **g**). In children, manifestations include pulmonary tuberculosis (part **h**; arrows show bilateral compression of the bronchi from lymphadenopathy due to pulmonary tuberculosis), bronchiectasis (part **i**; ellipses) and bronchiolitis obliterans (part **j**). Parts **i** and **j** courtesy of A.-M. du Plessis.