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Prevention

The World Health Organization has prioritized the eradication of tuberculosis and set the goal of reducing the incidence of TB to less than one per million population by 2050 in their STOP TB campaign. This requires commitment to finding and treating active cases of tuberculosis, and also to identifying latent infection. Improving socioeconomic conditions is vital in reducing transmission. There are ongoing studies of new treatments and vaccinations, but the only available vaccine currently is the BCG, which has limited evidence for effectiveness, protecting mainly against miliary disease and meningitis in children.

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18.4.5 Pulmonary complications of HIV infection

Julia Choy and Anton Pozniak

ESSENTIALS

Most HIV-positive individuals will experience at least one significant episode of pulmonary disease during their lifetime. The immune status of the HIV-infected patient is the primary determinant of the risk of developing specific pulmonary diseases: those with advanced immunosuppression are predisposed to opportunistic infections and malignancies; those with mild or no immunosuppression are at greater risk of conditions including community-acquired pneumonia, chronic obstructive pulmonary disease, pulmonary hypertension, and interstitial lung disease.

Pulmonary infections related to HIV infection with severe immunosuppression include: (1) *Pneumocystis jirovecii* pneumonia—typically presents with gradual onset of breathlessness and dry cough, and a chest X-ray showing diffuse bilateral infiltrates. Diagnosis requires direct visualization of fungal spores in respiratory secretions. First-line treatment is with high-dose trimethoprim/sulfamethoxazole. (2) Tuberculosis—is the leading cause of death among people with HIV. Presentation may be nonspecific and atypical, and tissue biopsy may be required for diagnosis. Treatment is as for HIV-uninfected patients, but great care is needed regarding drug interactions. (3) Fungal infections including aspergillosis and cryptococcosis.

Lung malignancies related to HIV infection with severe immunosuppression include: (1) Kaposi's sarcoma—caused by human herpesvirus (HHV-8), usually in patients with obvious mucocutaneous lesions and diagnosed by finding of purplish plaques at bronchoscopy; treatment is with systemic chemotherapy. (2) Lymphoma—typically non-Hodgkin's B-cell lymphoma or primary effusion lymphoma (also caused by HHV-8).

Introduction

In 2017, 37 million adults were living with HIV, mostly in Low and Middle Income Countries (LMIC). In many countries it is becoming chronic disease with life expectancies approximating normal due to the use of highly active combination antiretroviral therapy (cART). This is testimony to the fact that the risk of developing an opportunistic infection or malignancy is markedly reduced by being on cART and having an undetectable HIV-1 viral load. Nevertheless, with unequal access to diagnostics, treatment, and education worldwide, 1.8 million people are still infected every year and many develop opportunistic infections and HIV-associated neoplasms leading to almost one million AIDS-related deaths.

The lungs are commonly affected in HIV-positive individuals, 60% of whom will experience at least one significant episode of pulmonary disease during their lifetime. Subsequently, pulmonary disease remains a significant cause of morbidity and mortality. A wide range of conditions can occur, ranging from opportunistic infections and tumours to interstitial lung diseases. Available data suggest that both cellular and humoral lung immunity is impaired in HIV and that alveolar macrophages are an important reservoir for HIV in the lung.

This chapter will concentrate on common causes of HIV-related lung disease and can be divided into:

- HIV disease with mild or no immunosuppression (normal or near normal CD4 counts)—in these patients typical community-acquired infections occur at greater frequency than in the general population, and chronic obstructive pulmonary disease (COPD), pulmonary hypertension, interstitial lung disease, and lung cancers are common, partly related to immune defects and lifestyle factors.
- HIV disease with advanced immunosuppression—in these patients abnormalities of the innate and adaptive lung immunity predispose them to opportunistic infections and opportunistic malignancies.

Clearly, the differential diagnosis for specific pulmonary diseases in HIV is influenced by the immune status of the HIV-infected patient, which is the primary determinant for the risk of developing specific pulmonary disease. However, other elements such as demographic factors and the use of prophylactic antibiotics and cART also influence the differential.

Epidemiology

Immune status

In patients with HIV, the occurrence of specific infections/opportunistic infections is correlated with the degree of immunosuppression. The CD4 count of an uninfected adult/adolescent who is generally in good health ranges from 500 cells/mm^3 to 1200 cells/mm^3. There is an increased risk of developing a variety of illnesses when it falls below 350 cells/mm^3, and a very low CD4 count (less than 200 cells/mm^3) is associated with developing opportunistic infections and tumours. The CD4 + lymphocyte count is therefore a useful surrogate marker for immune function in HIV. It provides information about the type of pulmonary disease to which the patient is susceptible and also helps define the stage of HIV, although it should be noted that even at high CD4 counts opportunistic tumours and tuberculosis can occur.

The Pulmonary Complication of HIV Infection Study Group examined the incidence of pulmonary complications over 5 years. Together with data from the Strategic Timing of Antiretroviral Treatment (START) study, which looked at early versus late initiation of HIV treatment, a list of respiratory pathologies based upon HIV disease severity (as indicated by the CD4 + count and whether someone is on antiretroviral therapy) is detailed in Table 18.4.5.1.

TB and bacterial pneumonias often occur before subsequent opportunistic infections and neoplasms. With lower CD4 counts there is an increased incidence of all pulmonary pathologies, and different pulmonary infections occur with increasing frequency resulting in increased risk of bronchiectasis secondary to recurrent infections over time. The use of cART has dramatically diminished the incidence of all of these complications

Table 18.4.5.1 Respiratory pathologies in HIV infection

CD4 + Count (cells/mm^3)	Pulmonary Disease
Any CD4 + count	Sinusitis
	Bronchitis
	Bacterial pneumonia
	Tuberculous
	Kaposi's sarcoma
100–≤200 Advanced HIV—opportunistic infections (opportunistic infection)	Pneumocystis (PCP)
	Fungal
	Cytomegalovirus (CMV)
	Primary pulmonary lymphoma
≤100 Late-stage HIV	Non-TB mycobacteria
>350 and viral load (VL) undetectable Well-controlled HIV	Systemic lymphoma (non-Hodgkin's lymphoma)
	Chronic obstructive pulmonary disease
	Interstitial lung disease
	Pulmonary hypertension
	Lung cancers

Demographic factors

Injecting drug users are at increased risk of bacterial pneumonias compared to other persons with HIV. In this subgroup bacterial pneumonia is more common than *Pneumocystis jirovecii* pneumonia (PCP) and fungal pneumonias—especially invasive aspergillosis—are more common. Ethnicity and geography may also influence the risk of developing certain pulmonary diseases in HIV; for example, the risk of tuberculosis (TB) is higher in those living in or coming from developing countries, and those that are black or Hispanic. Conversely, the risk of PCP, HIV malignancies, and cytomegalovirus disease is higher in the white population. Consequently, there is a higher risk of PCP in Europe and the United States than there is in Africa, where TB is the most common pulmonary complication in HIV. There is a higher incidence of TB in enclosed populations, for example, in prisons and in hostels, and a higher incidence of fungal infections depending on the geographic distribution of endemic fungi (e.g. histoplasmosis pulmonary infections in HIV-positive individuals living in the Mississippi Delta or from Africa, and Coccidioidomycosis in California).

Prophylactic antibiotics and antiretroviral therapy

As described earlier, untreated HIV infection is associated with progressive reduction in cell-mediated immunity and an increased risk of opportunistic infection. This risk can be decreased by, firstly, starting cART to decrease HIV viral activity which leads to an increase in the CD4 count and improved immunity (the incidence of pulmonary opportunistic infection has declined dramatically following the widespread use of cART), and secondly, by putting patients on antimicrobial prophylaxis to decrease the risk of opportunistic infection at low CD4 counts. The risk of PCP without prophylaxis is 40–50% per year in those with a CD4 count less than 100: this risk is ninefold lower with the use of antibiotic prophylaxis.

Diagnosis of pulmonary disease in HIV infection

Patients with HIV-associated pulmonary diseases often present with nonspecific symptoms such as cough, with or without sputum production, dyspnoea, and wheezing. The initial diagnostic approach is the same as for any other patient (i.e. history, examination, and appropriate diagnostic tests). However, some specific considerations have to be recognized in the context of HIV. For example, neutropenia is a recognized complication of HIV, hence if neutropenia is present, empiric therapy covering *Pseudomonas aeruginosa* may be indicated. Elevated plasma levels of 1-3-beta-D-glucan, a component of the cell wall of *P. jirovecii*, have been found in HIV-infected patients with PCP. Lactate dehydrogenase levels may be useful to monitor response to treatment in PCP infection: they are often elevated in PCP but are nonspecific. Polymerase chain reaction (PCR) of respiratory fluid, in particular bronchoalveolar lavage (BAL), is increasingly used to make the diagnosis of PCP but cannot distinguish between colonization and disease. Blood cultures are helpful in the diagnosis of disseminated mycobacteria, fungi, and bacterial

pneumonia, in particular that due to *Streptococcus pneumoniae*. Routine collection of expectorated sputum for Gram stain and culture has low sensitivity and specificity in HIV infection, especially after antibiotics have been started. Induced sputum for PCP stain, AFB (acid fast) stain, and culture is the initial test of choice in most centres for diagnosis of *Pneumocystis jirovecii*, although sensitivity varies widely. This, along with exercise oximetry demonstration oxygen desaturation on exertion, is very useful in diagnosing PCP.

If no causative organism is isolated using standard techniques and/or the patient has failed to improve on empirical therapy for PCP and bacterial pneumonia, fibreoptic bronchoscopy with bronchoalveolar lavage +/- transbronchial biopsy may be performed. Bronchoalveolar lavage is highly sensitive for the diagnosis of PCP, and Kaposi's sarcoma is often diagnosed by visualizing the characteristic purple plaques, often without biopsy due to the risk of bleeding. Lung biopsy is likely to be necessary to establish an alternative diagnosis such as cytomegalovirus, Aspergillus, or lymphocytic interstitial pneumonitis, and video-assisted thoracoscopic biopsy can be useful in diagnosis of peripheral nodules or masses not reachable by bronchoscopic.

Pulmonary infections

The epidemiology of HIV-related pulmonary infections (Table 18.4.5.2) has changed as a consequence of advances in cART and prophylaxis. However, the most common respiratory infections are:

- Community-acquired pneumonia (CAP)
- *Pneumocystis jirovecii* pneumonia (PCP)
- *Mycobacterium tuberculosis (*TB)

In LMICs (e.g. sub-Saharan Africa), TB remains the most common pulmonary infection in HIV-infected patients, with CAP second. In resource-rich countries rates of PCP have decreased considerably with the use of co-trimoxazole prophylaxis and the introduction of cART. Rates of TB in HIV-infected patients have also decreased with the introduction of cART and with public health measures, such that bacterial CAP is now the most common pulmonary infection in HIV-infected individuals.

Table 18.4.5.2 Types of pulmonary infection patients with HIV

Type of pulmonary infection	Species
Bacterial community-acquired pneumonia	*Streptococcus pneumoniae*
	Haemophilus
	Staph Aureus
	Pseudomonas
	Klebsiella
	Nocardia
	Legionella
	Atypicals
	Rhodococcus
Tuberculosis (TB)	*Mycobacterium tuberculosis*
Non-TB mycobacterium	*Mycobacterium kansasii, avium, xenopi*
Fungal	*PCP*
	Cryptococcus
	Aspergillus
	Histoplasmosis (rare in United Kingdom)
Viral	*Cytomegalovirus* (CMV)

Bacterial community-acquired pneumonia

Although HIV affects cell-mediated immunity most profoundly, abnormalities in antibody production and (in advanced AIDS) neutrophil function all contribute to the increased risk of bacterial pneumonia. Bacterial pneumonia is a major cause of pulmonary infection in HIV-infected individuals and can occur at any CD4 count. The annual incidence of CAP in HIV patients is 5.5–29 per 100, compared to 0.7–10 per 100 in HIV-negative individuals. Use of cART has resulted in decreased incidence of bacterial pneumonia (from 22.7 to 9.1 episodes/100 patient years), but this still remains approximately 40 times higher than the risk of age-matched HIV-negative adults.

The epidemiology of bacterial pneumonia is influenced by both epidemiologic and immunological factors. Risk factors, apart from HIV infection *per se*, include CD4 count (<200 cells/mm^3), detectable viral load, neutropenia, not being on cART, having had prior PCP, IV drug abuse, smoking, alcohol abuse and other comorbidities, and steroid use.

Aetiology

The spectrum of pathogens, in general, does not differ significantly from those patients who are HIV negative (Table 18.4.5.2). Similarly, the clinical presentation of CAP is very similar to that in HIV-uninfected patients. *Streptococcus pnemoniae, Haemophilus influenza*, and *Staphylococcus aureus* are the most common bacterial pathogens, often giving a characteristic lobar/segmental focal consolidative picture on chest X-ray (Fig. 18.4.5.1), but diffuse bilateral infiltrates and cavitation can also occur (Fig. 18.4.5.2). There is a higher rate of bacteraemia in HIV-infected patients—HIV-positive adults are at approximately 40 times higher risk of invasive pneumococcal disease compared to age-matched HIV-negative adults.

Other causative organisms include Gram-negative pathogens, especially in the context of a low CD4 + count (e.g. *Pseudomonas*

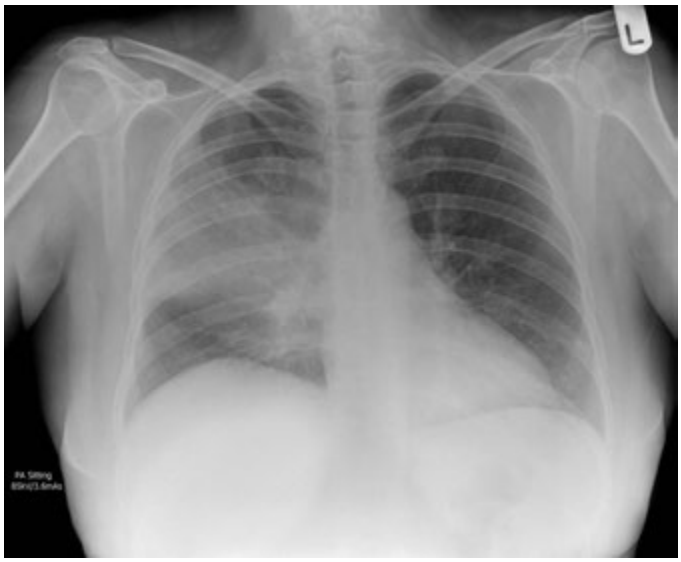

Fig. 18.4.5.1 Chest X-ray due to Strep pneumonia showing lobar pneumonia.

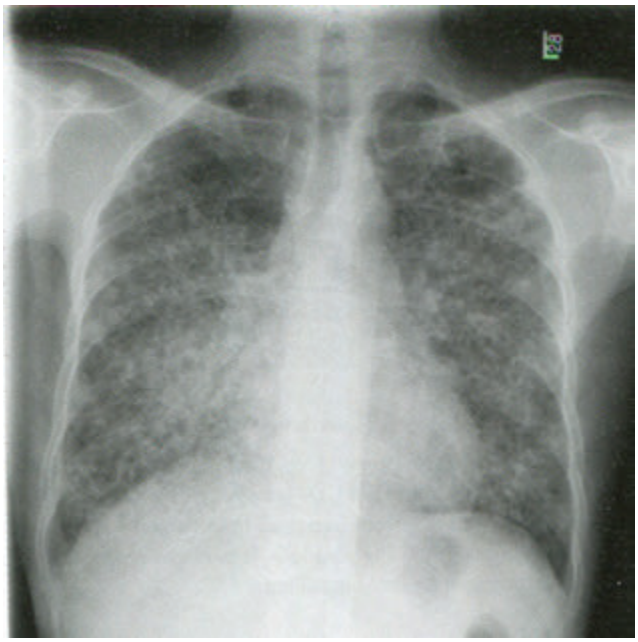

Fig. 18.4.5.2 Chest X-ray showing bilateral diffuse infiltrate due to Strep pneumonia, but mimicking *Pneumocystis jirovecii* pneumonia.

aeruginosa and *Klebsiella pneumoniae*). Atypical pathogens such as *Chlamydia, Mycoplasma*, and *Legionella* have been reported, but are relatively uncommon. Other uncommon pathogens causing CAP in HIV patients also include *Nocardia asteroids* and *Rhodococcus equi*.

Management, prognosis, and prevention

Treatment of CAP consists of a β-lactam plus a macrolide—quinolones are avoided due to the risk of quinolone resistant TB. If PCP has been excluded by sputum analysis, commencement of PCP prophylaxis should be considered if the CD4 + count is less than 200 cells/mm^3 or the CD4 percentage is 14% or less.

Compared with HIV-negative adults, HIV-positive persons show an increased risk of mortality after controlling for age and severity of presentation, and this risk is related to the CD4 cell count. With an increasing proportion of associated comorbidities in ageing HIV-positive populations (e.g. cirrhosis, chronic pulmonary disease) case fatality has tended to increase in recent years.

Pneumococcal vaccine is recommended for all HIV-infected people. Two types of pneumococcal vaccine are licensed in the United Kingdom; PPV-23, the pneumococcal polysaccharide vaccine, and PCV-13, the pneumococcal protein-conjugated vaccine. The most robust evidence for the use of pneumococcal vaccines in HIV-positive adults relates to PCV-13 use. The conjugated vaccines are immunogenic and have proven to be clinically effective in randomized controlled trials, including one undertaken in HIV-positive adults with low CD4 counts. Current British HIV Association (BHIVA) and European guidelines recommend that HIV-positive adults receive a single dose of PCV-13 irrespective of CD4 cell count, cART use, and viral load.

Pneumocystis

Pneumocystis jirovecii, formally called *Pneumocystis carinii*, is the cause of *Pneumocystis* pneumonia (PCP), a fungal pneumonia. The incidence of PCP has declined dramatically due to cART and PCP prophylaxis in those with low CD4 counts, but it still remains one of the leading opportunistic infections in HIV-infected persons with low CD4 counts. Most cases occur in those who have undiagnosed HIV, or those who are not receiving or are not engaged in care. Risk factors for PCP include a CD4 + count 200 cells/mm^3 or less, or a CD4% of 14% or less, a previous episode of PCP, a high viral load (>100 000 copies/ml), and/or the presence of oral thrush. PCP is unlikely in a patient on cART with a persistently undetectable viral load even with a CD4 count 200 cells/mm^3 or less.

Clinical features

PCP typically presents with gradually increasing dyspnoea and dry cough with fever over days to weeks. Symptoms are usually gradual in onset (being present on average for 3 weeks), as opposed to CAP. Purulent sputum suggests CAP, although this can be present in one-sixth of patients with PCP as a copathogen.

The chest X-ray usually displays diffuse bilateral infiltrates (Fig. 18.4.5.3), which strongly suggests the diagnosis, but sometimes shows nodular opacities, lobar consolidation, or can be normal in up to 25% of patients. Spontaneous pneumothoraces in patients with HIV should prompt the diagnosis of PCP. High resolution computed tomography (HRCT) has a high sensitivity for PCP among HIV-positive patients when patchy or nodular ground-glass attenuation are found. A negative HRCT scan makes the diagnosis of PCP unlikely.

There are no clinical features specific to PCP, but the diagnosis of PCP may be supported by adjunctive tests. Demonstration of a fall in oxygenation between rest and exercise has been validated as a reasonably specific test for PCP, but is not reliable enough to make a diagnosis without confirmatory microbiology. Patients with a diagnosis of PCP have significantly higher median 1-3-beta-D-glucan levels than patients without the disease and the test is used in supporting the diagnosis, though it can be positive in other fungal diseases. Lactate dehydrogenase levels are high in 90% of HIV-infected patients with PCP but have poor sensitivity and specificity diagnostically. A rising lactate dehydrogenase level despite appropriate treatment in PCP is a poor prognostic factor.

Microbiological diagnosis

PCP is a fungus that cannot be cultured. Diagnosis therefore requires direct visualization of the fungal spores in respiratory

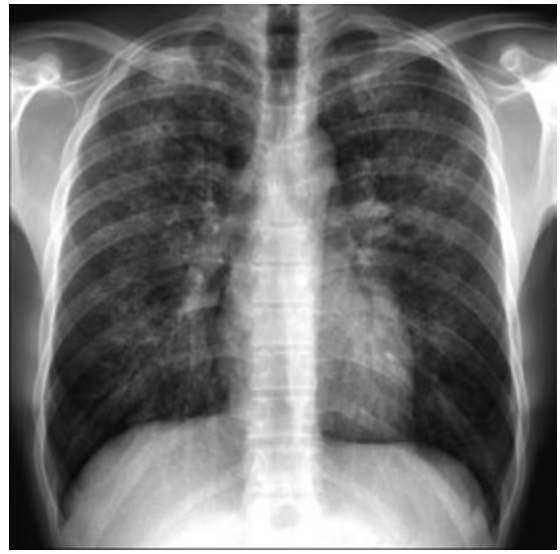

Fig. 18.4.5.3 Chest X-ray showing typical bilateral infiltrates in *Pneumocystis jirovecii* pneumonia.

secretions by immunofluorescence tests, for which adequate sputum specimens are required. These are most often obtained with induced sputum (sensitivity 50–90%), which is the least invasive technique. If induced sputum results are negative or inconclusive, then the patient should be assessed for bronchoscopy with bronchoalveolar lavage (diagnostic sensitivity >90%). Endotracheal aspirates and tissue biopsies may also be used in diagnosis. All specimens should be examined for the presence of acid-fast bacilli, fungi, and viral cellular inclusions, since patients with suspected PCP may have another infection, or may be co-infected with other pathogens.

Management

Treatment is started empirically in a patient with typical clinical and radiographic features and a CD4 less than 200 or 14% and an elevated 1-3-beta-D-glucan level. Pending diagnosis by cytological analysis of induced sputum samples or bronchoalveolar lavage fluid. Indeed, treatment should be started promptly if PCP is suspected, and not delayed for confirmation of the organism. Immunofluorescence tests for *Pneumocystis jirovecii* will remain positive for several days after treatment is commenced. CART should be started as soon as is practicable and within 2 weeks of PCP diagnosis.

Evaluation of the degree of hypoxia through arterial blood gas sampling helps assess the severity of the disease and the need to add glucocorticoids. A PaO_2 less than 9.3 kPa on room air indicates severe PCP infection and the need for glucocorticoids in addition to antimicrobial agents (Table 18.4.5.3) to suppress the robust inflammatory response to the *Pneumocystis* organism.

The British HIV Association and American Centre for Disease Control Guidelines recommend high-dose trimethoprim/sulfamethoxazole (TMP-SMX or co-trimoxazole) for 21 days as first-line treatment for PCP; patients with sulfa allergies require second-line regimens. If patients have concurrent gastrointestinal problems affecting swallowing or absorption (e.g. thrush/diarrhoea), or have moderate or severe disease, then TMP-SMX should be given intravenously rather than orally. Alternative therapies include atovoquone for mild disease and clindamycin-primaquine or IV pentamidine for severe disease.

Up to 10% of patients will fail first-line treatment with TMP-SMX (defined as deterioration after 5 days of first-line therapy) and will have to be switched to second-line treatments. The use of caspofungin as an adjunct therapy is still uncertain.

Prognosis

Despite highly active antiretroviral therapy, improvement in diagnostics, and the use of antipneumocystis prophylaxis, PCP pneumonia is still the most common cause of respiratory failure and admission to intensive care units in patients with HIV. When treatment is delayed or ineffective, severe PCP—resembling acute respiratory distress syndrome—may develop. Progressive respiratory deterioration while on therapy warrants early ICU/HDU input because acute progression of hypoxia in PCP is associated with high mortality (up to 60%) and morbidity. Other complications of PCP include pneumothorax.

Table 18.4.5.3 Treatment of *Pneumocystis jirovecii* pneumonia

Disease severity	Mild PaO_2 >9.3 kPa	Moderate–severe PaO_2 ≤9.3 kPa
First choice	Co-trimoxazole	Co-trimoxazole
Alternative therapy (second line)	Clindamycin-primaquine or Dapsone with trimethoprim or Atovaquone	Intravenous pentamidine or Clindamycin-primaquine or Dapsone with trimethoprim or Atovaquone
Steroids	No	Yes

Table 18.4.5.4 Indications for prophylaxis of *Pneumocystis jirovecii* pneumonia

Primary prophylaxis	CD4 ≤200 CD4 count ≤14% of total lymphocyte count
Secondary prophylaxis	All patients after an episode of PCP

Prevention

PCP prophylaxis is given to patients with a CD4 count of less than 200 cells/mm^3 who are at greatest at risk of PCP (Table 18.4.5.4). First-line choice for prophylaxis is co-trimoxazole; dapsone, atovaquone, and inhaled pentamidine are alternatives. Prophylaxis can be stopped in patients with an undetectable plasma viral load on cART who have maintained a CD4 count of more than 200 cells/mm^3 for 6 months.

Pulmonary tuberculous

HIV is a key driver in the global rise in TB cases through both accelerated progression of TB after exposure and greatly increased risk of reactivation. Most cases of TB in HIV-positive individuals represent reactivation of latent bacilli. The lifetime risk of developing active TB in an HIV-uninfected individual with latent TB infection is 10%, compared to 10% per year in an HIV-infected person not on cART. Active TB can occur at even relatively high CD4 counts (>350 cells/mm^3).

Many HIV-positive patients living in LMICs are exposed to TB due to the nature of their environment, especially overcrowding and poverty. Where the background prevalence of TB is low, the disease is uncommon in HIV-positive patients unless they can become exposed, for instance, through travel.

Clinical features and diagnosis

Typical clinical features of TB such as a subacute history of a productive cough, night sweats, and fevers accompanied with weight loss are common to both HIV-positive and HIV-negative patients. However, in advanced HIV disease/CD4 <200, symptoms of TB are often nonspecific and atypical, and many investigations have less diagnostic sensitivity than in an HIV-uninfected individual with TB (Table 18.4.5.5).

Table 18.4.5.5 Features of TB infection in presence and absence of HIV

	HIV uninfected	HIV infected CD4 <200
Symptoms	Focal symptoms predominate	Nonspecific symptoms predominate
Site	Pulmonary predominantly	Higher rates of extrapulmonary and disseminated disease
Sputum smear (AFB)	Good yield	Low yield
Mycobacterial burden (e.g. at biopsy/autopsy)	Low	High

Patients with profound immunosuppression (e.g. CD4 <200 cells/mm^3) are unable to control TB replication and hence have a greater mycobacterial burden. However, factors associated with reduced sputum smear positivity (e.g. lung cavitation), mean that sputum microscopy has a significantly lower diagnostic yield in HIV/TB co-infected patients. In HIV/TB co-infection mycobacterial blood cultures and tissue biopsy, for example, from a lymph node (for histology, TB culture, TB-PCR), may therefore be required to make a positive diagnosis of TB.

Patients with advanced HIV infection are more likely to develop extrapulmonary TB involving lymph nodes, blood, pericardium, lived, bone marrow, or meninges. Extra adjunct tests include adenosine deaminase levels in pleural or ascitic fluid, which are elevated in TB.

Immunological tests, such as the tuberculin skin test and ELISpot, performed to assess latent TB infection are often negative in HIV-infected individuals if CD4 counts show severe immunosuppression and have poor utility in making a diagnosis of active TB.

Radiographic features of TB in HIV-positive patients with low CD4 counts are different from those in HIV-negative patients (**Table 18.4.5.6**).

Treatment

Empirical TB treatment should start as soon as the diagnosis is confirmed and follows the same guidelines as for HIV-uninfected patients (i.e. a rifampicin-based regimen), but there are special considerations in TB/HIV co-infection. Firstly, adding cART to TB treatment improves treatment outcome and reduces mortality. Most patients benefit from stating cART within 2 weeks after anti-TB treatment, especially if CD4 is less than 50 cells/mm^3. For those with higher CD4 counts treatment for HIV can be delayed, but not beyond 8 weeks. Secondly, while initial TB therapy is empirical, therapy needs to be subsequently tailored to the drug resistance profile of the isolate, given the higher incidence of drug resistant TB in HIV. Thirdly, there should be close monitoring of treatment response and for immune reconstitution syndrome (IRIS), especially if the CD4 is less than 50 cells/mm^3. Lastly, rifampicin is a potent inducer of the cytochrome P450 enzyme, hence it interacts with drugs used in cART (especially protease inhibitors) leading to subtherapeutic levels, HIV treatment failure, and HIV drug resistance. A rifabutin-based regimen, rather than rifampicin, produces less drug-to-drug interactions with cART, but careful and expert dose management is required. Careful review for drug interactions is essential when initiating anti-TB therapy in patients taking cART (see https://www.hiv-druginteractions.org).

Table 18.4.5.6 Chest radiographic features of TB infection in presence and absence of HIV

HIV uninfected (typical TB)	TB in HIV/low CD4 counts
Upper zone cavitation	Pulmonary infiltrates with no particular preference for upper zones or cavitation
Bilateral hilar lymphadenopathy	Mediastinal lymphadenopathy
	Pleural effusions

Fungal pulmonary infections

Fungal infections of the respiratory tract are less common than viral or bacterial infections in HIV. However, CD4 cells are critical for antifungal defence, and a decline in CD4 cell numbers and cell function is a risk factor for invasive pulmonary infections in HIV-infected individuals. Other risk factors include neutropenia, long-term corticosteroid therapy, intravenous drug use, iatrogenic immunosuppression after organ transplantation, and abnormal lung architecture. In addition to PCP, the most prevalent pulmonary fungal infections in HIV are Aspergillosis and Cryptococcosis. With the introduction of cART, the prevalence of fungal infections has declined dramatically, but they still substantially contribute to AIDS-related mortality.

Aspergillosis

Aspergillosis refers to the illness caused by inhalation of spores of the fungal species Aspergillus from soil or air. Prior to cART, invasive aspergillosis was an important cause of death. Today, the infection is rarely seen in patients with HIV, except those with very low CD4 counts (<50 cells/mm^3) +/– other risk factors for fungal disease. US databases have showed that a diagnosis of aspergillosis was found only in 0.43% of HIV-infected patients. *Aspergillus fumigatus* is the most common species to cause disease: two clinical entities are recognized.

Invasive pulmonary parenchymal aspergillosis—this accounts for 80% of cases of disseminated aspergillosis in HIV-infected patients and is often fatal. Cavitating lesions form in the lung parenchyma, leading to fever, shortness of breath, productive cough, and haemoptysis. Signs of disseminated infection (e.g. neurological signs from brain involvement), may also be present. Imaging may reveal nodular or cavitating lesions on chest radiography. CT images may be may be very helpful in the early diagnosis of aspergillosis if they show a characteristic 'reverse halo sign' caused by an area of ground-glass infiltrate surrounding nodular densities.

Tracheobronchial aspergillosis—the disease site is predominately tracheal and bronchial involvement leading to airway obstruction, audible wheeze, and prominent shortness of breath.

As with PCP diagnosis, the rational first step to establishing the diagnosis of invasive Aspergillus involves the use of noninvasive modalities, such as serum biomarkers (galactomannan and β-D-glucan assays) and obtaining sputum for fungal staining and culture. If the diagnosis is not made by these methods, then a more invasive approach with bronchoscopy and bronchoalveolar lavage, transbronchial biopsy, CT-guided biopsy, or video-assisted thoracoscopic surgery is useful for histology, culture, and Aspergillus antigen assay. Treatment of aspergillosis is with voriconazole, although caspofungin is an alternative.

Cryptococcosis

Infections with the encapsulated yeast *Cryptococcus neoformans* in the most common fungal infection in HIV-infected individuals worldwide, but unusual in resource rich countries. Diagnosis of pulmonary cryptococcosis is based on culture of the organism in respiratory secretions or from lung biopsy, and detection of cryptococcal serum antigen. An HIV-infected patient is at greatest risk of disseminated extrapulmonary Cryptococcus (e.g. Cryptococcus meningoencephalitis when their CD4 is <100 cells/mm^3). Non-specific symptoms such as fever, cough, and shortness of breath

accompany chest radiographic changes including noncalcified pulmonary nodules, predominantly at the bases of the lungs, hilar lymphadenopathy, interstitial infiltrates, and lung masses. Treatment is with liposomal amphotericin (or oral fluconazole if not available) in combination with flucytosine.

Lung malignancy

Kaposi's sarcoma and non-Hodgkin's lymphoma may involve the lung, and patients with HIV appear to have both increased rates of lung cancer and more aggressive disease compared with uninfected controls.

Pulmonary Kaposi's sarcoma

Kaposi's sarcoma, caused by human herpesvirus (HHV-8), is the most common malignancy in persons with HIV infection. The skin is the major site of involvement, but visceral involvement with Kaposi's sarcoma is common in advanced disease, and may involve the airways, lung tissue, mediastinal lymph nodes, and pleura. The lung is the only site of disease in up to 15% of cases.

Patients with thoracic Kaposi's sarcoma usually have obvious mucocutaneous lesions, and a lesion on the palate suggests pulmonary involvement. Lung lesions cause dyspnoea, cough, or haemoptysis, accompanied in severe cases by constitutional symptoms such as night sweats, fevers, and weight loss. The presence of characteristic purplish plaque lesions at bronchoscopy is usually considered to be diagnostic.

The yield from bronchoscopic lung biopsy, which carries a risk of bleeding, is low, and even open-lung biopsy is nondiagnostic in about 10% of cases because of the focal distribution of the lesions. Pleural effusions are usually exudative and sanguineous, but cytological examination is nondiagnostic. Closed pleural biopsy specimens are rarely positive for Kaposi's sarcoma due to the focal nature of the pleural lesions and the predominant involvement of the visceral (rather than the parietal) pleura. Radiographic findings are variable, but bronchial wall thickening, Kerley B lines, and nodular infiltrates with peribronchovascular distribution and pulmonary effusions are common (Fig. 18.4.5.4). Treatment is with systemic chemotherapy, namely liposomal anthracyclines plus cART.

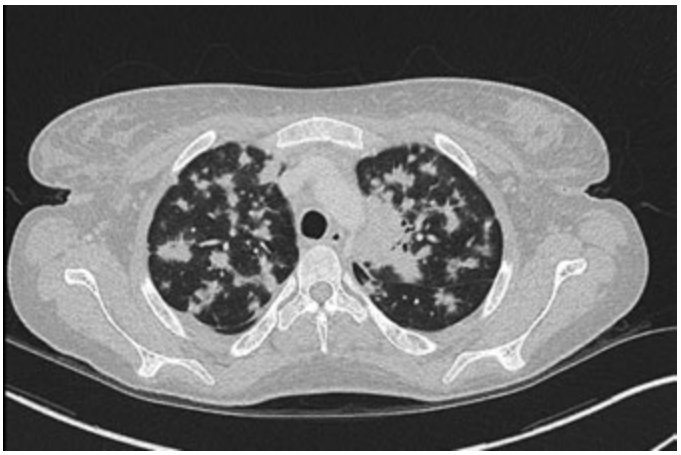

Fig. 18.4.5.4 CT scan showing nodular infiltrates with peribronchovascular distribution due to Kaposi's sarcoma.

Lymphoma

Non-Hodgkin's B-cell lymphoma is associated with HIV infection and continues to occur despite the use of cART. Although pulmonary involvement is usually clinically asymptomatic the lung is a common site of extranodal disease. Primary effusion lymphoma is most commonly a high-grade B-cell tumour associated closely with HHV8 and occurring in the setting of advance HIV infection.

Non-Hodgkin's B-cell lymphoma

The risk of developing non-Hodgkin's lymphoma is 200–600 times greater in persons with HIV compared with those who are uninfected. Non-Hodgkin's lymphoma associated with HIV infection is most commonly a high-grade B-cell tumour and tends to present more commonly with stage IV and extranodal disease. The lung is a site of extranodal disease, but in contrast to non-AIDS patients, mediastinal and hilar lymphadenopathy is generally not prominent. Pulmonary symptoms tend to occur late in the disease and can simulate common opportunistic infections (e.g. lobar consolidations, nodules, reticular opacities, and pleural effusions or thickening). Airway involvement may cause atelectasis. B-symptoms may also be present. The diagnosis is established by bronchoscopic or open-lung/pleural biopsy, or by cytological analysis of pleural fluid. Bronchoalveolar lavage has a very low diagnostic yield.

Primary effusion lymphoma

A few lymphomas are associated with HHV8. They present as body cavity lymphomas, causing pleural or peritoneal effusions (primary effusion lymphoma). In almost all cases tumour DNA shows HHV8, which is also the aetiological agent of Kaposi's sarcoma (as previously described).

Non-small cell carcinoma of the lung

It appears that the incidence of non-small cell lung cancer is increased in people living with HIV infection. Whether the increase simply reflects a higher smoking prevalence continues to be debated as there is no association with CD4 count, viral load, or the use of cART. Patients with lung cancer in the setting of HIV infection tend to be relatively young at presentation (mean age 45 years) and have mild or moderate immunosuppression. Most present with stage III or IV disease, and adenocarcinoma is the most common histological type, with its prognosis appearing to be worse in patients with HIV infection. The diagnostic and treatment approaches to HIV-associated lung cancer are the same as for those without HIV infection although there is a potential for drug interactions with cART.

Other pulmonary conditions

In addition infections and malignancies, HIV is associated with an increased risk of other pulmonary diseases such as immune reconstitution inflammatory syndrome (IRIS), pulmonary hypertension, COPD, interstitial lung disease, and lymphocytic interstitial pneumonitis.

Immune reconstitution inflammatory syndrome

IRIS refers to a disease- or pathogen-specific inflammatory response in HIV-infected patients that usually occurs after initiation

or re-initiation of cART. It has been reported as worsening of symptoms and signs in those with mycobacterial, fungal, viral, or bacterial infections, and worsening of tumours such as Kaposi's sarcoma.

Most cases occur in patients who have low CD4 counts (usually less than 100 cells/mm^3) at the time cART therapy is started and is usually coincident with a rapid increase in CD4 cell count. The time of presentation is usually within the first 8 weeks after starting cART therapy, but has been reported occurred many weeks after initiation. Treatment is with corticosteroids, but the course can be very prolonged in some. Pre emptive steroids can reduce TB IRIS by 30%.

Pulmonary hypertension

Pulmonary hypertension is 6–12 times more prevalent in HIV-infected patients compared to the general population. The pathogenesis still remains unclear and some cases are related to prior ARV use with Didanosine. Therapies for HIV-related pulmonary hypertension are nearly identical to those used in non-HIV patients, except the use of calcium channel blockers are not recommended.

Chronic obstructive pulmonary disease

There is high prevalence respiratory symptoms and COPD among HIV-infected patients. Currently, cigarette smoking and previous bacterial pneumonia seem to play a significant role in the development of respiratory symptoms and COPD. Smoking cessation is important, and COPD is managed as for the non-HIV-infected population. An important consideration is the drug interaction between the antivirals pharmaco boosting agents cobicistat and ritonavir with fluorinated steroids, which can cause Cushing's syndrome.

Asthma/bronchial hyper-responsiveness

Asthma and airway hyper-responsiveness may be more common among HIV-seropositive individuals treated with cART. Again, as with COPD, caution with drug interactions of inhaled fluorinated steroids and antiretroviral therapy is required.

Bronchiectasis

May result from severe or repeated opportunistic infection, including tuberculosis. In children risk factors include recurrent pneumonia, severe immunosuppression, and lymphoid interstitial pneumonitis.

Interstitial lung disease

Interstitial pneumonitis and lymphocytic interstitial pneumonitis were frequently described in HIV-infected adults prior to the use of cART. Post cART, these conditions are less frequent. However, sarcoidosis among HIV-infected persons is increasingly recognized and may represent an immune reconstitution phenomenon.

Table 18.4.5.7 compares clinical, radiological, and histological features of the main causes of interstitial lung disease seen in HIV.

Table 18.4.5.7 Clinical, radiological, and histological features of the main causes of interstitial lung disease seen in HIV

	NSIP	LIP	COP	HP	Sarcoid
Dyspnoea and cough	+/–	+	+	+	+/–
fevers	+/–	+	+	-	+/–
Usual CD4 count (cells/mm3/µl)	<200	>350	Any	Usually >350	>200
Chest X-ray	Interstitial or alveolar infiltrates Normal in up to 50%	Reticular or nodular shadowing	Consolidation	May be normal or diffuse nodules	BHL +/– reticulonodular opacities
HRCT: Ground-glass opacification	Basal, may be prominent	Present	Present	Diffuse or patchy	Occasional diffuse
HRCT: Consolidation	May be present	Not usually a feature	Dominant feature	Not usually a feature	May be present
HRCT: Honeycombing	Rarely may be present	Present in advanced disease	Not usually a feature	Present in advanced disease	May be present if fibrotic disease
Other HRCT features		Reticular and nodular shadowing	Cavitating nodules	Mosaic attenuation	Adenopathy and nodules on fissures
Histopathological features	Interstitial infiltrates of lymphocytes, plasma cells/mm^3 and macrophages	Interstitial infiltrates of polyclonal lymphocytes, some histiocytes and plasma cells/mm^3 with extension into alveolar septae	Organizing pneumonia, intraluminal polyps of granulation tissue	Peri-bronchiolar lymphocytic infiltrates and variable fibrosis in chronic disease	Noncaseating granuloma
Granulomata	Not present	Occasionally reported	Not present	Present	Prominent
Treatment and prognosis	Usually self-limiting Use of cART leads to improvement in lymphocytic alveolitis	May be stable without treatment Some role for steroids and cART Rarely progresses to respiratory failure	Responds rapidly to corticosteroids	May be self-limiting on removal of causative agent May require corticosteroids	May spontaneously remit May require steroids

HRCT, high-resolution computed tomography; NSIP, nonspecific interstitial pneumonia; LIP, lymphocytic interstitial pneumonia; COP, cryptogenic organizing pneumonia; HP, hypersensitivity pneumonitis and sarcoidosis.

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