HIV-related disease

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HIV remains a major global public health issue. It is estimated that in 2016 there were over 36 million people living with HIV (PLHIV), 1.8 million of who were new infections. Since the start of the epidemic around 35 million people are thought to have died. These sobering statistics are tempered by the remarkable impact of effective combination antiretroviral therapy (ART). This has transformed the lives of the estimated 57% of PLHIV who use it long term, and has led to a 50–90% fall in the incidence of many HIV-associated opportunistic infections, some malignancies, and death since the peak in 2005.

Most PLHIV experience at least one significant episode of respiratory disease during their lifetime. The associated reduction in mortality achieved by ART means that PLHIV have a life expectancy not much less than the general population. They are, therefore, now at risk of the non-communicable pulmonary conditions that arise generally in older age. Thus, PLHIV with respiratory symptoms require careful, systematic assessment to exclude both infectious and non-infectious causes of disease.

This chapter will focus on common causes of HIV-related respiratory illness in adults (Table 1). For a given individual, the aetiology is determined by factors that include their risk of exposure to pathogens (*e.g.* through where they live or have spent time, and lifestyle, such as injecting drug use); their ability to obtain and consistently use ART successfully; the use of specific preventive therapies such as co-trimoxazole; and co-factors such as cigarette smoking. Unfortunately, there remain a large number of people who present to healthcare services with severe respiratory disease and undiagnosed HIV infection. Irrespective of whether this occurs in a high or low HIV incidence setting, this is avoidable and represents a failure of societal medical care.

In the following sections we use blood absolute CD4 counts as an indicator of HIV-related immuncompromise. This is a reasonably accurate measure of systemic and local immunity: in HIV-uninfected individuals, the CD4 count is typically >500 cells.μL^{-1}. In PLHIV with preserved immunity, typical community-acquired infections occur although at a greater frequency than in the general population. With advancing HIV-induced immunosuppression (CD4 counts <200 cells.μL^{-1}), the risk of opportunistic infections and malignancy rapidly increases.

Infections

Bacterial infection

Prior to the use of ART, upper respiratory tract infections, acute bronchitis, and acute and symptomatic chronic sinusitis were considerably more common in PLHIV than the general population. It is unclear if this is still the case in people using ART long-term.

Bronchiectasis was an increasing concern in PLHIV prior to ART. This probably resulted from previous respiratory disease (such as tuberculosis, bacterial infection and recurrent *Pneumocystis jirovecii* pneumonia). In low HIV incidence, resource-rich settings this appears to be less of a problem now, though remains an issue elsewhere.

Compared with HIV-negative populations, bacterial pneumonia occurs six to 10 times more frequently in PLHIV not using ART. Injecting drug users are particularly vulnerable (with a risk approximately double that of other PLHIV). Other associations with bacterial pneumonia include advancing age, tobacco smoking, previous respiratory disease and advancing HIV-related immunosuppression.

The presentation of HIV-associated community-acquired bacterial pneumonia is similar to that in HIV-negative subjects. However, the chest radiograph may be atypical, and mimic *P. jirovecii* pneumonia in up to half of cases. The usual pathogens isolated are *Streptococcus pneumoniae* (in up to one-third of microbiologically confirmed epsiodes) or *Haemophilus influenzae* (10% cases). Infection with *Staphylococcus aureus* and Gram-negative organisms may occur in

advanced HIV disease. *Mycoplasma*, *Legionella* and *Chlamydia* species are probably no more frequent.

Bacteraemia is reported to be up to 100 times more common in PLHIV with bacterial pneumonia, irrespective of blood CD4 count. These data come from studies performed prior to ART. Even so, bacteraemia is still reported in around one in six cases of bacterial pneumonia – with *Streptococcus pneumoniae* being the main pathogen implicated. This highlights the importance of performing comprehensive investigation (including blood cultures) in PLHIV presenting with community-acquired pneumonia.

Complications of bacterial infection include intrapulmonary cavitation, abscess formation and empyema. There is a high relapse rate, despite appropriate antibiotic therapy in PLHIV with advanced HIV disease. However, in most recent studies overall mortality is similar to that in matched HIV-uninfected populations with bacterial pneumonia. Risk factors for poor outcome include advanced immunosuppression (blood CD4 <100 cells.μL^{-1}) and severe or progressive respiratory illness despite therapy.

Immunisation with pneumococcal vaccine is recommended in all adults and adolescents (at diagnosis of HIV infection and after 5 years). Conjugate vaccines, such as the 13-valent vaccine PCV-13) appear to offer better protection than polysaccharide vaccines (eg PPV-23). Humoral responses and clinical efficacy are probably impaired in those with CD4 counts <200 cells.μL^{-1}, although vaccination can be successfully re-administered to subjects on ART who have not developed protective immunity from prior vaccination when not using ART. There remains debate whether the combination of PCV-13 and PPV-23 provides better protection than the conjugate vaccine alone in people on long-term ART.

Viral infection

Over the last decade, the return of *Influenza A* as a pandemic condition has served as a reminder that opportunistic viral infections, such as *Cytomegalovirus* pneumonitis, are for many PLHIV much less of an issue than common viral pathogens. This includes *Rhinovirus* that appears to be frequently isolated from adults with HIV Infection admitted to hospital with

respiratory symptoms. In most reports, *Influenza H1N1* had a similar presentation and outcome in PLHIV to that seen in the general population. ART probably offers little specific protection against 'flu, and annual influenza immunisation is recommended.

Fungal infection

P. jirovecii, formerly *P. carinii*, is the cause of *Pneumocystis* pneumonia (PCP). It remains a common problem in individuals unaware of their HIV serostatus, as well as among PLHIV not taking ART (with consequent blood CD4 count <100 cells.μL^{-1} and high HIV load) and/or PCP prophylaxis.

Patients present with non-productive cough and progressive exertional breathlessness of several days' to weeks' duration, with or without fever. Examination may show features of impaired immunity such as oral candida infection. However on auscultation, the chest is usually clear, with in more severe cases end-inspiratory crackles audible. In early PCP, the chest radiograph may be normal (~10% of cases); though more frequently bilateral perihilar, interstitial infiltrates are present. These may progress to diffuse alveolar shadowing over a period of days. Atypical radiographic appearances include upper zone infiltrates resembling TB, hilar/mediastinal lymphadenopathy, intrapulmonary nodules and lobar consolidation (present in up to 20% of cases). CT chest usually confirms chest radiographic appearances, with ground-glass changes and interlobular septal thickening.

Treatment is usually started empirically in patients with typical clinical and radiological features and a CD4 count of <200 cells·μL^{-1}, pending diagnosis by cytological analysis of broncho-alveolar lavage (BAL) fluid or induced sputum samples. Recent interest in the use of molecular diagnostics for PCP has demonstrated that lung colonisation (distinct from infection and disease) is common; and that further refinements (including quantitative measures, and additional serum markers such as (1-3)-beta-D-glucan, a cell wall component of many fungi) are also needed to improve the sensitivity and specificity of these tests.

PCP can be stratified clinically as mild (PaO_2 >11.0 kPa, SaO_2 >96% breathing air at rest), moderate (PaO_2 8.0–11.0 kPa, SaO_2 91–96%) or severe (PaO_2 <8.0 kPa, SaO_2 <91%). This

categorisation is helpful, as oral therapy may be given to those with mild disease. The first-choice treatment for PCP of all severity is high-dose co-trimoxazole (initially sulphamethoxazole 100 mg·kg^{-1}·day^{-1} with trimethoprim 20 mg·kg^{-1}·day^{-1}, reduced by 25% at day 5-7 onwards if the patient is responding to treatment) in two to four divided doses orally or intravenously for 21 days. Approximately two-thirds of patients will successfully complete this regimen. Treatment-limiting drug toxicity (*e.g.* intense gastro-intestinal upset, rash, bone marrow suppression, or renal or liver dysfunction) is common, while <10% who tolerate therapy do not respond to treatment (defined by deterioration ≥5 days after initiation).

In patients with drug toxicity or poor response to co-trimoxazole, alternative therapy in mild/moderate disease includes clindamycin (450–600 mg four times daily orally or *i.v.*) plus oral primaquine (15 -30mg daily), oral dapsone (100 mg daily) with trimethoprim (20 mg·kg^{-1}·day^{-1}), or oral atovaquone suspension (750 mg twice daily). In severe disease, alternative therapy is clindamycin with primaquine or *i.v.* pentamidine (4 mg·kg^{-1} daily).

Co-trimoxazole, dapsone and primaquine should be avoided in patients with glucose-6-phosphate dehydrogenase deficiency, and testing for the enzyme deficiency is recommended as standard practice.

Patients with an admission PaO$_2$ ≤9.3 kPa should also receive adjunctive glucocorticoids within 72 h of starting specific anti-PCP treatment. A frequently used regimen is prednisolone, 40 mg twice daily for 5 days, with 40 mg daily on days 6–10, and 20 mg daily on days 11–21. Adjunctive glucocorticoids have been shown to reduce the need for ICU admission (and mechanical ventilation) and mortality. Patients should be monitored carefully for steroid-related adverse events, including hypertension, hyperglycaemia, and local and systemic viral reactivation.

Several factors present on admission to hospital, or shortly thereafter, predict poor outcome from PCP. These include increasing patient age, a second or third episode of PCP, hypoxaemia, low haemoglobin, co-existent pulmonary Kaposi sarcoma and medical comorbidity. Once

hospitalised, development of pneumothorax, admission to the intensive care unit and the need for mechanical ventilation are associated with a worse outcome.

Regimens for PCP prophylaxis are listed in Table 2.

Indications for primary prophylaxis are:

- blood absolute CD4 count <200 cells·μL^{-1};

- blood CD4 count <14% of total lymphocyte count;

- unexplained fever (>3 weeks' duration);

- persistent or recurrent oral/pharyngeal *Candida*;

- history of another AIDS-defining diagnosis, *e.g.* Kaposi sarcoma.

The indication for secondary prophylaxis is:

- all patients who have had a previous episode of PCP.

Indications for discontinuing secondary prophylaxis are:

- patients on ART with a sustained increase in blood CD4 count (>200 cells·μL^{-1}) and undetectable plasma HIV RNA for ≥3 months (note that if CD4 count subsequently falls below 200 cells·μL^{-1} and/or the HIV RNA load increases, prophylaxis should be re-instituted);

- based on the rates of recurrent PCP noted within observational cohorts, some clinicians will discontinue treatment if the HIV load is undetectable and blood CD4 is >100 cells·μL^{-1}.

It is recommended that, if possible, all patients with an episode of PCP start ART within 2 weeks of commencing their anti-*Pneumocystis* treatment.

Tuberculosis

All patients with TB and unknown HIV status should be offered an HIV test. Active TB is estimated to occur between 20 and 40 times more frequently in PLHIV. Worldwide, over 10% of new TB cases (>1,000,000) occur each year in PLHIV; and TB accounts for almost one-in three of all HIV-related deaths. TB is also covered in other chapters, so here the focus is on issues of particular relevance to HIV co-infection.

More than two-thirds of patients with TB/HIV present with pulmonary disease. When blood CD4 counts are normal or only slightly reduced (*e.g.* >350 cells·µL^{-1}), clinical features are similar to adult post-primary disease. Chest radiography often shows upper lobe infiltrates and cavitary changes. Sputum and BAL fluid are often smear positive.

In advanced HIV disease, and/or with a low blood CD4 count (<200 cells·µL^{-1}), the presentation is often with nonspecific malaise, fatigue, weight loss and fever. Chest radiographic abnormalities may not be specific for TB and include diffuse or miliary-type shadowing, mediastinal/hilar lymphadenopathy and pleural effusions; cavitation is uncommon. Sputum or BAL fluid is often smear negative though culture positive. Extrapulmonary TB is common in patients with CD4 counts <100 cells·µL^{-1}. Local or disseminated infection may involve lymph nodes and bone marrow, blood cultures may be positive and it is worth obtaining specimens from as many body sites or fluids as clinically practical. For example, the yield from early-morning urine cultures is reasonable.

If smears or un-speciated mycobacterial cultures are positive, treatment should initially include a four-drug anti-TB regimen with a rifamycin (usually either rifampicin or rifabutin) plus isoniazid, pyrazinamide and ethambutol, until mycobacterial identification and drug sensitivities are known. Some clinicians will also add in a macrolide antibiotic, if there is clinical concern that the causative agent may be a non-tuberculous mycobacteria, such as disseminated *M. avium-intracellulare* complex disease. It should be noted that rifamycins in particular can interact with components of ART, and expert advice should be sought when developing a treatment plan in PLHIV with TB, so as to avoid significant drug-drug interactions and treatment failure.

TB diagnosis using rapid nucleic acid amplification tests are increasingly sensitive in PLHIV, although, generally, less than in HIV-negative TB patients. Even so, their superior ability to diagnose TB compared to sputum and other tissue fluid smears, means that they are now recommended by the WHO as a first line test in TB/HIV endemic settings in preference to conventional microscopy and culture. The molecular probes can distinguish *Mycobacterium tuberculosis* from opportunistic mycobacteria, and identify common mutations in the *rpoB* gene associated with rifampicin resistance, as well as isoniazid (*katG* and *inhA* genes) and mutations associated with resistance to other anti-TB drugs, depending on the test kit used.

Rapid molecular diagnostic assays, such as the Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA), and its new variants, are increasingly simple to use in a field/non-specialist laboratory setting. They enable often scarce resources to be allocated effectively; for example, if a patient is shown to have rifampicin resistance using the probe, then an early decision can be made to treat for multidrug-resistant TB, and appropriate samples set up for mycobacterial culture and sensitivity testing, which may not be a part of local standard care.

Point-of-care rapid antigen assays using relatively easily obtained body fluids (*e.g.* the mycobacterial cell wall antigen lipoarabinomannan tested in urine) are of more value in PLHIV than HIV-uninfected individuals with suspected active TB. However, despite good specificity, their sensitivity means that they are of most use in patients with TB who are unwell and have advanced HIV infection (presumably due to there being a greater overall mycobacterial load).

The wider use of rapid mycobacterial detection systems has led to the discovery that 'subclinical' TB is common in PLHIV from TB endemic areas. Here, patients are generally well but have viable bacilli isolated from, for example, sputum and, hence, require treatment for TB. This has been reported in up to 20% of people being screened for active TB prior to starting ART. In lower TB prevalence areas, it is less common and probably occurs in, at most, 5%.

Short- and long-term response to treatment with a 6-month four-drug regimen is generally good, although patients with disseminated disease are often treated for 9–12 months. Given the reported increased risk of developing drug-resistant disease, it is recommended that PLHIV

with high mycobacterial loads (*e.g.* disseminated disease, as is often present in patients with low blood CD4 counts) receive daily and not higher-dose (twice- or thrice-weekly) intermittent therapy. Compared with non-HIV-infected individuals, there is possibly a greater incidence of adverse reactions to anti-TB drugs and an increased risk of death.

ART reduces short- and long-term mortality in co-infected patients and should be started as soon as is practicable in subjects receiving treatment for active TB. Generally, the lower the blood CD4 count, the more pressing is the clinical need to start ART (*e.g.* usually within 8-12 weeks of TB diagnosis, and if blood CD4 <50 cells·µL^{-1}, within 2 weeks of starting anti-TB treatment). An important exception to this is in patients with CNS TB, where the risk of severe intracranial immune reconstitution disease (with associated life-threatening pressure effects) is so high when ART is started early, that it should be deferred until several weeks into established anti-TB treatment, irrespective of blood CD4 count.

Issues with early use of ART in TB patients include:

- high pill burden;

- overlapping toxicities, *e.g.* neuropathy;

- drug–drug interactions, *e.g.* ART and rifamycins;

- poor adherence to complex regimens; and

- increased risk of immune reconstitution disease (IRD) (see later).

Multidrug- and extensively drug-resistant TB have been associated epidemiologically with HIV infection. This is probably due to the rapid development of active (and, hence, infectious) TB in the PLHIV exposed to drug-resistant cases and, hence, reflects general susceptibility to developing mycobacterial disease rather than to infection with specific drug-resistant strains.

Given the high risk of latent TB infection (LTBI) progressing to active disease, the World Health Organization recommends that PLHIV with LTBI should receive preventive treatment. As, by

definition, LTBI diagnosis requires a positive immune response (*e.g.* tuberculin skin test or blood interferon-γ release assay) in an asymptomatic individual, these assessments can be affected by the immune dysregulation present in PLHIV.

Malignant conditions

Kaposi sarcoma

Kaposi sarcoma is the most common HIV-associated malignancy. Before the advent of ART, 15–20% of AIDS diagnoses were due to Kaposi sarcoma. It is associated with *Human Herpes Virus-8* (also called Kaposi sarcoma-associated virus) co-infection. Pulmonary Kaposi sarcoma is almost always accompanied by cutaneous or lymphadenopathic Kaposi sarcoma (palatal disease strongly predicts the presence of pulmonary lesions). Presentation is with non-specific cough and progressive breathlessness; haemoptysis is uncommon.

As Kaposi sarcoma may involve both the airways and lung parenchyma; radiological findings include interstitial or nodular infiltrates and alveolar consolidation. Hilar/mediastinal lymphadenopathy occurs in ~25% of patients and up to 40% have a pleural effusion.

Diagnosis is confirmed at bronchoscopy in >50% cases by the appearance of multiple, raised or flat, red or purple endotracheal and endobronchial lesions. Biopsy is rarely performed as cutaneous Kaposi sarcoma is usually present, and diagnostic yield from biopsy is <20%. ART may induce remission of lesions and is used in addition to chemotherapy.

Lymphoma

High-grade B-cell non-Hodgkin lymphoma is the most common HIV-associated thoracic lymphoma and is usually found in association with disease elsewhere. Presenting symptoms are nonspecific. Chest radiographic abnormalities include mediastinal lymphadenopathy, pleural masses or effusions. The prognosis is considerably better if patients treated with chemotherapy also receive ART.

Bronchial carcinoma

Lung cancer is more frequently diagnosed than in the pre-ART era; and is now one of the commonest non-AIDS malignancies. Whilst in part this probably reflects the protection ART offers from other conditions that would have occurred, the impact of high rates of tobacco smoking in PLHIV cannot be ignored. Cohort studies suggest that lung cancer risk is increased almost twenty-fold in PLHIV smokers compared to non-smokers. It appears to be around twice as common in PLHIV than HIV-negative smokers. The clinical presentation is often late and, despite specific treatment, plus the use of ART if not already prescribed, the prognosis is, therefore, often poor. Whether targeted screening programmes will improve the outlook is unclear. Thus, effective smoking cessation programmes are central to HIV-related cancer care.

Nonmalignant, noninfectious conditions

Chronic obstructive pulmonary disease

PLHIV smokers are at increased risk (approximately 10–25%) of developing COPD. Although this does not approach the relative risk associated with many HIV-related respiratory infections, in a similar manner to lung cancer, the onset of symptoms appears to be at a younger age, and may be a more aggressive process once it starts. Some studies suggest that such individuals are more breathlessness and functionally disabled compared to HIV-negative COPD patients with equivalent lung function.

The large number of ageing PLHIV smokers together with the synergistic effects of smoking, recurrent bacterial and opportunistic infections, injecting drug use, and possibly the direct effect of HIV in the lung (as well as the inflammatory response generated by use of ART), argue strongly for scaling up smoking cessation services. This is important as in many settings, smoking rates in PLHIV are higher than national averages. Smoking cessation will also impact on other smoking-related illnesses such as cardiovascular disease and osteoporosis, which are increasingly prevalent in HIV-infected communities.

HIV-associated pneumonitis

Nonspecific pneumonitis mimics PCP but often occurs at higher blood CD4 counts. Diagnosis requires transbronchial, video-assisted thoracoscopic or open-lung biopsy. Most episodes are self-limiting, but prednisolone may be beneficial.

Lymphocytic interstitial pneumonitis is generally seen in children with HIV, and clinically resembles idiopathic pulmonary fibrosis. Diagnosis requires biopsy. Treatment with ART is often effective.

Pulmonary arterial hypertension

Pulmonary arterial hypertension is reported to be around ten times more common in PLHIV. The presentation and management are similar to immunocompetent individuals, although use of ART is associated with improved haemodynamics and survival.

Pneumothorax

This occurs more frequently in PLHIV than in the age-matched general medical population. Cigarette smoking and use of nebulised pentamidine are risk factors. PCP should be excluded in any patient presenting with a pneumothorax.

HIV therapy causing respiratory symptoms

The clear beneficial impact of ART on both short and long-term morbidity and mortality (in many cases due to its effect on reducing respiratory disease) means that starting ART immediately following HIV diagnosis or early during care is now a globally recommended standard for PLHIV. The changes in immunity that occur when it is first started can be intense. In up to 30% subjects who have documented or subclinical co-infection, the immune response may be over-exuberant and manifest as a clinical deterioration in health status. This has been given several names including immune reconstitution inflammatory syndrome and IRD. It has been reported to occur with many conditions, and in particular mycobacterial disease, and chronic fungal and viral infections.

The underlying mechanism is not completely understood, and its clinical features represent both innate and acquired host responses to exogenous antigen. The 'paradoxical' type of IRD is similar to that seen in non-HIV-infected patients being treated for TB, though in PLHIV is generally more intense. Here, subjects with known TB improving on treatment start ART and within a median of 2–3 weeks develop new clinical manifestations often at the site of their previous disease. This includes increasing peripheral lymphadenopathy, pleural or pericardial effusions or cerebral disease. There is no specific diagnostic test, and therefore drug resistance, patient non-adherence with treatment, drug-drug interactions and other disease processes occurring concurrently or *de novo* must be actively excluded. It is more common in PLHIV with low pre-treatment CD4 counts (<100 cells·µL^{-1}), faster suppression of HIV load and shorter time between starting anti-TB therapy and ART. IRD can be severe, though is rarely fatal. When this does happen it is generally due to the local pressure effects associated with a rapid increase in size of inflammatory lesions. Hence, care must be taken with IRD associated with cerebral, pericardial and, sometimes, mediastinal disease. Treatment is largely symptomatic (such as draining abscesses), though may require glucocorticoid therapy or other inflammatory- or immune-modulators.

A second form of IRD is the 'unmasking' of TB. Here, a patient with latent, asymptomatic infection will rapidly develop highly inflammatory active TB at a median of 3–6 weeks after starting ART. Treatment is generally directed at the underlying mycobacterial infection. In TB-endemic areas, such as sub-Saharan Africa and South-East Asia, screening subjects for subclinical TB prior to ART initiation is important. Studies have indicated that up to one in five of individuals who are minimally symptomatic will have sputum culture-positive TB and, hence, require treatment. The use of rapid molecular and mycobacterial diagnostic tests (described earlier in this chapter) are a useful and effective means of excluding TB in people prior to starting ART.

The antiretroviral nucleoside analogue abacavir can cause a hypersensitivity reaction (in around 3% of subjects) with fever, rash and pulmonary symptoms. In these cases, recovery occurs if the drug is withdrawn. It should not be given again. Individual risk of abacavir-related

hypersensitivity can be reduced by testing PLHIV prior to treatment for the presence of HLA-B*5701, with which it is strongly associated.

Key points

- In populations with access to antiretroviral therapy, use of combination antiretroviral therapy (ART) has led to a marked reduction in the incidence of many HIV-associated pulmonary diseases such as PCP, and improved overall outcome following a severe respiratory event.

- Despite ART, bacterial infections remain more common in PLHIV than in the general population.

- TB may occur at any stage of HIV infection, and is a common cause of HIV-related disease and death. Cases should be managed in line with appropriate public health and infection control guidance.

- In response to starting ART, there may be an over-exuberant and uncontrolled immune response to exogenous antigen such as mycobacteria. This phenomenon of immune reconstitution disease can mimic a variety of other conditions and may be life-threatening.

- Non-infectious respiratory complications of HIV are increasingly recognised in an ageing population. Many of these, such as COPD and lung cancer, are linked to smoking, and can run an accelerated course compared with the general population.

- Quitting smoking and immunisation are an integral component of long-term respiratory health maintenance in PLHIV.

Further reading

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Table 1. Common causes of HIV-associated respiratory disease

Infectious conditions	Non-infectious conditions
Upper respiratory tract infection	**Malignancy**
Acute sinusitis	Kaposi sarcoma
Chronic sinusitis	Lymphoma
Acute bronchitis	Bronchial carcinoma
Bronchiectasis	**Non-malignant conditions**
Bacterial pneumonia	COPD
Streptococcus pneumoniae	HIV-associated pneumonitis *e.g.* NSIP and LIP
Haemophilus influenzae	Pulmonary arterial hypertension
Viral infection	Pneumothorax
Influenza A	HIV therapy causing respiratory symptoms
Rhinovirus	*e.g.* IRD
Tuberculosis	
Fungal infection	
Pneumocystis pneumonia	
Histoplasma capsulatum	
Cryptococcus neoformans	

IRD: immune reconstitution disease; LIP: lymphocytic interstitial pneumonitis; NSIP: nonspecific interstitial pneumonitis

TABLE 2. Recommended PCP prophylaxis regimens

	Drug	Dosage	Notes
First choice	Co-trimoxazole (sulphamethoxazole + trimethoprim 5:1)	960 mg once daily# 480 mg once daily 960 mg thrice weekly	Protects against certain bacterial infections and reactivation of toxoplasmosis Adverse effects include nausea (40%), rash (up to 20%), bone marrow suppression (20%)
Second choice	Aerosolised pentamidine	300 mg once per month *via* jet nebuliser	Use once per fortnight if CD4 count <50 cells·μL^{-1}
	Dapsone	100 mg once daily	Plus oral pyrimethamine 25 mg once per week against reactivation of toxoplasmosis
Third choice	Atovaquone	Suspension 750 mg twice daily	
	Azithromycin	1250 mg once per week	

#: the use of lower doses of co-trimoxazole may be associated with fewer adverse events.