HIV and respiratory medicine

The end of the 20th century saw the start of an HIV pandemic that brought death and suffering to millions. Anti-HIV drug therapy has improved the lives of many, although HIV-related respiratory complications remain extremely common worldwide.

In 2006 there were an estimated 39.5 million people living with HIV/AIDS, and 4.3 million of these had new infections acquired that year. There have been an estimated 25 million deaths from AIDS. In the UK, up to March 2007, almost 87 000 adults were thought to have been infected with HIV. Of these, at least 17 400 had died (AVERT, 2007a,b).

Respiratory diseases are an important cause of morbidity and mortality in HIV-infected individuals. Early work, such as the Pulmonary Complications of HIV Infection cohort study from the USA (Wallace et al, 1993), demonstrated that almost half of the participants developed pulmonary disease. This included upper respiratory tract infections reported in 33%, acute bronchitis (16%), acute sinusitis (5%), and lower respiratory disease in 14% including bacterial pneumonia (5%) and *Pneumocystis carinii* (now reclassified as *Pneumocystis jirovecii*) pneumonia (4%) (*Table 1*). The widespread use of highly active antiretroviral therapy (HAART) since the mid-1990s has led to a fall in numbers of both major opportunistic illnesses and deaths. However, respiratory disease remains much more common than in non-infected individuals (Grubb et al, 2006). This article reviews the diagnostic strategies and management of common pulmonary complications of HIV.

Pathogenesis

The human immunodeficiency virus was isolated in 1983 following reports of severe opportunistic illnesses occurring in certain population demographics. These conditions were clustered under the epidemiological umbrella of AIDS, and in the developed world most commonly presented as homosexual men developing Kaposi's sarcoma and *Pneumocystis jirovecii* pneumonia (PCP).

HIV is a retrovirus belonging to the lentivirus family. It is usually transmitted within blood or genital secretions, and cannot infect by inhalation. Once within the body, host cell infection occurs via the binding of the virus to CD4 receptors, most commonly on T-helper lymphocytes. With viral replication (*Figure 1*), progressive immune dysregulation occurs through a combination of host cell death and aberrant activation. In what is usually several years, infected individuals move from an asymptomatic to increasingly symptomatic state associated with falling blood CD4 counts and physical evidence of impaired immunity. In general, the risk of life-threatening disease rises rapidly as CD4 counts fall below 200 cells/mm^3 (the usual lower limit in HIV-negative individuals being 400 cells/mm^3).

Since the mid-1990s HAART, which essentially means combinations of effective drugs directed against HIV, has become widely available in the developed world. Although these often have class-specific adverse effects, there is no doubt that the drugs work in both the short and medium term (years). The lack of HAART in resource-poor environments has served to widen the gap in outcomes between the developed and developing world. Globally, the most common serious respiratory conditions are bacterial pneumonia, tuberculosis and

Table 1. The 18-month incidence rates of lower respiratory disorders in 1116 HIV-seropositive people within the Pulmonary Complications of HIV Infection Study

Disorder	Number of patients	%
Bacterial pneumonia	53	4.8
Pneumocystis jirovecii	43	3.9
Non-tuberculous mycobacteria	12	1.1
Mycobacterium tuberculosis	10	0.9
Non-specific pneumonitis	8	0.7
Cryptococcus neoformans	5	0.5
Cytomegalovirus	3	0.3
Carcinoma	3	0.3
Kaposi's sarcoma	2	0.2
Congestive heart failure	2	0.2
Herpes simplex	1	0.1
Toxoplasma gondii	1	0.1
Histoplasma capsulatum	1	0.1
Lung abscess	1	0.1
Pulmonary embolism	1	0.1
Pneumothorax	1	0.1

From Wallace et al (1993)

Dr Swapna Mandal *is Respiratory Research Registrar at The London Chest Hospital, London,* **Dr Samantha Cooper** *is HIV/Respiratory Specialist Registrar and* **Dr Marc Lipman** *is HIV/Respiratory Consultant at The Royal Free Hospital, London NW3 2QG*

Correspondence to: Dr M Lipman

PCP, although a wide variety of diseases have been reported (*Table 2*).

Risk factors for respiratory disease

As discussed earlier, pulmonary disorders are generally much more common in HIV-infected populations, although several factors can further modify this risk. Declining blood CD4 count is a useful surrogate for impaired pulmonary immunity. Consequently the use of HAART (with subsequent enhanced local immunity) and preventative medication directed against specific pathogens (e.g. anti-pneumocystis prophylaxis) both reduce the risk of respiratory infection.

Injecting drug users and smokers are more likely to develop pulmonary disease. This is probably a result of local effects within the lung. These can also interact with other social factors, such as travel history. For example, tuberculosis is more frequently reported in injecting drug users than in homosexual males, although it is most common in subjects who have spent time in tuberculosis endemic areas.

Clinical approach to HIV-related lung disease

What becomes apparent in subsequent sections is that patient presentation can often be very non-specific. Diagnosis, therefore, relies on focussed investigation (usually with lung fluid sampling by either induced sputum or more commonly, bronchoscopy and bronchoalveolar lavage). Treatment may need to be started empirically, and should reflect likely pathogens, using risk assessment such as that described above. For example, an injecting drug user with a low blood CD4 count, e.g. <200 cells/mm^3, and infiltrates on the chest radiograph, should be segregated if admitted, until pulmonary tuberculosis has been ruled out, and treated initially both for bacterial pneumonia and PCP.

Bacterial respiratory infections

This may present in several ways: sinusitis, bronchitis, bronchiectasis and pneumonia. The clinical features are largely similar to those seen in HIV-negative individuals. The increasing recognition of bronchiectasis among HIV patients is thought to be the result of recurrent bacterial infections in the context of a dysregulated pulmonary immune response.

The spectrum of organisms causing HIV-related community-acquired pneumonia is similar to that seen in non-infected individuals. The most common pathogens are *Streptococcus pneumonia*, *Haemophilus influenzae* and *Staphylococcus aureus*. More unusual pathogens increase in incidence as local immunity declines. For example, *Pseudomonas* spp. pneumonia is rarely found in subjects with blood CD4 >100 cells/mm^3. HIV-positive subjects are more likely to develop pneumonic complications such as cavitation, pleural effusions and abscess formation.

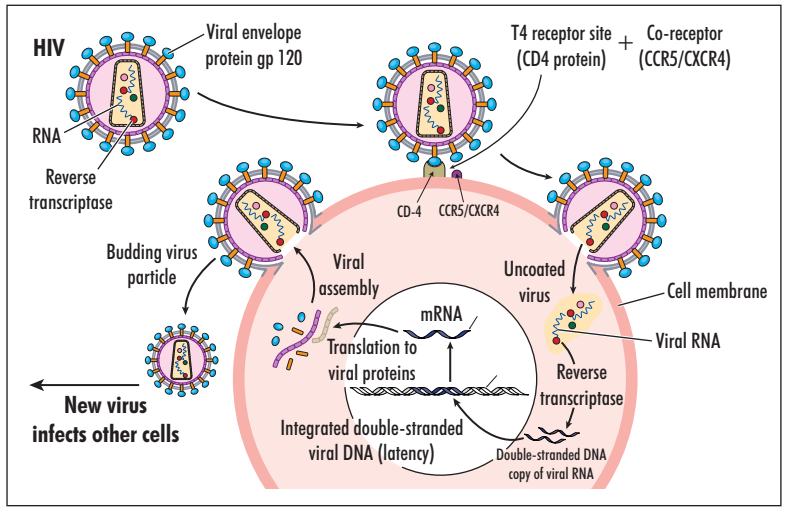


Figure 1. Schematic representation of HIV replication. From Lipman et al (2004).

Investigation is similar to that of non-HIV-infected individuals. Bacteraemia is reported as being up to 100 times more common, and blood cultures are mandatory

Table 2. Common aetiologies of HIV-related pulmonary diseases

Bacteria	*Streptococcus pneumoniae*
	Haemophilus influenzae
	Staphylococcus aureus
	Pseudomonas aeruginosa
	Escherichia coli
	Mycobacterium tuberculosis
	Mycobacterium avium-intracellulare complex
	Mycobacterium kansasii
Fungi	*Pneumocystis jirovecii*
	Cryptococcus neoformans
	Histoplasma capsulatum
	Aspergillus spp.
	Penicillium marneffei
Parasites	*Toxoplasma gondii*
	Cryptosporidium spp.
	Strongyloides stercoralis
Viruses	Cytomegalovirus
	Adenovirus
Non-infectious	Kaposi's sarcoma
	Lymphoma (Hodgkin's and non-Hodgkin's)
	Lung cancer
	Emphysema
	Immune reconstitution inflammatory syndrome
	Pulmonary hypertension
	Lymphoid interstitial pneumonitis
	Non-specific interstitial pneumonitis

in patients with respiratory infections. Chest radiographic findings are often non-specific and may mimic PCP (*Figure 2*).

Antibacterial treatment is similar to that for non-HIV-infected patients and should be directed by local/national guidelines. However, it is important to note that patients are often taking a large number of medications, making the likelihood of complex drug–drug interactions high. Therefore, expert opinion should be sought promptly if the patient does not appear to respond as expected, or if he/she is using a variety of HIV-related therapies.

Mycobacterial infections

HIV infection is the strongest acquired risk factor for the development of active mycobacterial infection (estimated at least 40-fold over background rates). Organisms of note include *Mycobacterium avium* complex, *Mycobacterium xenopi* and *Mycobacterium kansasii*. The most important of all, however, remains *Mycobacterium tuberculosis*, which unlike all the others can occur at any level of immunity. Although HAART reduces the risk of active tuberculosis by 70–80%, rates of tuberculosis are still much higher than in HIV-negative individuals.

The clinical presentation of tuberculosis depends on host immunity, and is therefore more often disseminated in subjects with low blood CD4 counts. This is also reflected in a transition in the radiographic findings from the typical pulmonary features of upper zone consolidation with associated cavitation in early HIV disease, to an extrapulmonary distribution with nodal disease and pleural effusions later on (*Figure 3*).

Given the importance of tuberculosis, it should be considered in any patient who presents with respiratory illness, disseminated disease or non-specific symptoms and risk factors for *Mycobacterium tuberculosis* acquisition. With this comes the need to segregate the person from others until pulmonary tuberculosis has been effectively ruled out.

Diagnosis may be achieved through identification of acid and alcohol-fast bacilli in sputum (several samples may be required) or lung fluid smears. It can be confirmed using nucleic acid amplification tests and culture. The latter is critical, given recent reports of various forms of clinically important drug resistance being often seen in HIV-infected subjects (World Health Organization, 2007). However, provided there is felt to be a low risk of such resistance, treatment can be started with a four-drug combination of a rifamycin (usually rifampicin or rifabutin), isoniazid, pyrazimanide and ethambutol, pending culture results. The rifamycins interact with HAART regimens and expert advice should be sought when considering using these together (Pozniak et al, 2005).

There is much debate regarding the duration of treatment required to cure drug-sensitive pulmonary tuberculosis. Most experts advise a 6-month course, although there is often a low threshold to extending this if there is any evidence of dissemination or very poor host immunity. The use of a package of care including directly observed short-course therapy has led to much better global outcomes.

Fungal infections

PCP is far and away the most important fungal pulmonary disease. It is still seen in the UK, although to a much lesser extent than before HAART and PCP prophylaxis were available. Presentation may be very non-spe-

Figure 2. Chest radiograph of* Streptococcus pneumoniae *pneumonia. The bilateral airspace shadowing in a predominantly peri-hilar distribution could be mistaken for severe* Pneumocystis jirovecii *pneumonia (PCP).

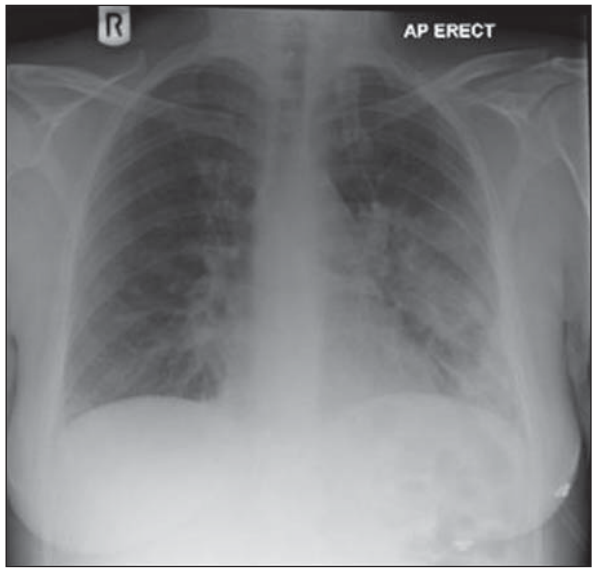
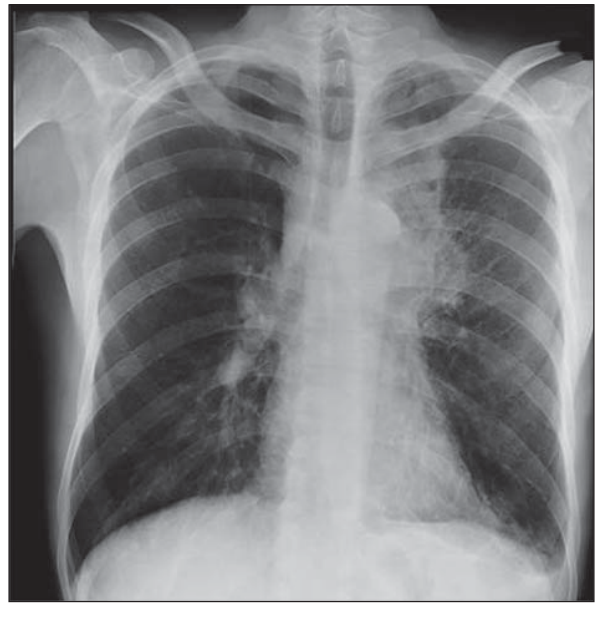


Figure 3. Chest radiograph demonstrating tuberculosis with bilateral hilar adenopathy, left upper zone consolidation, and a small left pleural effusion. From Lipman et al (2004).

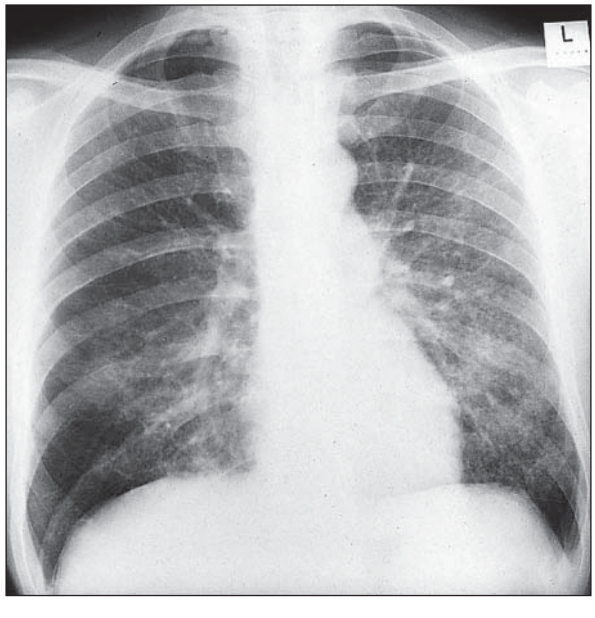


cific with days or weeks of dry cough, exertional breathlessness, fevers and malaise. Investigations include arterial blood gas and chest radiograph (which may be normal in up to 10% of cases, although most commonly demonstrates bilateral perihilar interstitial infiltrates) (*Figure 4*). In early PCP, exercise oxygen saturations may fall by >3% or to less than 90% in subjects with a normal or near-normal radiograph.

Currently the organism cannot be cultured and using nucleic acid amplification tests methods is too inaccurate. Therefore, lung fluid sampling is necessary to establish the diagnosis using either immunofluorescence or cytochemical staining of bronchoalveolar lavage or induced sputum.

High dose co-trimoxazole (trimethoprim plus sulphamethoxazole at a dose of 120 mg/kg for usually 3 weeks) is the drug of choice in the treatment of PCP, although other agents are available. Response rates are high, although in patients with a PaO_2 <9.3 kPa (<70 mmHg) this is further improved by the addition of corticosteroids, if started within 72 hours of anti-PCP treatment therapy. Respiratory support strategies in and out of the intensive care unit, such as continuous positive airway pressure, have also contributed to better overall outcome. Anti-pneumocystis prophylaxis is given to individuals who are at significant risk of PCP. This includes those with previous PCP, a blood CD4 count <200/mm^3 (14% of total lymphocytes), or evidence of impaired local immunity such as recurrent oral thrush. The most common drug used is lower dose oral co-trimoxazole, e.g. 960 mg daily. Adverse effects include rash, haematological, gastrointestinal and hepatic toxicity.

Figure 4.* Pneumocystis jirovecii *pneumonia (PCP) – a chest radiograph of typical PCP. Interstitial shadowing superimposed on vascular markings, changes are predominantly peri-hilar and there is peripheral sparring (Lipman et al, 2004).



Other respiratory tract fungal infections such as *Aspergillus fumigatus* or cryptococcal pneumonia are surprisingly uncommon. The clinical picture is usually dominated by severe extra-pulmonary symptoms, e.g. meningitis, skin lesions or sepsis in disseminated cryptococcal infection.

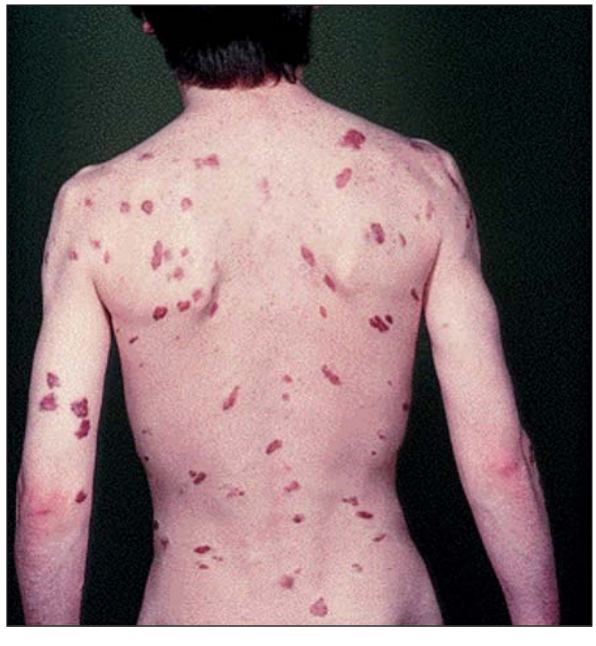
Viral infections

Cytomegalovirus is frequently found in HIV-infected individuals' lungs, although its significance has never been fully determined. This is in contrast to disease at other sites such as the retina, brain or gastrointestinal tract, which require specific treatment.

Non-infective conditions

Kaposi's sarcoma is the most common malignancy in HIV-infected individuals. Before HAART, it was at least 100 times more frequent in this population than in HIV-negative subjects. It is a virus-associated tumour, with host infection by human herpes virus 8 (HHV8) being a key step in its pathogenesis. Kaposi's sarcoma usually affects the skin, and pulmonary disease is often seen in individuals with extensive cutaneous involvement. Typical respiratory symptoms include progressive cough, breathlessness and haemoptysis associated with systemic symptoms. Radiology may show either interstitial changes or nodularity in the lung fields, as well as pleural effusions. When tapped, the fluid is typically sero-sanginous. Diagnosis is usually suspected by the clinical picture (*Figure 5*), and can be confirmed by careful tissue biopsy of these vascular tumours. Pulmonary disease may be difficult to treat, although good results have been achieved with newer chemotherapy strategies together with HAART.

Figure 5. Extensive cutaneous Kaposi's sarcoma. From Lipman et al (2004).



Non-Hodgkin's B-cell lymphoma is another common HIV-related tumour. It is also associated with herpes virus co-infection (Epstein–Barr virus). The lung is usually affected as part of multi-organ involvement. However, primary effusion lymphoma is also reported (and linked to HHV8 infection). Treatment is with HAART and chemotherapy.

There is increasing evidence of an association between HIV and lung cancer. These occur in smokers, and often present at a stage when cure is impossible. This may in part be caused by a more aggressive clinical course, although late diagnosis arising from HIV clinicians not expecting to see 'HIV-unrelated' disease could also be important. Smoking appears to predispose to an accelerated form of emphysema, as well as recurrent pneumonia, cardiovascular disease and overall mortality. It is imperative, therefore, to encourage sustained smoking cessation in HIV-infected individuals.

More recently, immune reconstitution inflammatory syndrome has been described. Here, a clinical and sometimes severe deterioration occurs following the start of HAART. This has been reported in up to a third of patients with major opportunistic diseases (Lipman and Breen, 2006). The most common of these are mycobacterial infections (in particular tuberculosis), fungal diseases (cryptococcus and pneumocystis) and viruses such as cytomegalovirus. Risk factors for immune reconstitution inflammatory syndrome include a short time between initiating treatment for these infections and starting HAART, and low blood CD4 counts. Treatment is usually supportive, and all therapies are continued. However, in some cases steroids may be required.

KEY POINTS

- Respiratory disease remains very common in HIV infection.
- Risk factor assessment (such as level of blood CD4 count) is a useful way of assessing risk of major opportunistic infection.
- Bacterial pneumonia, tuberculosis and *Pneumocystis jirovecii* pneumonia (PCP) must always be considered in the initial assessment of lower respiratory tract infection.
- Useful information can be obtained from chest radiology, blood oxygen assessment, and sputum and blood cultures.
- More complex tests are needed to diagnose PCP such as bronchoscopy or induced sputum.
- Pulmonary tuberculosis is infectious, and patients should be managed in line with good infection control policies.
- Malignancy is common in HIV infection and is associated with co-factors such as herpes viral infection and smoking.
- Highly active antiretroviral therapy has improved the outcome of HIV, although has specific adverse effects such as immune reconstitution inflammatory syndrome.
- Involvement of an HIV specialist should be considered at an early stage in patients with complex respiratory disease.

Conclusions

The natural history of HIV-related respiratory disease continues to evolve. Without effective antiretroviral therapy the majority of individuals develop severe pulmonary infection. The non-specific presentation makes careful assessment mandatory. The wide range of potential pathogens often requires expert input, and for best outcome this should be early in the course of respiratory illness. HAART has undoubtedly improved things, although it has also brought with it associated clinical syndromes and drug–drug interactions. For sustained benefit, future work should focus on modification of lifestyle factors such as smoking cessation programmes. **BJHM**

Conflict of interest: none.

Albert RK, Spiro SG, Jett JR (2004) *Clinical Respiratory Medicine.* 2nd edn. Elsevier Health Sciences, Denver

AVERT (2007a) *AIDS around the world.* AVERT, Horsham, West Sussex (www.avert.org/aroundworld.htm accessed 18 February 2008)

AVERT (2007b) *HIV and AIDS in the UK.* AVERT, Horsham, West Sussex (www.avert.org/aidsuk.htm accessed 18 February 2008)

Grubb JR, Moorman AC, Baker RK, Masur H (2006) The changing spectrum of pulmonary disease in patients with HIV infection on antiretroviral therapy. *AIDS* **20**(8): 1095–107

Lipman MCI, Baker RW, Johnson MA (2004) *An Atlas of Differential Diagnosis in HIV Disease.* 2nd edn. Parthenon Publishing Group, San Francisco

Lipman M, Breen R (2006) Immune reconstitution inflammatory syndrome in HIV. *Curr Opin Infect Dis* **19**(1): 20–5

Pozniak AL, Miller RF, Lipman MC et al (2005) BHIVA guidelines for TB/HIV infection. *HIV Med* **6**(suppl 2): 62–83

Wallace JM, Rao AJ, Glassroth J et al (1993) Respiratory illness in persons with human immunodeficiency virus infection. *Am Rev Resp Dis* **148:** 1523–9

World Health Organization (2007) *Stop TB strategy.* World Health Organization, Geneva (www.who.int/tb/strategy/en/ accessed 18 February 2008)