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With progressive HIV disease, subjects are at an increased risk of opportunistic disease. For example, the North American Prospective Study of Pulmonary Complications of HIV Infection (PSPC), a multicenter cohort drawn from all HIV risk groups at various stages of immunosuppression, revealed over an 18-month study period that of approximately 1000 subjects who were not using HAART:

- 33% reported an upper respiratory tract infection
- 16% had an episode of acute bronchitis
- 5% had acute sinusitis
- 5% had bacterial pneumonia
- 4% had PCP develop

The immune dysregulation that arises from HIV infection means that bacteria, mycobacteria, fungi, viruses, and protozoa can all cause disease in subjects with advanced infection. Table 34-1 shows the organisms that typically infect the lung in HIV disease. Of these, bacterial infections, tuberculosis, and PCP are the most important. In the West, 40% of AIDS diagnoses are due to PCP. This chapter provides a brief general overview of the epidemiology and pathogenesis of HIV infection before concentrating on HIV and its infectious pulmonary complications.

It is reported that by the end of 2006, 39.5 million individuals worldwide had acquired HIV infection (Figure 34-1). Of these, more than 40% are thought to have had AIDS develop (for definition of AIDS, see Tables 34-2 and 34-3, and Box 34-1). Globally, 4.3 million individuals acquired HIV infection in 2006, and over this time 2.9 million died of AIDS. The developing world has been most affected. Sub-Saharan Africa is the current epicenter of the pandemic (two thirds of all infections); here, one in five adults is HIV infected. South and Southeast Asia are responsible for almost a fifth of the estimated HIV global burden. In Central-Eastern Europe and Central Asia, there are currently 1.7 million HIV-infected individuals. In the developed world, North America and Western Europe account for approximately 1.4 million and 740,000 infections, respectively. Most of these are spread through sexual contact, although vertical (mother-to-child) and bloodborne infections are also common. In the developing world, heterosexual transmission is the norm; however, in North America and Europe, homosexual and bisexual men constitute the largest group of infected individuals.

**Virology and Immunology of the Human Immunodeficiency Virus**

HIV was first isolated in 1983 from patients with symptoms and signs of immune dysfunction. Two subtypes (HIV-1 and HIV-2) have subsequently been identified. HIV-1 (hereafter...
referred to as HIV) is responsible for most infections, has a more aggressive clinical course, and is the focus of this chapter.

HIV is a human retrovirus belonging to the lentivirus family. Cell-free or cell-associated HIV infects through attachment of its viral envelope protein (gp120) to the CD4 antigen complex on host cells. The CD4 receptor is found on several cell types, although the T-helper lymphocyte is the main site of HIV infection in the body. HIV gp120 must also bind to a cell surface protein coreceptor called chemokine receptor 5 (CCR5) or to other co-receptors, including CXCR4, depending on the host cell type. Polymorphisms in genes for CCR5 may affect disease progression by reducing the ability of HIV to enter and infect cells. However, at a population level, this effect is small.

Once HIV is inside the cell, it can, by use of the enzyme reverse transcriptase (RNA-dependent DNA polymerase), transcribe its HIV RNA into a DNA copy that can translocate to the nucleus and integrate with host cell DNA by use of its viral integrase. The virus (as proviral DNA) remains latent in many cells until the cell itself becomes activated. This may arise from cytokine or antigen stimulation. The viral genetic material is then transcribed into new RNA, which, in the form of a newly created virion, buds from the cell surface and is free to infect other CD4-bearing cells.

HIV infection directly attacks the immune system and in particular the T-helper cells that are central to a coordinated immune response. This leads to progressive immune dysfunction and an inability to resist opportunistic disease. The pathogenic process is not well defined, although it is thought that at the time of primary infection, HIV spreads to the lymph nodes, circulating immune cells, and thymus. This is a massive viral infection of the human host; and although there seems to be a relatively potent immune response, in fact, this initial onslaught is so devastating (targeting as it does specific memory T cells responsible for sustaining long-term protective immunity) that the scene is set for progressive immune failure. This occurs through a combination of direct cell killing by HIV replicating within cells, as well as the negative effects of chronic immune activation. Ultimately, these lead in most individuals to immune system destruction and dysfunction.

### TABLE 34-1 Common Etiologies of HIV-Related Pulmonary Infections

| Bacteria                        | Fungi                      | Parasites        | Viruses              |
|--------------------------------|----------------------------|------------------|----------------------|
| Streptococcus pneumoniae       | Pneumocystis jirovecii     | Toxoplasma gondii| Cytomegalovirus      |
| Haemophilus influenzae         | Cryptococcus neoformans    | Cryptosporidium sp. |
| Staphylococcus aureus          | Histoplasma capsulatum     | Microsporidium sp. |
| Pseudomonas aeruginosa         | Candida albicans           | Leishmania sp.    |
| Nocardia asteroides           | Aspergillus sp.            | Strongyloides stercoralis |
| Rochalimaea henselae          | Penicillium marneffi       |                  |
| Mycobacterium tuberculosis    |                            |                  |
| Mycobacterium avium-intracellulare |                      |                  |
| Mycobacterium kansasii        |                            |                  |

FIGURE 34-1 Estimated number of adults and children with human immunodeficiency virus (HIV) infection (to December 2006) by regions of the world. (Source: UNAIDS/WHO AIDS epidemic update: December 2006.)
This is reflected not only by clinical disease indicating profound immunosuppression but also by a measurable reduction in the circulating absolute CD4 cell count, the percentage of T cells expressing CD4 markers, and in the progressive reduction in CD4/CD8 T-cell ratio.

**Natural History of Human Immunodeficiency Virus Infection**

The use of HAART, as well as preventative (prophylactic) therapies for opportunistic infections, has changed the clinical picture of HIV disease in countries where these interventions are available. Death rates have fallen to one sixth of their previous levels. However, in the absence of such treatments, the median interval between HIV seroconversion and progression to AIDS in the developed world has been estimated to be 10 years, although rather less in resource-poor countries. Almost all individuals have AIDS develop if untreated, and without HAART, 95% of these will die within 5 years. In many parts of the world, the main causes of death in patients with HIV infection include bacterial pneumonia, tuberculosis, and PCP.

### Table 34-2: Centers for Disease Control and Prevention Classification

| Group | Infection |
|-------|-----------|
| I     | Acute primary |
| II    | Asymptomatic |
| III   | Persistent generalized lymphadenopathy |
| IV    | Other disease |
| Subgroup A | Constitutional disease (e.g., weight loss >10% of body weight or >4.5 kg; fevers >38.5°C lasting >1 month; diarrhea lasting >1 month) |
| Subgroup B | Neurologic disease (e.g., HIV encephalopathy, myelopathy, peripheral neuropathy) |
| Subgroup C | Secondary infectious diseases |
| Subgroup C1 | AIDS-defining secondary diseases (e.g., Pneumocystis jirovecii pneumonia, cerebral toxoplasmosis, cytomegalovirus retinitis) |
| Subgroup C2 | Other specified secondary infectious diseases (e.g., oral candida, multidermatomal varicella zoster) |
| Subgroup D | Secondary cancers (e.g., Kaposi sarcoma, non-Hodgkin lymphoma) |
| Subgroup E | Other conditions (e.g., lymphoid interstitial pneumonitis) |

### Table 34-3: Revised (1993) CDC Classification System for HIV Infection—Clinical Categories

| CD4 T-cell Categories (cells/mL) | A: Acute (primary) HIV, Asymptomatic or Persistent Lymphadenopathy | B: Symptomatic (not A or C) | C: AIDS Indicator Conditions |
|----------------------------------|---------------------------------------------------------------|----------------------------|----------------------------|
| >500                             | A1                                                            | B1                         | C1                         |
| 200–499                          | A2                                                            | B2                         | C2                         |
| <200                             | A3                                                            | B3                         | C3                         |

Patients are stratified clinically (A–C) and immunologically (1–3). Category B consists of symptomatic conditions that are not included within AIDS indicator diseases (category C) but can either be attributed to, or are complicated by, HIV infection. Examples include persistent candidiasis, thrombocytopenia, and peripheral neuropathy.

The course of HIV infection can be divided clinically into several distinct periods:

- Acquisition of the virus
- Seroconversion, with or without a clinical illness (primary HIV infection)
- Clinically silent period, lasting several months to years
- Development of symptoms and signs indicating some degree of immunosuppression
- AIDS (where the subject has opportunistic disease implying profound immunosuppression [e.g., PCP])

### Table 34-4: Centers for Disease Control and Prevention Classification

**BOX 34-1: Adult AIDS Indicator Diseases (1993)**

- Candidiasis of esophagus, trachea, bronchi, or lungs
- Cervical carcinoma, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, with diarrhea for >1 month
- Cytomegalovirus diseases (not in liver, spleen, or lymph nodes)
- Encephalopathy caused by HIV (AIDS-dementia complex)
- Herpes simplex: ulcers for >1 month, or pneumonitis, esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, with diarrhea for >1 month
- Kaposi sarcoma
- Lymphoma: Burkitt or immunoblastic or primary in CNS
- Mycobacteriosis (including pulmonary tuberculosis)
- Pneumocystis jirovecii pneumonia
- Pneumonia recurrent within a 12-month period
- Progressive multifocal leukoencephalopathy
- Salmonellal (nontyphoidal) septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome caused by HIV

The time from acquisition of HIV infection to development of detectable antibodies (the “window” period) is usually approximately 6–8 weeks. Between 30 and 70% of individuals who become infected will have a seroconversion illness. HIV antibody is normally present within 2–3 weeks of these symptoms, although this can take longer. HIV RNA in peripheral blood is detectable before this and is often used to confirm infection.

The nonspecific features of primary HIV infection are almost always self-limiting, and typically seroconversion mimics a “flulike” illness or glandular fever. Most individuals with primary HIV infection recover from the acute symptoms within 4 weeks. A proportion may have persistent symmetric pulmonary infections.
generalized lymphadenopathy. There is no difference in prognosis in this group compared with asymptomatic HIV-positive individuals.

**Chronic Human Immunodeficiency Virus Infection**

Although a proportion of individuals remain completely well without any treatment for an extended period (approximately 20% after 10 years), many HIV-infected individuals have minor symptoms and signs suggesting immune dysfunction. Examples of these include new or worsening rashes (including herpes simplex), tiredness, cough, and low-grade anemia. Certain clinical symptoms and signs provide important prognostic information. Most studies have shown that oral candidiasis and constitutional symptoms (e.g., malaise, idiopathic fever, night sweats, diarrhea, and weight loss) are the strongest clinical predictors of progression to AIDS.

The term AIDS was created as an epidemiologic tool to capture those conditions that early in the HIV epidemic seemed to suggest significant immune destruction. Over time, it has been modified to incorporate the expanding spectrum of recognized diseases affecting immunosuppressed individuals, such as cervical carcinoma and recurrent bacterial pneumonia (see Box 34-1). The 1993 Centers for Disease Control and Prevention (CDC) classification included an immunologic criterion for AIDS (CD4 count <200 cells/µL or CD4 percentage <14% of total lymphocytes) regardless of clinical symptoms (see Table 34-3). These data are used to define a point at which the risk of severe opportunistic infection rises dramatically. An example of this can be seen in the Multicenter AIDS Cohort Study (MACS) of homosexual and bisexual men without AIDS, which found that the incidence of PCP in subjects who did not use prophylaxis rose from 0.5% at 6 months in men with a baseline CD4 count >200 cells/µL to 8.4% in those with a CD4 count <200 cells/µL.

Apart from cervical carcinoma, AIDS indicator diseases differ little between men and women. Injecting drug users have a high incidence of wasting syndrome, recurrent bacterial pneumonia, and tuberculosis. Geographic differences in diseases occur that reflect the opportunistic pathogens present in the local environment (e.g., histoplasmosis or visceral leishmaniasis usually occur only in patients from endemic areas). In the developed world, sexual, racial, and HIV risk factor survival differences after an AIDS diagnosis mainly arise from variation in ease of access to medical care. It is certainly the case, however, that better treatment outcomes are associated with genuine specialist care provided by people with extensive experience in the field.

In countries where HAART is available, the spectrum of HIV-related disease has changed. In the EuroSIDA cohort (a pan-European prospective study of HIV infection), between 1994 and 2002, opportunistic infections associated with very low CD4 counts (e.g., cytomegalovirus [CMV] retinitis and Mycobacterium avium-intracellulare complex [MAC] infection) were observed less frequently over time. Malignant disease, such as non-Hodgkin lymphoma, increased as an AIDS-defining event between 1994 and 2004.

Although death rates have fallen in HAART-treated populations, there has been a rise in the proportion of non-AIDS deaths. In some series, this accounts for most events. Causes include liver disease (often caused by viral hepatitis) and cancer, as well as cardiovascular disease and drug-related toxicity. In such circumstances, AIDS deaths usually occur among patients who have not accessed medical care regularly and who are initially seen with advanced HIV disease.

A new manifestation of opportunistic infection has been described in patients commencing HAART. The immune reconstitution disease, IRIS, may cause severe, if temporary, clinical illness as the individual’s immunity recovers. Patients will appear to develop a relapse of their original (and partially treated) disease. This is often seen in MAC infection, tuberculosis, hepatitis B, CMV retinitis, and herpesviral infection. Metabolic complications of HAART, such as ischemic heart disease and diabetes, are a potential problem in HIV practice in the developed world. A significant number of individuals taking HAART also experience drug toxicity. An increasing number of patients are also surviving to manifest symptoms associated with chronic hepatitis B and C infection. HIV-associated nephropathy (often with chronic kidney disease) is common in black Africans and is a significant cause of long-term morbidity.

**Prognostic Markers**

Laboratory markers and clinical symptoms (e.g., oral thrush) can independently reflect the immune changes that lead to serious disease. Staging systems have been developed that can predict the risk of progression to severe opportunistic disease (AIDS). The fall in absolute blood CD4 T-lymphocyte count is the most widely used prognostic marker, although CD4 counts may be affected by a number of factors apart from HIV, including intercurrent infection, cigarette smoking, exercise, time of day, and laboratory variation. The percentage of CD4 cells and ratio of CD4/CD8 cells are more stable measures and may be used if the CD4 absolute counts seem to vary widely from visit to visit.

Measurement of plasma HIV RNA “viral load” provides important prognostic information that can both guide therapy and suggest long-term outcome. It has a particular value in subjects who are clinically well and have high CD4 counts, because it can give some indication of the expected speed of clinical progression.

**Pulmonary Immune Response During Human Immunodeficiency Virus Infection**

It is clear from the frequency with which HIV-related respiratory disease occurs that the pulmonary immune response is profoundly dysregulated. However, the mechanism underlying this has not been fully explained. In part, this is because the alterations that arise reflect the complex interplay between systemically derived HIV and other circulating antigens trafficking through the pulmonary vasculature, local immune cells, and airborne antigen. Most studies investigating the pulmonary immune response have used *in vitro* cell culture systems that seek to mimic the pulmonary environment or in some cases bronchoscopy and bronchoalveolar lavage (BAL) to recover lung cells from infected individuals. Until recently, these have been performed on symptomatic patients who required bronchoscopy as a diagnostic procedure. Such subjects generally have advanced HIV infection, are often taking a number of different drugs (including antiretrovirals), and may have any number of different pathogens causing their pulmonary disease—which by themselves can influence the immune findings. Finally, the question of whether BAL fluid truly represents the site of the immune response (the lung parenchyma) remains unclear. For all these reasons, reported data should be interpreted with some care.
Risk Factors for Respiratory Disease

An individual’s risk for respiratory disease is determined by his or her medical history (e.g., receipt of effective preventative or antiretroviral therapy), place of residence and travel history (e.g., the influence of geography on mycobacterial and fungal disease), and state of host immunity. Falling blood CD4 counts or high plasma RNA “viral loads” increase the chance of respiratory infection, with an increased spectrum of potential organisms responsible for infection in the more immunosuppressed individual. For example, HIV-infected individuals with a CD4 count <200 cells/μL are four times more likely to have one episode of bacterial pneumonia per year than those with higher CD4 cell counts. More exotic organisms are found in subjects with very low CD4 counts. These include bacteria such as *Rhodococcus equi* and *Nocardia asteroides* and fungi such as *Aspergillus* species and *Penicillium marneffei*. Just as with *P. jirovecii*, this reflects the importance of T-cell depletion and macrophage dysfunction in the loss of host immunity (a process that has been confirmed by animal experiments).

Among HIV-infected patients, injecting drug users are at greatest risk for development of bacterial pneumonia and tuberculosis. Individuals who have had previous respiratory episodes (PCP or bacterial pneumonia) seem to be at increased risk of further disease. Whether this relates to host or environmental factors is not certain, although it seems likely that structural lung damage and abnormal pulmonary physiology would, in part, contribute to this. This argument is supported by the increased rates of pneumonia in HIV-infected smokers compared with nonsmokers. Recent work has shown chronic obstructive pulmonary disease (COPD) and lung cancer occur more frequently among HIV-infected individuals compared with the general population. Given that a large number of HIV-infected individuals smoke heavily, there is a pressing need to target this population for smoking cessation. This is reinforced by the association demonstrated in some (but not all) studies between smoking and a more rapid progression to first AIDS illness and death.

CLINICAL FEATURES

Bacterial Infection

Bronchitis

The presentation mimics bacterial exacerbations of chronic obstructive lung disease; most patients have a productive cough and fever. The pathogens commonly identified are similar to those in the general population (i.e., *Streptococcus pneumoniae* and *Haemophilus influenzae*). However, patients with advanced disease may be infected with *Pseudomonas aeruginosa* or *Staphylococcus aureus*. Response to appropriate antibiotic therapy in conventional doses is good, although relapses frequently occur.

Bronchiectasis

Bronchiectasis is increasingly recognized in HIV-infected patients with advanced HIV disease and low CD4 lymphocyte counts. It probably arises secondary to recurrent bacterial or *P. jirovecii* infections. The diagnosis is most often made by high-resolution/fine-cut computed tomography (CT) scanning. Its prevalence has not been accurately determined, although with improved survival from both opportunistic infections and HIV disease, it is likely that it will be increasingly common in clinical practice. The pathogens isolated in patients with bronchiectasis are those seen in bronchitis. In addition, *Pseudomonas cepacia* and *Moraxella catarrhalis* have been described.

Pneumonia

Community-acquired bacterial pneumonia occurs more frequently in HIV-infected patients than in the general population. It is especially common in HIV-infected injecting drug users. The spectrum of bacterial pathogens is similar to that in non-HIV–infected individuals (see Table 34-1). *S. pneumoniae* is the most common cause, followed by *H. influenzae*. HIV-infected individuals with *S. pneumoniae* pneumonia are frequently bacteremic. In one study, the rate of pneumococcal bacteremia in HIV-infected individuals was 100 times that of an HIV-negative population. More recent work has confirmed this to be the case for all causes of HIV-related bacterial pneumonia. Typically, blood cultures have a 40-fold increased pickup rate in HIV-positive patients. The widespread use of HAART has led to some decrease in rates of bacterial pneumonia and bacteremia, although they are still considerably higher than those seen in a non-HIV–infected population.

Bacterial pneumonia has a similar presentation in HIV-infected and uninfected individuals. Chest radiographs are frequently atypical, mimicking PCP in up to 50% of cases (Figure 34-2). By contrast, radiographic lobar or segmental consolidation may also be seen in a wide range of bacterial organisms (Figure 34-3); these include *S. pneumoniae*, *P. aeruginosa*, *H. influenzae*, and *Mycobacterium tuberculosis*. PCP may also present with lobar or segmental consolidation.

In subjects with more advanced HIV disease and low CD4 lymphocyte counts, *P. aeruginosa* and *S. aureus* also cause pneumonia.

Complications of bacterial pneumonia frequently occur, and pleural effusions are twice as likely in HIV infection (often occurring with *S. aureus* infection); empyema and intrapulmonary abscess formation are present in up to 10% of patients. Inevitably, the mortality rate is high (approximately 10%).

![FIGURE 34-2 Chest radiograph showing bilateral, diffuse, interstitial infiltrates mimicking *Pneumocystis jirovecii* pneumonia. Etiology is *Streptococcus pneumoniae*](image)
**Other Bacteria**

**Nocardia Asteroides Infection.** This has been reported in patients with advanced HIV disease and low CD4 lymphocyte counts. The widespread use of trimethoprim/sulfamethoxazole (TMP/SMX) for prophylaxis of PCP may have reduced the incidence of infection. The clinical presentation is often indistinguishable from that of other bacterial infections. Chest radiographic appearances may mimic tuberculosis (see later), with upper lobe consolidation, cavitation, interstitial infiltrates, pleural effusion, and hilar lymphadenopathy. The diagnosis is made by identification of the organism in sputum/BAL fluid or lung tissue.

**Rhodococcus equi.** R. equi usually produces pneumonia in patients who have advanced HIV infection and have been in contact with farm animals or with soil from fields or barns where animals are housed. The presentation is subacute, with 2–3 weeks of cough, dyspnea, fever, and pleuritic chest pain. The chest radiograph typically shows consolidation with cavitatory lesions. Pleural effusions are common. The diagnosis is usually made by culture of sputum or blood; bronchoscopy with BAL or pleural aspiration may be necessary in some cases.

**Bartonella henselae.** B. henselae is a gram-negative bacillus that causes bacillary angiomatosis in HIV-infected patients. Clinically, the cutaneous lesions may mimic Kaposi sarcoma, from which they may be distinguished by demonstration of organisms in tissue with Warthin–Starry silver stain. Bacillary angiomatosis may also infect the lungs, where it produces endobronchial red or violet polypoid angiomatous lesions, which may resemble Kaposi sarcoma. Biopsy is necessary to confirm a diagnosis.

**Mycobacterial Infections**

**Tuberculosis**

HIV infection is associated with at least a 40-fold increased risk of an individual having active tuberculosis develop compared with noninfected subjects. Taken together with its ability to infect both the immunosuppressed and immunocompetent, tuberculosis is perhaps, therefore, the single most important disease associated with HIV infection. It is estimated that there are at least 13 million individuals with HIV-tuberculosis coinfection. As such, tuberculosis is a major cause of HIV-related morbidity and mortality. It is also a major driver in both resource-rich and resource-poor countries for the current overall increase in tuberculosis rates. Where HIV infection is endemic, tuberculosis control at a population level is almost impossible if treatment for both infections is not available.

In the United Kingdom, many centers routinely offer HIV antibody testing to all patients with tuberculosis, regardless of risk factors for HIV infection. In the United States, the CDC now recommends HIV testing as a routine part of health care for all patients aged 13–64 accessing medical services. The advantage of this is that individuals who are found to be HIV infected can be given HAART. Furthermore, strategies to modify high-risk behavior and reduce ongoing HIV transmission may be offered.

Active tuberculosis can occur at any stage of HIV infection, and unlike almost every other HIV-related infection, may do so despite effective antiretroviral therapy. In the United States, United Kingdom, and most European countries, reporting of tuberculosis in both HIV-infected and non-HIV–infected individuals is mandatory.

Clinical disease in HIV-infected patients may arise in several different ways: by reactivation of latent tuberculosis, by rapid progression of pulmonary infection, and by reinfection from an exogenous source.

Pulmonary disease is the most common presentation; and clinical manifestations are related to the level of an individual’s cell-mediated immunity. For example, subjects with early HIV disease have clinical features similar to “normal” adult postprimary disease (Table 34-4). Symptoms typically include

| TABLE 34-4 Tuberculosis and HIV Infection |
|------------------------------------------|
| **Stage of HIV Disease** | **Early** | **Late** |
| Chest radiograph | Upper lobe infiltrates and cavities (c.f. postprimary infection) | Lymphadenopathy, effusions, miliary or diffuse infiltrates (c.f. primary infection) |
| | | Normal |
| Sputum or bronchoalveolar lavage “smear positive” | Frequently | Less commonly |
| Tuberculin test positive | Frequently | Less commonly |
weight loss, fever with sweats, cough, sputum, dyspnea, hemoptysis, and chest pain. These patients may have no clinical features to suggest associated HIV infection. The chest radiograph frequently shows upper lobe consolidation, and cavitary change is common (Figure 34-4). The tuberculin skin test (purified protein derivative [PPD]) is usually positive, and the likelihood of spontaneously expectorated sputum or BAL fluid being smear positive for acid-fast bacilli is high.

In individuals with advanced HIV disease (i.e., low CD4 lymphocyte counts and clinically apparent immunosuppression), it may be difficult to diagnose tuberculosis. The clinical presentation here is often with nonspecific symptoms. Fever, weight loss, fatigue, and malaise may be mistakenly ascribed to HIV infection itself. In this context, pulmonary tuberculosis is often similar to primary infection, with the chest radiograph showing diffuse or military-type shadowing (Figure 34-5), hilar or mediastinal lymphadenopathy, or pleural effusion; cavitary is unusual. In up to 10% of patients the chest radiograph may appear normal; in others, the pulmonary infiltrate can be bilateral, diffuse, and interstitial in pattern, thus mimicking PCP. Hilar lymphadenopathy and pleural effusion may also be produced by pulmonary Kaposi sarcoma or lymphoma, with which M. tuberculosis may coexist. The tuberculin skin test is usually negative, and spontaneously expectorated sputum and BAL fluid are often smear negative (but culture positive).

In addition to pulmonary tuberculosis, extrapulmonary disease occurs in a high proportion of HIV-infected individuals with low CD4 lymphocyte counts (<150 cells/μL). Mycobacteremia and lymph node infection (Figure 34-6) are common, but involvement of bone marrow, liver, pericardium, meninges, and brain also occurs.

Evidence of extrapulmonary tuberculosis should be sought in any HIV-infected patient with suspected or confirmed pulmonary tuberculosis, by culture of stool, urine, and blood or bone marrow. Traditional solid phase culture and speciation techniques may take 6–10 weeks. Liquid culture methods (e.g., BACTEC, Becton Dickinson) that detect early growth may provide a diagnosis in only 2–3 weeks. Molecular diagnostic tests that use M. tuberculosis genome detection (e.g., by polymerase chain reaction [PCR]) offer the possibility of yet more rapid diagnosis (within hours), but are not yet in routine clinical use. They are also less useful in primary samples with low bacterial load (e.g., smear negative sputum)—which is often when they will be most needed in HIV-coinfected patients. The recent description of simple, but highly sensitive

FIGURE 34-4 Chest radiograph of pulmonary tuberculosis in early-stage human immunodeficiency virus infection. Upper lobe infiltrates and cavities are shown.

FIGURE 34-5 Chest radiograph showing miliary tuberculosis. Patient’s CD4 count was 80 cells/μL.

FIGURE 34-6 Mediastinal lymph node showing necrotic tissue surrounded by poorly developed granulomatous inflammation (left insert). A Ziehl Neelsen stain showed numerous acid-fast bacilli (right insert). (Reproduced with permission from Miller RF, Shahmanesh M, Talbot MD, Wiselka MJ, Shaw PJ, Bacon C, Robertson CM: Progressive symptoms and signs after institution of highly active antiretroviral therapy and subsequent antituberculosis therapy: Immune reconstitution syndrome or infection? Sexually Transmitted Infections 2006; 82: 111–116, BMJ Publishing Group.)
and specific, methods that use the inoculation of large quantities of, for example, sputum onto microscopic plates with subsequent rapid detection (in days) of both mycobacterial growth and resistance patterns (MODS) is of great potential significance.

Until the results of culture and speciation are known, acid-fast bacilli identified in respiratory samples, biopsy tissue, an aspirate, or blood in an HIV-infected individual, regardless of the CD4 lymphocyte count, should be regarded as being $M. tuberculosis$, and conventional antituberculosis therapy should be commenced. If culture fails to demonstrate $M. tuberculosis$ and instead another mycobacterium (see later) is identified, treatment can be modified.

Drug-Resistant Tuberculosis

Multiple drug-resistant (MDR) tuberculosis—that is, $M. tuberculosis$ that is resistant to isoniazid and rifampicin (rifampin), with or without other drugs, is now an important clinical problem in HIV-infected individuals in the United States, where it is responsible for approximately 3% of all tuberculosis in HIV-infected patients. Outbreaks of MDR tuberculosis have occurred in both HIV-infected and non-HIV-infected individuals in the United States in prison facilities, hostels, and hospitals. Similar outbreaks have also been documented among HIV-infected patients in Europe. Inadequate treatment (including case management and supervision of medication) of tuberculosis and poor patient compliance with antituberculosis therapy are the most important risk factors for development of MDR tuberculosis. Other cases have arisen because of exogenous reinfection of profoundly immunosuppressed HIV-infected patients who are already receiving treatment for drug-sensitive disease.

Despite antituberculosis therapy, the median survival in HIV-infected individuals with MDR-tuberculosis was initially only 2–3 months. Recently this has improved, largely because of an increased awareness of the condition with early initiation of suitable therapy as determined by drug sensitivity testing.

Extensively Drug-Resistant Tuberculosis

Extensively drug-resistant (XDR) tuberculosis—that is, $M. tuberculosis$ resistant to isoniazid and rifampicin (rifampin), plus any fluoroquinolone and one or more of the three injectable second-line drugs (capreomycin, kanamycin and amikacin)—is an increasingly important clinical problem. Originally described in South Africa in association with HIV infection, XDR tuberculosis has also been identified in most parts of the world. As of March 2007, 35 countries had reported at least one case; although in many places, testing for fluoroquinolone sensitivity is not standard practice; this number may be, in fact, a huge underestimate. What is of concern about XDR tuberculosis is that, despite specific therapy, mortality is high among HIV-infected individuals. The current picture seems to mirror early reports of MDR tuberculosis in HIV infection: in the original South African study from KwaZulu Natal, survival was less than 3 weeks from the time of receipt of the first sputum sample.

Mycobacteria Other Than Tuberculosis

**Mycobacterium avium-intracellulare Complex.** Before the widespread availability of HAART, disseminated MAC infection developed in up to 50% of HIV-infected patients. It remains a problem in patients with advanced HIV disease not receiving antiretroviral therapy and who have CD4 lymphocyte counts <50 cells/µL. Clinical presentation is nonspecific and may be confused with the effects of HIV itself. Fever, night sweats, weight loss, anorexia, and malaise are common. Anemia, hepatosplenomegaly, abdominal pain, and chronic diarrhea are frequent findings. The diagnosis of disseminated MAC infection is based on culture of the organism from blood, bone marrow, lymph node, or liver biopsy specimens. Also, MAC is frequently identified in BAL fluid, sputum, stool, and urine, but detection of the organism at these sites is not diagnostic of disseminated infection. Evidence of pulmonary MAC infection is not usually obtained from a chest radiograph, which may be negative or show nonspecific infiltrates. Rarely, focal consolidation, nodular infiltrates, and apical cavitiation (resembling $M. tuberculosis$) have been reported.

**Mycobacterium kansasi.** $Mycobacterium kansasi$ is the second most common nontuberculous opportunistic mycobacterial infection in HIV-infected individuals and usually appears late in the course of HIV infection in patients with CD4 lymphocyte counts <100 cells/µL. The most frequent presentation is with fever, cough, and dyspnea. In approximately two thirds of those who have $M. kansasi$ infection, the disease is localized to the lungs; the remainder have disseminated disease that affects bone marrow, lymph node, skin, and lungs. The diagnosis is made by culture of the organism from respiratory secretions or from bone marrow, lymph node aspirate, or skin biopsy. Focal upper lobe infiltrates with diffuse interstitial infiltrates are the most common radiographic abnormalities; thin-walled cavitary lesions and hilar adenopathy have also been reported.

**Mycobacterium xenopi.** $Mycobacterium xenopi$ may occasionally be isolated from sputum or BAL fluid samples, but its significance is uncertain. Patients have low CD4 counts, and $M. xenopi$ is usually accompanied by isolation of a pathogen, such as $P. jirovecii$. Treatment of the latter condition is associated in most cases with resolution of symptoms. There is some evidence that starting HAART prevents disease recurrence, provided there is an adequate immune response.

**Pneumocystis jirovecii Pneumonia.** The development of PCP is largely related to underlying states of immunosuppression induced by malignancy or treatment thereof, organ transplantation, or HIV infection. In 2007 in the United States, United Kingdom, Europe, and Australasia, PCP is largely seen only in HIV-infected individuals unaware of their serostatus or in those who are intolerant of, or noncompliant with, anti-$P. jirovecii$ prophylaxis and HAART.

Until recently, $P. jirovecii$ was regarded taxonomically as a protozoan, on the basis of its morphology and the lack of response to antifungal agents such as amphotericin B. The organism has now been ascribed to the fungal kingdom. The demonstration of antibodies against $P. jirovecii$ in most healthy children/adults suggests that organisms are acquired in childhood and persist in the lungs in a dormant phase. Subsequent immunosuppression (e.g., as a result of HIV infection) allows the fungus to propagate in the lung and cause clinical disease. However, this “latency” hypothesis is challenged by several observations:

- $P. jirovecii$ cannot be identified in the lungs of immunocompetent individuals.
- “Case clusters” of PCP in health care facilities suggest recent transmission.
Different genotypes of *P. jirovecii* are identified in each episode in HIV-infected patients who have recurrent PCP. Genotypes of *P. jirovecii* in patients who have PCP correlate with place of diagnosis and not with their place of birth—suggesting infection has been recently acquired.

Taken together, these data suggest that PCP arises by reinfection from an exogenous source.

The clinical presentation of PCP is nonspecific, with an onset of progressive exertional dyspnea over days or weeks, together with a dry cough with or without expectoration of minimal quantities of mucoid sputum. Patients often complain of an inability to take a deep breath, which is not due to pleurisy (Table 34-5). Fever is common, yet patients rarely complain of temperatures or sweats. In HIV-infected patients, the presentation is usually more insidious than in patients receiving immunosuppressive therapy, with a median time to diagnosis from onset of symptoms of more than 3 weeks in those with HIV compared with less than 1 week in non-HIV–infected patients. In a small proportion of HIV-positive individuals, the disease course of PCP is fulminant, with an interval of only 5–7 days between onset of symptoms and progression to development of respiratory failure. In others, it may be much more indolent, with respiratory symptoms that worsen almost imperceptibly over several months. Rarely, PCP may present without respiratory symptoms as a fever of undetermined origin.

Clinical examination is usually remarkable only for the absence of physical signs; occasionally, fine, basal, end-inspiratory crackles are audible. Features that would suggest an alternative diagnosis include a cough productive of purulent sputum or hemoptysis, chest pain (particularly pleural pain), and signs of focal consolidation or pleural effusion (see Table 34-5). It should be noted that infection with more than one pathogen occurs in almost one fifth of individuals, and thus symptoms may be the product of several agents.

The chest radiograph in PCP is typically unremarkable initially. Later, diffuse reticular shadowing, especially in the perihilar regions, is seen and may progress to diffuse alveolar consolidation that resembles pulmonary edema if untreated or if the patient is seen late in disease. At this stage, the lung may be massively consolidated and almost airless (Figure 34-7). Up to 20% of chest radiographs are atypical, showing lobar consolidation, honeycomb lung, multiple thin-walled cystic air space formation (pneumatocoeles), intrapulmonary nodules, cavitory lesions, pneumothorax, and hilar and mediastinal lymphadenopathy. Predominantly apical changes, resembling tuberculosis, may occur in patients who have PCP develop having received anti-*P. jirovecii* prophylaxis with nebulized pentamidine (Figure 34-8). All these radiographic changes

![Figure 34-7 Chest radiograph of severe *Pneumocystis jirovecii* pneumonia. Diffuse bilateral interstitial infiltrates are shown.](image)

| TABLE 34-5 Presentation of *Pneumocystis jirovecii* Pneumonia |
|-------------------------------------------------------------|
| **Examination** | **Typical Presentation** | **Atypical Presentation** |
| Symptoms | Progressive exertional dyspnea over days or weeks | Sudden onset of dyspnea over hours or days |
| | Dry cough ± mucoid sputum | Cough productive of purulent sputum |
| | Difficulty in taking in a deep breath not because of pleuritic pain | Hemoptysis |
| | Fever ± sweats | Chest pain (pleuritic or “crushing”) |
| | Tachypnea | |
| Signs | Normal breath sounds or fine end-inspiratory basal crackles | Wheeze, signs of focal consolidation or pleural effusion |
| Chest radiograph | Early: perihilar “haze” or bilateral interstitial shadowing | |
| | Late: alveolar-interstitial changes or “white out” (marked alveolar consolidation with sparing of apices and costophrenic angles) | |
| Arterial blood gases | $P_{aO_2}$: early, normal; late, low | |
| | $P_{aCO_2}$: early, normal or low; late, normal or high | |
are nonspecific, and similar changes occur with other pulmonary pathogens, including pyogenic bacterial, mycobacterial, and fungal infection, as well as Kaposi sarcoma and nonspecific interstitial pneumonitis. Respiratory symptoms in an immunosuppressed, HIV-infected individual with a negative chest radiograph should not be discounted, because over an interval of 2–3 days radiographic abnormalities may appear.

The diagnosis of PCP is made by demonstration of the organism in induced sputum, BAL fluid, or lung biopsy material by use of histochemical or immunofluorescence techniques. The early promise of molecular diagnostic techniques has not been borne out.

Fungal Infections
Many fungal infections of the lung are confined to specific geographic regions, although with widespread travel, they may present in patients outside these areas. *Candida*, *Aspergillus*, and *Cryptococcus* species are ubiquitous and occur worldwide.

Candidal Infection
In contrast to infections of the oropharynx and esophagus, candidal infection of the trachea, bronchi, and lungs is rare in HIV-infected patients, as are candidemia, disseminated candidiasis, and deep focal candidiasis. The clinical presentation of pulmonary candidal infection has no specific features. Chest radiography is equally nonspecific—it may be negative or show patchy infiltrates. Isolation of *Candida* from sputum may simply represent colonization and does not mean the patient has candidal pneumonia. Indirect evidence may be obtained from positive cultures or rising antibody titers. However, in HIV-infected patients, a high antibody titer alone is a less reliable indicator, and antibodies may be absent in proven cases of invasive candidal infection. Some correlation occurs between identification of large quantities of *Candida* species in BAL fluid and *Candida* species as the cause of pneumonia. Definitive diagnosis is made by lung biopsy.

Aspergillus Infection
By contrast with patients immunosuppressed and rendered neutropenic by systemic chemotherapy, infection with *Aspergillus* species is relatively rare in HIV-positive individuals. Risk factors for aspergillosis are neutropenia, which is commonly drug induced (zidovudine or ganciclovir), or patient’s receipt of corticosteroids. Fever, cough, and dyspnea are the most common presenting symptoms, but pleuritic chest pain and hemoptysis are found in approximately one third of patients.

Patterns of pulmonary disease include cavitating upper lobe disease, focal radiographic opacities resembling bacterial pneumonia, bilateral diffuse and patchy opacities (nodular or reticular-nodular in pattern), pseudomembranous aspergillosis, which may obstruct the lumen of airways, and tracheobronchitis. Diagnosis of pulmonary aspergillosis is made by the identification of fungus in sputum, sputum casts, or BAL fluid associated with respiratory tract tissue invasion (Figure 34-9). The role of antigen testing (such as galactomannan assays), which is commonplace in hematology patients at risk of invasive aspergillosis, has not been clearly defined in HIV-infected individuals.

Cryptococcal Infection
Infection may present in one of two ways: either as primary cryptococcosis or complicating cryptococcal meningitis as part of disseminated infection with cryptococccemia, pneumonia, and cutaneous disease (umbilicated papules mimicking molluscum contagiosum; Figure 34-10). Primary pulmonary cryptococcosis presents in a very nonspecific way and is frequently indistinguishable from other pulmonary infections. In disseminated infection, the presentation is frequently overshadowed by headache, fever, and malaise (caused by meningitis). The duration of onset may range from only a few days to several weeks. Examination may reveal skin lesions, lymphadenopathy, and meningism. In the chest, signs may be absent or crackles may be audible. Arterial blood gas tensions may be normal or show hypoxemia. The most common abnormality on the chest radiograph is focal or diffuse interstitial infiltrates.
Less frequently, masses, mediastinal or hilar lymphadenopathy, nodules, and effusion are noted.

The diagnosis of cryptococcal pulmonary infection (Figure 34-11) is made by identification of *Cryptococcus neoformans* (by staining with India ink or mucicarmine, and by culture) in sputum, BAL fluid, pleural fluid, or lung biopsy. Cryptococcal antigen may be detected in serum by use of the cryptococcal latex agglutination (CrAg) test. Titers are usually high but may be negative in primary pulmonary cryptococcosis, in which case BAL fluid (CrAg) is positive. In patients with disseminated infection, *C. neoformans* may also be cultured from blood and cerebrospinal fluid. The mortality rate is high in this disseminated form (up to 80%).

**Histoplasmosis**

Progressive, disseminated histoplasmosis in patients with HIV typically presents with a subacute onset of fever and weight loss; approximately 50% of patients have mild respiratory symptoms with a nonproductive cough and dyspnea. Hepatosplenomegaly is frequently found on examination, and a rash (similar to that produced by *Cryptococcus* species) may be seen. Rarely, the presentation may be rapidly fulminant, with clinical features of the sepsis syndrome, including anemia or disseminated intravascular coagulation. The chest radiograph may be unremarkable (in up to one third of patients), although characteristic abnormalities are bilateral, widespread nodules 2–4 mm in size. Other radiographic features are nonspecific and include interstitial infiltrates, reticular nodular shadowing, and alveolar consolidation. Histoplasmosis may disseminate to the central nervous system and produce meningoencephalitis or mass lesions. The diagnosis is made reliably by identification of the organism in Wright-stained peripheral blood or by Giemsa staining of bone marrow, lymph node, skin, sputum, BAL fluid, or lung tissue. It is important that identification is confirmed by detection of *H. capsulatum* var. *capsulatum* polysaccharide antigen by radioimmunoassay, which has a high sensitivity. False-positive results may occur in patients infected with Blastomycosis and Coccidioides species. Tests for Histoplasma antibodies by complement fixation or immunodiffusion may be negative in immunosuppressed, HIV-positive patients.

**Coccidioidomycosis**

The clinical presentation of coccidioidomycosis is variable. The chest radiograph may show focal pulmonary disease with focal alveolar infiltrates, adenopathy, and intrapulmonary cavities or, alternately, diffuse reticular infiltrates. Diagnosis is made by isolation of the organism in sputum or BAL fluid. Disseminated disease is identified by isolating the fungus in blood, urine, or cerebrospinal fluid. Serologic tests may also be used for diagnosis.

**Blastomycosis**

Blastomycosis presents in patients who have advanced HIV infection, when CD4 lymphocyte counts are usually less than 200 cells/μL. Clinical symptoms include cough, fever, dyspnea, and weight loss. Patients may present late in respiratory failure. Disseminated disease can occur with both pulmonary and extrapulmonary features. There is frequently multiple involvement of the skin, liver, brain, and meninges. Chest radiographic abnormalities include focal pneumonic change, miliary shadowing, or diffuse reticular infiltrates. Diagnosis is made by culture from BAL fluid, skin, and blood. In this infection, cytologic or histologic diagnosis is important for early diagnosis, because culture of the organism may take 2–4 weeks. The mortality rate is high in patients with disseminated infection.

**Penicillium marneffei Infection**

*P. marneffei* infection is particularly common in Southeast Asia. Most HIV-infected patients present with disseminated infection and solitary skin or oral mucosal lesions, or with multiple infiltrates in the liver or spleen, or bone marrow (leading to presentation with pancytopenia). Pulmonary infection has no specific clinical features, and chest radiographs may be
negative or show diffuse, small nodular infiltrates. Diagnosis is made by identifying the organism in bone marrow, skin biopsy samples, blood films, or BAL fluid. The differential diagnosis of *P. marneffei* infection includes both PCP and tuberculosis.

**Viral Infections**

**Community-Based Respiratory Viral Infections**

These occur with equal frequency in HIV-infected and non-HIV-infected patients; however, respiratory complications after influenza infection are increased in patients affected with underlying conditions such as cardiac or pulmonary disease and immunosuppression. In prospective studies of HIV-infected patients undergoing bronchoscopy for evaluation of suspected lower respiratory tract disease, the community-acquired respiratory viral infections (i.e., influenza, parainfluenza, respiratory syncytial virus, rhinovirus, coronavirus and adenovirus) are found only rarely, if at all.

**Cytomegalovirus**

CMV chronically infects most HIV-infected individuals, and up to 90% of homosexual HIV-infected men shed CMV intermittently in urine, semen, and saliva. Clinical disease may be caused by CMV in patients who have advanced HIV infection and CD4 counts <100 cells/μL. Chorioretinitis is most frequently encountered, but encephalitis, adrenalitis, esophagitis, and colitis are also seen. Frequently, CMV is isolated from BAL fluid, being found in 40% of samples from patients with CD4 counts <100 cells/μL. However, the role of CMV in causing disease in this context is unclear (see later).

In patients who have CMV as the sole identified pathogen, clinical presentation and chest radiographic abnormalities (usually diffuse interstitial infiltrates) are nonspecific. Diagnosis of CMV pneumonitis is made by identifying characteristic intranuclear and intracytoplasmic inclusions, not only in cells in BAL fluid but also in lung biopsy specimens (Figure 34-12).

**Protozoal Infections**

**Leishmaniasis**

Pulmonary involvement with *Leishmania* species may rarely occur as part of the syndrome of visceral leishmaniasis in HIV-infected patients. Patients usually have advanced HIV disease with CD4 lymphocyte counts less than 300 cells/μL and present with unexplained fever, splenomegaly, and leukopenia. Respiratory symptoms are often absent. Diagnosis of visceral leishmaniasis is most often made by staining a splenic or bone marrow aspirate and subsequent culture. Occasionally, the parasite is found by chance in a skin or rectal biopsy or BAL fluid taken for other purposes. The chest radiograph may be negative or show reticular-nodular infiltrates.

**Toxoplasmosis**

*Toxoplasma gondii* infection in patients who have AIDS usually occurs as a result of reactivation of latent, intracellular protozoa acquired in a primary infection. Patients are invariably systemically unwell, with malaise and pyrexia. Clinical disease in association with HIV infection is most commonly seen in the central nervous system, where it produces single or multiple abscesses. Multisystem infection with *T. gondii* is uncommon in patients who have HIV infection.

Toxoplasmic pneumonia is frequently difficult to distinguish from PCP. Nonproductive cough and dyspnea are the symptoms most commonly reported. Chest radiographic abnormalities include diffuse interstitial infiltrates indistinguishable from those of PCP (Figure 34-13), as well as micronodular infiltrates, a coarse nodular infiltrate, cavitory change, and lobar consolidation. The diagnosis is made by

**FIGURE 34-12** Bronchoalveolar lavage fluid containing cytomegalovirus inclusions.

**FIGURE 34-13** Chest radiograph of *Toxoplasma gondii* pneumonia. The diffuse bilateral infiltrates resemble *P. jirovecii* pneumonia. (Reproduced with permission from Miller RF, Lucas SB, Bateman NT: Disseminated *Toxoplasma gondii* infection presenting with a fulminating pneumonia. Genitourinary Med 1996; 72:139–143, BMJ Publishing Group.)
Cryptosporidiosis
The most frequent manifestation of infection with Cryptosporidium species in HIV infection is a noninflammatory diarrhea that may be of high volume, intractable, and life threatening. Cryptosporidium species may colonize epithelial surfaces, including the trachea and lungs, occasionally resulting in pulmonary infection. Most cases of pulmonary cryptosporidiosis have co-pathology such as PCP or bacterial pneumonia; ascertaining the exact role of cryptosporidiosis as the cause of respiratory symptoms may be difficult. Diagnosis is made by Ziehl–Neelsen or auramine-rhodamine staining of BAL fluid or transbronchial biopsy specimens.

Microsporidiosis
Pulmonary Microsporidia infection may occur as part of systemic dissemination from gastrointestinal infection with Septata intestinalis or Encephalitozoon hellem. The organism may be identified by conventional staining in BAL fluid. Electron microscopy is necessary to distinguish the two species.

Strongyloidiasis
The nematode Strongyloides stercoralis is endemic in warm countries worldwide. In immunosuppressed patients, the organism has an increased ability to reproduce parthenogenetically in the gastrointestinal tract without the need for repeated exposure to new infection—so-called autoinfection. This results in a great increase in worm load and a hyperinfection syndrome ensues; massive acute dissemination with S. stercoralis may occur in the lungs, kidneys, pancreas, and brain. Although infection with S. stercoralis is more severe in immunocompromised patients, it is no more common in patients who have HIV infection. Presentation with hyperinfection may be with fever, hypotension secondary to bacterial sepsis, or disseminated intravascular coagulation. The clinical features of respiratory S. stercoralis infection are nonspecific. S. stercoralis in sputum or BAL fluid (Figure 34-14) may be identified in HIV-positive patients in the absence of symptoms elsewhere; this can predate disseminated infection and, as such, requires prompt treatment.

Diagnosis
It is apparent from the foregoing discussion that HIV-related pneumonia of any cause may present in a similar manner. A wide range of investigations is available to aid diagnosis. These are listed in Table 34-6. If the subject is producing sputum, it is important to obtain samples for bacterial and mycobacterial detection. In up to one third of cases, these will assist in diagnosis. Three samples on consecutive days (preferably either with overnight or early morning production) is the critical first step in the diagnosis of pulmonary tuberculosis. This is considerably easier and safer for health care personnel than obtaining hypertonic saline-induced sputum or BAL fluid. Blood cultures are also important, because very high rates of bacteremia have been reported in both bacterial and mycobacterial disease (see earlier).

A patient who is initially seen with symptoms and signs consistent with pneumonia should have chest radiography and arterial oxygen assessments performed at his or her first consultation. The question at this stage is usually whether this infectious episode is due to bacterial infection, tuberculosis, or PCP. In general, alveolar and interstitial shadowing is taken as evidence for PCP, although important caveats apply.

Arterial Oxygen Assessments
Transcutaneous pulse oximetry and arterial blood gas analysis are useful tests for hypoxemia. They can be used to distinguish an alveolar condition (i.e., PCP) from bacterial pneumonia. The alveolitis produces a greater impairment of oxygen transfer (especially during exercise), such that for a given clinical situation there will be more hypoxemia and a wider alveolar–arterial oxygen gradient (A–aO2) in those with PCP. With pulse oximetry, this manifests as low oxygen saturations at rest that decrease further with exercise. In general, more information

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**TABLE 34-6 Tests Available to Aid Diagnosis of HIV-Related Pneumonia**

| Type          | Test                                                                 |
|---------------|----------------------------------------------------------------------|
| Physiologic   | Transcutaneous pulse oximetry                                       |
|               | Arterial blood gas analysis                                         |
|               | Lung function                                                       |
| Radiologic    | Chest radiography                                                   |
|               | Computed tomography of thorax                                       |
| Pathologic    | Serology (antigen or antibody testing)                              |
|               | Serum lactate dehydrogenase enzyme measurement                     |
|               | Microscopy and culture of body fluid/tissue (e.g., sputum, blood, bronchoalveolar lavage fluid, lung tissue) obtained by: |
|               | Sputum induction                                                    |
|               | Bronchoscopy and bronchoalveolar lavage fluid                      |
|               | Bronchoscopy and transbronchial biopsy                              |
|               | Thorascopic biopsy                                                  |
|               | Open-lung biopsy                                                    |
|               | Nucleic acid detection of specific organisms (e.g., polymerase chain reaction for Pneumocystis jirovecii in bronchoalveolar lavage fluid or sputum) |

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**FIGURE 34-14** Bronchoalveolar lavage fluid containing Strongyloides stercoralis.
can be obtained from arterial blood gas analysis, although this advantage is offset by the need for direct arterial puncture.

Of patients with PCP, fewer than 10% have a normal \( \text{PaO}_2 \) and a normal \( \text{A-aO}_2 \). These measures are sensitive, although not particularly specific for PCP, and similar results may occur with bacterial pneumonia, pulmonary Kaposi sarcoma, and \( M. \text{ tuberculosis} \) infection. The diagnostic value of identifying exercise-induced desaturation, measured by transcutaneous oximetry, has been validated only in HIV-infected patients who have PCP and a normal or “near normal” appearance on chest radiographs. The test’s value has not been confirmed in patients with abnormal chest radiographs because of PCP or other pathogens. Exercise-induced desaturation may persist for many weeks after treatment and recovery from PCP, even in the absence of active pulmonary disease.

**Lung Function Testing**

Abnormalities of lung function are well documented with HIV infection. The most common of these relate to tests measuring gas exchange, rather than the size of the conducting airways. In general, an overall reduction in diffusing capacity for carbon monoxide (DL\( \text{CO} \)) occurs at all stages of HIV infection, with the largest changes found in HIV-infected patients with PCP. Thus, to some extent, patients who have probable PCP can be differentiated and treatment guided. A normal DL\( \text{CO} \) in an individual who has symptoms but a negative or unchanged chest radiograph makes the diagnosis of PCP extremely unlikely. Data from the North American PSPC cohort study suggest that individuals with rapid rates of decline in DL\( \text{CO} \) are at an increased risk for development of PCP. Recent work suggests that HIV-infected smokers are at increased risk of early-onset emphysema. Smoking history must, therefore, be taken into account when assessing a patient’s lung function results in the context of possible PCP.

**Computed Tomography Scanning**

High-resolution (fine-cut) CT scanning of the chest may be helpful when the chest radiograph is normal, unchanged, or equivocal. The characteristic appearance of an alveolitis (i.e., areas of ground-glass attenuation through which the pulmonary vessels can be clearly identified) may be present, which indicates active pulmonary disease (Figure 34-15). This feature, however, is neither sensitive nor specific for PCP, although its sensitivity can be improved if evidence for reticulation and/or small cystic lesions is added to this. Hence, a negative test result implies an alternative diagnosis.

**Lactate Dehydrogenase Enzyme**

In the context of an HIV-infected patient who is seen with an acute or subacute pneumonitis, an elevated serum lactate dehydrogenase (LDH) enzyme level is strongly suggestive of PCP. When interpreting such results, it is important to remember that other pulmonary disease processes (e.g., pulmonary embolism, nonspecific pneumonitis, and bacterial and mycobacterial pneumonia) and extrapulmonary disease (Castleman disease and lymphoma) may also cause elevations of LDH and may need to be considered in the correct clinical context.

From the previous information, it is evident that noninvasive tests cannot reliably distinguish the different infecting agents from each other but may be useful in excluding acute opportunistic disease. Thus, the clinician is left with either proceeding to diagnostic lung fluid or tissue sampling (by either induced sputum collection or bronchoscopy and BAL with or without transbronchial biopsy Table 34-7) or treating an unknown condition empirically. HAART has also altered the investigation of respiratory disease. The numbers of invasive procedures performed are falling and tend to be in patients

![Figure 34-15 CT scan of thorax showing diffuse bilateral ground-glass shadowing typical of PCP.](image)

| TABLE 34-7 Induced Sputum, Bronchoalveolar Lavage, and Surgical Biopsy in Diagnosis of Pneumocystis jirovecii Pneumonia |
|-------------------------------------------------------------|
| **Technique** | **Ease of Procedure** | **Diagnostic Sensitivity (%)** | **Cost** | **Notes** |
|----------------|-----------------------|------------------------------|----------|----------|
| Induced sputum  | Simple once technique established | 50–90 | Low | Requires dedicated health care worker(s) and facility Risk to health care workers from expectorated aerosol |
| Bronchoalveolar lavage | Moderate | 90–95 | Moderate | Risk of deterioration post procedure Risk to health care workers from coughed secretions Sensitivity may be increased by two-lobe lavage |
| Surgical biopsy | Complex | >95 | High | Requires health care workers with surgical expertise |
special care should be exercised when sedation is used with antiretroviral protease inhibitor (PI) therapy. Mean that infection diagnosis is vital. The drug interactions associated with a pathology department with experience in opportunistic etiology may also provide etiologic clues—cooperation of bacteria, viruses, fungi, and protozoa. Inspection of the cellular component may also enhance the yield of induced sputum compared with standard cytochemistry.

\textbf{Induced Sputum}

Spontaneously expectorated sputum is inadequate for diagnosis of PCP. Sputum induction by inhalation of ultrasonically nebulized hypertonic saline may provide a suitable specimen (see Table 34-7). The technique requires close attention to detail and is much less useful when samples are purulent. Sputum induction must be carried out away from other immuno-suppressed patients and health care workers, ideally in a room with separate negative-pressure ventilation, to reduce the risk of nosocomial transmission of tuberculosis. Although very specific (>95%), the sensitivity of induced sputum varies widely (55–90%), and therefore a negative result for \textit{P. jirovecii} prompts further diagnostic studies. The use of immunofluorescence staining enhances the yield of induced sputum compared with standard cytochemistry.

\textbf{Bronchoscopy}

Fiberoptic bronchoscopy with BAL is commonly used to diagnose HIV-related pulmonary disease. When a good “wedged” sample is obtained, the test has a sensitivity of more than 90% for detection of \textit{P. jirovecii} (Figure 34-16). Just as with induced sputum, fluorescent staining methods increase the diagnostic yield, which makes it the technique of choice in most centers. More technically demanding (both of the patient and the operator) than induced sputum collection, bronchoscopy and BAL have the advantage that direct inspection of the upper airway and bronchial tree can be performed and, if necessary, biopsies taken. Transbronchial biopsies may marginally increase the diagnostic yield of the procedure. This is relevant for the diagnosis of mycobacterial disease, although the relatively high complication rate in HIV-infected individuals (pneumothorax and the possibility of significant pulmonary hemorrhage in up to 10%) outweighs the advantages of the technique for routine purposes.

Samples of BAL fluid are examined for bacteria, mycobacteria, viruses, fungi, and protozoa. Inspection of the cellular component may also provide etiologic clues—cooperation of a pathology department with experience in opportunistic infection diagnosis is vital. The drug interactions associated with antiretroviral protease inhibitor (PI) therapy mean that special care should be exercised when sedation is used with either benzodiazepine or opiate drugs. Prolonged sedation and life-threatening arrhythmias have been reported.

A diagnostic strategy, therefore, includes sputum induction and, if results are nondiagnostic or if the test is unavailable, bronchoscopy and BAL. If this does not yield a result and consideration is given to either a repeat bronchoscopy and BAL with transbronchial biopsies or surgical biopsy. The latter can be performed as either an open lung or thoracoscopic procedure. Surgical biopsy has a high sensitivity.

\textbf{Empirical Diagnosis and Therapy}

Although empirical therapy is usually reserved for the management of presumed bacterial pneumonias, and at first sight may seem unwise when dealing with possible opportunistic infection, in reality PCP is almost invariably a diagnosis of exclusion, and certain clinical and laboratory features may guide the assessment of an HIV-infected individual’s risk for this condition. The likelihood that \textit{P. jirovecii} is the causative organism increases if the subject is not taking effective anti-
\textit{Pneumocystis} drug prophylaxis or has a previous medical history with clinical or laboratory features that suggest systemic immunosuppression (i.e., recurrent oral thrush, longstanding fever of unknown cause, clinical AIDS, or blood CD4 count <200 cells/\mu L). Hence, some centers advocate use of empirical therapy for HIV-infected patients who are seen with symptoms and chest radiographic and blood gas abnormalities typical of mild PCP, without the need for bronchoscopy. Invasive measures are reserved for those with an atypical radiographic presentation, those who fail to respond to empirical therapy by day 5, and those who deteriorate at any stage.

Most clinicians in North America and the United Kingdom would seek to obtain a confirmed diagnosis in every case of suspected PCP. In practice, both strategies seem to be equally effective, although a number of caveats should be borne in mind when empirical treatment is given for PCP. Patients who have PCP typically take 4–7 days to show clinical signs of improvement, so a bronchoscopically proven diagnosis ensures that the treatment being given is correct, particularly in the first few days of therapy, when it may not be well tolerated. In addition, the diagnosis of PCP has implications for the infected individual, because it may influence the decision to start either HAART or anti-
\textit{Pneumocystis} prophylaxis. Finally, empirical therapy requires the patient to be maximally adherent to treatment, because nonresolution of symptoms may be seen as failure of therapy rather than of compliance.

\textbf{Nucleic Acid Detection}

Molecular biologic techniques (such as PCR) are increasingly used in the diagnosis of respiratory disease. Two examples of this are DNA amplification of loci of the \textit{P. jirovecii} and \textit{M. tuberculosis} genomes. The advantages of molecular methods are that the diagnosis may be made by use of samples that are more readily obtained than BAL fluid (i.e., expectorated sputum or nasopharyngeal secretions) and also that these methods are rapid (the answer may be available within a working day, compared with conventional mycobacterial culture, which may take weeks). Despite encouraging results in the research setting (sensitivity and specificity have been reported as 60–100% and 70–100%, respectively), problems persist when these techniques are applied to routine diagnostic samples. These include extraction of nucleic acid from clinical material, cross-contamination with the products of previous assays, and clinical interpretation of a test result. Currently,
molecular methods are not part of the standard diagnostic workup.

**TREATMENT**

Individuals infected with HIV, compared with the non-HIV-infected general population, have an increased likelihood of adverse reactions to therapy. This includes TMP/SMX (see later) and other antibacterial and antifungal agents. In addition, there are complex drug interactions with other medications, particularly components of HAART. Before instituting therapy for any infectious complication in an HIV-infected individual, it is important to consult with a physician experienced in the care of patients with HIV infection and to seek advice from a specialist pharmacist.

**Bacterial Pneumonia**

The main organisms causing pneumonia in HIV-infected individuals are similar to those found in the general population with community-acquired pneumonia. Thus, bacterial pneumonia in HIV-infected patients should be treated in a similar manner to that in HIV-negative individuals, by use of the published American Thoracic Society (ATS) and British Thoracic Society (BTS) guidelines. In addition, expert advice on local antibiotic resistance patterns should be sought from infectious disease or microbiology colleagues, because treatment is usually begun on an empirical basis before the causative organism is identified and antibiotic sensitivities known. The same clinical and laboratory prognostic indices that are described for the general population apply to HIV-infected patients and should be documented on presentation.

Response to appropriate antibiotic therapy is usually rapid and is similar to that seen in the non-HIV-infected individual. Early relapse of infection after successful treatment is well described. Those HIV-infected patients who have presumed PCP and are being treated empirically with high-dose TMP/SMX, and who have infection with either *S. pneumoniae* or *H. influenzae* rather than *P. jiroveci*, may also improve. In addition, in those patients who are treated with benzylpenicillin for proven *S. pneumoniae* pneumonia but do not respond, and penicillin resistance can be discounted as the cause, it is important to consider whether there is a second pathologic process, such as PCP. Co-pathogens are reported in up to 20% of cases of pneumonia.

**Pneumocystis jirovecii Pneumonia**

Before instituting treatment, assessment of the severity of PCP should be performed on the basis of history, findings on examination, arterial blood gas estimations, and chest radiographic abnormalities. Patients can then be stratified into those with mild, moderate, or severe disease (Table 34-8). This is important, because some drugs are of unproven benefit and others are known to be ineffective for the treatment of severe disease. In addition, adjunct glucocorticoid therapy may be given to patients with moderate or severe pneumonia. Patients with glucose-6-phosphate dehydrogenase deficiency should not receive TMP/SMX, dapsone, or primaquine, because these drugs increase the risk of hemolysis.

**Trimethoprim-Sulfamethoxazole**

Several drugs are effective in the treatment of PCP. TMP/SMX is the drug of first choice (Tables 34-9 and 34-10). Overall it is effective in 70–80% of individuals when used as first-line therapy. Adverse reactions to TMP/SMX are common and usually become apparent between days 6 and 14 of treatment. Neutropenia and anemia (in up to 40% of patients), rash and fever (up to 30%), and biochemical abnormalities of liver function (up to 15%) are the most frequent adverse reactions. Hematologic toxicity induced by TMP/SMX is neither attenuated nor prevented by coadministration of folic or folinic acid. Furthermore, the use of these agents may be associated with reduced therapeutic success. During treatment with TMP/SMX, full blood count, liver function, and urea and electrolytes should be monitored at least twice weekly.

It is not known why HIV-infected individuals, especially those with higher CD4 counts, have such a high frequency of adverse reactions to TMP/SMX. The optimum strategy for an HIV-infected patient who has PCP and who becomes intolerant of high-dose TMP/SMX has not been established. Many physicians “treat through” minor rash, often adding an antihistamine and a short course of oral prednisolone (30 mg every 24 h, reducing to zero over 5 days).

**Other Therapy**

If treatment with TMP/SMX fails, or is not tolerated by the patient, several alternative therapies are available (see Tables 34-9 and 34-10).

| TABLE 34-8 Grading of Severity of Pneumocystis Jirovecii Pneumonia |
|---------------------------------------------|
| **Symptoms and signs** | Mild | Moderate | Severe |
| Dyspnea on exertion with or without cough and sweat | Dyspnea on minimal exertion and occasionally at rest; cough and fever | Dyspnea and tachypnea at rest; persistent fever and cough |
| Oxygenation PaO2 room air, at rest (kPa; mmHg) | >11.0; >83 | 8.1–11.0; 61–83 | ≤8.0; ≤60 |
| SaO2, room air | >96 | 91–96 | <91 |
| SaO2, on exercise | >90 | <90 | 90 |
| A-aO2 (kPa; mmHg) | <4.7; <35 | 4.7–6.0; 35–45 | >6.0; >45 |
| Chest radiograph | Normal or minor perihilar shadowing | Diffuse interstitial shadowing | Extensive interstitial shadowing with or without diffuse alveolar shadowing |
| | | | |
Clindamycin-Primaquine

The combination of clindamycin and primaquine is widely used for treatment of PCP whatever the severity, although there is no license in the United Kingdom or United States for this indication. The combination is as effective as oral TMP/SMX and oral trimethoprim-dapsone for the treatment of mild and moderate-severity disease. As a second-line treatment it is effective in up to 90% of patients. Methemoglobinemia caused by primaquine occurs in up to 40% of patients. If 15 mg four times daily of primaquine is used, rather than 30 mg four times daily, the likelihood of methemoglobinemia is reduced. Diarrhea develops in up to 33% of patients receiving clindamycin. If this occurs, stool samples should be analyzed for the presence of Clostridium difficile toxin.

Trimethoprim-Dapsone

This oral combination is as effective as oral TMP/SMX and oral clindamycin plus primaquine (see earlier) for treatment of mild and moderate-severity PCP. The combination has not been shown to be effective in patients who have severe PCP. Most patients experience methemoglobinemia (caused by dapsone), which is usually asymptomatic. Up to one half of patients have mild hyperkalemia (<6.1 mmol/L) caused by trimethoprim.

Trimetrexate

A methotrexate analog, trimetrexate, is given intravenously together with folinic acid “rescue” to protect human cells from trimetrexate-induced toxicity. In patients who have moderate...
to severe disease, trimetrexate-folinic acid is less effective than high-dose TMP/SMX, but serious treatment-limiting hematologic toxicity occurs less frequently with trimetrexate-folinic acid.

**Atovaquone**

Atovaquone is licensed for the treatment of mild and moderate-severity PCP in patients who are intolerant of TMP/SMX. In tablet formulation (no longer available), this drug was less effective but was better tolerated than TMP/SMX or intravenous pentamidine for treatment of mild or moderate-severity PCP (see Tables 34-9 and 34-10). There are no data from prospective studies that compare the liquid formulation (which has better bioavailability) with other treatment regimens. Common adverse reactions include rash, fever, nausea and vomiting, and constipation. Absorption of atovaquone is increased if it is taken with food.

**Intravenous Pentamidine**

Intravenous pentamidine is now seldom used for the treatment of mild or moderate-severity PCP because of its toxicity. Intravenous pentamidine may be used in patients who have severe PCP, despite its toxicity, if other agents have failed (see Tables 34-9 and 34-10). Nephrotoxicity develops in almost 60% of patients given intravenous pentamidine (indicated by elevation in serum creatinine), leukopenia develops in approximately half, and up to 25% have symptomatic hypotension or nausea and vomiting. Hypoglycemia occurs in approximately 20% of patients. Given the long half-life of the drug, this may occur up to several days after the discontinuation of treatment. Pancreatitis is also a recognized side effect.

**Adjuvant Glucocorticoids**

For patients who have moderate and severe PCP, adjuvant glucocorticoid therapy reduces the risk of respiratory failure by up to half and the risk of death by up to one third (see Tables 34-9 and 34-10). Glucocorticoids are given to HIV-infected patients with confirmed or suspected PCP who have a PaO$_2$ <9.3 kPa (<70 mmHg) or an A–aO$_2$ of >4.7 kPa (<33 mmHg). Oral or intravenous adjunctive therapy is given at the same time as (or within 72 h of starting) specific anti–P. jirovecii therapy. Clearly, in some patients treatment is commenced on a presumptive basis, pending confirmation of the diagnosis. In prospective studies, adjuvant glucocorticoids have not been shown to be of benefit in patients with mild PCP. However, it would be difficult to demonstrate this, given that survival in such cases approaches 95% with standard treatment.

**General Management of Pneumocystis jirovecii Pneumonia**

Patients with mild PCP may be treated with oral TMP/SMX as outpatients if they are able to manage at home, willing to attend the outpatient clinic for regular review, and that there is clinical and radiographic evidence of recovery. If the patient is intolerant of oral TMP/SMX despite clinical recovery, either the treatment is given intravenously or treatment may be changed to oral clindamycin plus primaquine. All patients with moderate and severe PCP should be hospitalized and given intravenous TMP/SMX or intravenous clindamycin and oral primaquine (plus adjuvant steroids). Patients with moderate or severe disease who show clinical and radiographic response by day 7–10 of therapy may be switched to oral TMP/SMX to complete the remaining 14 days of treatment. If the patient has failed to respond within 7–10 days or deteriorates before this time while receiving TMP/SMX, then treatment should be changed to clindamycin and primaquine or trimetrexate plus folic acid.

**Deterioration in the Patient with Pneumocystis jirovecii Pneumonia**

Deterioration in a patient who is receiving anti–P. jirovecii therapy may occur for several reasons (Table 34-11). Before ascribing deterioration to treatment failure and considering a change in therapy, these alternatives should be evaluated carefully. It is also important to consider treating any co-pathogens present in BAL fluid, to perform bronchoscopy if the diagnosis was made empirically, to repeat the procedure, or to carry out open lung biopsy to confirm that the diagnosis is correct.

**Intensive Care**

Most centers advocate admission to the ICU for PCP with respiratory failure and for acute severe deterioration after bronchoscopy. The prognosis for severe PCP in such circumstances has improved over the past decade. This is likely because of a greater understanding of successful general ICU management of respiratory failure and acute respiratory distress syndrome (ARDS) rather than specific improvements in PCP care. Factors associated with poor outcome include increasing patient age, need for mechanical ventilation, and development of a pneumothorax. The latter reflects both the association between this complication and PCP, as well as the subsequent difficulty in successful mechanical ventilation of such individuals.

**Treatment of Mycobacterial Diseases**

**Treatment of Tuberculosis**

The treatment of HIV-related mycobacterial disease is complex. Not only do individuals have to take prolonged courses of relatively toxic agents, but also these antimycobacterial drugs have side effects similar to those of other prescribed drugs.
medications, especially HAART. Drug–drug interactions are also extremely common.

**Overlapping Toxicity**

In the developed world, isoniazid-related peripheral neuropathy is rare in HIV-negative subjects taking pyridoxine. The nucleoside reverse transcriptase inhibitors (RTI) didanosine and stavudine, which are now less frequently used in the United States and the United Kingdom but which remain a mainstay of HAART in the developing world, can also cause a painful peripheral neuropathy. This complication develops in up to 30% of patients if stavudine and isoniazid are co-administered. Rash, fever, and biochemical hepatitis are common adverse events with rifamycins, pyrazinamide, and isoniazid (occurring more frequently in patients with tuberculosis who have HIV infection with hepatitis C coinfection). The nonnucleoside RTI drugs (e.g., nevirapine) have a similar toxicity profile. If treatment for both HIV and tuberculosis is co-administered, ascribing a cause may be problematic.

**Drug–Drug Interactions**

Drug–drug interactions between medications used to treat tuberculosis and HIV infection occur because of their common pathway of metabolism through the hepatic cytochrome P-450 enzyme system. Rifampin is a potent inducer of this enzyme (rifabutin less so), which may result in subtherapeutic levels of nonnucleoside RTI and PI antiretroviral drugs, with the potential for inadequate suppression of HIV replication and the development of resistance to HIV. In addition, the PI class of antiretroviral drugs inhibits the metabolism of rifamycins, which leads to increases in their plasma concentration and is associated with increased drug toxicity. The non-nucleoside RTI drugs are inducers of this enzyme pathway. Co-administration of rifabutin with efavirenz requires an increase in the dose of rifabutin to compensate for the increase in its metabolism induced by efavirenz (see later).

**Type and Duration of Therapy for Tuberculosis**

The optimal duration of treatment of tuberculosis, by use of a rifamycin-based regimen, in a patient who has HIV infection is unknown. Current recommendations (Joint Tuberculosis Committee of the BTS and the ATS/CDC/Infectious Disease Society of North America [IDSA]) are to treat tuberculosis in HIV-infected patients in the same way as for the general population (i.e., for 6 months for drug-sensitive pulmonary TB). In addition, ATS/CDC/IDSA guidelines recommend that treatment be extended to 9 months in those who have cavitation on the original radiograph, continuing signs, or a positive culture after 2 months of therapy. Recent work has highlighted the increased risk for development of rifampin monoresistance in HIV-infected individuals on treatment. This is especially so if intermittent regimens are used and may arise from a lack of efficacy of the other drugs present in the combination (e.g., intermittent isoniazid). Hence, daily medication regimens are recommended and should be closely supervised in all HIV-positive patients. It should be remembered that although rifabutin is usually given three times a week with ritonavir-boosted protease inhibitors, this seems to achieve adequate rifamycin levels; there have been no reports of this leading to rifamycin resistance in patients who are appropriately adherent. Directly observed therapy (DOT) is an important, although fairly labor-intensive, strategy that has the support of the World Health Organization.

**When to Start Antiretroviral Therapy in a Patient with Tuberculosis**

The best time to start therapy in patients being treated for tuberculosis is unknown. Decision analyses show that early treatment with antiretroviral therapy leads to a marked reduction in further opportunistic disease. Against this is balanced the risk of needing to discontinue antituberculosis therapy or HIV therapy because of drug toxicity or drug–drug interactions. IRIS is reported to be more likely if the treatments are started at the same time as each other.

Pragmatically, delaying the start of antiretroviral therapy simplifies patient management and may reduce or prevent adverse drug reactions and drug–drug interactions and may also reduce the risk of IRIS. On the basis of current evidence, patients with CD4 counts >200 cells/µL have a low risk of HIV disease progression or death during 6 months of treatment for tuberculosis. In these patients, the CD4 count should be closely monitored, and antiretroviral therapy may be deferred until treatment for tuberculosis is completed. In patients who have CD4 counts from 199–100 cells/µL, many centers currently delay starting antiretroviral therapy until after the first 2 months of treatment for tuberculosis have been completed; patients are given concomitant PCP prophylaxis. In patients who have CD4 counts of <99 cells/µL, antiretroviral therapy is started as soon as possible after beginning treatment for tuberculosis. This is based on evidence that shows a significant short-term risk of HIV disease progression and death in this patient group if antiretroviral therapy is delayed.

Two options exist for starting antiretroviral therapy in a patient already being treated for tuberculosis. First, the rifampin-based regimen is continued, and antiretroviral therapy is commenced, for example, with a combination of two nucleoside RTIs and a non-nucleoside RTI, such as efavirenz (if the patient weighs <50 kg, the efavirenz dose is often increased to 800 mg once daily to compensate for rifampin-induced metabolism of efavirenz). Alternately, the rifampin is stopped and rifabutin is started: Antiretroviral therapy is given, with a combination of two nucleoside RTIs and a non-nucleoside RTI, such as efavirenz (if the patient weighs <50 kg, the efavirenz dose is often increased to 800 mg once daily to compensate for rifampin-induced metabolism of efavirenz). Here the dose of rifabutin is adjusted to take into account the pharmacokinetic effect of the co-administered drug. With a boosted PI, it is usually prescribed at a dose of 150 mg three times weekly and with efavirenz it is increased to 450 mg once a day.

**Immune Reconstitution Inflammatory Syndrome**

Before the advent of antiretroviral therapy, it was recognized by tuberculosis physicians that patients who were apparently responding to their antimycobacterial treatment would sometimes have a short period of clinical deterioration develop. This “paradoxical reaction” (in the face of overall treatment response) was seen as an interesting and probable immune-based phenomenon of generally little consequence. The widespread introduction of HAART has led to an increased awareness by clinicians of similar, but generally more severe, events in HIV-infected individuals. In the context of HIV, these are termed IRIS, or immune reconstitution disease.

They can present in a number of ways and with a range of opportunistic conditions. Perhaps the most common of these
is similar to a paradoxical reaction. Here, after initiation of antiretroviral therapy in a patient being treated for tuberculosis, for example, there arises the return of the original or the development of new symptoms and signs. These are often of a systemic nature and may be associated with marked radiographic changes. Examples of this include fever, dyspnea, lymphadenopathy, effusions, parenchymal pulmonary infiltrates, or expansion of cerebral tuberculomas. This form of IRIS is seen most frequently with mycobacteria (commonly tuberculosis or MAC), fungi (notably, Cryptococcus), and viruses (hepatitis and herpes viridae).

IRIS develops in up to one third of HIV-infected patients being treated for tuberculosis when antiretroviral therapy is started. The median onset of tuberculosis-related IRIS is approximately 4 weeks from beginning antituberculosis treatment or 2 weeks from commencing HAART. It seems to be more likely in patients who have disseminated tuberculosis (and hence presumably more antigen present as well as more potential for significant inflammatory reactions) and a lower baseline blood CD4 count. A rapid fall in HIV load, as well as a large increase in CD4 counts in response to HAART, may also predict IRIS. The relationship between early use of HAART and low blood CD4 counts suggests that care must be taken when starting antiretrovirals in patients with TB at sites where rapid expansion of an inflammatory mass could be life threatening. Examples of this would include cerebral, pericardial, or peritracheal disease (Figure 34-17).

It is important to note that IRIS is currently a diagnosis of exclusion. There is no laboratory test available to assist with this; it should be made only after progressive or (multi) drug-resistant tuberculosis, poor drug adherence (to either antituberculosis or antiretroviral agents) and drug absorption, or an alternative pathologic process have been excluded as an explanation for the presentation. Criteria have been drawn up that seek to provide clinical diagnostic criteria (Table 34-12).

The mechanism leading to IRIS is unclear. It is not due to failure of treatment of tuberculosis or to another disease process; if anything, it is most likely to represent an exuberant and uncontrolled response to mycobacterial antigens (from both dead and live organisms).

Current treatments include nonsteroidal antiinflammatory drugs or glucocorticoids. The latter are undoubtedly effective, although they can lead to hyperglycemia and hypertension. Recent preliminary data suggest that the leukotriene receptor antagonist montelukast may be of benefit in IRIS (this drug is unlicensed for this indication). Recurrent aspiration of lymph nodes or effusion may also be needed. Although IRIS is often self-limiting, it may persist for several months. Rarely, temporary discontinuation of antiretroviral therapy is required. In this situation there may be precipitous falls in CD4 counts; patients are at risk of other opportunistic infections.

Attention has also focused on what is possibly more of a concern—the form of IRIS referred to as “unmasking phenomenon.” Here, individuals with presumably latent tuberculosis infection who start HAART have systemic active (and often infectious) tuberculosis develop within a 3-month period. Although it is likely that the patient’s disease would have presented in time anyway and that some of the reported cases may, in fact, represent ascertainment bias, the current view is that this is real and represents an adverse effect of HAART. Given that the people most at risk live in countries with limited facilities for pre-HAART screening, this has major implications for antiretroviral therapy roll-out programs in resource-poor areas.

**Treatment of Disseminated Mycobacterium avium-intracellulare Complex Infection**

Combination antymycobacterial therapy by itself does not cure MAC infection. A commonly used regimen is oral rifabutin, 300 mg once daily, with oral ethambutol, 15 mg/kg once daily,
A frequently used regimen includes rifampin, isoniazid, and ethambutol in conventional doses; all drugs are given by mouth.

**TABLE 34-12 Immune Reconstitution Inflammatory Syndrome in HIV-Infected Individuals with Tuberculosis**

| Evidence supporting diagnosis | A. Initial diagnosis of tuberculosis confirmed by laboratory methods or by appropriate response to treatment |
|------------------------------|---------------------------------------------------------------------------------------------------------|
|                              | B. Development of new clinical phenomena temporally associated with starting HAART. This includes, but is not limited to: |
|                              | 1. New or enlarging lymphadenopathy, cold abscesses, or other focal tissue involvement |
|                              | 2. New or worsening central nervous system disease |
|                              | 3. New or worsening radiological features of tuberculosis |
|                              | 4. New or worsening serositis (pleural effusion, ascites, pericardial effusion, or arthritis) |
|                              | 5. New or worsening constitutional symptoms such as fever, night sweats, and/or weight loss |
|                              | 6. Retrospective review indicating that a clinical or radiologic deterioration occurred with no change having been made to tuberculosis treatment |
|                              | C. Immune restoration, e.g., a rise in CD4 lymphocyte count in response to HAART |
|                              | D. A fall in HIV “viral load” in response to HAART |

| Alternative diagnoses to be excluded | Progressive underlying infection |
|--------------------------------------|-------------------------------|
|                                      | Treatment failure due to drug resistance (MDR or XDR) |
|                                      | Treatment failure from poor adherence |
|                                      | Adverse drug reaction |
|                                      | Another diagnosis coexisting (e.g., non-Hodgkin lymphoma) |

**Treatment of Fungal Infections**

The treatment regimens for fungal infections complicating HIV infection are shown in Table 34-13.

**Cryptococcosis**

A combination of sulfadiazine and pyrimethamine is the regimen of choice for *T. gondii* infection. The most frequent dose-limiting side effects are rash and fever. Adequate hydration must be maintained to avoid the risk of sulfadiazine crystalluria and obstructive uropathy. Alternate regimens are given in Table 34-14. Once treatment is completed, lifelong maintenance is necessary to prevent relapse, unless antiretroviral therapy achieves adequate immune restoration (blood CD4 count >250 cells/µL and undetectable HIV load).

**Penicillium marneffei Infection**

Oral itraconazole has now replaced amphotericin B as the treatment of choice for *P. marneffei* infection, apart from the subgroup who are acutely unwell. Fluconazole is less effective than itraconazole. After initial treatment, lifelong suppressive therapy with itraconazole is needed. There are no data on the impact of antiretroviral therapy on which to base decisions about discontinuation of secondary prophylaxis.

**Toxoplasmosis**

A combination of sulfadiazine and pyrimethamine is the regimen of choice for *T. gondii* infection. The most frequent dose-limiting side effects are rash and fever. Adequate hydration must be maintained to avoid the risk of sulfadiazine crystalluria and obstructive uropathy. Alternate regimens are given in Table 34-14. Once treatment is completed, lifelong maintenance is necessary to prevent relapse, unless antiretroviral therapy achieves adequate immune restoration (blood CD4 count >250 cells/µL and undetectable HIV load).

**Visceral Leishmaniasis**

Visceral leishmaniasis is usually treated with liposomal amphotericin B, although this is still associated with a high rate of relapse. Second-line therapy (or first-line in resource-poor environments) is to use sodium stibogluconate (see Table 34-14).
STRONGYLOIDES STERCORALIS INFECTION

The treatment of choice is ivermectin. Risk of treatment failure with thiabendazole in HIV-infected individuals is higher than that in non-HIV–infected patients.

TREATMENT OF VIRAL INFECTIONS

Cytomegalovirus pneumonitis is treated with intravenous ganciclovir, 5 mg/kg every 12 h, for 14 days. Drug-induced neutropenia is managed with granulocyte colony-stimulating factor. Some centers use valganciclovir, an oral formulation of ganciclovir, at a dose of 900 mg orally every 12 h, to treat CMV pneumonitis. Side effects and their management are as for ganciclovir. There are no data that demonstrate efficacy for cidofovir for treatment of CMV pneumonitis, but this agent is used as second-line therapy in many centers. Phosphonoformate (foscarnet) can be used for treatment of CMV end-organ disease (e.g., pneumonitis), although it has an extensive toxicity profile. It is also a moderately effective antiretroviral agent. This effect is occasionally used as an adjunct in controlling nonresponsive viral infections.

TREATMENT OF FUNGAL PULMONARY INFECTION IN HIV-INFECTED INDIVIDUALS

| Infectious Cause | Drug | Notes |
|------------------|------|-------|
| Candida spp.     | Amphotericin B IV for 2–20 weeks | Continue until clinical/mycologic response is achieved |
| Aspergillus spp. | Amphotericin B 1 mg/kg or liposomal amphotericin 3 mg/kg IV q24h or itraconazole 200 mg PO q12h or voriconazole 6 mg/kg q12h | Use for severely ill patients Monitor renal function Adjust dose to measured trough levels |
| Cryptococcus neoformans | Amphotericin B 0.8–1.0 mg/kg or liposomal amphotericin 3 mg/kg IV q24h for 2–4 weeks and fluconazole 25–50 mg/kg IV q6h or fluconazole 300–400 mg PO q12h for 2–4 weeks | Monitor renal function Monitor blood count, liver and renal function |
| Histoplasma capsulatum | Itraconazole 200 mg PO q8h for 3 days, then 200 mg PO q12h for 6–12 weeks Amphotericin B 0.7 mg/kg or liposomal amphotericin 4 mg/kg IV q24h for 2–4 weeks | Adjust dose to measured trough levels Use for severely ill patients Monitor renal function |
| Coccioidoides immittis | Amphotericin B 0.5–1 mg/kg or liposomal amphotericin 4 mg/kg IV q24h for 2–4 weeks | Monitor renal function |
| Penicillium marneffei | Itraconazole 400 mg PO q24h for 4–6 weeks Amphotericin B 0.6–1.0 mg/kg or liposomal amphotericin 3 mg/kg IV q24h for 2–4 weeks | Adjust dose to measured trough levels Use for severely ill patients Monitor renal function |

TREATMENT OF PARASITIC INFECTIONS IN HIV-INFECTED INDIVIDUALS

| Infectious Cause | Drug | Notes |
|------------------|------|-------|
| Toxoplasma gondii | Sulfadiazine 2 g PO q8h and pyrimethamine 50 mg PO q24h and folic acid 15 mg PO q24h for 14–28 days | Rash and fever are common |
| Second choice | Clindamycin 450–600 mg PO q6h and pyrimethamine 50 mg PO q24h and folic acid 15 mg PO q24h for 14–28 days | If diarrhea develops, analyze stool for Clostridium difficile |
| Leishmania spp. | Liposomal amphotericin B 2–5 mg/kg IV q24h for 10 days | |
| Second choice | Sodium stibogluconate (equivalent to pentavalent antimony 10 g/mL) 10–20 mg/kg IV q24h for 3–4 weeks | |
| Strongyloides stercoralis | Ivermectin 200 μg/kg PO q24h × 4 doses over 16 days | |

STRONGYLOIDES STERCORALIS INFECTION

The treatment of choice is ivermectin. Risk of treatment failure with thiabendazole in HIV-infected individuals is higher than that in non-HIV–infected patients.

TREATMENT OF VIRAL INFECTIONS

Cytomegalovirus pneumonitis is treated with intravenous ganciclovir, 5 mg/kg every 12 h, for 14 days. Drug-induced neutropenia is managed with granulocyte colony-stimulating factor. Some centers use valganciclovir, an oral formulation of ganciclovir, at a dose of 900 mg orally every 12 h, to treat CMV pneumonitis. Side effects and their management are as for ganciclovir. There are no data that demonstrate efficacy for cidofovir for treatment of CMV pneumonitis, but this agent is used as second-line therapy in many centers. Phosphonoformate (foscarnet) can be used for treatment of CMV end-organ disease (e.g., pneumonitis), although it has an extensive toxicity profile. It is also a moderately effective antiretroviral agent. This effect is occasionally used as an adjunct in controlling nonresponsive viral infections.

CLINICAL COURSE AND PREVENTION

Within the past few years, drug therapy has radically altered the depressingly predictable nature of progressive HIV infection. Combinations of specific opportunistic infection prophylaxis and antiretroviral therapy can reduce both the incidence and the mortality associated with common conditions. The observational North American MACS cohort demonstrated that the risk of PCP in individuals with blood CD4 counts of <100 cells/μL can be reduced almost fourfold if both specific prophylaxis and HAART are taken (from 47% to 13%). However, as common conditions are prevented, so other less treatable illnesses may arise.

The initial impact of P. jirovecii prophylaxis was a reduction in the incidence of PCP at the expense of an increase in cases of disseminated MAC infection, CMV infection, esophageal candidiasis, and wasting syndrome. New prophylactic therapies targeting those conditions associated with high morbidity and mortality (in particular MAC) have further improved survival. It has become apparent that specific infection prophylaxis may also confer protection against other agents. This “cross-
prophylaxis” is particularly seen with the use of TMP/SMX for *Pneumocystis*, which also provides cover against cerebral toxoplasmosis and several common bacterial infections (although not *S. pneumoniae*) and with macrolides for MAC infection, which further reduce the incidence of bacterial disease and also PCP. Use of large amounts of antibiotic raises the possibility of future widespread drug resistance. This is clearly of concern, and recent reports suggest that, indeed, in some parts of the world the incidence of pneumococcal TMP/SMX resistance is rising. Current preventive therapies pertinent to lung disease focus on *P. jirovecii*, MAC, *M. tuberculosis*, and certain bacteria (Table 34-15).

**Pneumocystis jirovecii Prophylaxis**

Numerous studies have demonstrated the greatly increased risk in subjects who do not take adequate drug therapy with blood CD4 counts <200 cells/µL. Clinical symptoms are also an independent risk factor for PCP, and hence the current guidelines recommend lifelong prophylaxis against *P. jirovecii* in HIV-infected adults who have had prior PCP, CD4 counts <200 cells/µL, constitutional symptoms (documented oral thrush or fever of unknown cause of <37.8°C that persists for more than 2 weeks), or clinical AIDS. The importance of secondary prophylaxis (i.e., used after an episode of PCP) becomes clear from historical data, which indicate a 60% risk of relapse in the first 12 months after infection.

The increase in systemic and local immunity that occurs with HAART has led to several studies evaluating the need for prolonged prophylaxis in individuals with sustained elevations in blood CD4 counts and low HIV RNA load. In summary, it seems that both primary and secondary PCP prophylaxis can be discontinued once CD4 counts are >200 cells/µL for more than 3 months. A caveat to this is that the patient should have a low or undetectable HIV RNA load, that the CD4 percentage is stable or rising and is >14%, and that the individual plans to continue HAART long term with good adherence.

The risk of PCP recurrence is real if the CD4 count falls below 200 cells/µL. If this does happen, PCP prophylaxis should be restarted. Similar algorithms have been successfully used for all the major infections except tuberculosis. They all rely on an estimation of the general blood CD4 count above which clinical disease is highly unlikely. For example, secondary prophylaxis of MAC may be discontinued once the blood CD4 count is consistently >100 cells/µL. This is a general guideline, however, and patients must be assessed on an individual basis.

**Trimethoprim-Sulfamethoxazole**

As with treatment strategies, TMP/SMX is the drug of choice for prophylaxis (Table 34-16). It has the advantages of being highly effective for both primary and secondary prophylaxis (with 1-year risk of PCP while on the drug being 1.5 and 3.5%, respectively). It is cheap, can be taken orally, acts systematically, and provides some cross-prophylaxis against other infections, such as toxoplasmosis, *Salmonella* species, *Staphylococcus* species, and *H. influenzae*. Its main disadvantage is that adverse reactions are common (see earlier), occurring in up to 50% of individuals taking the prophylactic dose.

The standard dose of TMP/SMX is one double-strength tablet (160 mg trimethoprim, 800 mg sulfamethoxazole) per day. Other regimens have been tried; these include one “double-strength” tablet three times weekly and one single-strength tablet per day. In general, when used for primary prophylaxis, these regimens are tolerated well (if not better than the standard) and seem as efficacious as one double-strength tablet per day. The data are less clear on secondary prophylaxis, in which subjects are at a much higher risk of recurrent PCP. Attempts to desensitize patients who are intolerant of TMP/SMX have met with some success.

**Dapsone**

In patients who cannot tolerate TMP/SMX, dapsone is a safe and inexpensive alternative. It has been studied in a number of trials as both primary and secondary prophylaxis and is effective at an oral dose of 100 mg/day. When combined with pyrimethamine (25 mg three times weekly), it provides a degree of cross-prophylaxis against toxoplasmosis. Before starting dapsone, patients are tested for glucose-6-phosphate dehydrogenase deficiency.

| Organism                        | Preventive Method | Specific Agent                          | Indications                                      | Cost     | Notes                                                                 |
|---------------------------------|-------------------|----------------------------------------|-------------------------------------------------|----------|----------------------------------------------------------------------|
| *Pneumocystis jirovecii*        | Regular drug      | Trimethoprim-sulfamethoxazole (daily)  | Persistent thrush, fever, AIDS                   | Cheap    | Provides cross-protection May lead to resistance                      |
| *Mycobacterium tuberculosis*    | Regular drug      | Isoniazid (6–12 months)                | Purified protein derivative positive             | Cheap    | Compliance a potential problem, therefore resistance possible        |
| *Mycobacterium avium-intracellulare complex* | Regular drug | Clarithromycin (daily) or azithromycin (weekly) | CD4 count <50 cells/µL  | Expensive | Provides cross-protection May lead to resistance                      |
| *Streptococcus pneumoniae*      | Immunization      | 23-valent capsular polysaccharide      | All subjects at diagnosis and at 5 years        | Cheap    | Uncertain protection Transient increase in HIV “load”                |
| *Influenza virus*               | Immunization      | Whole or split virus                   | All subjects                                    | Cheap    | Uncertain protection Transient increase in HIV “load”                |
TABLE 34-16 Primary and Secondary Prophylaxis Regimens for Pneumocystis jirovecii

| Drug                          | Dose                                    | Notes                                                                 |
|-------------------------------|-----------------------------------------|----------------------------------------------------------------------|
| Trimethoprim-sulfamethoxazole | 1 Double-strength* tablet PO q24h       | Other options for primary prophylaxis: 1 double-strength* tablet PO q24h three times a week or 1 single-strength† tablet PO q24h Protects against toxoplasmosis and certain bacteria |
| Dapsone                       | 100 mg PO q24h                          | With pyrimethamine (25 mg PO q24h three times a week) protects against toxoplasmosis |
| Pentamidine                   | 300 mg via Respirgard II (jet) nebulizer every 4 weeks | Less effective in subjects with CD4 <100 cells/μL Provides no cross-prophylaxis |
| Atovaquone                    | 750 mg PO q12h                          | Absorption increased if administered with food Protects against toxoplasmosis |
| Azithromycin                  | 1250 mg PO once weekly                  | Protects against Mycobacterium avium-intracellulare complex and certain bacteria |

*160 mg trimethoprim, 800 mg sulfamethoxazole.
†80 mg trimethoprim, 400 mg sulfamethoxazole.

Pentamidine

Nebulized pentamidine has largely fallen from use as a prophylactic agent. This is despite it being better tolerated and having a similar efficacy to TMP/SMX for primary preventive therapy. However, its breakthrough rate is higher in subjects who have lower CD4 counts (i.e., <100 cells/μL) and in those who take it as secondary prophylaxis. Other disadvantages include equipment costs and complexity (alveolar deposition is crucial, and hence the nebulizer system used is important), the risk of transmission of respiratory disease (e.g., tuberculosis) to other patients and staff during the nebulization procedure, an alteration in the clinical presentation of PCP while on pentamidine (increased frequency of radiographic upper zone shadowing, increased incidence of pneumothorax), and a lack of systemic protection against Pneumocystis and other infectious agents. There is also an acute bronchoconstriction effect during nebulization. Long-term follow-up studies have not demonstrated any significant negative effect on lung function.

Atovaquone

Atovaquone oral suspension is used as a second-line prophylactic agent in subjects intolerant of TMP/SMX. It seems to have similar efficacy to dapsone (given together with weekly pyrimethamine), with a reduced incidence of side effects, of which the most frequent are rash, fever, and gastrointestinal disturbance.

Azithromycin

Azithromycin is used in many centers as a third-line prophylactic agent. It is given at a dose of 1250 mg once weekly, and may provide protection against some bacterial infections, as well as MAC.

Predictors of Pneumocystis Prophylaxis Failure

A low blood CD4 count (<50 cells/μL) is the current best laboratory predictor of prophylaxis failure. This is not particularly surprising given that the median blood CD4 count of subjects not on prophylaxis who have PCP develop is below 50 cells/μL. Persistent fever of unknown cause is an important clinical risk factor for PCP. Used as preventive therapy, TMP/SMX significantly reduces the chance for development of Pneumocystis. It is, therefore, vital that subjects who are most vulnerable be encouraged to use this drug on a regular basis. The PSPC cohort study revealed that 21% of subjects with a CD4 count <200 cells/μL were not receiving any form of PCP prophylaxis.

Bacterial Infection Prophylaxis

The effective and safe (i.e., replication incompetent) bacterial vaccines that are available would be expected to be widely used to prevent HIV-related disease. In fact, uptake of both pneumococcal and the H. influenzae type b (Hib) vaccines is poor (current estimates for the former are at most only 40% of the infected population with the recommended 23-valent vaccine). One reason for this may be that the protection conferred by vaccination (90%) in the general population is not seen in immunosuppressed HIV-infected individuals, reflecting their inability to generate adequate memory B-cell responses (especially those subjects with CD4 counts <200 cells/μL). However, in North America, CDC/IDSA recommend the pneumococcal vaccine as a single dose as soon as HIV infection is diagnosed, with a booster at 5 years, or if an individual’s blood CD4 count was <200 cells/μL and subsequently increased on HAART. Several studies show pneumococcal immunization reduces the risk of invasive pneumococcal infection in this population. This does not seem to be the case in a developing world setting, where not only is the 23-valent vaccine ineffective against both invasive and noninvasive pneumococcal disease, but the overall incidence of pneumonia is increased.

Infection with H. influenzae type b is much less common in HIV-infected adults and, therefore, immunization with Hib vaccine is not routinely recommended.

There is little evidence to suggest that the high frequency of bacterial infections in the HIV population is related to bacterial colonization. Therefore, continuous antibiotics are rarely indicated, although both TMP/SMX and the macrolides (clarithromycin and azithromycin) given as long-term prophylaxis for opportunistic infections have been shown to reduce the incidence of bacterial pneumonia, sinusitis/otitis media, and infectious diarrhea. The use of TMP/SMX also confers a survival advantage in many studies performed in resource-poor settings. There is little evidence, however, that TMP/SMX protects against pneumococcal infection.
Mycobacterium tuberculosis Prophylaxis

The interaction between HIV and tuberculosis is of fundamental importance, because the annual risk for the development of clinical tuberculosis in a given individual is estimated to be 5–15% (i.e., similar to a non-HIV–infected subject’s lifetime risk). HIV-infected individuals with pulmonary tuberculosis are less likely to be smear positive than their HIV-negative counterparts, although they can still transmit tuberculosis. Thus, within a community, tuberculosis prevention involves case finding and treatment of active disease, as well as specific prophylactic drug therapies for those exposed. If possible, HIV-positive subjects should make every effort to avoid encountering tuberculosis (e.g., at work, homeless shelter, health care facility).

One of the problems with standard methods of tuberculosis contact tracing in HIV infection is that both tuberculin skin test results and chest radiology may be unreliable. However, in the absence of bacillus Calmette–Guérin (BCG) immunization, a positive PPD (e.g., <5 mm induration with 5 tuberculin units) indicates a greatly increased risk (6- to 23-fold compared with nonanergic, PPD-negative, HIV-infected subjects) of future active disease. The chance that HIV-infected subjects may contract disseminated infection if given BCG means that (having excluded active infection) the only option in these circumstances is to use a preventative drug regimen. Options include at least 6 months of isoniazid (together with pyridoxine to prevent peripheral neuropathy). This is safe and well tolerated, although compliance is a problem (especially with regimens longer than 6 months), and DOT may need to be instituted (e.g., 900 mg isoniazid twice weekly). There is little evidence to suggest that this single-agent regimen leads to isoniazid resistance, which probably reflects the low mycobacterial load present in such individuals.

Attempts to shorten the length of treatment for latent infection have produced variable results. Recent studies used rifampin and pyrazinamide for short-course prophylaxis (2 months). This was as effective as 12 months of isoniazid in HIV-coinfected individuals, although it was associated with fatal hepatotoxicity (almost exclusively in the HIV-negative population). Hence, it is currently out of favor. If used, liver function should be closely monitored, and it is recommended that this regimen not be given to patients with preexisting liver disease (e.g., because of alcohol or viral hepatitis). Because rifampin should not be used by subjects taking PIs, this may also limit widespread application of the two-drug regimen. The same applies to combinations of isoniazid and rifampin taken for at least 3 months, which are also effective in HIV-negative individuals. Alternate protocols also exist for subjects thought to be resistant to first-line prophylactic agents. These have not been widely clinically evaluated. It is recommended that HIV-infected subjects who have had close contact with an active case of tuberculosis should also receive prophylaxis. There is little evidence to suggest that anergy confers an increased risk for development of clinical disease. However, patients who have not had BCG, have a negative skin test, and have started HAART may benefit from regular skin tests, because some studies suggest that cutaneous responses may return with increasing CD4 counts, and that this may help in identifying newly infected individuals requiring prophylaxis.

In populations where the prevalence of tuberculosis is low and BCG may be given during childhood or adolescence (e.g., the United Kingdom), the value of PPD testing is more limited. Here, an arbitrary cutoff of 10 mm for tuberculin reactions is used to define who should receive preventive therapy. The introduction of immune-based blood tests that can accurately distinguish between BCG vaccination and tuberculosis infection may be helpful when screening for evidence of latent tuberculosis. The two currently available commercial tests use fairly specific CD4-directed mycobacterial antigen responses with consequent production of detectable interferon-γ. The need for reasonably intact CD4 function means that they may, in fact, be less useful in HIV infection, especially in those subjects with very low blood CD4 counts, who are possibly at greatest risk of developing active tuberculosis.

Secondary tuberculosis prophylaxis may be important, because studies indicate a high rate of relapse in endemic areas. Here, no specific guidelines exist, although 6 months of isoniazid and rifampin after a full treatment course shows a greatly reduced risk of relapse within the subsequent 2 years. Whether this is enough to prevent clinical disease (which may also arise from reinfection in areas of high tuberculosis prevalence) without concomitant antiretroviral therapy is unclear. In the developed world, secondary prophylaxis is usually not recommended.

The use of HAART also can reduce the risk of tuberculosis in endemic areas. Work in South Africa indicates that this is most beneficial in patients with advanced disease and leads to a reduction in RR of at least 80%.

Mycobacterium avium-intracellulare Complex Prophylaxis

Data from North America indicate that the prevention of disseminated MAC infection has an effect on survival (25% reduction in mortality rate in subjects taking clarithromycin). The US guidelines advise prophylaxis with a macrolide (either clarithromycin, 500 mg orally twice per day, or azithromycin, 1250 mg orally, once a week) in all HIV-infected individuals with blood CD4 counts >50 cells/μL. In Europe, where the prevalence of disseminated MAC infection is probably lower (perhaps because of previous BCG vaccination), this may be less relevant. Here, surveillance cultures of blood may be more cost-effective in the at-risk HIV population with low CD4 counts. Routine stool and sputum cultures probably do not add much to this strategy, because disseminated MAC is much more common than isolated organ disease.

Single-agent prophylaxis may lead to antibiotic resistance. This does not seem to be reduced by the addition of a second drug (rifabutin) to the prophylactic regimen. The latter is now a second-line prophylactic agent, largely as a result of its rather worse protective effect and its adverse interaction profile with PIs. As mentioned earlier, if an individual sustains a rise in CD4 count >100 cells/μL for >6 months, it is safe to discontinue prophylaxis.

PROGNOSIS

Pneumocystis jirovecii

Several clinical and laboratory features have prognostic significance in HIV-infected individuals with PCP (Box 34-2). A severity score on the basis of the serum LDH levels, the A-aO2, and the percentage of neutrophils in the BAL fluid can predict survival reasonably accurately, with the highest scores indicating the worst outcome. Other workers have shown that increased age (<50 years) leads to an increased
mortality rate—in part as a result of late, “unsuspected” diagnosis. The overall mortality rate from an episode of PCP is approximately 14% and has not changed since the advent of HAART.

Among individuals with access to HAART, post-PCP survival has improved. In 1981, the median survival after PCP was 9 months. By 1995, this had risen to 20 months. The introduction of HAART has led to a further improvement, with survival in the period up to year 2000 of 40 months. In those without access to HAART and/or prophylaxis, survival post-PCP, unfortunately, remains poor.

**Bacterial Infection**

In general, mortality from bacterial respiratory infection in HIV-infected individuals is similar to that seen in the general population. Clinical and laboratory markers of disease severity that have been defined in the adult general population (e.g., those described in the ATS or the BTS Guidelines for the management of community-acquired pneumonia in adults) apply to HIV-infected patients. These are confusion, raised respiratory rate, abnormal renal function, and low blood pressure. Recurrent pneumonia is common (reported in up to 55% of cases) and may lead to chronic pulmonary disease (see earlier).

**Mycobacterium Tuberculosis**

Although tuberculosis normally responds to standard multiple-drug therapy, work from Africa has highlighted the increased mortality rate in HIV-infected compared with non-HIV-infected individuals. A relationship has also been described between mortality and declining blood CD4 count: HIV-infected patients with CD4 counts <200 cells/μL have a mortality rate of 10% compared with 4% in those with CD4 counts from 200–499 cells/μL. Compared with HIV-infected individuals without tuberculosis, the main effect on mortality is seen in patients with higher CD4 counts (>200 cells/μL), where the relative risk of death is three times that of the non-tuberculous population.

**Mycobacterium avium-intracellulare Complex**

Several case-controlled studies have indicated that in the absence of effective treatments, MAC-infected patients have a reduced survival compared with blood CD4 level-matched control subjects (approximately 4 months vs 9 months, respectively). Currently available treatment regimens may reduce this difference, although severe anemia seems to be an independent predictor of mortality.

**Cytomegalovirus**

The presence of CMV in BAL fluid also containing *P. jirovecii* has been related to outcome (see earlier). The mortality rate at 3 and 6 months after bronchoscopy is greater in those with CMV detected at bronchoscopy. However, CMV recovered as a sole pathogen does not impact on survival.

**PITFALLS AND CONTROVERSIES**

The Effect of Antiretroviral Therapy on Opportunistic Infections

The introduction of HAART, together with the wide availability of accurate methods of determining plasma RNA viral load, has led to profound changes in both clinical practice and HIV outcome. Although it is still the case that respiratory disease remains above non-HIV infected background levels, in particular, bacterial pneumonia, TB, and lung cancer are more common, despite apparently effective HAART, in HIV-infected subjects. Overall data indicate that clinical progression is rare in subjects who are able to adhere rigorously to at least 95% of their antiretroviral drug regimen. Mortality rates have fallen by 80% for almost all conditions, and it seems that a damaged immune system can, to a clinically significant extent, be reconstituted for a period of at least several years. Hence, clinicians need to consider not only opportunistic infection but malignancy within their diagnostic workup but also the effects of drug therapy itself. The side effect profile of HAART (e.g., metabolic and mitochondrial toxicities, liver damage, and neuropsychiatric disorders), as well as the large number of drug-drug interactions, makes this a very complex area of management. The best example of this is HIV-related tuberculosis. Here, not only is there overlapping toxicity and pharmacologic interaction, but IRIS is common. Research is needed to address this area. Studies should inform the decision on when to start HAART in patients already on antituberculosis medication. Other work needs to focus on understanding
why full pulmonary immunity is not restored. This may reflect abnormalities in the innate immune response, which is currently poorly described in HIV infection.

Predictors of Disease

Despite the benefits of HAART, it is likely that in the long term many patients will progress to severe disease. There is currently little research in this area. Research should focus on correlating clinical and laboratory findings. An example of this would be assessing the risk of an individual for development of active tuberculosis. It is clear that much of the excess mortality in HIV-tuberculosis coinfection occurs early in HIV infection. Thus, if tests can be devised that indicate who has latent tuberculosis infection (and who is, therefore, most likely to have clinical disease develop), steps can be taken to prevent illness.

As discussed previously, immune-based tests have shown promise in immunocompetent individuals with tuberculosis infection. If these can be refined to work consistently in patients with HIV infection at a reasonable cost, there is the possibility of targeting those at risk of future tuberculosis, or of tuberculosis “unmasking” after starting HAART.

The other role for a test such as this would be in rapid diagnosis of active tuberculosis. It is common to be faced with a patient who has nonspecific symptoms and a wide differential diagnosis. Often treatment is multiple and empirical. A quantitative test would help resolve some of these dilemmas by indicating the chance of the condition being caused by a particular disease. An example would be the patient from an endemic tuberculosis area, with low CD4 counts, who has both pulmonary and central nervous system disease. Is this tuberculosis, toxoplasmosis, cryptococcosis, or viral or bacterial infection? Any such test for tuberculosis would also have to distinguish between the different states of old (treated), old (inactive), old (latent), and active. Although not insurmountable, at present, this is not possible.

Rapid diagnostic assays that assess organism viability are also important. If a clinician can receive early feedback on whether treatment is producing a suitable killing effect, therapy can be tailored to the individual. This enables regimens to be “dose adjusted” as needed and removes the element of concern that is often present when patients are slow to respond. Examples of this would be in the treatment of PCP or mycobacterial disease.

Bacterial Infections

The frequency of bacterial infection (often recurrent) with its attendant sequelae makes effective strategies for vaccination an important priority. It is uncertain why there is a differential response to vaccination; even in the United States, African Americans do not seem to derive the same benefit as whites. This needs further research, together with more emphasis on identifying the local immune response present in the lung in such individuals.

Bacterial infections may be clinically indistinguishable from other pathogens, and only two thirds of all respiratory infections are formally diagnosed. There is a need for improved methods to assist with this. The use of rapid antigen tests may be one way forward. This is especially so given the high incidence of (potentially fatal) bacteremia present in such populations. For maximum benefit, this needs to use a system that is simple and cheap, and hence suitable to both resource-rich and resource-poor countries.

Mycobacterial Diseases

*M. tuberculosis* is globally the most important HIV-related pathogen. Strategies of control and prevention are vital to ensure that millions of people do not become coinfected and that those who are do not go on to have clinical disease develop. Rapid diagnostics are critical. The encouraging reports of the simple and cheap method of MODS to both diagnose tuberculosis and then provide resistance data in field settings (see earlier) argues for large-scale roll out and evaluation.

Beyond public health measures, such as DOT, fixed-dose combination drugs, case management, and education, research needs to improve on current drug therapy. Long-acting preparations such as rifapentine show promise but, as the problem with rifampicin monoresistance demonstrates, there is still much work to be done. For the first time in many years, there are several antimycobacterial drugs that are in various stages of clinical trials. All are promising, and several have novel mechanisms of action. The Global Alliance and the WHO “Stop TB” campaigns have been crucial in this regard. The fluoroquinolones, moxifloxacin and gatifloxacin, are closest to the market. They are potent drugs with considerable ability both to kill and also sterilize mycobacteria-infected sites. Trials of treatment-shortening regimens are ongoing worldwide.

Vaccination against *M. tuberculosis* with BCG has understandably not been widely used in an immunosuppressed HIV-infected population. However, a safe vaccine may be the only affordable way of protecting large parts of the world from tuberculosis. So far there seems to be more success in vaccines to either enhance or replace the primary protective effects of BCG. The use of immunotherapy (e.g., with heat-killed *Mycobacterium vaccae*) in combination with chemotherapy has been disappointing in clinical trials.

Pneumocystis jirovecii

Newer methods of diagnosis (e.g., PCR tests on saliva) may prove invaluable for quick and easy disease confirmation, although their applicability to routine samples needs further evaluation.

*P. jirovecii* prophylaxis was the first important HIV treatment widely available. However, despite the efficacy of TMP/SMX, compliance remains a problem. Regimens that use a gradual increase in dosage when starting prophylaxis may help. One concern with widespread use of prophylaxis is that resistance will start to occur to TMP/SMX. Reports have indicated that there are mutations in the *P. jirovecii* dihydropyroate synthase gene that confer resistance. These seem to be increasing over time, although they do not seem to be present in many patients who fail treatment for PCP with TMP/SMX. The implications of this are uncertain but could include a greater likelihood of treatment failure and the possibility of worsening patterns of global bacterial drug resistance.

Smoking-Related Diseases

HIV-infected populations in the developed world have high rates of smoking. The evidence that this is harmful above those effects seen in the general population continues to accrue. The accelerated course of both obstructive lung disease and cancer, together with the increased risk of respiratory infection in smokers, persuasively argues the case for targeted smoking.
cessation. That HIV infection and HAART have profound (and probably negative) effects on blood lipids and insulin resistance further support the need to reduce smoking rates in this population. It seems that we are starting to see increased rates of cardiovascular disease in this now aging population.

The natural history of HIV-related respiratory disease continues to evolve. HAART and newer therapeutic strategies have made a significant impact on morbidity and mortality. Yet individuals continue to become HIV infected, progress, and die from an ever-expanding range of conditions. *P. jirovecii* remains the most common AIDS-defining event in the developed world, whereas *M. tuberculosis* is globally the most common cause of death. Bacterial respiratory infection is not far behind. Given the huge number of individuals with HIV infection, the only effective way to manage this disease is to find simple ways of treating HIV itself, and thus contain the worst ravages of this illness.

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