Matthew Fei, MD

Laurence Huang, MD

HIV-ASSOCIATED PNEUMONIAS

Respiratory symptoms, including cough, shortness of breath, labored breathing, and chest pain, are common complaints in the setting of HIV infection. The spectrum of respiratory infections ranges from mild, self-limited viral upper respiratory infections to severe, life-threatening pneumonias requiring urgent hospitalization and treatment. In the United States, bacterial pneumonia and *Pneumocystis* pneumonia (PCP) are the two most common HIV-associated pneumonias. Although less common in the U.S., tuberculosis (TB) is the leading HIV-associated pneumonia worldwide.

While the overall incidence of opportunistic infections has decreased since the introduction of highly active antiretroviral therapy (HAART) in 1996, HIV-associated pneumonias remain a significant source of illness, and any respiratory complaint that may be due to pneumonia must be taken seriously. This review focuses on the most common HIV-related pulmonary infections—bacterial pneumonia, *Pneumocystis* pneumonia, and tuberculosis—and will provide an overview of the epidemiology, characteristic clinical and chest radiograph findings, diagnosis, treatment, and prevention of these pneumonias.

Epidemiology

Following the introduction of HAART and the use of preventive antibiotics for PCP, the prevalence of different HIV-associated pneumonias has changed. From the beginning of the HIV/AIDS epidemic through the early 1990s, PCP was the most common pneumonia seen in most U.S. institutions. At San Francisco General Hospital (SFGH), for example, approximately 25 cases of PCP were diagnosed monthly in 1992. In the mid-1990s, HAART became available and cases of PCP declined. Today, bacterial pneumonia is the most common HIV-associated pulmonary infection seen at SFGH, with significantly fewer cases of PCP—roughly three or four cases per month. (Unfortunately, over 20% of the people diagnosed with PCP at SFGH in the post-HAART era are unaware of their HIV positive status at the time of presentation with PCP, emphasizing the need for early HIV testing.)

Globally, TB is the major pulmonary infection associated with the HIV epidemic. In sub-Saharan Africa, TB is probably the most common pulmonary complication of HIV infection: approximately one-third of persons with TB in Africa are also HIV positive. In contrast, as reported in the January 2002 issue of *AIDS,* TB accounted for less than 5% of pneumonias in a prospective study of 230 people admitted with HIV and pneumonia to an academic medical center in Atlanta, Georgia.

Risk for HIV-Associated Pneumonias

The relative health of the immune system, as measured by the CD4 cell count, is the most important factor in assessing the risk for various opportunistic pulmonary infections (Table 1). Typically, the severity of HIV infection can be stratified by CD4 cell count into several stages: above 500, 200–500, 50–200, and below 50 cells/mm³. A CD4 cell count above

TABLE 1

HIV-Associated Opportunistic Respiratory Infections

RISK INCREASED AT	INFECTION
Any CD4 cell count	Bacterial pneumonia (community-acquired pneumonia) Tuberculosis
CD4 <200 cells/mm³	*Pneumocystis* pneumonia *Cryptococcus neoformans* pneumonia, usually associated with disseminated disease
CD4 <100 cells/mm³	*Toxoplasma gondii* pneumonia, usually associated with disseminated disease
CD4 <50 cells/mm³	Endemic fungal pneumonia: *Histoplasma capsulatum* or *Coccidioides immitis* pneumonia, usually associated with disseminated disease Cytomegalovirus pneumonia *Mycobacterium avium* complex pneumonia, usually associated with disseminated disease *Aspergillus* species pneumonia

500 cells/mm³ is indicative of a relatively intact immune system, and is typically seen in early HIV infection or after initiation of HAART and successful immune reconstitution. A CD4 cell count between 200 and 500 cells/mm³ signals immune suppression. When the CD4 cell count decreases below 200 cells/mm³, HIV infection has progressed to AIDS as defined by the U.S. Centers for Disease Control and Prevention (CDC).

Among the various opportunistic pulmonary infections, bacterial pneumonia and TB are unique in that HIV infection increases the risk of contracting both illnesses even if the CD4 cell count is relatively preserved (above 500 cells/mm³). In addition, the overall risk of contracting bacterial pneumonia or TB increases as the CD4 cell count decreases. In contrast, pulmonary infections such as PCP, fungal pneumonias, *Toxoplasma gondii* pneumonia, and cytomegalovirus (CMV) pneumonia are typically seen only in the setting of severe immune suppression, after the CD4 cell count falls below 200 cells/mm³.

In addition to the CD4 cell count, several key factors increase and decrease the likelihood of pulmonary infection. Injection drug use increases the risk of bacterial pneumonia. A prior diagnosis of PCP is a significant risk factor for subsequent PCP infection, while prophylactic use of trimethoprim-sulfamethoxazole (TMP-SMX, Septra, Bactrim) when the CD4 cell count falls below 200 cells/mm³ substantially decreases the risk of subsequent PCP. Cigarette smoking has been linked to increased risk of bacterial pneumonia and TB in both HIV positive and HIV negative individuals.

HIV infection is a risk factor for progression of latent tuberculosis infection (LTBI) to active tuberculosis disease. LTBI indicates prior infection with *Mycobacterium tuberculosis* and is defined by a positive purified protein derivative (PPD) skin test (which involves injecting 0.1 ml of sterile *M. tuberculosis* proteins under the skin of the forearm and assessing for swelling at the injection site 48 to 72 hours later), along with a normal chest radiograph (X-ray) and no symptoms con-

cerning for active TB. HIV positive individuals who have LTBI face a 10% per year risk of progressing from latent to active tuberculous disease, compared with an approximately 10% lifetime risk in the general population. Thus, all HIV positive persons are advised to be screened annually for LTBI, and those diagnosed with LTBI should receive therapy.

Symptoms

While there is no one sign or symptom that indicates a pulmonary infection, a cluster of complaints that suggests the need for further evaluation includes the presence of fever, cough, fatigue, or shortness of breath. Chest pain worsened by breathing or a decrease in the ability to exercise or perform usual daily activities are concerning as well. The duration and acuity of symptoms is important to note (Table 2). For example, bacterial pneumonia classically presents with the rapid onset of fevers, chills, cough, and shortness of breath over the course of three to five days, whereas PCP typically presents with the sub-acute, gradual progression of fever, cough, and shortness of breath over the course of two to four weeks. The production or non-production of sputum (material discharged from infected airways) is also noteworthy. While PCP typically causes a dry, non-productive cough, bacterial pneu-

monia is often associated with the production of thick, purulent (pus-containing) sputum. These observations, however, are generalizations, and exceptions to the rule can and do occur. For example, cases of PCP have presented with a productive cough (though usually of thin, clear sputum), and bacterial pneumonia can on occasion present with a sub-acute onset of symptoms over one week or more.

The presence of non-pulmonary signs and symptoms must also be noted, as these can be related to a primary pulmonary infection. Prolonged fevers over weeks to months, drenching night sweats, loss of appetite, and weight loss are commonly seen in the setting of active tuberculosis, *Mycobacterium avium* complex (MAC) that is disseminated (spread to other organs besides the lungs), and endemic fungal infections such as *Coccidioides immitis* (the causal pathogen of "Valley Fever," common to the California Central Valley and the American Southwest). The common portal of entry for these organisms is the lungs, and disseminated infection can present with pneumonia. Confusion and headache may indicate both neurologic and pulmonary involvement by the fungus *Cryptococcus neoformans.* Blurry vision and abdominal pain may herald concur-

rent CMV infections of the eye, gastrointestinal tract, and lung.

Finally, it must be emphasized that two or more opportunistic infections may present concurrently in the setting of HIV infection, especially with advanced immune suppression. For example, simultaneous infection with two different entities—such as PCP and bacterial pneumonia—may occur. The following sections discuss in more detail the three most common HIV-associated pulmonary infections: bacterial pneumonia, PCP, and TB.

Bacterial Pneumonia

HIV positive persons are at greater risk for bacterial pneumonia than are HIV negative individuals. Bacterial pneumonia is a frequent complication of HIV infection, and it often precedes other opportunistic infections. In many people, bacterial pneumonia may be the first manifestation of undiagnosed HIV infection.

Epidemiology

In HIV positive people, bacterial pneumonia is frequently recurrent; in fact, recurrent bacterial pneumonia, defined as two or more episodes within 12 months, became an AIDS-defining illness in the CDC's *1993 Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults.* Persons with multiple episodes of bacterial pneumonia may develop bronchiec-

TABLE 2

Signs and Symptoms of Common HIV-Associated Pulmonary Infections

CLINICAL FEATURES	BACTERIAL PNEUMONIA	*PNEUMOCYSTIS* PNEUMONIA	TUBERCULOSIS
Organism	*Streptococcus pneumoniae, Haemophilus* species, *Pseudomonas aeruginosa,* and others	*Pneumocystis jirovecii*	*Mycobacterium tuberculosis*
Signs and symptoms	Cough with purulent sputum, fever, chills Acute onset, symptoms <1 week	Nonproductive cough, shortness of breath, fever Gradual onset, symptoms >2 weeks	Cough, fever, night sweats, weight loss, swollen lymph nodes Gradual onset, symptoms >2 weeks

tasis (permanent destruction and dilatation of the bronchial airways) and other irreversible damage to their lungs.

In 1995, the Pulmonary Complications of HIV Infection Study group (PCHIS) published a paper describing the increased risk of bacterial pneumonia in the setting of HIV infection. The PCHIS was a multicenter study with six sites across the United States, one of which was SFGH. The study authors found that the rate of bacterial pneumonia was higher in the HIV positive population, even when the CD4 cell count was greater than 500 cells/mm^3. In addition, the rate of bacterial pneumonia increased as the CD4 cell count declined. In this study, the incidence of bacterial pneumonia among injection drug users was significantly higher than the rates found among both female heterosexuals and men who had sex with men. Among persons with CD4 cell counts less than 200 cells/mm^3, those who smoked cigarettes had a higher incidence of bacterial pneumonia compared with non-smokers.

Etiology

Many bacterial pathogens have the potential to cause HIV-associated pneumonia. Studies have found that two of the most common bacteria are *Streptococcus pneumoniae* and *Haemophilus influenzae.* "Atypical" organisms, such as *Mycoplasma, Legionella,* and *Chlamydophila,* can also cause pneumonia. *Pseudomonas aeruginosa* and *Staphylococcus aureus* are both reported as community-acquired pathogens seen with an increased frequency in HIV positive persons. However, it is not uncommon to never identify the infectious organism despite culturing samples of blood and sputum. In the aforementioned Atlanta study, which investigated the microbiologic cause of 230 cases of HIV-associated pneumonia, the authors were unable to isolate the causative organism in 33% of cases. Nevertheless, in the majority of cases

FIGURE 1

Chest radiograph of an HIV positive individual with a CD4 cell count above 200 cells/mm^3, revealing right upper lobe consolidation. Sputum and blood cultures were positive for *Streptococcus pneumoniae. Courtesy of Laurence Huang, MD.*

of "culture-negative" bacterial pneumonia, symptomatic improvement and recovery occur with antibiotics appropriate for the diagnosis of bacterial pneumonia.

Clinical and radiographic presentation

The clinical and radiographic presentation of bacterial pneumonia in HIV positive persons is similar to that in HIV negative individuals. Persons with pneumonias due to *Streptococcus pneumoniae* and *Haemophilus* species characteristically present with an acute onset (three to five days) of symptoms, including fevers, chills, rigors, chest pain, cough productive of purulent sputum, and dyspnea (labored breathing). The patient's white blood cell (WBC) count is usually elevated. Persons with bacterial pneumonia characteristically present with unilateral (on one side only), focal

(having a clear focus), segmental (located in a specific segment of the lungs), or lobar (located in a specific lobe, or side, of the lungs) consolidation on chest radiograph (Figure 1). However, the frequency of these typical radiographic findings may depend on the underlying bacterial pathogen. HIV positive persons may present with multifocal or multilobar involvement and with parapneumonic effusions—accumulations of fluid between layers of the membrane that lines the lung and the chest wall—more frequently than HIV negative individuals.

Diagnosis

The evaluation for bacterial pneumonia typically involves an attempt to isolate the infectious pathogen in cultures of blood, sputum, and potentially other sterile areas such as pleural fluid (fluid accumulating in the pleural space, which surrounds the lungs

in the chest cavity). While it is quite uncommon for PCP to disseminate and cause infection outside of the lung, pathogens responsible for bacterial pneumonia can often invade the lung barrier to gain access to the normally sterile bloodstream. From there, these bacteria can cause widespread infections of not only the blood (bacteremia) but also the heart valves (endocarditis), the pleural space (empyema), and the tissue layer surrounding the brain, or meninges (meningitis). In the setting of disseminated disease, the sequelae of infection can be quite morbid—long-term neurologic defects following *S. pneumoniae* meningitis are seen up to 25% of the time, and surgical replacement of infected heart valves is required in some instances of endocarditis.

Treatment

Treatment approaches for bacterial pneumonia differ based on whether the illness is severe enough to warrant hospital admission. Outpatient treatment for mild cases of bacterial pneumonia can be accomplished and usually involves seven to ten days of oral antibiotics. In the hospital setting, intravenous antibiotics are typically administered. The U.S. Public Health Service and Infectious Diseases Society of America recommend that HIV positive persons with suspected or confirmed bacterial pneumonia and who are being treated as inpatients should receive an intravenous beta-lactam antibiotic plus either a macrolide or doxycycline. The preferred beta-lactam antibiotics are ceftriaxone (Rocephin), cefotaxime (Calforan), or ampicillin (Omnipen, Polycillin, Principen).

Prevention

Because of the increased risk of disseminated disease with bacterial pneumonia, it is recommended that all HIV positive adults with a CD4 cell count greater than 200 cells/mm^3 receive the 23-valent polysaccharide pneumococcal vaccine (PPV). The PPV works by stimulating an antibody response against sugars in the protective capsule of *S. pneumoniae*. The PPV may lose some efficacy if given after the CD4 cell count falls below 200 cells/mm^3, as a protective immune response may fail to mobilize. In these persons, revaccination may be considered if the CD4 cell count rises above 200 cells/mm^3, as a result of HAART.

Pneumocystis Pneumonia

Pneumocystis pneumonia (PCP) is caused by the fungal pathogen *Pneumocystis jirovecii* (formerly known as *P. carinii*). PCP is the most common AIDS-defining opportunistic infection in the United States and typically causes disease only when the CD4 cell count falls below 200 cells/mm^3. PCP research has been hampered by the inability to culture this organism.

Epidemiology

On the basis of antibody testing, it is believed that the majority of people are infected with *Pneumocystis* early in childhood. The conventional theory is that PCP results from reactivation of this latent childhood infection, but studies suggest that PCP may also result from a recent exposure and infection. The route of transmission of PCP and its natural reservoir are incompletely understood, though a respiratory route of infection has been implicated in well-controlled animal
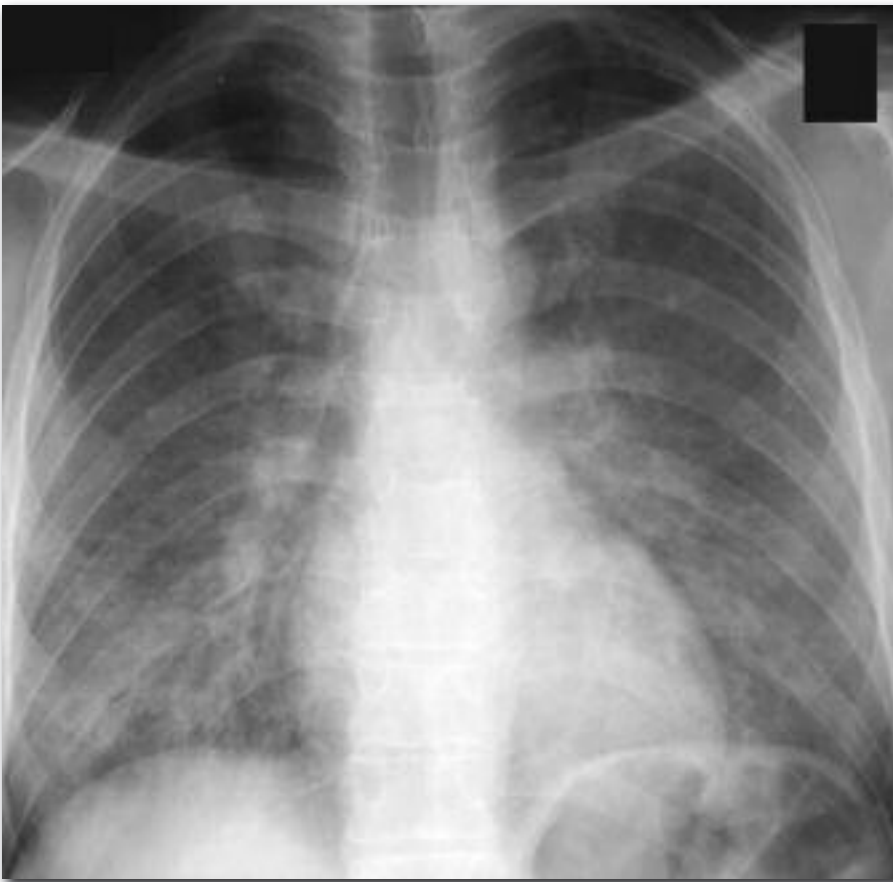
FIGURE 2

Figure 2. Chest radiograph of an HIV positive person with a CD4 cell count below 200 cells/mm^3, demonstrating the characteristic bilateral granular opacities of PCP. Bronchoscopy with bronchoalveolar lavage fluid microscopic examination revealed *Pneumocystis* cysts and trophic forms. *Courtesy of Laurence Huang, MD.*

studies. Currently, there is evidence that person-to-person transmission does occur, and recent molecular studies have shown that the organism can reside in the lungs without causing symptoms (referred to as "colonization"). The significance of colonization is unknown. Nevertheless, unlike management of TB, respiratory isolation for PCP is not routinely recommended at this time.

Clinical and radiographic presentation

The clinical presentation of PCP in HIV positive persons differs from the presentation in other immunocompromised persons; in general, HIV positive individuals present with a sub-acute onset (two to four weeks) and a longer symptom duration. Classically, PCP presents with fever, cough, and shortness of breath. The cough is usually dry and non-productive unless a concurrent bacterial infection is present. The cough may be exacerbated by deep breathing and occasionally accompanied by "chest tightness." Symptoms are often subtle at the onset but are gradually progressive and may be present for weeks and occasionally months before diagnosis.

No current laboratory test is specific for PCP. The serum lactate dehydrogenase (LDH) is usually found to be elevated; however, the LDH can be elevated in response to a variety of pulmonary and non-pulmonary conditions. On chest radiograph, persons with PCP characteristically present with bilateral (on both sides), reticular (network-like), or granular (grainy-looking) opaque areas, or opacities (Figure 2). Occasionally, persons with PCP may have a normal or minimally abnormal chest radiograph and may undergo high-resolution computed tomography (HRCT) of the chest for further evaluation. On chest HRCT, persons with PCP characteristically present with bilateral, patchy areas called "ground-glass" opacities (Figure 3).

FIGURE 3
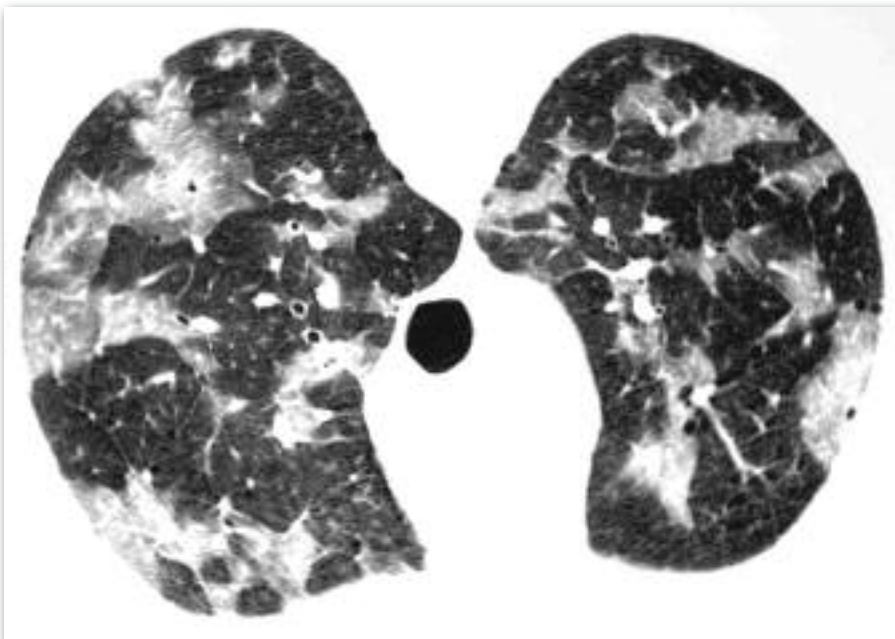
Chest high-resolution computed tomography (HRCT) scan of an HIV positive person with a CD4 cell count below 200 cells/mm^3 whose chest radiograph was normal. Chest HRCT scan revealed the characteristic patchy ground-glass opacities of PCP. Induced sputum microscopic examination revealed *Pneumocystis* cysts and trophic forms. *Courtesy of Laurence Huang, MD.*

Diagnosis

There is no universally agreed-upon approach to the management of HIV positive persons with suspected PCP. Many institutions treat persons with suspected PCP based solely on the patients' symptoms and chest radiographic presentation, while other institutions (such as SFGH) pursue a definitive microscopic diagnosis. Because *Pneumocystis* cannot be cultured, the diagnosis of PCP relies on microscopic examination of the characteristic cysts and/or trophic forms (different stages of the pathogen's life cycle) on respiratory specimens that have been stained to make their microscopic structures more clearly visible. Typically, these respiratory specimens are obtained from sputum induction (a procedure to stimulate sputum production through the inhalation of hypertonic saline mist) or bronchoscopy with bronchoalveolar lavage (BAL; a procedure, performed by a pulmonary specialist, in which a fiberoptic bronchoscope is passed into the throat and wedged deep into an airway, saline is instilled, and fluid is aspirated back and sent for study). Several studies have examined the utility of applying a sensitive and specific molecular assay (e.g., polymerase chain reaction, or PCR) to a simple, non-invasive, 60-second procedure called oropharyngeal washing (OPW) to collect specimens for PCP diagnosis. However, although results indicate that PCR with OPW is a sensitive and specific test for PCP, it is mainly a research tool at present.

Treatment

Unfortunately, the health consequences of PCP infection can be severe. Outpatient treatment may be appropriate in cases of mild infection but most people with PCP require hospitalization and close observation. Indications for hospital admission include low oxygen saturation of the blood, severe shortness of breath, and persistent or worsening symptoms de-

spite the use of appropriate oral PCP treatment. In the HIV positive population, PCP remains the most common reason for respiratory failure and need for mechanical ventilation ("breathing machine"). While the number of PCP infections has declined substantially since the introduction of PCP prophylaxis and HAART, mortality from severe PCP requiring admission to an intensive care unit and subsequent mechanical ventilation remains high ($>50\%$).

First-line therapy for PCP is the fixed-dose combination drug trimethoprim-sulfamethoxazole (TMP-SMX). Typically, PCP treatment is for a total duration of three weeks. Common side effects of therapy include gastrointestinal upset (nausea, vomiting), rash, fever, and bone marrow suppression (anemia). In cases of

moderate to severe PCP, corticosteroids are indicated to decrease the inflammatory reaction in the lung and subsequent respiratory failure, and have been shown in controlled trials to decrease mortality. Second-line therapy includes intravenous pentamidine (Nebupent), clindamycin (Cleocin) plus primaquine (Primaquine); trimethoprim (Trimpex, Proloprim, Primsol) plus dapsone (Dapsone); and atovaquone (Mepron) suspension.

Prevention

Prevention of PCP, also called PCP prophylaxis, should begin when the CD4 cell count falls below 200 cells/mm³. Other indications for PCP prophylaxis include a diagnosis of oral thrush or following a documented episode of PCP. The most effective

prophylaxis regimen is daily TMP-SMX with either a double-strength or single-strength tablet. One double-strength tablet three times a week is an alternative prophylaxis regimen. Unfortunately, some persons are allergic to or intolerant of TMP-SMX. In these persons, dapsone with or without pyrimethamine, atovaquone suspension, and monthly aerosolized pentamidine are potential options. Rigorous adherence decreases the risk of PCP infection substantially, but no preventive regimen is 100% effective. PCP has been known to occur despite antibiotic prophylaxis, especially in the setting of severe immune suppression. PCP prophylaxis can typically be stopped when the CD4 cell count has risen above 200 cells/mm³ for a period of three months as a result of antiretroviral treatment.

The widespread use of TMP-SMX for PCP prophylaxis has led to increasing concerns about the potential for TMP-SMX drug resistance. Unfortunately, the inability to culture *Pneumocystis* has precluded the demonstration of drug resistance *in vitro.* Several studies using molecular and epidemiologic tools have found a strong association between the use of TMP-SMX for PCP prophylaxis and the presence of specific mutations in *Pneumocystis,* and have found in some instances that the presence of these mutations is associated with increased mortality and increased TMP-SMX PCP treatment failure. However, the clinical significance of these *Pneumocystis* mutations is unclear at present, since these studies also have noted that the majority of persons with these mutations still respond to TMP-SMX therapy.

Tuberculosis

Coinciding with the onset of the HIV epidemic, there was a surge in cases of *Mycobacterium tuberculosis* infection in the 1980s and early 1990s, and like recurrent bacterial pneumonia, pulmonary TB became an AIDS-defining illness in the CDC's *1993 Expanded Surveillance Case Definition for*
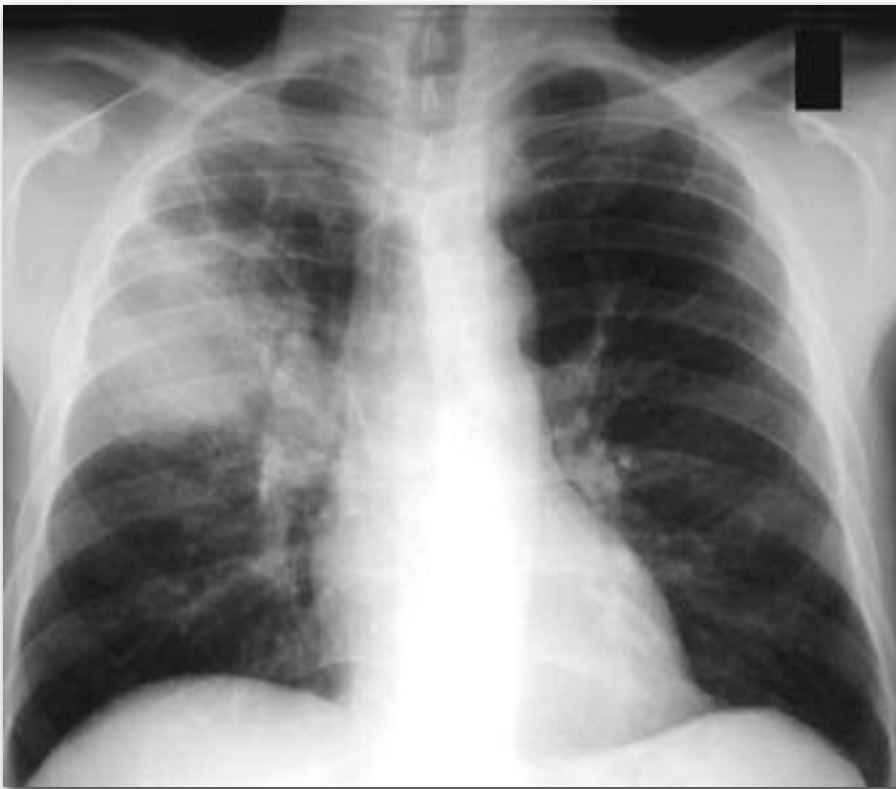
FIGURE 4

Figure 4. Chest radiograph of an HIV positive individual with a CD4 cell count above 200 cells/mm³, revealing right upper lobe consolidation with areas of cavitation. Multiple sputum acid-fast bacillus stains were smear microscopy-positive and mycobacterial cultures grew *Mycobacterium tuberculosis. Courtesy of Laurence Huang, MD.*

AIDS. While various public health and infection control measures have subsequently decreased the number of TB cases per year in the U.S., HIV remains a major risk factor for TB infection.

Epidemiology

M. tuberculosis is a bacterium spread by person-to-person transmission via respiratory droplets. Transmission of infection typically requires close proximity of several hours or more to a person who has active pulmonary tuberculosis and is coughing. Among HIV negative persons, exposure to and subsequent infection with *M. tuberculosis* is asymptomatic in at least 90% of cases, resulting in LTBI, a prolonged carrier state in which dormant bacteria with the potential to cause future infection remain in the body for life. Primary progressive TB, an active pneumonia following initial exposure to the bacteria, is quite rare. The lifetime risk of progressing from LTBI to active tuberculosis is approximately 10% in HIV negative people. In contrast, people living with HIV are at an increased risk of progressing from LTBI to active tuberculosis at a rate of approximately 5%–10% per year. In addition, HIV increases the risk of primary progressive TB and development of an active pneumonia following initial exposure to tuberculosis.

Clinical and radiographic presentation

There are several features which are notable in HIV-associated tuberculosis. First, the chest radiograph is less likely to show the "classic" upper lung zone cavitary (chest cavity) disease (Figure 4), and the absence of the typical radiographic appearance may delay diagnostic evaluation for TB and the initiation of TB therapy. In HIV positive persons with advanced immune suppression, the chest radiograph may reveal disease in the middle and/or lower lung zone (Figure 5), nodules (aggregations of cells), or a "miliary" pattern characterized by nu-

FIGURE 5
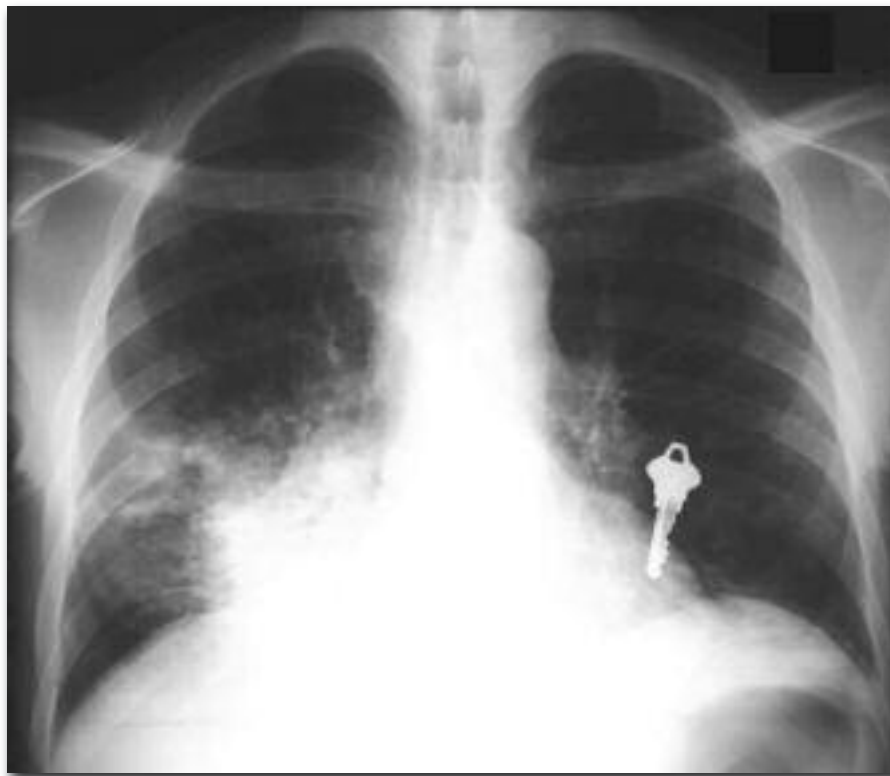
Chest radiograph of an HIV positive person with a CD4 cell count below 200 cells/mm^3, revealing right lower lung zone consolidation without cavitation. Sputum acid-fast bacillus stains were smear microscopy-negative but mycobacterial cultures grew *Mycobacterium tuberculosis* that was mono-rifampin-resistant. In this case, the key to the diagnosis of TB was knowledge of the person's CD4 cell count and understanding that TB can present with this chest radiographic picture in an individual with a CD4 cell count below 200 cells/mm^3. *Courtesy of Laurence Huang, MD.*

merous small lesions. Persons with TB may also present with pleural effusions on chest radiograph. While most cases of active tuberculosis will have some abnormal findings on chest radiograph to suggest presence of infection, even a normal radiograph does not rule out the diagnosis of tuberculosis in the setting of HIV infection. Second, much like bacterial pneumonia, HIV-associated tuberculosis has a tendency to cause widespread, disseminated disease. Tuberculosis can spread to almost any organ in the body, but commonly will affect the lymph nodes, pleural space, meninges, pericardium (the tissue layer surrounding the heart), and bone marrow.

Diagnosis

Since TB is transmitted from person to person, individuals who are admitted with suspected TB should be placed in respiratory isolation while undergoing diagnostic evaluation. Sputum acid-fast bacilli (AFB) smears and mycobacterial culture are the standard diagnostic tools used to evaluate suspected TB. Sputum is obtained on three consecutive days, ideally from the first specimen produced each morning. Serial sampling of expectorated sputum is appropriate for persons with a productive cough; sputum induction should be performed in persons with a non-productive cough. Occasionally, bronchoscopy with BAL and transbronchial biopsies is per-

formed to diagnose TB. Thoracentesis (a procedure to remove fluid from the space between the pleura, the lining of the outside of the lungs, and the wall of the chest) with pleural biopsies may be performed to diagnose pleural TB.

Treatment

Effective treatment of active tuberculosis requires multiple antibiotics taken for a minimum of six months. If the infecting *M. tuberculosis* is susceptible to all antibiotics tested in sputum samples or tissue cultures, HIV infection does not significantly change the type or duration of recommended anti-TB therapy. A typical regimen would involve treatment with isoniazid (INH; Niazid, Nydrazid), a rifamycin drug (RIF; commonly rifampin [Rifadin] or rifabutin [Mycobutin]), pyrazinamide, and ethambutol (Myambutol) for two months, followed by four additional months of INH and RIF. All of these antibiotics can be given as oral medications, without the need for injections. These general guidelines must be tailored to each individual case; the type of antibiotic may be changed and duration of therapy lengthened if there is any indication that the TB infection is not being adequately treated.

HIV-associated tuberculosis has been reported to have similar outcomes (rates of cure and disease relapse) compared with HIV negative cases when the tuberculosis organism is antibiotic susceptible, although overall mortality (from both TB and other AIDS-related illnesses) is higher in HIV positive persons. A recently published retrospective analysis of TB cases in San Francisco, however, described higher rates of TB relapse in people with HIV. While these findings may eventually lead to changes in recommended therapy for patients with both TB and HIV, further research is necessary to clarify this important clinical question.

When undergoing treatment for active tuberculosis, it is extremely important to adhere strictly to recommended therapy and avoid missed doses of antibiotics. One of the greatest risks for developing drug-resistant TB is intermittent antibiotic use and failure to comply with recommended TB therapy. Intermittent exposure to antibiotics will select for TB organisms that are resistant to first-line antibiotics, making further treatment more difficult (often requiring the use of intravenous or injectable antibiotics) and lengthening the duration of therapy. While the treatment period for drug-susceptible TB is approximately six months, treatment for different strains of drug-resistant TB may take two years or longer and typically involves combinations of four to six or more medications, one of which is usually injected. The treatment of multidrug-resistant TB requires the use of second-line antibiotics, which have decreased efficacy compared to first-line drugs like INH and RIF and more side effects. Despite these intensified regimens for drug-resistant TB, treatment failure rates and mortality are increased, especially in the HIV positive population. For these reasons, directly observed therapy (DOT) is recommended for all cases of HIV-associated TB. DOT is defined as a situation in which a health care provider observes a person taking their medications. In various studies, DOT has been shown to decrease rates of drug resistance as well as relapse of TB disease.

Multidrug-Resistant TB and Extensively Drug-Resistant TB

Multidrug-resistant TB (MDR-TB) is defined as infection with an organism resistant to the two main first-line drugs, INH and RIF, while extensively drug-resistant TB (XDR-TB) is defined as infection with an organism resistant to INH, RIF, any fluoroquinolone, and at least one of the injectable antibiotics used in TB therapy. In the U.S., where new cases of TB and drug-resistant TB must be reported to state health departments and the CDC, there were 121 cases of MDR-TB in 2005 and 15 cases of XDR-TB be-

tween 2000 and 2005. In San Francisco, typically one to four cases of MDR-TB are diagnosed yearly, and the overall number of newly diagnosed active TB cases declined to 120 in 2006—an all-time low.

Drug-resistant TB can be acquired either by primary infection from another person with resistant TB, or when a previously sensitive organism becomes resistant, usually through inadequate treatment or nonadherence to treatment. Drug resistance occurs because any TB-positive individual harbors a mixed population of tuberculosis organisms, some with inherent, natural resistance to various antibiotics. Thus, the rationale for combination antibiotic therapy is based on the extremely low likelihood that any one organism is resistant to two or more antibiotics. However, if drug therapy is taken sporadically or if prescribed treatment is inadequate, selection for the antibiotic-resistant strains will occur.

In published studies of drug-resistant TB, concomitant HIV infection is seen in disproportionate numbers. Multiple outbreaks of drug-resistant TB were reported in U.S. hospital and jail settings in the early 1990s, with most cases occurring in HIV positive individuals. In contrast to the outcomes seen with antibiotic-susceptible TB, mortality was extremely high in cases of HIV co-infection with MDR-TB, ranging from 72% to 89%. In a case series of all people with MDR-TB treated at SFGH between 1982 and 2000, the cure rate and survival in HIV negative people was 97% (32 of 33 cured); in contrast, all 11 of the HIV positive individuals died of either TB or another AIDS-related illness during the study period. All of the HIV positive participants in this study had advanced AIDS, and only two were on HAART. Fortunately, outside of institutional outbreak settings, which were attributed to poor infection-control practices, there has not been a consistent association to suggest that HIV infection increases one's risk of acquiring MDR-TB.

Highly Active Antiretroviral Therapy

In addition to anti-TB medications, HIV positive persons may also require HAART to treat their underlying HIV infection. While there are varying opinions on when to start HAART, most guidelines advocate earlier initiation in settings of more severe immune suppression. Thus, anti-HIV and anti-TB treatment may need to be given concurrently if the CD4 cell count is less than 200 cells/mm³, whereas it may be a better option to defer antiretroviral therapy until TB treatment is completed in those persons with higher CD4 cell counts. One recently reported study of HIV-associated TB found that initiation of HAART during TB treatment led to decreases in HIV viral load, AIDS-related illnesses, and mortality. This study enrolled 188 people, all of whom had severe immune compromise, with a median CD4 cell count of 90 cells/mm³. Unfortunately, concomitant use of HAART and anti-tuberculosis therapy was associated with an increase in medication side effects, sometimes requiring cessation or changes in therapy. Similar results were noted in a 2007 retrospective study of 264 patients with HIV-associated TB in San Francisco, in which the authors found that use of HAART was associated with a decrease in mortality.

Several factors can complicate the co-administration of anti-tuberculosis and antiretroviral agents. Toxicities and side effects of HAART and anti-TB medications are common and can overlap (Table 3). In general (and when possible), it is wise to initiate anti-tuberculosis therapy first and ensure that it is well tolerated for a period of at least two weeks before starting HAART. Second, there are complex drug-drug interactions between the rifamycins, which represent a cornerstone of TB therapy, and two classes of antiretroviral medications—the protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). These interactions can lead to increased blood levels of rifamycin and decreased blood levels of the PIs and NNRTIs. Clinically, this change in blood levels can increase the risk for rifamycin side effects and potentially require discontinuation of this important medication. In addition, decreased drug levels of PIs and NNRTIs can lead to resistance to both classes of drugs and seriously complicate future attempts to treat HIV. Fortunately, there are regimens which can simultaneously treat TB and HIV which minimize the likelihood of side effects and drug-drug interactions (although these problems remain significant in resource-limited settings, where fewer antiretroviral drugs are available). For the highest chance of success, it is strongly recommended that cases of HIV-associated TB be treated by health care providers who have significant experience in these fields.

Prevention

Because antibiotic therapy can substantially decrease the risk of progression from LTBI to active tuberculosis, annual screening for LTBI in those with HIV infection is strongly advised. The recommended screening exam is the PPD skin test, described above. While false positives and negatives are possible (the latter especially in the setting of advanced HIV), the PPD skin test cannot cause tuberculosis infection. In HIV positive persons, a diagnosis of LTBI is typically confirmed

TABLE 3

Common Antibiotics for Tuberculosis, and Possible Side Effects

DRUG	SIDE EFFECTS	ADDITIONAL INFORMATION
First-line drugs		
isoniazid (Niazid, Nydrazid)	Hepatitis, neuropathy	Vitamin B6 (pyridoxine) supplementation recommended to decrease risk of neuropathy.
rifamycin (rifampin [Rifadin], rifabutin [Mycobutin])	Hepatitis, rash, itching	Orange discoloration of body fluids (saliva, urine, tears, sweat) is normal and to be expected. Rifabutin has fewer interactions with common antiretroviral drugs.
pyrazinamide	Hepatitis, joint pains, gout flare, rash	
ethambutol (Myambutol)	Decreased visual acuity or color discrimination	Eye exam recommended prior to treatment and following any changes in vision.
Second-line drugs		
Injectables: streptomycin amikacin (Amikin) kanamycin (Kantrex) capreomycin (Capastat)	Hearing loss, renal failure (kidney injury)	
Fluoroquinolones: levofloxacin (Levaquin) moxifloxacin (Avelox)		All fluoroquinolones can be taken orally, and are commonly used to treat non-tuberculosis-related bacterial infections.

by the presence of a 5-mm or larger patch of hardened or inflamed skin at the site of the PPD test 48 hours following the injection.

An alternative screening exam for LTBI is the interferon-gamma release assay (IGRA), which is a blood test; unlike the PPD, the IGRA does not require a repeat visit for interpretation. While the IGRA has been approved by the U.S. Food and Drug Administration to assist in the diagnosis of tuberculosis infection, its accuracy in HIV positive persons has not been well characterized. Prior to initiating antibiotic treatment for LTBI, active tuberculosis disease must be excluded, with a chest radiograph and medical exam by a health care provider experienced in tuberculosis diagnosis and treatment. Recommended regimens for treatment of LTBI in the setting of HIV infection include nine months of isoniazid, rifampin for four months, or rifabutin for four months.

When to Seek Medical Evaluation

While HIV does increase the risk of serious pulmonary infections, it is also quite common (and normal) to experience relatively minor episodes of cough, runny nose, sore throat, and other respiratory symptoms which may indicate the "common cold," bronchitis, or related viral upper respiratory infections. When is it important to seek medical care? Gauging both the severity and duration of symptoms is key to answering this question. High fevers, severe shortness of breath, and cough are extremely worrisome even if symptoms are of short duration. Similarly, low-grade fevers and progressive shortness of breath and cough are concerning if symptoms persist for more than one week. Erring on the side of caution is advisable; early diagnosis and prompt initiation of appropriate treatment will result in improved outcomes for all HIV-related pulmonary diseases.

Medical Evaluation

A battery of tests assists the health care provider in arriving at the correct diagnosis. As mentioned above, basic blood work and cultures of sputum and blood may be performed. An arterial blood gas test may be conducted to evaluate the levels of oxygen and carbon dioxide in the arteries. A chest radiograph will provide a significant amount of information, as each HIV-associated pneumonia has a characteristic pattern. If the diagnosis remains unclear with these initial tests, a computed tomography (CT) scan of the chest can provide additional diagnostic information. If PCP is suspected, sputum induction and/or bronchoscopy with BAL may be performed; bronchoscopy requires specialized equipment and is usually performed by a pulmonary specialist. If active tuberculosis infection is suspected, hospital admission and respiratory isolation is usually indicated. The diagnosis of TB requires submission of daily sputum samples to search for *M. tuberculosis* organisms.

Conclusion

Pulmonary complications of HIV are common and can range from minor upper respiratory infections to life-threatening pneumonias. Because of the health consequences of a delayed or incorrect diagnosis, empiric therapy (often with antibiotics) is not recommended and pursuit of a definitive microbiologic or pathologic diagnosis is encouraged whenever possible. The most common HIV-associated pulmonary infections in the United States are bacterial pneumonia, PCP, and tuberculosis. While drug-resistant TB is not a particularly common problem in the U.S., the consequences of developing MDR-TB in the setting of HIV infection are severe. Treatment of HIV and TB co-infection should be done by a health care provider with significant experience in both of these fields.

While regimens to treat HIV and TB can be quite complex and require multiple medications, it is extremely important to adhere to the recommended medication schedule to prevent development of antibiotic resistance. Because the risk of HIV-associated pneumonias typically increases with a progressive decline in CD4 cell count, antiretroviral therapy and appropriate use of preventive antibiotics are highly recommended in the appropriate clinical setting.

Matthew Fei, MD, is a clinical fellow in the Division of Pulmonary and Critical Care Medicine at San Francisco General Hospital and the University of California, San Francisco.

Laurence Huang, MD, is a Professor of Medicine at the University of California, San Francisco, and an attending physician in the Division of Pulmonary and Critical Care Medicine and the HIV/AIDS Division at San Francisco General Hospital. He is actively involved in clinical research studies on HIV-associated pneumonias, including PCP, TB, and bacterial pneumonia.

Selected Sources

Centers for Disease Control and Prevention. Guidelines for preventing opportunistic infections among HIV-infected persons—2002 recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. *Morbidity and Mortality Weekly Report* 51(RR08):1–46. June 14, 2002.

Centers for Disease Control and Prevention. Treatment of tuberculosis, American Thoracic Society, CDC, and Infectious Diseases Society of America. *Morbidity and Mortality Weekly Report* 52(RR11):1–77. June 20, 2003.

Hirschtick, R. and others. Bacterial pneumonia in persons infected with the human immunodeficiency virus. *New England Journal of Medicine* 333(13):845–51. September 28, 1995.

McIlleron, H. and others. Complications of antiretroviral therapy in patients with tuberculosis: drug interactions, toxicity, and immune reconstitution inflammatory syndrome. *The Journal of Infectious Diseases* 196:S63–S75. August 15, 2007.

Nahid, P. and others. Treatment outcomes of patients with HIV and tuberculosis. *American Journal of Respiratory and Critical Care Medicine* 175:1199–1206. June 1, 2007.

Onyebujoh, P. and others. Treatment options for HIV-associated tuberculosis. *The Journal of Infectious Diseases* 196:S35–S45. August 15, 2007.

Rimland, D. and others. Prospective study of etiologic agents of community-acquired pneumonia in patients with HIV infection. *AIDS* 16:85–95. January 4, 2002.

Wells, C. and others. HIV infection and multidrug-resistant tuberculosis—the perfect storm. *The Journal of Infectious Diseases* 196:S86–S107. August 15, 2007.

World Health Organization. *TB/HIV: A Clinical Manual,* 2nd edition. 2004.