Tuberculosis Update

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Cover Illustration by Christine Armstrong
INTRODUCTION

Despite major therapeutic advances in the 20th century, tuberculosis (TB) continues to be the leading infectious cause of adult mortality worldwide, resulting in an estimated 2 to 3 million deaths per year.1 Whereas cases of active TB are quite prevalent, latent infection with Mycobacterium tuberculosis is even more common; it is estimated that as many as a third of the world’s population (or approximately 2 billion people) are currently infected with \textit{M. tuberculosis}.2 Moreover, the advent of the HIV/AIDS epidemic, which has inflicted its heaviest burden in areas where TB is endemic, has altered the dynamics of TB. In certain parts of the world, as much as one third of the increased incidence of TB can be attributed to HIV.3

This manual reviews the epidemiology, diagnosis, and management of latent infection with \textit{M. tuberculosis} and of active TB in an attempt to provide a fuller understanding of this disease. Coinfection with \textit{M. tuberculosis} and HIV is also discussed. A case-based format is used on occasion to illustrate major points.

GENERAL EPIDEMIOLOGY

TB is of enormous global concern, given its significant worldwide morbidity and mortality. Approximately 8.7 million cases of TB occur each year throughout the world (Figure 1), with the number of TB cases increasing almost 2% per year.4 The greatest burden of both \textit{M. tuberculosis} infection and active TB disease is disproportionately borne by the developing world, with 54% of all reported cases occurring in Asia and Africa.1 Approximately 95% of all cases of TB and more than 98.6% of all TB deaths occur in countries in which TB is endemic and medical services are substandard.5

In the United States, it is estimated that 15 million persons are infected with \textit{M. tuberculosis}, comprising a large reservoir from which active TB may develop in ensuing years. A resurgence of TB in the United States occurred between 1985 and 1992, with cases increasing by 20%. This increase has been attributed to several factors, including the HIV/AIDS epidemic, deterioration of the infrastructure for TB services, immigration of persons from countries where TB is endemic, TB transmission in institutional settings, and the appearance of multidrug-resistant TB. Since 1993, however, the number of reported cases of TB in the United States has been declining. In 2001, a total of only 15,991 cases of TB were reported in all 50 states and the District of Columbia; this figure represented a 2% decrease from 2000 and a 40% decrease from 1992.4 The case rate was 5.6 per 100,000 persons, and 50% of cases occurred in foreign-born persons. The proportion of TB cases among foreign-born persons has steadily increased since the mid-1980s. Currently, the TB case rate for foreign-born persons remains at least 4 to 6 times higher than that for persons born in the United States.7

In addition, surveillance data have shown that TB in the United States affects racial and ethnic minorities disproportionately. Compared with non-Hispanic white persons, African Americans are 8 times more likely to have TB.7 Similarly, Hispanic persons, Native Americans, and Alaskan natives are 5 times more likely and Asians are 16 times more likely to have TB than are non-Hispanic white persons.

The threat of growing multidrug resistance is also of great concern. In the year 2000, an estimated 273,000 (3.2%) of the 8.7 million new TB cases were multidrug resistant,8 with higher percentages occurring in areas such as Estonia (14%), Latvia (9%), and the Ivanovo (9%) and Tomsk (7%) provinces in Russia. In 2001 in the United States, the percentage of isoniazid (INH)-resistant strains of TB was 4.5% among those born in the country and 9.6% among those born in foreign countries.8 The percentage of strains resistant to both INH and rifampin was 0.6% among those born in the United States and 1.4% among those born in foreign countries.

DIAGNOSIS AND MANAGEMENT OF LATENT INFECTION

CASE 1 PRESENTATION

A 45-year-old homeless man goes to a local clinic to establish primary care. He has a prior history of alcoholic liver disease, hypertension, and a seizure disorder for
which he takes phenytoin. He has been staying in shelters for the past 5 years but is unaware of any contact with persons who had active TB. He reports no cough, fever, night sweats, or weight loss. His physical examination is unremarkable, except for some mild palmar erythema and telangiectasias on his trunk. There are no additional stigmata of liver disease. Results of a tuberculin skin test show 12 mm of induration at 72 hours.

- What do this patient’s test results suggest?
- What is the most appropriate treatment?

DIAGNOSING CASES OF LATENT INFECTION

The use of targeted tuberculin testing to detect latent infection is a strategic component of TB control that identifies high-risk persons who would benefit from preventive treatment of their latent infection. Based on the sensitivity and specificity of the tuberculin skin test and the prevalence of TB among different groups, 3 cut points have been recommended for defining a positive tuberculin reaction (ie, ≥5 mm, ≥10 mm, ≥15 mm of induration). Table 1 describes in further detail the criteria constituting positive results on a tuberculin skin test.

Persons at higher risk than normal for acquisition of *M. tuberculosis* infection include close contacts of persons with known or suspected TB, persons born in countries where TB is endemic, employees and residents of high-risk congregate settings (eg, correctional institutions, homeless shelters), health care workers serving high-risk patients, injection drug users and other substance abusers (eg, crack cocaine users), and children exposed to adults in high-risk categories. This risk is also typically higher in medically underserved, low-income populations and in high-risk racial or ethnic minorities. Once infected with *M. tuberculosis*, persons are at higher risk for developing TB if their infection is recent (ie, was acquired within the past 2 years), if they have HIV infection or certain other medical conditions (Table 2), if they are injection drug users, or if they previously had TB that was inadequately treated.

TREATMENT

Once patients have been identified as having latent TB infection, an initial clinical evaluation should be performed. Active TB should be excluded if signs, symptoms, or radiographic findings suggest potentially active disease. All patients with positive results on tuberculin skin testing but no evidence of disease who cannot document prior prophylaxis should be offered treatment for latent infection, regardless of age. Table 3 lists recommended regimens for treatment of latent *M. tuberculosis* infection.

A history of bacille Calmette-Guérin vaccination should not influence the decision of whether or not to treat latent TB infection. The criteria provided in Table 1 should still apply without modification.

CLINICAL AND LABORATORY MONITORING DURING TREATMENT

Routine baseline and laboratory monitoring are no longer required for most patients receiving treatment for latent *M. tuberculosis* infection, with the exception of HIV-positive persons, pregnant women, persons with chronic liver disease, or regular alcohol users. If patients develop signs and symptoms of potential adverse drug effects, prompt evaluation is recommended. If patients are receiving a single drug to treat their latent infection (ie, INH or rifampin), they should be followed monthly. If patients are receiving rifampin plus pyrazinamide (not recommended for most patients owing to the risk of severe liver injury and death), they
should be closely monitored at 2, 4, 6, and 8 weeks. Clinical evaluations should include assessment for adverse drug effects and evaluation for signs or symptoms of hepatitis. Baseline laboratory testing is currently indicated only in the following groups: persons whose initial evaluation suggests an underlying liver disorder, pregnant women, women within 3 months of the postpartum period, persons with HIV infection, and persons with chronic liver disease (eg, chronic hepatitis B or C, alcoholic liver disease).

Follow-up liver function tests are indicated in patients with abnormal results on baseline tests, in patients at risk for hepatic disease, or in patients who become symptomatic. Some experts recommend withholding INH if a patient is symptomatic and has transaminase levels that are more than 3 times the upper limit of normal or if the patient is asymptomatic and has transaminase levels that are more than 5 times the upper limit of normal.4

Because of reports of severe hepatotoxicity when the combination of rifampin and pyrazinamide is given, this regimen should be reserved for persons in whom longer courses of therapy with INH (eg, 9 months) or rifampin (eg, 4 months) are not possible. Monitoring for hepatotoxicity should be performed at 2, 4, and 6 weeks of treatment.

**OTHER MANAGEMENT CONSIDERATIONS**

Pregnant women with latent *M. tuberculosis* infection may be treated during pregnancy if they were recently infected or are at high risk for developing active TB. INH and rifampin can be given to pregnant women, but toxicity should be monitored. Pyrazinamide should be avoided during the first trimester. All pregnant women and, subsequently, their infants (if the mother breast feeds) should receive pyridoxine.

**CHANGES FROM PRIOR RECOMMENDATIONS**

Emphasis has shifted to targeted tuberculin testing in persons who are at high risk for latent *M. tuberculosis* infection or have comorbid conditions that increase the risk for TB, regardless of age. The cutoff of 5 mm or more of induration for patients with organ transplants and immunosuppressed patients also represents a change.

**FOLLOW-UP DISCUSSION OF PATIENT 1**

Results of patient 1’s chest radiograph are normal. Lacking any focal symptoms attributable to active TB, the patient begins a daily regimen of INH chemoprophylaxis for 9 months. Because of his history of alcoholic liver disease, he also undergoes periodic liver function testing during this time. Moreover, because INH can result in higher serum levels of phenytoin, his serum level of phenytoin is likewise carefully monitored.

**DIAGNOSIS AND MANAGEMENT OF ACTIVE TUBERCULOSIS**

**CASE 2 PRESENTATION**

A 30-year-old woman who recently immigrated to the United States from Cape Verde comes to a community
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Table 2. Conditions Other Than HIV Infection That Increase Risk for Developing Active TB

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic malabsorption syndromes</td>
</tr>
<tr>
<td>Conditions requiring prolonged use of corticosteroids or other immunosuppressive therapy</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>End-stage renal disease</td>
</tr>
<tr>
<td>Head and neck cancers</td>
</tr>
<tr>
<td>Hematologic and reticuloendothelial diseases</td>
</tr>
<tr>
<td>Low body weight*</td>
</tr>
<tr>
<td>Prior intestinal bypass or gastrectomy</td>
</tr>
<tr>
<td>Silicosis</td>
</tr>
</tbody>
</table>

*More than 10% below ideal body weight.

Table 3. Regimens Recommended for Treatment of Latent Tuberculosis

<table>
<thead>
<tr>
<th>Drug and Dosage</th>
<th>Interval and Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred therapy</td>
<td>INH 300 mg Daily for 9 mo*</td>
</tr>
<tr>
<td>Alternative therapies</td>
<td>INH 900 mg Twice weekly for 9 mo</td>
</tr>
<tr>
<td></td>
<td>INH 300 mg Daily for 6 mo†</td>
</tr>
<tr>
<td></td>
<td>INH 900 mg Twice weekly for 6 mo†</td>
</tr>
<tr>
<td></td>
<td>RIF 600 mg Daily for 4 mo</td>
</tr>
</tbody>
</table>

INH = isoniazid; RIF = rifampin.

*Preferred for both HIV-positive and HIV-negative patients.
†For HIV-positive patients, offer only when other options cannot be given.


Patients may have no further disease or may develop progressive primary infection. Dissemination of the disease may occur, with development of miliary, meningeal, or other extrapulmonary sites. Finally, the disease may enter a dormant phase, with disease reactivation occurring years or decades later.

Pulmonary Tuberculosis

In persons who are HIV-negative, pulmonary TB accounts for approximately 85% of reported cases; extrapulmonary disease accounts for the remaining 15% of cases. The most common presenting symptom of pulmonary TB is cough, which initially may be nonproductive but with ongoing inflammation and tissue necrosis can become productive. Hemoptysis is a rare presenting symptom, and dyspnea is likewise highly unusual unless there is extensive disease. With regard to systemic symptoms, fever occurs in 37% to 80% of patients; loss of appetite, weight loss, and night sweats are also common. Common laboratory abnormalities include anemia (10% of patients), leukocytosis or leukopenia, and (in some cases) monocytosis or eosinophilia. Hyponatremia can occur in 11% of patients and is usually attributed to the syndrome of inappropriate secretion of antidiuretic hormone.

Radiographs in patients with pulmonary TB are nearly always abnormal, with the exception of cases of endobronchial TB, which may not be associated with radiographic abnormalities. In cases of TB reactivation, the most common sites of involvement are the apical and posterior segments of the upper lobes. As TB progresses,
infected material may spread via the airways into other parts of the lungs, leading to a patchy bronchopneumonia. Cavitary disease in the apices or the apex of the lower lobe is common and carries an extremely large bacillary burden, which serves frequently as a nidus for infection of other portions of the lung, because bacilli can be spread via coughing to other areas (ie, bronchogenic spread).

**Extrapulmonary Tuberculosis**

Nonsuppurative sites of TB reactivation are less common, accounting for 15% of cases. These sites include bone (especially the thoracic spine), joints, viscera (pleural or pericardial), and the renal system. Meningitis and miliary disease are also associated with TB reactivation. Involvement by TB of almost every organ has been described.

**DIAGNOSTIC METHODS**

Although tuberculin skin tests are often performed in patients suspected of having pulmonary TB, it is worth noting that positive test results do not confirm that pulmonary infiltrates result from TB. By the same token, negative tuberculin skin test results have been reported in 17.4% to 21% of cases of active pulmonary TB, with even higher proportions of negative results (as many as 50%) noted in cases involving miliary disease. Therefore, the cornerstone of diagnosis in cases of TB is the use of an acid-fast bacillus smear and culture. The sensitivity of acid-fast bacillus smears in the diagnosis of pulmonary TB ranges from 65% to 75% in patients with multiple specimens and 30% to 40% in patients with a single specimen. The best specimen for the diagnosis of pulmonary TB is an early morning sputum sample; if a patient cannot produce sputum, then sputum induction with normal or hypertonic saline should be attempted.

Several studies have shown that there must be 5000 to 10,000 bacilli per milliliter of specimen to allow the detection of bacteria in stained smears, whereas only 10 to 100 organisms are needed for a culture to be considered positive; this fact explains the higher sensitivity of culture (80%–85%); specificity is 98%. Rapid molecular diagnostic tests (ie, nucleic acid probes with amplification) can provide rapid diagnosis of M. tuberculosis infection on smear-positive or smear-negative sputum samples. Specifications for each testing method vary, and caution must be used in interpretation, given possible false-positive and false-negative results. These tests are particularly useful both in determining the mycobacterial species in patients with positive smears and in establishing the diagnosis of TB in the setting of recent antimicrobial therapy.

**TREATMENT OF ACTIVE TUBERCULOSIS**

**General Treatment Considerations**

The goal of therapy in cases of active tuberculosis is to eradicate M. tuberculosis bacilli in the various environments in which they reside and to prevent the emergence of drug resistance. Four basic environments in which organisms thrive are targeted by chemotherapy: (1) Extracellular organisms grow along cavity walls and in liquid necrotic medium; they comprise the largest load of bacilli. (2) Slower growing, semidormant, extracellular organisms are sometimes found in caseous material; they may have only spurs of activity. (3) Slowly growing or semidormant bacilli are found intracellularly in the acidic environment of macrophages. (4) Dormant organisms are found in inactive, fibrotic granulomas; they cannot be killed until they begin to grow. The need to achieve a rapid decrease of the bacillary burden and to prevent emergence of resistant strains form the basis of multidrug chemotherapy.

The introduction of rifampin has enabled the shortening of the course of TB therapy from 18 months (with INH and ethambutol) to 9 months (with INH and rifampin). Currently, with the addition of pyrazinamide, the course has been further shortened to 6 months in cases of TB caused by drug-susceptible strains. The ability to use thrice-weekly or twice-weekly therapy after the induction phase is possible because of the bacilli’s slow replication time; these regimens have had similar efficacy compared with daily administration in susceptible strains.

The slow-growing nature of mycobacteria precludes the use of in vitro susceptibility testing to guide initial treatment. However, all patients should have their sputum or tissue sampled for culture and drug susceptibility testing to guide therapy in the event of drug resistance and to enable epidemiologic surveillance. In addition, strong consideration should be given to treating all TB patients with directly observed therapy to maximize adherence and prevent the development of resistance during therapy. Directly observed therapy is mandatory in patients who are on twice-weekly or thrice-weekly regimens.

**Table 4** lists acceptable regimens for patients with active TB.

**Special Considerations in the Treatment of Extrapulmonary Disease**

The management of extrapulmonary disease, as a rule, should include the same regimens used for treatment of pulmonary TB in adults and children. Extrapulmonary disease usually only requires 6 months of treatment with standard regimens. However, a few exceptions exist, including miliary TB, TB of the bone and joints, and tuberculous meningitis in infants and children.
### Table 4. Regimens Used in the Treatment of Active Tuberculosis

<table>
<thead>
<tr>
<th>Indication</th>
<th>Total Duration (wk)</th>
<th><strong>Induction Phase</strong></th>
<th><strong>Continuation Phase</strong></th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary and extra-pulmonary TB in adults and children*</td>
<td>26</td>
<td>INH, RIF, PZA, and either EMB or SM†</td>
<td>Daily or 5 d/wk for 8 wk</td>
<td>INH, RIF, Daily, twice weekly, or 5 d/wk for 18 wk</td>
</tr>
<tr>
<td>Pulmonary and extra-pulmonary TB in adults and children*</td>
<td>26</td>
<td>INH, RIF, PZA, and either EMB or SM†</td>
<td>Daily for 2 wk, then twice weekly for 6 wk or 5 d/wk for 2 wk, then twice weekly for 6 wk</td>
<td>INH, RIF, Daily for 8 wk</td>
</tr>
<tr>
<td>Pulmonary and extra-pulmonary TB in adults and children, when PZA is contra-indicated*</td>
<td>26</td>
<td>INH, RIF, PZA, and either EMB or SM†</td>
<td>Thrice weekly for 8 wk</td>
<td>INH, RIF, Thrice weekly for 18 wk</td>
</tr>
<tr>
<td>Pulmonary and extra-pulmonary TB in adults and children, when PZA is contra-indicated*</td>
<td>39</td>
<td>INH, RIF, and either EMB or SM†</td>
<td>Daily or 5 d/wk for 8 wk</td>
<td>INH, RIF, Daily, twice weekly, or 5 d/wk for 31 wk</td>
</tr>
<tr>
<td>Smear- and culture-negative pulmonary TB in adults*</td>
<td>16</td>
<td>INH, RIF, PZA, and either EMB or SM†</td>
<td>Daily for 8 wk, or daily for 2 wk then twice weekly for 6 wk or thrice weekly for 8 wk</td>
<td>INH, RIF, Daily, twice weekly, or 5 d/wk for 8 wk</td>
</tr>
</tbody>
</table>

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EMB = ethambutol; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; RPT = rifapentine; SM = streptomycin; TB = tuberculosis.

*In patients with miliary TB and bone/joint TB and in infants and children with TB meningitis, the total duration of therapy should be 12 months.

†Because of increased frequency of resistance, SM is not recommended as being interchangeable with EMB unless the organism is known to be susceptible to the drug or the patient is from a population in which SM resistance is unlikely.
These conditions should be treated with a full 12 months of chemotherapy.

Bacteriologic evaluation of extrapulmonary disease might be difficult, given the site(s) of involvement, and so response to treatment is often assessed by clinical and radiographic findings. In addition, the utility of surgery varies, depending on the clinical setting; surgery may be needed in cases of constrictive pericarditis, spinal cord compression, acute/progressive neurologic deterioration from Pott’s disease, or some instances of tuberculous empyema.

The Role of Corticosteroids

The role of adjuvant corticosteroids in the management of TB is complex. In patients with pulmonary TB, the typical signs and symptoms of tuberculous pneumonia reactivation, tuberculous pleurisy, and probably even primary tuberculous disease with associated lymphadenopathy appear to rapidly decrease with administration of corticosteroids. Yet, no differences in long-term outcomes have been noted. At the same time, most studies have not shown any delay in conversion of sputum smears or cultures or any additional deleterious effects of corticosteroid use, as long as concomitant effective chemotherapy with at least 2 effective anti-TB agents was administered.

In cases of tuberculous meningitis, the use of adjuvant corticosteroids (eg, dexamethasone 8–12 mg per day or a prednisone equivalent) tapered over 6 to 8 weeks appears to reduce sequelae and improve survival in patients with moderate to severe disease.

In cases of tuberculous pericarditis, adjuvant corticosteroids are useful in the management of the acute phase of pericarditis, reducing the size of pericardial effusion, reducing the need for drainage procedures, and decreasing mortality. Use of corticosteroids, however, does not alter the incidence of progression to constrictive disease when used in the acute or intermediate stage.

Finally, in cases of tuberculous pleurisy, dyspnea, fever, and pain appear to resolve faster with the use of adjuvant corticosteroids. However, a reduction in subsequent restrictive pleural disease has not been shown.

FOLLOW-UP DISCUSSION OF PATIENT 2

A stain of patient 2’s morning expectorated sputum reveals rare acid-fast bacilli (Figure 2). The patient is treated empirically with INH, rifampin, pyrazinamide, and ethambutol for 8 weeks, followed by INH and rifampin for another 16 weeks to complete a 24-week (6-month) course. Results of susceptibility testing confirm that the \( M. \text{tuberculosis} \) organism is sensitive to all agents. Results of HIV testing are negative for infection.

COINFECTION WITH MYCOBACTERIUM TUBERCULOSIS AND HIV

EPIDEMIOLOGY

TB accounts for approximately 11% of all AIDS deaths worldwide. An estimated 8% of the world’s population is coinfected with HIV and \( M. \text{tuberculosis} \). In the United States, the Centers for Disease Control and Prevention reports approximately 9000 cases of TB in HIV-infected persons, accounting for 10% of TB cases.

THE LINK BETWEEN MULTIDRUG-RESISTANT TUBERCULOSIS AND HIV/AIDS

HIV infection/AIDS is a well-recognized risk factor for multidrug-resistant TB. Although the link between multidrug resistance and HIV/AIDS is not yet fully understood, there are several considerations that may help explain this important association.

\( M. \text{tuberculosis} \) strains with lower genetic fitness, manifested as a decreased capacity to cause disease after infection, may appear only in immunosuppressed persons. Laboratory experiments have shown that resistant strains are less viable than are sensitive strains in vitro; some studies have shown similar findings in guinea pigs. However, there are no human studies definitively showing that multidrug-resistant strains are less virulent than drug susceptible strains.

TB among patients with HIV infection is likely the result of recent infection, and a higher proportion of recent infections are drug resistant. In addition, there are shared risk factors for infection with either HIV or drug-resistant strains of \( M. \text{tuberculosis} \), including injection drug use and hospitalization. (The latter risk factor

Figure 2. Photomicrograph of sputum from patient 2 showing the acid-fast bacilli (pink) characteristic of \( M. \text{tuberculosis} \) (Kinyoun carbol fuchsin, original magnification × 120).
explains the large numbers of reported nosocomial outbreaks of multidrug resistance among AIDS patients.) Because they are immunosuppressed, HIV patients might have a higher bacillary burden and, therefore, be more apt to fail standard regimens. Moreover, resistance is likely to emerge more readily if the microorganisms are more genetically diverse. Finally, patients with HIV infection may be subject more often to functional monotherapy because of other indications for rifampin and because of drug-drug interactions.25

**ROLE OF HIV IN DETERMINING SUSCEPTIBILITY TO TUBERCULOSIS**

Persons coinfect with HIV and *M. tuberculosis* are estimated to be more than 100 times as likely as HIV-negative persons infected with *M. tuberculosis* to develop TB after a given exposure. The annual risk for developing active TB is 7% to 10% in persons with HIV infection and positive results on tuberculin skin tests.26–28 For HIV-negative persons with positive results on tuberculin skin tests, 7% to 10% comprises the lifetime risk for developing active TB.

Of interest, although HIV-infected persons are at markedly increased risk for both primary and reactivated disease, molecular studies have confirmed that exogenous reinfection plays an equally important role, especially in areas where TB is endemic.29–31

**ROLE OF TUBERCULOSIS IN THE COURSE OF HIV INFECTION**

TB itself has known detrimental effects on the course of HIV infection. In vitro studies have shown that TB increases HIV replication up to 160-fold.32,33 Clinical studies also have noted that the risk for death of patients coinfect with *M. tuberculosis* and HIV is twice that of HIV-positive patients without TB, independent of CD4 + cell count.34 Additional factors associated with increased morality from TB among HIV-infected patients include prior opportunistic infections, low CD4 + cell counts, and negative results on tuberculin skin tests.35

**CLINICAL AND RADIOGRAPHIC FEATURES OF TUBERCULOSIS IN HIV-INFECTED PERSONS**

The clinical presentation of TB in HIV-infected persons is closely related to the degree of immunosuppression. In persons with HIV infection but relatively preserved immune function, TB presents similarly to how it presents in persons without HIV (eg, fevers, night sweats, weight loss, upper lobe cavitary disease on chest radiography).36 As immunosuppression progresses, however, the clinical presentation becomes more protean; middle or lower lobe disease, a miliary pattern, and much higher rates of extrapulmonary disease and mycobacteremia are more common.37 In cases of advanced HIV infection, the diagnosis of TB in an extrapulmonary site (eg, lymph node, bone marrow) is often associated with positive sputum cultures, even in the absence of abnormalities on chest radiographs. The use of antiretroviral therapy may be associated with significant immune-reconstitution syndromes and paradoxical worsening of TB.38,39

**DIAGNOSIS OF TUBERCULOSIS IN HIV-POSITIVE PERSONS**

The diagnosis of TB in HIV-positive persons is also intricately linked to the degree of immunosuppression.40 An important difference is the higher proportion of extrapulmonary disease, which can exist in more than 50% of patients with HIV, especially if CD4+ cell counts are less than 100/mm3.41 The relevance of this finding is that sites outside the lung may yield the diagnosis of TB in this population. In advanced stages of AIDS, as many as 49% of patients are mycobacteremic.41

Regarding the yield and sensitivity of sputum examinations in an HIV-infected population, there is conflicting evidence. Whereas initial studies reported a higher sensitivity of sputum smears in this population, several other studies have shown the contrary to be true, including a large study of 289 patients with culture-proven pulmonary mycobacterial disease.42 This study looked at the positive-predictive accuracy of a positive smear in diagnosing pulmonary TB in HIV-positive versus HIV-negative patients; the respective positive-predictive values were 80% versus 90%. Another study showed that only 29% of AIDS patients versus 61% of controls had an initial positive smear; after 5 smears were obtained, the sensitivity among AIDS patients increased to 40% versus 87.1% in the control group.43 The assumption is that the lower rate of cavitary disease and necrosis in AIDS patients leads to a lower proportion of positive results. The utility of bronchoscopy in the diagnosis of TB in HIV-positive persons varies, with rates of smear positivity ranging from 10% to 47% and culture positivity ranging from 43% to 89%.44–46

**TREATMENT ISSUES**

Treatment recommendations for HIV-infected patients with TB are outlined in Table 5.

In patients with latent *M. tuberculosis* infection, preventive therapy is critical in reducing the risk for active TB and has led to prolonged survival in persons coinfect with HIV and *M. tuberculosis*.57,48 Consequently, all HIV-positive patients (regardless of their CD4+ cell count) who have a tuberculin skin test induration of 5 mm or more, close contact with an active case of TB,
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Table 5. Treatment of Active Tuberculosis in HIV-Positive Persons

For active infection in persons not taking protease inhibitors or NNRTIs
8-week induction period

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>300 mg orally daily</td>
</tr>
<tr>
<td>Rifampin</td>
<td>600 mg orally daily</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>25 mg/kg body weight orally daily</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15 to 20 mg/kg orally daily^a</td>
</tr>
</tbody>
</table>

Subsequent 18-week treatment period

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH and rifampin (at same daily doses as during the 8-week induction period)</td>
<td></td>
</tr>
</tbody>
</table>

For active infection in persons taking either protease inhibitors or NNRTIs†
8-week induction period

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>300 mg orally daily</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>150 mg orally daily‡</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>25 mg/kg orally daily</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15 to 20 mg/kg orally daily</td>
</tr>
</tbody>
</table>

Subsequent 18-week treatment period

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH and rifabutin (at same daily doses as during the 8-week induction period)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Because these recommendations are frequently revised, obtaining the most up-to-date information from the Centers for Disease Control and Prevention Web site (www.cdc.gov/nchstp/tb) is advised.

INH = isoniazid; NNRTI = nonnucleoside reverse transcriptase inhibitor.

^aMay substitute streptomycin 15 mg/kg intramuscularly daily for ethambutol during the 8-week induction period.

†All HIV-positive persons must have susceptibility testing performed and therapy tailored accordingly. Length of therapy should be extended if cultures are persistently positive (verify that acquired resistance has not occurred) or if there is a delayed clinical response.

‡Rifabutin is contraindicated in patients taking delavirdine or hard-gel saquinavir. The dosage of rifabutin should be decreased to 150 mg orally daily from the standard dose of 300 mg orally daily if used concurrently with nelfinavir, indinavir, or amprenavir or to 150 mg orally every 48 h (or thrice weekly) if used with ritonavir; increase the rifabutin dosage to 450 to 600 mg orally daily if used concurrently with efavirenz. The dosage of efavirenz or protease inhibitors may also have to be increased by 20% to 25%. Monitor rifabutin toxicity (eg, arthralgia, uveitis, leukopenia) closely.


or known prior positive results on tuberculin skin testing without treatment must receive chemoprophylaxis for latent infection. Because of the poor predictive value of using skin test controls with HIV patients, this step is no longer recommended for tuberculin testing.49

Tuberculosis and Combination Antiretroviral Therapy

Whereas the advent of antiretroviral therapy has improved the prognosis of HIV-infected patients, it also has added significant complexity to the treatment of patients coinfected with HIV and M. tuberculosis. Some of the factors contributing to this complexity include the significant drug-drug interactions between rifampicin drugs and the protease inhibitors and nonnucleoside reverse transcriptase inhibitors (NNRTIs) used against HIV infection, the higher rates of adverse drug reactions to TB medications among patients with HIV infection, and the higher rates of drug resistance (in particular, to rifampin) in HIV-infected patients.50

All HIV-positive patients with confirmed TB should have susceptibility testing performed to ensure appropriate tailoring of therapy, especially because HIV-infected patients are at increased risk for rifampin monoresistance. Moreover, HIV-infected patients with drug-susceptible TB whose current drug regimens include neither protease inhibitors nor NNRTIs should receive standard 4-drug therapy for 2 months followed by INH/rifampin for a minimum of 4 months. Although some studies have shown higher relapse rates in HIV-infected persons with TB who were treated for 6 months as opposed to 12 months, there was no significant survival difference.51 HIV-infected patients who are on a protease inhibitor–containing regimen or NNRTI-containing regimen generally should receive rifabutin rather than rifampin, because rifampin can lead to subtherapeutic levels of both protease inhibitors and NNRTIs. However, rifampin can be used with certain combinations of antiretroviral agents.52,53 Treatment guidelines are frequently revised; up-to-date information on treatment recommendations can be obtained at the website of the CDC Division of Tuberculosis Elimination (www.cdc.gov/nchstp/tb). Close monitoring for synergistic drug toxicity and drug interactions is essential throughout the course of therapy.

The timing of antiretroviral therapy in persons coinfected with HIV and M. tuberculosis is the subject of much debate; the best timing remains largely unknown. In a recent study of 188 patients with HIV infection and tuberculosis, 45% of patients initiated combination antiretroviral therapy during TB treatment.54 An AIDS-defining illness developed in 10% of patients with CD4+ cell counts of more than 100/mm³, compared with 20%
of patients with CD4+ cell counts of less than 100/mm³. Given the high proportion (54%) of adverse drug effects in this cohort—a finding that correlated with concomitant antiretroviral and antitubercular treatment—the authors recommended starting antiretroviral therapy early in persons with advanced HIV disease (ie, CD4+ cell counts ≤ 100/mm³) and deferring antiviral therapy for at least 2 months in persons with CD4+ cell counts of more than 100/mm³. Further studies are needed to better establish the proper timing of initiation of antiretroviral therapy in patients with both tuberculosis and HIV infection.

SUMMARY

Despite advances in public health measures and the availability of more sophisticated diagnostic and therapeutic technologies, TB remains among the most morbid diseases worldwide. A critical trend arises from the synergy between TB and HIV/AIDS, which is reflected in recent changes in chemoprophylactic and treatment guidelines. Directly observed therapy is recommended for all affected patients and is required for those on twice- or thrice-weekly regimens.

REFERENCES


