Update on the Treatment of Tuberculosis

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Approximately one third of the world's population, including more than 11 million persons in the United States, is latently infected with *Mycobacterium tuberculosis*. Although most cases of tuberculosis in the United States occur in foreign-born persons from endemic countries, the prevalence is generally greater in economically disadvantaged populations and in persons with immunosuppressive conditions. Delays in detection and treatment allow for greater transmission of the infection. Compared with the traditional tuberculin skin test and acid-fast bacilli smear, newer interferon-gamma release assays and nucleic acid amplification assays lead to more rapid and specific detection of *M. tuberculosis* infection and active disease, respectively. Nine months of isoniazid therapy is the treatment of choice for most patients with latent tuberculosis infection. When active tuberculosis is identified, combination therapy with isoniazid, rifampin, pyrazinamide, and ethambutol should be promptly initiated for a two-month "intensive phase," and in most cases, followed by isoniazid and a rifamycin product for a four- to seven-month "continuation phase." Directly observed therapy should be used. Although currently limited in the United States, multidrug-resistant and extensively drug-resistant strains of tuberculosis are increasingly recognized in many countries, reaffirming the need for prompt diagnosis and adequate treatment strategies. Similarly, care of persons coinfected with human immunodeficiency virus and tuberculosis poses additional challenges, including drug interactions and immune reconstitution inflammatory syndrome. (*Am Fam Physician*. 2008;78(4):457-465, 469-470. Copyright © 2008 American Academy of Family Physicians.)

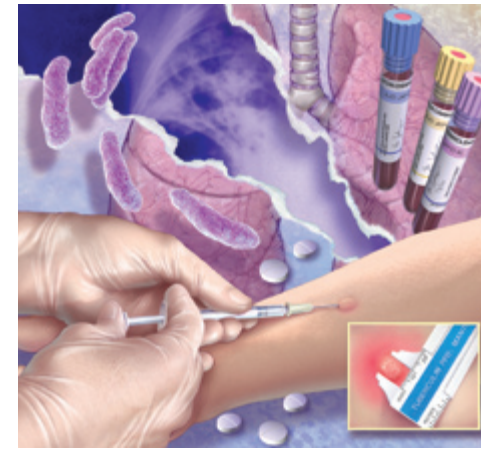

ILLUSTRATION BY STEVE OH

▶ **Patient information:** A handout on tuberculosis, written by the authors of this article, is provided on page 469.

AFP This article exemplifies the AAFP 2008 Annual Clinical Focus on infectious disease: prevention, diagnosis, and management.

There were 13,293 cases of active tuberculosis identified in the United States in 2007.[1] Although this number continues to decrease, the rate of decline has slowed. In the United States, foreign-born persons from endemic countries are at the greatest risk of *Mycobacterium tuberculosis* infection, with a rate almost 10 times higher than that of persons born in the United States.[1] Most of the ethnic and racial disparities in identified tuberculosis cases may also be attributed to the differences in prevalence in persons who are foreign-born[1] or who have risk factors associated with lower socioeconomic status. In 2007, 11.3 percent of persons in the United States with tuberculosis were coinfected with human immunodeficiency virus (HIV). However, this estimate is not comprehensive because coinfection data from California was not reported and HIV status may have been absent in some identified tuberculosis cases.[1] Delays in detection and treatment of patients with active pulmonary tuberculosis or those at high risk of reactivation of latent tuberculosis infection allow for greater transmission of the infection. Appropriate treatment of all persons with latent tuberculosis infection and active tuberculosis is essential for tuberculosis control.[2]

New Diagnostic Tests

Random screening for *M. tuberculosis* infection is not advised; a more targeted approach of screening persons at high risk of latent tuberculosis infection or progression to active disease is recommended.[3] Treatment is recommended in persons with latent infection who are at risk of progression to active disease *(Table 1*[3]*)*.[2] The tuberculin skin test (TST), also referred to as the Mantoux test or purified protein derivative test, has longevity in clinical practice and a low cost. The TST is the standard test for diagnosis of *M. tuberculosis*

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
A targeted approach to screening for *Mycobacterium tuberculosis* infection is recommended. Screening should only be conducted in persons at high risk of infection or progression to active disease.	C	3
Antigen-specific interferon-gamma release assays are useful for screening for *M. tuberculosis* infection, especially in persons with previous bacille Calmette-Guérin vaccination or possible nontuberculosis mycobacteria.	C	5-9
Isoniazid monotherapy is the treatment of choice for most patients with latent tuberculosis infection, except those suspected to have primary drug-resistant tuberculosis.	C	3
Although uncommon in the United States, extensively drug-resistant tuberculosis and multidrug-resistant tuberculosis underscore the need for combination drug therapy and directly observed therapy in patients with tuberculosis.	C	3, 36, 37

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see http://www.aafp.org/afpsort.xml.

infection despite its poor sensitivity, low specificity, variability in test placement, and often inadequate patient follow-up for test reading.[4] Nontuberculosis mycobacteria infection, bacille Calmette-Guérin (BCG) vaccination (especially if recent), and subjective interpretation of test results (skin induration) may cause false-positive TST findings.[4] Although U.S. guidelines do not include BCG vaccination history in TST interpretation, newer diagnostic assays may distinguish recent BCG vaccination from *M. tuberculosis* infection.[3]

M. tuberculosis antigen-specific interferon-gamma release assays detect interferon-gamma release from previously sensitized memory T cells via in vitro simulation by *M. tuberculosis*–specific proteins. Interferon-gamma release assays do not produce false-positive results in patients with previous BCG vaccination or most types of nontuberculosis mycobacteria infection,[5] allowing for greater specificity in the identification of *M. tuberculosis*.[6,7] Like the TST, interferon-gamma release assays are only designed to identify *M. tuberculosis* and, when used alone, cannot distinguish latent infection from active disease. Additionally, HIV infection and immunosuppressive conditions, which impair T-cell function, could potentially cause false-negative or indeterminate results with the TST and interferon-gamma release assays.[8-10] Therefore, a negative interferon-gamma release assay or TST result alone should never exclude a diagnosis of tuberculosis.

Active tuberculosis is diagnosed with a combination of a thorough history and physical examination, chest radiography, sputum or other tissue cultures, and occasionally, tissue biopsy. If active tuberculosis is suspected, additional diagnostic evaluation should be performed before the interferon-gamma release assay or TST results are available. Several nucleic acid amplification assays offer a more rapid and sensitive diagnosis of active tuberculosis and complement the acid-fast bacillus smear and mycobacteria culture.

Table 1. High-Risk Populations Needing Targeted Tuberculin Testing and Treatment of Latent Infection

Persons at high risk of exposure to and infection with *Mycobacterium tuberculosis*
Persons in close contact with someone who has confirmed active tuberculosis
Foreign-born persons from endemic countries who have been living in the United States for five years or less (especially children younger than four years)
Residents and employees of congregate settings (e.g., correctional facilities, long-term care facilities, homeless shelters)
Health care workers with high-risk patients
Medically underserved, low-income populations
Infants, children, and adolescents exposed to adults in high-risk categories
Persons at high risk of progression from latent tuberculosis infection to active disease
Persons with human immunodeficiency virus infection
Persons recently (within the past two years) infected with *M. tuberculosis*
Children younger than four years
Patients who are immunosuppressed (e.g., those with diabetes, chronic or end-stage renal disease, silicosis, cancer, malnutrition, prolonged steroid use, or organ transplants; those taking tumor necrosis factor-alpha inhibitors)

Information from reference 3.

Latent Tuberculosis Infection

Approximately one third of the world's population, including more than 11 million persons in the United States, is latently infected with *M. tuberculosis*.[11] The predicted lifetime risk of reactivation in most immunocompetent patients is 5 to 10 percent.[12] However, variations in immunologic fitness (e.g., HIV infection, diabetes, immunosuppressive conditions) increase this risk. Patients with HIV infection have a substantially greater reactivation risk of

Table 2. Treatment Options for Latent Tuberculosis Infection

Drug	*Daily dosage (maximum)*	*Adult intermittent dosage (maximum)*	*Duration*
Isoniazid*†[3]	5 mg per kg (300 mg)	15 mg per kg (900 mg per dose) twice per week	Nine months in adults and children (six months may be an alternative treatment duration in adults)
Rifampin (Rifadin)*‡[3]	10 mg per kg (600 mg)	10 mg per kg (600 mg per dose); daily dosing required when used alone	Four months in adults; six months in children

NOTE: *Rifampin plus pyrazinamide is no longer recommended for the treatment of latent tuberculosis infection.[13]*

HIV = human immunodeficiency virus.

**—Rifampin plus isoniazid (same dosing) for three months may be an alternative treatment option in select patients, but risk of hepatotoxicity may increase.[14,15]*

†—*To reduce neuropathy risk, isoniazid should be supplemented with 25 to 50 mg daily of pyridoxine (vitamin B_6) in high-risk patients (e.g., pregnant women; patients with diabetes, alcoholism, preexisting neuropathy, uremia, malnutrition, HIV infection, or seizure disorders).[3]*

‡—*Not recommended as monotherapy in patients with HIV infection because of increased rates of resistance and drug interactions with many antiretrovirals.[3]*

Information from references 3 and 13 through 15.

10 percent per year compared with patients who do not have HIV infection.[12] The greatest risk of active tuberculosis occurs during the first two years after infection.[3,4] Persons at high risk of reactivation should receive additional education regarding the risks of developing active tuberculosis and a strong recommendation to begin treatment for latent tuberculosis infection.

Isoniazid monotherapy is the treatment of choice for most patients with latent tuberculosis infection, except those with suspected isoniazid resistance.[3] Treatment options for latent tuberculosis infection are listed in *Table 2*.[3,13-15] Treatment with isoniazid for nine months diminishes the rate of reactivation during granuloma dissolution, providing an effectiveness rate of approximately 90 percent in compliant patients.[12,16,17] Nine months of treatment with isoniazid is also recommended in patients with HIV infection and in children younger than four years to reduce the risk of treatment failure or drug resistance.[12] Older age alone is no longer an indication for baseline laboratory testing or treatment exclusion.

Although not preferred and less effective, six months of treatment with isoniazid can be considered in patients unable or unwilling to complete nine months of treatment. The shortened isoniazid treatment period may reduce the discontinuation rate in nonadherent patients unable to take rifampin (Rifadin), potentially increasing effectiveness.[18] Treatment compliance remains a challenge, especially for patients who do not understand the benefits of treatment.[19,20] Methods for increasing treatment adherence are presented in *Table 3*.[21]

Four months of rifampin is an alternative treatment for patients who are unable to tolerate isoniazid or in patients who have known or suspected isoniazid-resistant latent tuberculosis infection.[22] Rifampin may offer less hepatotoxicity and a greater treatment completion rate compared with nine months of isoniazid.[23,24] However, the potential for extensive drug interactions and the risk of noncompliant patients developing resistance to rifampin is a significant concern. Rifampin monotherapy in patients with HIV infection is not recommended because of the higher rate of rifampin-resistant tuberculosis in these patients and because of the consequence of drug interactions with many combinations of antiretroviral therapy.[22]

Although it is not a first-line treatment, combination therapy with isoniazid and rifampin for three months is another alternative treatment option in select circumstances. A meta-analysis of five trials comparing this regimen with six to 12 months of isoniazid monotherapy suggested no difference in safety or effectiveness (failure rates of 4.2 and 4.1 percent, respectively).[14] Treatment with rifampin and pyrazinamide for two months has been eliminated as a treatment option because of cases of significant hepatotoxicity in the setting of preventive therapy.[13,15]

Proper application, education, and clinical monitoring of these antituberculosis therapies minimize the risk of toxicity. The risk of isoniazid-associated hepatotoxicity is 0.1 to 1.0 percent; this risk increases with chronic liver disease (e.g., alcoholism, viral hepatitis) and older age.[25] Baseline liver function test monitoring is only recommended in patients with chronic liver diseases, alcoholism, or HIV infection—and during pregnancy and three months after delivery. Longitudinal monitoring is only recommended for patients with abnormal liver function test results at baseline and for those with chronic liver disease. Age alone does not mandate liver function test monitoring; monitoring can be considered on a case-by-case basis. Pregnant women, patients at a higher risk of isoniazid-associated peripheral neuropathy (e.g., those with diabetes,

Table 3. Challenges of Treatment Adherence and Possible Solutions in Patients with Latent Tuberculosis Infection

Challenges	*Examples*	*Solutions*
Access to care	Inconvenient office hours, long waits, lack of privacy, poor physician-patient communication, patient concerns about being scolded for nonadherence	Offer extended hours and reduced waits (e.g., at the end of the day, first thing in the morning) Make sure the physician-patient relationship is supportive by establishing a rapport
Interpretation of wellness	Lack of understanding about why they are taking medication, the proper treatment duration, or adverse effects Concerns over symptoms	Educate patients on the risks of the disease and benefits of therapy Be sure to mention potential adverse effects of medication; offer solutions or guidance about when to contact the physician's office
Financial burden	Loss of time from work Medical expenses associated with treatment visits (e.g., laboratory tests, monitoring)	Work with state and local health departments to determine methods for avoiding additional costs outside of providing free medications
Attitude, knowledge, and beliefs about treatment	Lack of knowledge about the purpose and effectiveness of therapy Mistrust of traditional medicine, potentially related to cultural beliefs	Discussions should occur in the patient's primary language (this could involve an interpreter), which would help to avoid misunderstandings and assist in identifying potential cultural and religious barriers
Laws and immigration status	Concerns that the diagnosis may affect immigration status	Make sure the patient is aware that the diagnosis will not alter the patient's immigration status
Patient characteristics	Mental health problems, high-risk behaviors, religious beliefs, concern about being labeled as "difficult"	Take into account underlying psychiatric or medical conditions (e.g., depression), religious beliefs, or patient concerns that may hinder medication adherence
Family, community, and household influences	Stigma of disease within the family Community and households limit disclosure and reduce social and economic support	Provide educational materials to the patient, family, and employer to reduce unnecessary stigma or concerns

Information from reference 21.

alcoholism, preexisting neuropathy, uremia, malnutrition, HIV infection), and patients with an underlying seizure disorder should receive pyridoxine (vitamin B_6) supplementation with isoniazid. *Table 4* summarizes key points of antituberculosis therapy monitoring.[25,26]

If latent tuberculosis infection is not treated, immunologic impairment increases the risk of reactivation and progression to active disease. Populations at greatest risk of reactivation or progression to active disease include young children; patients with untreated or suboptimally treated previous tuberculosis; patients who are immunosuppressed (e.g., those with HIV infection, diabetes, chronic or end-stage renal disease, silicosis, cancer, malnutrition); and patients taking immunosuppressive agents, such as tumor necrosis factor (TNF)-alpha inhibitors (e.g., infliximab [Remicade], etanercept [Enbrel], adalimumab [Humira]).[27,28] All patients prescribed TNF-alpha inhibitors should be screened for latent tuberculosis infection before initiating therapy.[29]

Active Tuberculosis

Treatment of active tuberculosis with combination drug therapy remains the cornerstone of mycobacterial killing and tissue sterilization, thus aiding in the prevention of drug resistance, which is of increasing concern. The development of drug resistance is twofold. Extensive replication of up to 10^8 tubercles in some cavitary lesions can produce primary drug resistance. Secondary drug resistance may be a product of inappropriate drug therapy (e.g., too few drugs, inactive drugs, subtherapeutic drug concentrations) that likely results from poor patient adherence or inadequate prescribing.

Two stages of treatment are recommended for active tuberculosis. First is an initial or "intensive phase" using a four-drug regimen of isoniazid, rifampin, pyrazinamide, and ethambutol (Myambutol) for two months. Multiple drugs are used to support the elimination of actively replicating and semidormant tubercle bacilli. Most medication regimens are administered five to seven times per week via directly observed therapy *(Table 5)*.[26] A "continuation phase" follows in most patients with pulmonary or extrapulmonary drug-susceptible tuberculosis; this consists of isoniazid and a rifamycin (rifampin, rifabutin [Mycobutin], or rifapentine [Priftin]) administered daily or intermittently for four to seven months.[26] The continuation phase of treatment

Table 4. Main Adverse Effects of Antituberculosis Drugs

Drug	*Main adverse effects*	*Monitoring parameters*
Isoniazid	Hepatotoxicity	Monitor LFTs and for flushing and decreased sensation in extremities
	Lupus-like syndrome Peripheral neuropathy	LFTs should be monitored monthly in patients who are at a higher risk of hepatotoxicity,* have preexisting liver disease, or develop abnormal LFT results
		LFTs should also be checked in patients who develop clinical symptoms of hepatitis; isoniazid should be discontinued if findings on LFTs increase by more than five times the upper limits of normal in patients without symptoms of hepatotoxicity and by more than three times the upper limits of normal in patients with symptoms†
	Monoamine toxicity	If flushing occurs, patients should be counseled to avoid foods with high concentrations of monoamines (e.g., aged cheeses, wine)
Rifampin (Rifadin)‡	Drug Interactions Hepatotoxicity Immunologic reactions Acute renal failure Influenza-like symptoms Hemolytic anemia, thrombocytopenia (with potential for acute renal failure) Pruritus (with or without rash)	Baseline laboratory tests (including complete blood count and serum creatinine measurements) and monthly; every-other-month; or one-, three-, or six-month monitoring of LFTs and clinical symptoms are acceptable for most patients, but not required LFTs should be monitored monthly or twice monthly in patients who are at a higher risk of hepatotoxicity,* have preexisting liver disease, or develop abnormal LFT results
	Orange discoloration of body fluids	Patients should be counseled about the risk of contact lens discoloration
Pyrazinamide	Arthralgias Gastrointestinal upset Hepatotoxicity Rash	Baseline LFTs; serum creatinine may be assessed at baseline for dosing adjustments LFTs should be monitored monthly or twice monthly in patients who are at a higher risk of hepatotoxicity* or who have underlying hepatic dysfunction
	Hyperuricemia	Check uric acid levels if patient is symptomatic
Ethambutol (Myambutol)	Optic neuritis	Baseline and monthly testing of visual acuity and color discrimination; serum creatinine may be assessed at baseline for dosing adjustments

LFT = liver function test.

**—Risk factors include genetic alteration (slow acetylators); hepatitis B or C; concomitant hepatotoxic medication use (acetaminophen, anticonvulsants, methotrexate); alcohol consumption; age older than 50 years; pregnancy (up to three months postpartum); and malnourishment.*

†*—Symptoms of hepatotoxicity include nausea, vomiting, abdominal pain (50 to 75 percent), fever (10 percent), and rash (5 percent). Jaundice, dark-colored urine, abnormal stools, coagulopathy, hyperalbuminemia, and hypoglycemia indicate worsening of hepatotoxic effects and are not common.*

‡*—Rifampin, a potent hepatic enzyme inducer, has several clinically significant drug interactions; a medication may require dosage adjustment or may be contraindicated with concomitant use of rifampin.*

Information from references 25 and 26.

typically lasts four months in most patients. An extended seven-month continuation phase of treatment should be used for patients whose initial intensive phase of treatment did not contain pyrazinamide; patients with cavitary pulmonary disease caused by drug-susceptible tuberculosis, whose sputum culture collected at the end of the intensive phase remains positive for *M. tuberculosis*; and patients receiving once-weekly isoniazid plus rifapentine, whose sputum culture collected at the end of the intensive phase remains positive for *M. tuberculosis*. Once-weekly rifapentine may be used in the continuation phase of treatment in patients who are HIV-negative with noncavitary pulmonary disease and negative sputum acid-fast bacilli smear at the completion of the initial phase of treatment.[26]

HIV-negative patients with culture-negative tuberculosis who are clinically and radiographically improving with treatment can receive a shortened two-month continuation phase, for a total treatment duration of four months.[26] However, many physicians still prescribe a total combination drug treatment duration of six months in these patients.

Recent trials of 400 mg of moxifloxacin (Avelox) support its use as a potential alternative to ethambutol in patients with visual toxicities or drug-resistant tuberculosis.[30] Moxifloxacin and ethambutol appear to be

Table 5. Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

Initial phase			*Continuation phase*	
Regimen	*Drugs*	*Interval and doses* (minimal duration)*	*Regimen*	*Drugs*
1	Isoniazid Rifampin Pyrazinamide Ethambutol	Seven days per week for 56 doses (eight weeks) *or* five days per week for 40 doses (eight weeks)‡	1a 1b 1c‖	Isoniazid/rifampin Isoniazid/rifampin Isoniazid/rifapentine
2	Isoniazid Rifampin Pyrazinamide Ethambutol	Seven days per week for 14 doses (two weeks), *then* twice weekly for 12 doses (six weeks) *or* five days per week for 10 doses (two weeks),‡ *then* twice weekly for 12 doses (six weeks)	2a 2b‖	Isoniazid/rifampin Isoniazid/rifapentine
3	Isoniazid Rifampin Pyrazinamide Ethambutol	Three times weekly for 24 doses (eight weeks)	3a	Isoniazid/rifampin
4	Isoniazid Rifampin Ethambutol	Seven days per week for 56 doses (eight weeks) *or* five days per week for 40 doses (eight weeks)‡	4a 4b	Isoniazid/rifampin Isoniazid/rifampin

HIV= human immunodeficiency virus.

Definitions of evidence ratings: A = preferred; B = acceptable alternative; C = offer when A and B cannot be given; E = should never be given; I = randomized clinical trial; II = data from clinical trials that were not randomized or were conducted in other populations; III = expert opinion.

**—When directly observed therapy is used, drugs may be given five days per week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.*

†—Patients with cavitation on the initial chest radiograph and positive culture results at completion of two months of therapy should receive a seven-month (31-week; either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.

‡—Five-day-a-week administration is always given by directly observed therapy. Rating for five-day-a-week regimens is AIII.

equivalent in smear conversion from positive to negative after two months of treatment. Thus, moxifloxacin may provide additional sterilizing capacity, which could potentially shorten treatment duration.[30] In the meantime, ethambutol may be discontinued in patients in whom full susceptibility has been determined. *Table 5* summarizes active tuberculosis treatment recommendations and dosing schedule.[26] Additionally, recommendations for preventing *M. tuberculosis* transmission in the health care setting is presented in *Table 6*.[31] Patients with smear-negative tuberculosis who are not suspected to have drug-resistant tuberculosis may be considered noninfectious after two to three weeks of drug therapy.[26]

DRUG RESISTANCE

Testing to determine the drug susceptibility of *M. tuberculosis* isolates should be performed in all patients. Approximately 1.1 percent of all *M. tuberculosis* cases in the United States are multidrug-resistant strains (tuberculosis characterized by resistance to isoniazid and rifampin).[1] Treatment with four to six therapeutic agents to which the infection is susceptible is recommended. The estimated average cost of treatment is $250,000 per patient, which is more than 10 times the cost of treatment of nonresistant strains.[32-34] In 2006, the definition of extensively drug-resistant tuberculosis was revised to include strains resistant to isoniazid and rifampin, with additional resistance to fluoroquinolones and at least one injectable agent (amikacin [Amikin], capreomycin [Capastat], or kanamycin [Kantrex; brand not available in the United States]).[35] Multidrug-resistant and extensively drug-resistant tuberculosis require at least 18 to 24 months of therapy, depending on the patient's response to treatment. Thoracic surgery for resection of the lung lesion is often considered as adjunctive therapy.

Extensively drug-resistant tuberculosis outbreaks have been limited, but have poor survival rates. Air travel is common around the world, which enables infectious pathogens to spread to new locations. Primary factors contributing to the development of multidrug-resistant or extensively drug-resistant tuberculosis include poor patient compliance with current or previous tuberculosis treatment regimens, inappropriate drug selection or modification by the health care professional, and virulent strain adaptation.[36,37] To optimize patient drug

Interval and doses*† (minimal duration)	Range of total doses (minimal duration)	Rating (evidence)	
		HIV–	HIV+
Seven days per week for 126 doses (18 weeks) *or* five days per week for 90 doses (18 weeks)‡	182 to 130 (26 weeks)	A (I)	A (II)
Twice weekly for 36 doses (18 weeks)	92 to 76 (26 weeks)	A (I)	A(II)§
Once weekly for 18 doses (18 weeks)	74 to 58 (26 weeks)	B (I)	E (I)
Twice weekly for 36 doses (18 weeks)	62 to 58 (26 weeks)	A (II)	B (II)§
Once weekly for 18 doses (18 weeks)	44 to 40 (26 weeks)	B (I)	E (I)
Three times weekly for 54 doses (18 weeks)	78 (26 weeks)	B (I)	B (II)
Seven days per week for 217 doses (31 weeks) *or* five days per week for 155 doses (31 weeks)‡	273 to 195 (39 weeks)	C (I)	C (II)
Twice weekly for 62 doses (31 weeks)	118 to 102 (39 weeks)	C (I)	C (II)

§—Not recommended for patients with HIV infection and CD4 cell counts of less than 100 cells per mm³.

||—Options 1c and 2b should be used only in patients without HIV who have negative sputum smears at the time of completion of two months of therapy and who do not have cavitation on the initial chest radiograph. For patients started on this regimen and found to have a positive culture from the two-month specimen, treatment should be extended an extra three months.

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compliance and tolerability, directly observed therapy through the county or state health department is strongly recommended so that an expert in tuberculosis management may assist with the incorporation of multiple second-line agents.[36]

HIV AND TUBERCULOSIS COINFECTION

Every patient diagnosed with tuberculosis should be tested for HIV.[38] In patients coinfected with HIV and tuberculosis, treatment for tuberculosis infection or active disease should be promptly initiated. HIV infection significantly increases the risk of developing active tuberculosis, irrespective of CD4 cell counts. HIV-mediated immunosuppression leads to an increased risk of extrapulmonary and miliary tuberculosis, as well as more variable clinical and radiologic pulmonary presentations. Tuberculosis is an acquired immunodeficiency syndrome (AIDS)–defining illness in patients with HIV, and the diagnosis of one necessitates screening for the other.[38,39]

Treatment with once- or twice-weekly isoniazid plus rifapentine should not be used in patients with HIV infection because of a higher rate of treatment failure and relapse (often with rifamycin-resistant *M. tuberculosis)*. For a similar reason, twice-weekly treatment with isoniazid and rifampin during the continuation phase is not recommended in patients wth HIV infection who have CD4 counts below 100 cells per mm³.[26]

Although immediate antiretroviral therapy may be considered in patients with life-threatening AIDS-associated conditions, patient tolerance and compliance may be optimized if therapy is delayed until two weeks to two months after starting antituberculosis therapy. Highly active antiretroviral therapy reduces the risk of progression to active tuberculosis[39,40] and reduces tuberculosis mortality in patients with a CD4 cell count of less than 200 cells per mm³, but complications may include immune reconstitution inflammatory syndrome or drug toxicity.[41] Rifampin induces hepatic drug metabolism, potentially decreasing the effectiveness of concomitant antiretroviral drug therapy (specifically, the protease inhibitors and non-nucleoside reverse transcriptase inhibitors).[39] Rifabutin may be substituted to decrease some potential antiretroviral drug interactions. A team approach to treating HIV and tuberculosis is recommended.

Table 6. Recommendations for Prevention of *Mycobacterium tuberculosis* Transmission in the Health Care Setting

Each physician's office should develop a protocol for suspected tuberculosis.
All patients should be asked about history of tuberculosis exposure, infection, and active disease.
Patient screening forms should include symptoms and signs of active tuberculosis, and conditions that would categorize patients as high risk.
Interviews should be in the patient's primary language when possible (translator resources are available at http://www.atanet.org).
Patients suspected of having active tuberculosis should be transferred from waiting areas to separate rooms (if possible, to rooms that meet isolation requirements for airborne infection); the door should be closed as soon as possible to reduce the risk of exposure to other persons.
Patients with symptoms of active tuberculosis should be given a surgical or procedure mask and instructed on respiratory hygiene and cough etiquette.
Patients with suspected or confirmed tuberculosis should be immediately reported to the local health department so that tracking, contact investigations, and case management may be arranged.
All family members (especially children) and persons exposed to active tuberculosis (including health care workers) should immediately receive screening for symptoms and a TST, followed by another screen and TST eight to 10 weeks after exposure; treatment may be considered for high-risk patients and children in the testing interim.
A TST should be considered positive if there is any induration of 5 mm or greater in patients without prior induration, or an increase in induration of 10 mm in those with prior induration.
Patients with positive TST results should receive chest radiography (and potentially other diagnostic evaluation).
All test conversions and cases of tuberculosis among health care workers should be recorded and reported according to the Occupational Safety and Health Administration standard 29 Code of Federal Regulations.

TST = tuberculin skin test.

Information from reference 31.

PREGNANCY

Pregnancy alone is not a significant risk factor for progression from latent tuberculosis infection to active disease. Pregnant women with positive TST or interferon-gamma release assay results should receive prompt clinical evaluation and chest radiography (with abdominal shielding) to exclude active disease. For most immunocompetent pregnant women without HIV, treatment for latent tuberculosis infection may be delayed during pregnancy and for the first three months postpartum to decrease the risk of isoniazid toxicities.[3] Women at increased risk of progression to active tuberculosis (e.g., those recently infected, those with HIV infection or other immunosuppressive conditions) should receive treatment during pregnancy. Isoniazid (with pyridoxine) and rifampin are safe to use during pregnancy with liver function test monitoring.[25] Breastfeeding is not contraindicated with isoniazid or rifampin. However, because small amounts of isoniazid have been detected in breast milk, the breastfeeding infant, as well as the mother, should receive supplemental pyridoxine.[3]

EXTRAPULMONARY TUBERCULOSIS

Treatment of extrapulmonary tuberculosis incorporates the same principles as treatment of pulmonary tuberculosis. However, treatment durations are extended up to nine months for bone and joint tuberculosis and nine to 12 months for central nervous system tuberculosis, including meningitis. Additionally, adjunctive steroid therapy is recommended in patients with meningitis or pericarditis to decrease morbidity and improve survival rates.[26]

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