Clinical Infectious Diseases

IDSA GUIDELINE

Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

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The American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of America jointly sponsored the development of this guideline for the treatment of drug-susceptible tuberculosis, which is also endorsed by the European Respiratory Society and the US National Tuberculosis Controllers Association. Representatives from the American Academy of Pediatrics, the Canadian Thoracic Society, the International Union Against Tuberculosis and Lung Disease, and the World Health Organization also participated in the development of the guideline. This guideline provides recommendations on the clinical and public health management of tuberculosis in children and adults in settings in which mycobacterial cultures, molecular and phenotypic drug susceptibility tests, and radiographic studies, among other diagnostic tools, are available on a routine basis. For all recommendations, literature reviews were performed, followed by discussion by an expert committee according to the Grading of Recommendations, Assessment, Development and Evaluation methodology. Given the public health implications of prompt diagnosis and effective management of tuberculosis, empiric multidrug treatment is initiated in almost all situations in which active tuberculosis is suspected. Additional characteristics such as presence of comorbidities, severity of disease, and response to treatment influence management decisions. Specific recommendations on the use of case management strategies (including directly observed therapy), regimen and dosing selection in adults and children (daily vs intermittent), treatment of tuberculosis in the presence of HIV infection (duration of tuberculosis treatment and timing of initiation of antiretroviral therapy), as well as treatment of extrapulmonary disease (central nervous system, pericardial among other sites) are provided. The development of more potent and better-tolerated drug regimens, optimization of drug exposure for the component drugs, optimal management of tuberculosis in special populations, identification of accurate biomarkers of treatment effect, and the assessment of new strategies for implementing regimens in the field remain key priority areas for research. See the full-text online version of the document for detailed discussion of the management of tuberculosis and recommendations for practice.

Keywords. *Mycobacterium tuberculosis*; HIV infections; antitubercular agents; case management; public health.

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These guidelines were endorsed by the European Respiratory Society (ERS) and the US National Tuberculosis Controllers Association (NTCA). It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The sponsoring and endorsing societies consider adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

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EXECUTIVE SUMMARY

The American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC), and Infectious Diseases Society of America (IDSA) jointly sponsored the development of this guideline on the treatment of drug-susceptible tuberculosis, which is also endorsed by the European Respiratory Society (ERS) and the US National Tuberculosis Controllers Association (NTCA). This guideline provides recommendations on the clinical and public health management of tuberculosis in children and adults in settings in which mycobacterial cultures, molecular

Table 1. Interpretation of "Strong" and "Conditional" Grading of Recommendations Assessment, Development, and Evaluation-Based Recommendations

Implications for:	Strong Recommendation	Conditional Recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policy	The recommendation can be adopted as policy in most situations.	Policymaking will require substantial debate and involvement of various stakeholders.

Source: Grading of Recommendations Assessment, Development and Evaluation Working Group [1, 2].

and phenotypic drug susceptibility tests, and radiographic studies, among other diagnostic tools, are available on a routine basis. Nine PICO (population, intervention, comparators, outcomes) questions and associated recommendations, developed based on the evidence that was appraised using GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology [1, 2], are summarized below. A carefully selected panel of experts, screened for conflicts of interest, including specialists in pulmonary medicine, infectious diseases, pharmacokinetics, pediatrics, primary care, public health, and systematic review methodology were assembled and used GRADE methods to assess the certainty in the evidence (also known as the quality of evidence) and strength of the recommendations (see Supplementary Appendix A: Methods and Table 1). This executive summary is a condensed version of the panel's recommendations. Additional detailed discussion of the management of pulmonary and extrapulmonary tuberculosis is available in the full-text version of this guideline.

OBJECTIVES OF ANTITUBERCULOSIS THERAPY

Treatment of tuberculosis is focused on both curing the individual patient and minimizing the transmission of *Mycobacterium tuberculosis* to other persons, thus, successful treatment of tuberculosis has benefits both for the individual patient and the community in which the patient resides.

The objectives of tuberculosis therapy are (1) to rapidly reduce the number of actively growing bacilli in the patient, thereby decreasing severity of the disease, preventing death and halting transmission of *M. tuberculosis*; (2) to eradicate populations of persisting bacilli in order to achieve durable cure (prevent relapse) after completion of therapy; and (3) to prevent acquisition of drug resistance during therapy.

The decision to initiate combination chemotherapy for tuberculosis is based on clinical, radiographic, laboratory, patient, and public health factors (Figure 1). In addition, clinical judgment and the index of suspicion for tuberculosis are critical in making a decision to initiate treatment. For example, in patients (children and adults) who, based on these considerations, have a high likelihood of having tuberculosis or are seriously ill with a disorder suspicious for tuberculosis, empiric treatment with a 4-drug regimen (Tables 2 and 3) should be initiated promptly even before the results of acid-fast bacilli (AFB) smear microscopy, molecular tests, and mycobacterial culture are known.

Sixty-five years of investigation, including many clinical trials, have consistently supported the necessity of treating with multiple drugs to achieve these treatment objectives, minimize drug toxicity, and maximize the likelihood of treatment completion [3, 4]. The success of drug treatment, however, depends upon many factors, and numerous studies have found an increased risk of relapse among patients with signs of more extensive disease (ie, cavitation or more extensive disease on chest radiograph) [5–9], and/or slower response to treatment (ie, delayed culture conversion at 2–3 months) [4, 6, 10, 11].

ORGANIZATION AND SUPERVISION OF TREATMENT

Because of the public health implications of prompt diagnosis and effective treatment of tuberculosis, most low-incidence countries designate a government public health agency as legal authority for controlling tuberculosis [12, 13]. The optimal organization of tuberculosis treatment often requires the coordination of public and private sectors [14–16]. In most settings, a patient is assigned a public health case manager who assesses needs and barriers that may interfere with treatment adherence [17]. With active input from the patient and healthcare providers, the case manager, together with the patient, develops an individualized "case management plan" with interventions to address the identified needs and barriers [18–20] (see PICO Question 1 and Supplementary Appendix B, Evidence Profiles 1–3). The least restrictive public health interventions that are effective are used to achieve adherence, thereby balancing the rights of the patient and public safety. Given that tuberculosis treatment requires multiple drugs be given for several months, it is crucial that the patient be involved in a meaningful way in making decisions concerning treatment supervision and overall care. International standards have been developed that also emphasize the importance of using patient-centered approaches to the management of tuberculosis [14–16].

Key considerations when developing a case management plan include (1) improving "treatment literacy" by educating the

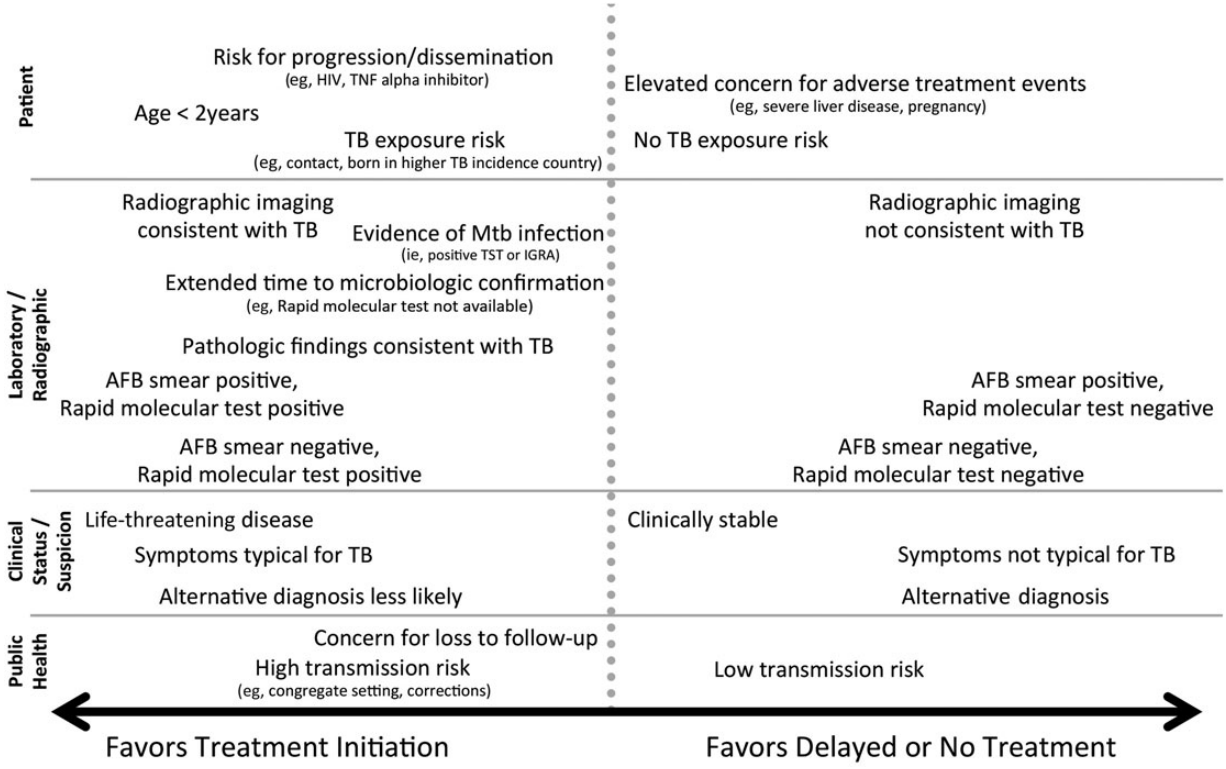

Figure 1. Factors to be considered in deciding to initiate treatment empirically for active tuberculosis (TB) (prior to microbiologic confirmation). Abbreviations: AFB, acid-fast bacilli; HIV, human immunodeficiency virus; IGRA, interferon-γ release assay; Mtb, *Mycobacterium tuberculosis*; TNF, tumor necrosis factor; TST, tuberculin skin test.

patient about tuberculosis and its treatment, including possible adverse effects [21, 22]; (2) discussing expected outcomes of treatment, specifically the ability to cure the patient of the disease; (3) reviewing methods of adherence support and plans for assessing response to therapy; and (4) discussing infectiousness and infection control measures using terminology that is appropriate to the culture, language, age, and reading level of the patient [23]. For non-English-speaking patients, the use of medical interpreter services is preferred over using family or friends as interpreters [24]. Relevant information should be reinforced at each visit. Other components of the case management plan include, but are not limited to, setting up patient reminders and systems to follow-up missed appointments [23, 25–29], use of incentives and enablers [30, 31], field and home visits [32], and integration and coordination of tuberculosis care with the patient's primary and specialty care (including mental health services, if appropriate and requested by the patient) (Table 4).

PICO Question 1: Does adding case management interventions to curative therapy improve outcomes compared to curative therapy alone among patients with tuberculosis? (Case management is defined as patient education/counseling, field/home visits, integration/coordination of care with specialists and medical home, patient reminders, and incentives/enablers).

Recommendation 1: We suggest using case management interventions during treatment of patients with tuberculosis *(conditional recommendation; very low certainty in the evidence).*

Given the critical importance of chemotherapy, both to the patient and to the public, approaches to ensuring adherence to the treatment regimen are a major focus of the overall management plan. To maximize completion of therapy, management strategies should utilize a broad range of approaches (see "Patient-Centered Care and Case Management" in the full-text version of the guideline). Among these, directly observed therapy (DOT), the practice of observing the patient swallow their antituberculosis medications, has been widely used as the standard of practice in many tuberculosis programs, and deserves special emphasis (see PICO Question 2 and Supplementary Appendix B, Evidence Profile 4). The systematic review conducted to obtain evidence in support of this practice guideline did not find any significant differences between self-administered therapy (SAT) and DOT when assessing several outcomes of interest, including mortality, treatment completion, and relapse. However, DOT was significantly associated with improved treatment success (the sum of patients cured and patients completing treatment) and with increased sputum smear conversion during treatment, as compared to SAT. Because DOT is a multifaceted public health intervention that is not amenable to the conventional clinical trial approaches to assessing benefits, and because participation in DOT can be advantageous for early recognition of adverse drug reactions and treatment irregularities, for allowing providers to establish

Table 2. Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

	Intensive Phase		Continuation Phase				
Regimen	Drug[a]	Interval and Dose[b] (Minimum Duration)	Drugs	Interval and Dose[b,c] (Minimum Duration)	Range of Total Doses	Comments[c,d]	Regimen Effectiveness
1	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	7 d/wk for 126 doses (18 wk), or 5 d/wk for 90 doses (18 wk)	182–130	This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis.	Greater
2	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	110–94	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	78	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.	
4	INH RIF PZA EMB	7 d/wk for 14 doses then twice weekly for 12 doses[e]	INH RIF	Twice weekly for 36 doses (18 wk)	62	Do not use twice-weekly regimens in HIV-infected patients or patients with smear-positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior.	Lesser

Abbreviations: DOT, directly observed therapy; EMB, ethambutol; HIV, human immunodeficiency virus; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin.

[a] Other combinations may be appropriate in certain circumstances; additional details are provided in the section "Recommended Treatment Regimens."

[b] When DOT is used, drugs may be given 5 days per week and the necessary number of doses adjusted accordingly. Although there are no studies that compare 5 with 7 daily doses, extensive experience indicates this would be an effective practice. DOT should be used when drugs are administered <7 days per week.

[c] Based on expert opinion, patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-week) continuation phase.

[d] Pyridoxine (vitamin B6), 25–50 mg/day, is given with INH to all persons at risk of neuropathy (eg, pregnant women; breastfeeding infants; persons with HIV; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or patients with advanced age). For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/day.

[e] See [426]. Alternatively, some US tuberculosis control programs have administered intensive-phase regimens 5 days per week for 15 doses (3 weeks), then twice weekly for 12 doses.

rapport with the patient and for addressing treatment complications expeditiously, DOT remains the standard of practice in the majority of tuberculosis programs in the United States [33–35] and Europe [15] (Table 5). To be consistent with the principles of patient-centered care noted previously, decisions regarding the use of DOT must be made in concert with the patient [14–16]. For example, DOT can be provided in the office, clinic, or in the "field" (patient's home, place of employment, school, or any other site that is mutually agreeable) by appropriately trained personnel [32].

PICO Question 2: Does self-administered therapy (SAT) have similar outcomes compared to directly observed therapy (DOT) in patients with various forms of tuberculosis?

Recommendation 2: We suggest using DOT rather than SAT for routine treatment of patients with all forms of tuberculosis *(conditional recommendation; low certainty in the evidence)*.

RECOMMENDED TREATMENT REGIMENS

The preferred regimen for treating adults with tuberculosis caused by organisms that are not known or suspected to be drug resistant is a regimen consisting of an intensive phase of 2 months of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) followed by a continuation phase of 4 months of INH and RIF (see Tables 2, 3, 10, 11, and Supplementary Appendix C) [3, 36, 37]. The intensive phase of treatment consists of 4 drugs (INH, RIF, PZA, EMB) because of the current proportion of new tuberculosis cases worldwide caused by organisms that are resistant to INH [38–41]; however, if therapy is being initiated after drug susceptibility test results are known and the patient's isolate is susceptible to both INH and RIF, EMB is not necessary, and the intensive phase can consist of INH, RIF, and PZA only. EMB can be discontinued as soon as the results of drug susceptibility studies demonstrate that the isolate is susceptible to INH and RIF. Pyridoxine (vitamin B6) is given with INH to all persons at risk of neuropathy (eg, pregnant women; breastfeeding infants; persons infected with human immunodeficiency virus [HIV]; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or those who are of advanced age) [42, 43].

With respect to administration schedule, the preferred frequency is once daily for both the intensive and continuation phases (see PICO Questions 3 and 4 and Supplementary Appendix B, Evidence Profiles 5–11). Although administration of antituberculosis drugs using DOT 5 days a week has been reported in a large number of studies, it has not been compared with 7-day administration in a clinical trial. Nonetheless, on the basis of substantial clinical experience, experts believe that 5-days-a-week drug administration by DOT is an acceptable alternative to 7-days-a-week administration, and either approach

Table 3. Doses[a] of Antituberculosis Drugs for Adults and Children[b]

Drug	Preparation	Population	Daily	Once-Weekly	Twice-Weekly	Thrice-Weekly
First-line drugs						
Isoniazid	Tablets (50 mg, 100 mg, 300 mg); elixir (50 mg/5 mL); aqueous solution (100 mg/mL) for intravenous or intramuscular injection. Note: Pyridoxine (vitamin B6), 25–50 mg/day, is given with INH to all persons at risk of neuropathy (eg, pregnant women; breastfeeding infants; persons with HIV; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or patients with advanced age). For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/d.	Adults	5 mg/kg (typically 300 mg)	15 mg/kg (typically 900 mg)	15 mg/kg (typically 900 mg)	15 mg/kg (typically 900 mg)
		Children	10–15 mg/kg	. . .	20–30 mg/kg	. . .[b]
Rifampin	Capsule (150 mg, 300 mg). Powder may be suspended for oral administration. Aqueous solution for intravenous injection.	Adults[c]	10 mg/kg (typically 600 mg)	. . .	10 mg/kg (typically 600 mg)	10 mg/kg (typically 600 mg)
		Children	10–20 mg/kg	. . .	10–20 mg/kg	. . .[b]
Rifabutin	Capsule (150 mg)	Adults[d]	5 mg/kg (typically 300 mg)	. . .	Not recommended	Not recommended
		Children	Appropriate dosing for children is unknown. Estimated at 5 mg/kg.			
Rifapentine	Tablet (150 mg film coated)	Adults		10–20 mg/kg[e]	. . .	. . .
		Children	Active tuberculosis: for children ≥12 y of age, same dosing as for adults, administered once weekly. Rifapentine is not FDA-approved for treatment of active tuberculosis in children <12 y of age.			
Pyrazinamide	Tablet (500 mg scored)	Adults	See Table 10	. . .	See Table 10	See Table 10
		Children	35 (30–40) mg/kg	. . .	50 mg/kg	. . .[b]
Ethambutol	Tablet (100 mg; 400 mg)	Adults	See Table 11	. . .	See Table 11	See Table 11
		Children[f]	20 (15–25) mg/kg	. . .	50 mg/kg	. . .[b]
Second-line drugs						
Cycloserine	Capsule (250 mg)	Adults[g]	10–15 mg/kg total (usually 250–500 mg once or twice daily)	There are inadequate data to support intermittent administration.		
		Children	15–20 mg/kg total (divided 1–2 times daily)			
Ethionamide	Tablet (250 mg)	Adults[h]	15–20 mg/kg total (usually 250–500 mg once or twice daily)	There are inadequate data to support intermittent administration.		
		Children	15–20 mg/kg total (divided 1–2 times daily)			
Streptomycin	Aqueous solution (1 g vials) for IM or IV administration.	Adults	15 mg/kg daily. Some clinicians prefer 25 mg/kg 3 times weekly. Patients with decreased renal function may require the 15 mg/kg dose to be given only 3 times weekly to allow for drug clearance.			
		Children	15–20 mg/kg [427]	. . .	25–30 mg/kg[i]	. . .
Amikacin/kanamycin	Aqueous solution (500 mg and 1 g vials) for IM or IV administration.	Adults	15 mg/kg daily. Some clinicians prefer 25 mg/kg 3 times weekly. Patients with decreased renal function, including older patients, may require the 15 mg/kg dose to be given only 3 times weekly to allow for drug clearance.			
		Children	15–20 mg/kg [427]	. . .	25–30 mg/kg[i]	. . .
Capreomycin	Aqueous solution (1 g vials) for IM or IV administration.	Adults	15 mg/kg daily. Some clinicians prefer 25 mg/kg 3 times weekly. Patients with decreased renal function, including older patients, may require the 15 mg/kg dose to be given only 3 times weekly to allow for drug clearance.			
		Children	15–20 mg/kg [427]	. . .	25–30 mg/kg[i]	. . .
Para-amino salicylic acid	Granules (4 g packets) can be mixed in and ingested with soft food (granules should not be chewed). Tablets (500 mg) are still available in some countries, but not in the United States. A solution for IV administration is available in Europe.	Adults	8–12 g total (usually 4000 mg 2–3 times daily)	There are inadequate data to support intermittent administration.		
		Children	200–300 mg/kg total (usually divided 100 mg/kg given 2 to 3 times daily)			
Levofloxacin	Tablets (250 mg, 500 mg, 750 mg); aqueous solution (500 mg vials) for IV injection.	Adults	500–1000 mg daily	There are inadequate data to support intermittent administration.		
		Children	The optimal dose is not known, but clinical data suggest 15–20 mg/kg [427]			

Table 3 continued.

Drug	Preparation	Population	Daily	Once-Weekly	Twice-Weekly	Thrice-Weekly
Moxifloxacin	Tablets (400 mg); aqueous solution (400 mg/250 mL) for IV injection	Adults	400 mg daily	There are inadequate data to support intermittent administration.[j]		
		Children	The optimal dose is not known. Some experts use 10 mg/kg daily dosing, though lack of formulations makes such titration challenging. Aiming for serum concentrations of 3–5 μL/mL 2 h postdose is proposed by experts as a reasonable target.			

Abbreviations: FDA, US Food and Drug Administration; HIV, human immunodeficiency virus; IM, intramuscular; INH, isoniazid; IV, intravenous.

[a] Dosing based on actual weight is acceptable in patients who are not obese. For obese patients (>20% above ideal body weight [IBW]), dosing based on IBW may be preferred for initial doses. Some clinicians prefer a modified IBW (IBW + [0.40 × (actual weight – IBW)]) as is done for initial aminoglycoside doses. Because tuberculosis drug dosing for obese patients has not been established, therapeutic drug monitoring may be considered for such patients.

[b] For purposes of this document, adult dosing begins at age 15 years or at a weight of >40 kg in younger children. The optimal doses for thrice-weekly therapy in children and adolescents have not been established. Some experts use in adolescents the same doses as recommended for adults, and for younger children the same doses as recommended for twice-weekly therapy.

[c] Higher doses of rifampin, currently as high as 35 mg/kg, are being studied in clinical trials.

[d] Rifabutin dose may need to be adjusted when there is concomitant use of protease inhibitors or nonnucleoside reverse transcriptase inhibitors.

[e] TBTC Study 22 used rifapentine (RPT) dosage of 10 mg/kg in the continuation phase of treatment for active disease [9]. However, RIFAQUIN and PREVENT TB safely used higher dosages of RPT, administered once weekly [164, 210]. Daily doses of 1200 mg RPT are being studied in clinical trials for active tuberculosis disease.

[f] As an approach to avoiding ethambutol (EMB) ocular toxicity, some clinicians use a 3-drug regimen (INH, rifampin, and pyrazinamide) in the initial 2 months of treatment for children who are HIV-uninfected, have no prior tuberculosis treatment history, are living in an area of low prevalence of drug-resistant tuberculosis, and have no exposure to an individual from an area of high prevalence of drug-resistant tuberculosis. However, because the prevalence of and risk for drug-resistant tuberculosis can be difficult to ascertain, the American Academy of Pediatrics and most experts include EMB as part of the intensive-phase regimen for children with tuberculosis.

[g] Clinicians experienced with using cycloserine suggest starting with 250 mg once daily and gradually increasing as tolerated. Serum concentrations often are useful in determining the appropriate dose for a given patient. Few patients tolerate 500 mg twice daily.

[h] Ethionamide can be given at bedtime or with a main meal in an attempt to reduce nausea. Clinicians experienced with using ethionamide suggest starting with 250 mg once daily and gradually increasing as tolerated. Serum concentrations may be useful in determining the appropriate dose for a given patient. Few patients tolerate 500 mg twice daily.

[i] Modified from adult intermittent dose of 25 mg/kg, and accounting for larger total body water content and faster clearance of injectable drugs in most children. Dosing can be guided by serum concentrations.

[j] RIFAQUIN trial studied a 6-month regimen. Daily isoniazid was replaced by daily moxifloxacin 400 mg for the first 2 months, followed by once-weekly doses of moxifloxacin 400 mg and RPT 1200 mg for the remaining 4 months. Two hundred twelve patients were studied (each dose of RPT was preceded by a meal of 2 hard-boiled eggs and bread). This regimen was shown to be noninferior to a standard daily administered 6-month regimen [164].

may be considered as meeting the definition of "daily" dosing. There are alternative regimens that are variations of the preferred regimen, which may be acceptable in certain clinical and/or public health situations (see "Other Regimens" and "Treatment in Special Situations" in the full-text version of the guideline).

PICO Question 3: Does intermittent dosing in the intensive phase have similar outcomes compared to daily dosing in the intensive phase for treatment of drug-susceptible pulmonary tuberculosis?

Recommendation 3a: We recommend the use of daily rather than intermittent dosing in the intensive phase of therapy for drug-susceptible pulmonary tuberculosis *(strong recommendation; moderate certainty in the evidence)*.

Recommendation 3b: Use of thrice-weekly therapy in the intensive phase (with or without an initial 2 weeks of daily therapy) may be considered in patients who are not HIV infected and are also at low risk of relapse (pulmonary tuberculosis caused by drug-susceptible organisms, that at the start of treatment is noncavitary and/or smear negative) *(conditional recommendation; low certainty in the evidence)*.

Recommendation 3c: In situations where daily or thrice-weekly DOT therapy is difficult to achieve, use of twice-weekly therapy after an initial 2 weeks of daily therapy may be considered for patients who are not HIV-infected and are also at low risk of relapse (pulmonary tuberculosis caused by drug-susceptible organisms, that at the start of treatment is noncavitary and/or smear negative) *(conditional recommendation; very low certainty in the evidence)*. Note: If doses are missed in a regimen using twice-weekly dosing, then therapy is equivalent to once weekly, which is inferior (see PICO Question 4).

Table 4. Possible Components of a Multifaceted, Patient-Centered Treatment Strategy

Enablers	Incentives
Interventions to assist the patient in completing therapy [130]	Interventions to motivate the patient, tailored to individual patient wishes and needs and, thus, meaningful to the patient [130]
Transportation vouchers [30]	Food stamps or snacks and meals [30]
Convenient clinic hours and locations [30]	Restaurant and grocery store coupons [30]
Clinic personnel who speak the languages of the populations served [428]	Assistance in finding or provision of housing [429]
Reminder systems and follow-up of missed appointments [28]	Clothing or other personal products [30]
Social service assistance (referrals for substance abuse treatment and counseling, housing, and other services) [429]	Books [428]
Outreach workers (bilingual/bicultural as needed; can provide many services related to maintaining patient adherence, including provision of directly observed therapy, follow-up on missed appointments, monthly monitoring, transportation, sputum collection, social service assistance, and educational reinforcement) [428]	Stipends [30]
Integration of care for tuberculosis with care for other conditions [428]	Patient contract [30]

Table 5. Examples of Priority Situations for the Use of Directly Observed Therapy

Patients With the Following Conditions/Circumstances [17, 130, 137, 139, 430, 431]:
• Positive sputum smears
• Delayed culture conversion (sputum obtained at/after completion of intensive-phase therapy is culture-positive)
• Treatment failure
• Relapse
• Drug resistance
• Homelessness
• Current or prior substance abuse
• Use of intermittent dosing
• HIV infection
• Previous nonadherence to therapy
• Children and adolescents
• Mental, emotional or physical disability (ie, cognitive deficits such as dementia; neurological deficits; medically fragile patients; or patients with blindness or severe loss of vision)
• Resident at correctional or long-term care facility
• Previous treatment for active or latent tuberculosis

Abbreviation: HIV, human immunodeficiency virus.

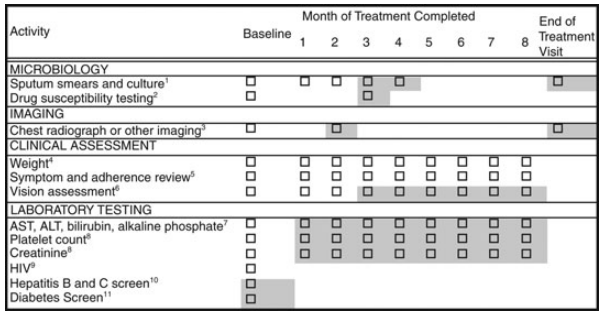

Figure 2. Baseline and follow-up evaluations for patients treated with first-line tuberculosis medications. Shading around boxes indicates activities that are optional or contingent on other information. [1]Obtain sputa for smear and culture at baseline, then monthly until 2 consecutive specimens are negative. Collecting sputa more often early in treatment for assessment of treatment response and at end of treatment is optional. At least one baseline specimen should be tested using a rapid molecular test. [2]Drug susceptibility for isoniazid, rifampin, ethambutol (EMB), and pyrazinamide should be obtained. Repeat drug susceptibility testing if patient remains culture positive after completing 3 months of treatment. Molecular resistance testing should be performed for patients with risk for drug resistance. [3]Obtain chest radiograph at baseline for all patients, and also at month 2 if baseline cultures are negative. End-of-treatment chest radiograph is optional. Other imaging for monitoring of extrapulmonary disease. [4]Monitor weight monthly to assess response to treatment; adjust medication dose if needed. [5]Assess adherence and monitor improvement in tuberculosis symptoms (eg, cough, fever, fatigue, night sweats) as well as development of medication adverse effects (eg, jaundice, dark urine, nausea, vomiting, abdominal pain, fever, rash, anorexia, malaise, neuropathy, arthralgias). [6]Patients on EMB: baseline visual acuity (Snellen test) and color discrimination tests, followed by monthly inquiry about visual disturbance and monthly color discrimination tests. [7]Liver function tests only at baseline unless there were abnormalities at baseline, symptoms consistent with hepatotoxicity develop, or for patients who chronically consume alcohol, take other potentially hepatotoxic medications, or have viral hepatitis or history of liver disease, human immunodeficiency virus (HIV) infection, or prior drug-induced liver injury. [8]Baseline for all patients. Further monitoring if there are baseline abnormalities or as clinically indicated. [9]HIV testing in all patients. CD4 lymphocyte count and HIV RNA load if positive. [10]Patients with hepatitis B or C risk factor (eg, injection drug use, birth in Asia or Africa, or HIV infection) should have screening tests for these viruses. [11]Fasting glucose or hemoglobin A1c for patients with risk factors for diabetes according to the American Diabetes Association including: age >45 years, body mass index >25 kg/m^2, first-degree relative with diabetes, and race/ethnicity of African American, Asian, Hispanic, American Indian/Alaska Native, or Hawaiian Native/Pacific Islander. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Recommended baseline and follow-up evaluations for patients suspected of having tuberculosis and treated with first-line medications are summarized in Figure 2. During treatment, a sputum specimen for AFB smear and culture are obtained at monthly intervals until 2 consecutive specimens are negative on culture. Duration of the continuation phase regimen hinges on the microbiological status at the end of the intensive phase of treatment; thus, obtaining sputum specimens at the time of completion of 2 months of treatment is critical if sputum culture conversion to negative has not already been documented. The culture result of a sputum specimen obtained at the completion of the intensive phase of treatment (2 months) has been shown to correlate with the likelihood of relapse after completion of treatment for pulmonary tuberculosis, albeit with low sensitivity [9, 44–46]. Cavitation on the initial chest radiograph has also been shown to be a risk factor for relapse [9, 47]. In patients treated for 6 months, having both cavitation and a positive culture at completion of 2 months of therapy has been associated with rates of relapse of approximately 20% compared with 2% among patients with neither factor [9, 45].

In view of this evidence, for patients who have cavitation on the initial chest radiograph and who have positive cultures at completion of 2 months of therapy, expert opinion is to extend the continuation phase with INH and RIF for an additional 3 months (ie, a continuation phase of 7 months in duration, corresponding to a total of 9 months of therapy). Additional factors to be considered in deciding to prolong treatment in patients with either cavitation or a positive culture at 2 months (but not both) might include being >10% below ideal body weight; being an active smoker; having diabetes, HIV infection, or any other immunosuppressing condition; or having extensive disease on chest radiograph [46, 48–52].

Interruptions in therapy are common in the treatment of tuberculosis. When interruptions occur, the person responsible for supervision must decide whether to restart a complete course of treatment or simply to continue as intended originally. In general, the earlier the break in therapy and the longer its duration, the more serious the effect and the greater the need to restart treatment from the beginning (Table 6). Continuous treatment is more important in the intensive phase of therapy when the bacillary population is highest and the chance of developing drug resistance greatest. During the continuation phase, the number of bacilli is much smaller and the goal of therapy is to kill the persisting organisms. The duration of the interruption and the bacteriologic status of the patient prior to and after the

Table 6. Management of Treatment Interruptions[a]

Time Point of Interruption	Details of Interruption	Approach
During intensive phase	Lapse is <14 d in duration	Continue treatment to complete planned total number of doses (as long as all doses are completed within 3 mo)
	Lapse is ≥14 d in duration	Restart treatment from the beginning
During continuation phase	Received ≥80% of doses and sputum was AFB smear negative on initial testing	Further therapy may not be necessary
	Received ≥80% of doses and sputum was AFB smear positive on initial testing	Continue therapy until all doses are completed
	Received <80% of doses and accumulative lapse is <3 mo in duration	Continue therapy until all doses are completed (full course), unless consecutive lapse is >2 mo If treatment cannot be completed within recommended time frame for regimen, restart therapy from the beginning (ie, restart intensive phase, to be followed by continuation phase)[b]
	Received <80% of doses and lapse is ≥3 mo in duration	Restart therapy from the beginning, new intensive and continuation phases (ie, restart intensive phase, to be followed by continuation phase)

Abbreviation: AFB, acid-fast bacilli.

[a] According to expert opinion, patients who are lost to follow-up (on treatment) and brought back to therapy, with interim treatment interruption, should have sputum resent for AFB smear, culture, and drug susceptibility testing.

[b] The recommended time frame for regimen, in tuberculosis control programs in the United States and in several European countries, is to administer all of the specified number of doses for the intensive phase within 3 months and those for the 4-month continuation phase within 6 months, so that the 6-month regimen is completed within 9 months.

interruption are also important considerations (see "Interruptions in Therapy" in the full-text version of the guideline).

PICO Question 4: Does intermittent dosing in the continuation phase have similar outcomes compared to daily dosing in the continuation phase in patients with drug-susceptible pulmonary tuberculosis patients?

Recommendation 4a: We recommend the use of daily or thrice-weekly dosing in the continuation phase of therapy for drug-susceptible pulmonary tuberculosis *(strong recommendation; moderate certainty in the evidence)*.
Recommendation 4b: If intermittent therapy is to be administered in the continuation phase, then we suggest use of thrice-weekly instead of twice-weekly therapy *(conditional recommendation; low certainty in the evidence)*. This recommendation allows for the possibility of some doses being missed; with twice-weekly therapy, if doses are missed then therapy is equivalent to once weekly, which is inferior.
Recommendation 4c: We recommend against use of once-weekly therapy with INH 900 mg and rifapentine 600 mg in the continuation phase *(strong recommendation; high certainty in the evidence)*. In uncommon situations where more than once-weekly DOT is difficult to achieve, once-weekly continuation phase therapy with INH 900 mg plus rifapentine 600 mg may be considered for use only in HIV-uninfected persons without cavitation on chest radiography.

PRACTICAL ASPECTS OF TREATMENT

Guidance on the practical aspects of tuberculosis treatment, drug–drug interactions, therapeutic drug monitoring (TDM), and management of adverse effects are available in the full-text version of this guideline. In brief, mild adverse effects usually can be managed with treatment directed at controlling the symptoms; severe effects usually require the offending drug(s) to be discontinued, and may require expert consultation on management. If a drug is permanently discontinued, then a replacement drug, typically from a different drug class, is included in the regimen. Patients with severe tuberculosis often require the initiation of an alternate regimen during the time the offending drug(s) are held. In general, for complicated diagnostic or management situations, consultation with local and state health departments is advised. In the United States, the Centers for Disease Control and Prevention's Division of Tuberculosis Elimination funds tuberculosis regional training and medical consultation centers (http://www.cdc.gov/tb/education/rtmc/), which provide medical consultation to programs and health providers on management of tuberculosis. In Europe, the World Health Organization (WHO)/ERS Tuberculosis Consilium (https://www.tbconsilium.org) provides similar consultation services regarding the diagnosis and treatment of tuberculosis.

Gastrointestinal reactions are common, especially early in therapy [53]. The optimum approach to management of epigastric distress or nausea with tuberculosis drugs is not clear. To minimize symptoms, patients receiving SAT may take the medications at bedtime. Gastrointestinal intolerance not associated with hepatotoxicity can be treated with antacids, which have less impact on absorption or peak concentration of first-line drugs than administration with food [54]. Any combination of otherwise unexplained nausea, vomiting, and abdominal pain is evaluated with a physical examination and liver function tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and alkaline phosphatase to assess for possible hepatotoxicity [55]. Drug-induced hepatitis is the most frequent serious adverse reaction to the first-line drugs. INH, RIF, and PZA can cause drug-induced liver injury (DILI), which is suspected when the ALT level is ≥3 times the upper limit of normal in the presence of hepatitis symptoms, or ≥5 the upper limit of normal in the absence of symptoms. In either situation, hepatotoxic drugs are stopped immediately and the patient is evaluated carefully. Other causes of abnormal liver function tests must be excluded before diagnosing drug-induced hepatotoxicity (Table 7). An official American Thoracic Society statement on the hepatotoxicity of antituberculosis

Table 7. Other Causes of Abnormal Liver Function Tests That Should Be Excluded

Viral hepatitis (hepatitis A, B, and C in all patients; Epstein-Barr virus, cytomegalovirus, and herpes simplex in immunosuppressed patients)
Biliary tract disease
Alcohol
Other hepatotoxic drugs (eg, acetaminophen, acetaminophen-containing multiagent preparations, lipid-lowering agents, other drugs)
Select herbal and dietary supplements

Source: American Thoracic Society [56].

therapy (http://www.thoracic.org/statements/resources/mtpi/hepatotoxicity-of-antituberculosis-therapy.pdf) provides additional details on the management of tuberculosis in the setting of drug-induced liver injury, as well as suggestions on drug rechallenge [56]; however, the optimal approach to reintroducing tuberculosis treatment after hepatotoxicity is still not known [57, 58].

TREATMENT IN SPECIAL SITUATIONS

Detailed recommendations on the management of tuberculosis in special situations (HIV infection, extrapulmonary tuberculosis, culture-negative pulmonary tuberculosis, advanced age, children, tuberculosis during pregnancy and breastfeeding, renal disease, and hepatic disease, among others) are available in the full-text version of this guideline. Five PICO questions with summary recommendations pertinent to the management of tuberculosis in HIV patients, steroid use in pericardial or meningeal tuberculosis, and culture-negative tuberculosis are summarized below.

HIV Infection

Treatment of tuberculosis in patients with HIV infection has several important differences compared with treatment of patients who do not have HIV infection. The need for antiretroviral therapy (ART), the potential for drug–drug interactions, especially between the rifamycins and antiretroviral agents (Table 8), paradoxical reactions that may be interpreted as clinical worsening, and the potential for developing resistance to rifamycins when using intermittent tuberculosis therapy are some of these differences. Detailed information on these topics is provided in the full-text version of this practice guideline. In regard to duration of treatment for drug-susceptible pulmonary tuberculosis in the presence of HIV infection, our updated systematic review of randomized trials and cohort studies comparing various durations of tuberculosis therapy (6 months vs 8 months or longer), most of which were conducted prior to the era of highly active ART, showed that the risk of recurrence is lower when the continuation phase of treatment is extended. However, it is important to note that the majority of these studies were reports on nonrandomized cohorts, most were completed prior to the era of routine antiretroviral use, many tested intermittent regimens and few distinguished between reinfection and relapse (see "HIV Infection" in the full-text version of the guideline). As discussed below, based on data that show significant reductions in mortality and AIDS-defining illnesses, patients with HIV infection and tuberculosis should receive ART in conjunction with daily antituberculosis medications. For HIV-infected patients receiving ART, we suggest using the standard 6-month daily regimen consisting of an intensive phase of 2 months of INH, RIF, PZA, and EMB followed by a continuation phase of 4 months of INH and RIF for the treatment of drug-susceptible pulmonary tuberculosis. In the uncommon situation in which an HIV-infected patient does not receive ART during tuberculosis treatment, we suggest extending the continuation phase with INH and RIF for an additional 3 months (ie, a continuation phase of 7 months in duration, corresponding to a total of 9 months of therapy) for treatment of drug-susceptible pulmonary tuberculosis (see PICO Question 5 and Supplementary Appendix B, Evidence Profile 12). As is noted for drug-susceptible pulmonary tuberculosis in patients without HIV coinfection, the continuation phase is extended in specific situations that are known to increase risk for relapse, as well as for selected extrapulmonary sites of disease, namely tuberculous meningitis, and bone, joint, and spinal tuberculosis (see "Identification and Management of Patients at Increased Risk of Relapse" and "Extrapulmonary Tuberculosis" in the full-text version of the guideline).

PICO Question 5: Does extending treatment beyond 6 months improve outcomes compared to the standard 6-month treatment regimen among pulmonary tuberculosis patients coinfected with HIV?

Recommendation 5a: For HIV-infected patients receiving ART, we suggest using the standard 6-month daily regimen consisting of an intensive phase of 2 months of INH, RIF, PZA, and EMB followed by a continuation phase of 4 months of INH and RIF for the treatment of drug-susceptible pulmonary tuberculosis *(conditional recommendation; very low certainty in the evidence)*.

Recommendation 5b: In uncommon situations in which HIV-infected patients do NOT receive ART during tuberculosis treatment, we suggest extending the continuation phase with INH and RIF for an additional 3 months (ie, a continuation phase of 7 months in duration, corresponding to a total of 9 months of therapy) for treatment of drug-susceptible pulmonary tuberculosis *(conditional recommendation; very low certainty in the evidence)*.

Use of intermittent tuberculosis treatment regimens in HIV-infected patients has been associated with high rates of relapse and the emergence of drug resistance [9, 59]. In a trial of rifabutin (RFB)–based antituberculosis therapy in combination with antiretroviral drugs, patients treated with twice-weekly RFB had a relapse rate of 5.3%, but 8 of 9 patients with relapse had acquired rifamycin resistance [60]. Relapse and resistance were associated with low CD4 lymphocyte counts, as all recurrences occurred in patients with baseline CD4 lymphocyte counts <100 cells/μL. In the pharmacokinetic substudy of the trial, lower plasma concentrations of RFB and INH were identified as key risk factors for acquiring rifamycin resistance [61]. More recently, the use of a thrice-weekly RIF-based regimen during the intensive and continuation phases of treatment was associated with a higher rate of relapse and emergence of

Table 8. Clinically Significant Drug–Drug Interactions Involving the Rifamycins[a]

Drug Class	Drugs Whose Concentrations Are Substantially Decreased by Rifamycins	Comments
Antiretroviral agents	HIV-1 protease inhibitors (lopinavir/ritonavir, darunavir/ritonavir, atazanavir, atazanavir/ritonavir)	RFB preferred with protease inhibitors. For ritonavir-boosted regimens, give RFB 150 mg daily. Double-dose lopinavir/ritonavir can be used with RIF but toxicity increased. Do not use RIF with other protease inhibitors.
	NNRTIs Nevirapine Efavirenz Rilpivirine Complera (fixed-dose combination tablet containing emtricitabine, rilpivirine, TDF) Etravirine	RIF decreases exposure to all NNRTIs. If nevirapine is used with RIF, lead-in nevirapine dose of 200 mg daily should be omitted and 400 mg daily nevirapine dosage given. With RIF, many experts advise that efavirenz be given at standard dosage of 600 mg daily, although FDA recommends increasing efavirenz to 800 mg daily in persons >60 kg. In young children double-dose lopinavir/ritonavir given with RIF results in inadequate concentrations – super-boosted Lopinavir/ritonavir is advised (if available) by some experts. Rilpivirine and etravirine should not be given with RIF. RFB can be used with nevirapine and etravirine at usual dosing. Efavirenz and RFB use requires dose increase of RFB to 600 mg daily, as such RIF is preferred. Rilpivirine should not be given with RFB.
	INSTIs Raltegravir Dolutegravir Elvitegravir (coformulated with cobicistat, tenofovir and emtricitabine as Stribild) Genvoya (fixed-dose combination tablet containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide)	Increase dose of raltegravir to 800 mg twice daily with RIF, although clinical trial data show similar efficacy using 400 mg twice daily. Dolutegravir dose should be increased to 50 mg every 12 h with RIF. Do not use RIF with elvitegravir. RFB can be used with all INSTIs.
	CCR5 inhibitors Maraviroc	RIF should not be used with maraviroc. RFB can be used with maraviroc.
Anti-infectives	Macrolide antibiotics (azithromycin, clarithromycin, erythromycin)	Azithromycin has no significant interaction with rifamycins. Coadministration of clarithromycin and RFB results in significant bidirectional interactions that can increase RFB to toxic levels increasing the risk of uveitis. Erythromycin is a CYP3A4 substrate and clearance may increase in setting of rifamycin use.
	Doxycycline	May require use of a drug other than doxycycline.
	Azole antifungal agents (ketoconazole, itraconazole, voriconazole, fluconazole, posaconazole, isavuconazole)	Itraconazole, ketoconazole, and voriconazole concentrations may be subtherapeutic with any of the rifamycins. Fluconazole can be used with rifamycins, but the dose of fluconazole may have to be increased.
	Atovaquone	Consider alternate form of *Pneumocystis jirovecii* treatment or prophylaxis.
	Chloramphenicol	Consider an alternative antibiotic.
	Mefloquine	Consider alternate form of malaria prophylaxis.
Hormone therapy	Ethinylestradiol, norethindrone	Women of reproductive potential on oral contraceptives should be advised to add a barrier method of contraception when on a rifamycin.
	Tamoxifen	May require alternate therapy or use of a non-rifamycin-containing regimen.
	Levothyroxine	Monitoring of serum TSH recommended; may require increased dose of levothyroxine.
Narcotics	Methadone	RIF and RPT use may require methadone dose increase. RFB infrequently causes methadone withdrawal.
Anticoagulants	Warfarin	Monitor prothrombin time; may require 2- to 3-fold warfarin dose increase.
Immunosuppressive agents	Cyclosporine, tacrolimus	RFB may allow concomitant use of cyclosporine and a rifamycin; monitoring of cyclosporine and tacrolimus serum concentrations may assist with dosing.
	Corticosteroids	Monitor clinically; may require 2- to 3-fold increase in corticosteroid dose.
Anticonvulsants	Phenytoin, lamotrigine	TDM recommended; may require anticonvulsant dose increase.
Cardiovascular agents	Verapamil, nifedipine, diltiazem (a similar interaction is also predicted for felodipine and nisoldipine)	Clinical monitoring recommended; may require change to an alternate cardiovascular agent.
	Propranolol, metoprolol	Clinical monitoring recommended; may require dose increase or change to an alternate cardiovascular drug.
	Enalapril, losartan	Monitor clinically; may require a dose increase or use of an alternate cardiovascular drug.
	Digoxin (among patients with renal insufficiency), digitoxin	TDM recommended; may require digoxin or digitoxin dose increase.
	Quinidine	TDM recommended; may require quinidine dose increase.
	Mexiletine, tocainide, propafenone	Clinical monitoring recommended; may require change to an alternate cardiovascular drug.
Theophylline	Theophylline	TDM recommended; may require theophylline dose increase.
Sulfonylurea hypoglycemics	Tolbutamide, chlorpropamide, glyburide, glimepiride, repaglinide	Monitor blood glucose; may require dose increase or change to an alternate hypoglycemic drug.
Hypolipidemics	Simvastatin, fluvastatin	Monitor hypolipidemic effect; may require use of an alternate antihyperlipidemic drug.

Table 8 continued.

Drug Class	Drugs Whose Concentrations Are Substantially Decreased by Rifamycins	Comments
Psychotropic drugs	Nortriptyline	TDM recommended; may require dose increase or change to alternate psychotropic drug.
	Haloperidol, quetiapine	Monitor clinically; may require a dose increase or use of an alternate psychotropic drug.
	Benzodiazepines (eg, diazepam, triazolam), zolpidem, buspirone)	Monitor clinically; may require a dose increase or use of an alternate psychotropic drug.

Abbreviations: CCR5, C chemokine receptor type 5; CYP, cytochrome P450; FDA, US Food and Drug Administration; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; RFB, rifabutin; RIF, rifampin; RPT, rifapentine; TDF, tenofovir disoproxil fumarate; TDM, therapeutic drug monitoring; TSH, thyroid-stimulating hormone.

[a] See the following useful websites for updated information regarding drug interactions: AIDSinfo, Centers for Disease Control and Prevention, University of California San Francisco, University of Liverpool, Indiana University, and University of Maryland.

rifamycin resistance in HIV-infected individuals not receiving antiretrovirals compared with HIV-infected patients also receiving antiretrovirals or HIV-uninfected patients [62]. Based in part on systematic reviews conducted to obtain evidence in support of this guideline, our expert opinion is that treatment of HIV-related tuberculosis be given daily in both the intensive and continuation phases to avoid recurrent disease and the emergence of rifamycin resistance (see "Recommended Treatment Regimens" in the full-text version of the guideline).

Mortality among patients with HIV and tuberculosis is high, principally due to complications of immunosuppression and occurrence of other HIV-related opportunistic diseases. Cotrimoxazole (trimethoprim-sulfamethoxazole) prophylaxis has been shown to reduce morbidity and mortality in HIV-infected patients with newly diagnosed tuberculosis [63–65]. Whereas cotrimoxazole is recommended by WHO for all HIV-infected people with active tuberculosis disease regardless of the CD4 cell count [66], in high-income countries, co-trimoxazole is primarily used in HIV-infected patients with CD4 counts <200 cells/μL [67]. The use of ART during tuberculosis treatment in persons with HIV infection also reduces mortality rates significantly and decreases the risk of developing AIDS-related conditions. We performed a systematic review and meta-analysis to address the concurrent initiation of ART with tuberculosis treatment. On the basis of high certainty in the evidence that the benefits outweigh the harms, we recommend that patients with tuberculosis and HIV infection receive ART during antituberculosis treatment. ART should ideally be started within 2 weeks for those patients with a CD4 count <50 cells/μL and by 8–12 weeks for those with a CD4 count ≥50 cells/μL (see PICO Question 6 and Supplementary Appendix B, Evidence Profile 13). An exception is HIV-infected patients with tuberculous meningitis, in whom ART is not initiated in the first 8 weeks of antituberculosis therapy (see full-text version of the guideline). The concurrent administration of antiretrovirals and rifamycins is a major therapeutic challenge, and additional details on the coadministration of these medications, including the use of RFB, are available in the full-text version of this guideline.

PICO Question 6: Does initiation of ART during tuberculosis treatment compared to at the end of tuberculosis treatment improve outcomes among tuberculosis patients coinfected with HIV?

Recommendation 6: We recommend initiating ART during tuberculosis treatment. ART should ideally be initiated within the first 2 weeks of tuberculosis treatment for patients with CD4 counts <50 cells/μL and by 8–12 weeks of tuberculosis treatment initiation for patients with CD4 counts ≥50 cells/μL *(strong recommendation; high certainty in the evidence)*. Note: an exception is patients with HIV infection and tuberculous meningitis (see Immune Reconstitution Inflammatory Syndrome).

Patients with HIV infection and tuberculosis are at increased risk of developing paradoxical worsening of symptoms, signs, or clinical manifestations of tuberculosis after beginning antituberculosis and antiretroviral treatments. These reactions presumably develop as a consequence of reconstitution of immune responsiveness brought about by ART, and are designated as the immune reconstitution inflammatory syndrome (IRIS). Tuberculosis IRIS has been noted to be more common in participants with earlier ART initiation and $CD4^+$ cell counts <50 cells/μL [68]. Signs of IRIS may include high fevers, worsening respiratory symptoms, increase in size and inflammation of involved lymph nodes, new lymphadenopathy, expanding central nervous system lesions, worsening of pulmonary parenchymal infiltrations, new or increasing pleural effusions, and development of intra-abdominal or retroperitoneal abscesses [69]. Such findings are attributed to IRIS only after excluding other possible causes, especially tuberculosis treatment failure from drug-resistant tuberculosis or another opportunistic disease, such as non-Hodgkin lymphoma or infection.

Management of IRIS is symptomatic. Based on expert opinion, for most patients with mild IRIS, tuberculosis and antiretroviral therapies can be continued with the addition of anti-inflammatory agents such as ibuprofen. For patients with worsening pleural effusions or abscesses, drainage may be necessary. For more severe cases of IRIS, treatment with corticosteroids is effective. In a placebo-controlled trial of prednisone for patients with moderate IRIS, prednisone 1.25 mg/kg/day significantly reduced the need for hospitalization or surgical

procedures [70]. For patients who develop IRIS, prednisone may be given at a dose of 1.25 mg/kg/day (50–80 mg/day) for 2–4 weeks, with tapering over a period of 6–12 weeks or longer.

Tuberculous Pericarditis

Based on small studies that have shown mortality and morbidity benefits [71–73], corticosteroids have previously been universally recommended in combination with a standard 6-month regimen (Table 2) for treating tuberculosis pericarditis; however, a recent placebo-controlled randomized clinical trial with 1400 participants did not find a difference in the combined primary endpoint of the trial, which included mortality, cardiac tamponade, or constrictive pericarditis, between patients treated with adjunctive corticosteroids vs placebo [74]. A subgroup analysis, however, did suggest a benefit in preventing constrictive pericarditis. Similarly, a systematic review conducted to obtain evidence in support of this guideline did not find a statistically significant benefit in terms of mortality or constrictive pericarditis from the use of corticosteroids [71–75]. Therefore, we suggest that adjunctive corticosteroids should not be used routinely in the treatment of patients with pericardial tuberculosis (see PICO Question 7 and Supplementary Appendix B, Evidence Profile 14). However, selective use of corticosteroids in patients who are at the highest risk for inflammatory complications might be appropriate. Such patients might include those with large pericardial effusions, those with high levels of inflammatory cells or markers in pericardial fluid, or those with early signs of constriction [76].

PICO Question 7: Does the use of adjuvant corticosteroids in tuberculous pericarditis provide mortality and morbidity benefits?

Recommendation 7: We suggest initial adjunctive corticosteroid therapy not be routinely used in patients with tuberculous pericarditis *(conditional recommendation; very low certainty in the evidence).*

Tuberculous Meningitis

Chemotherapy for tuberculous meningitis is initiated with INH, RIF, PZA, and EMB in an initial 2-month phase. After 2 months of 4-drug therapy, for meningitis known or presumed to be caused by susceptible strains, PZA and EMB may be discontinued, and INH and RIF continued for an additional 7–10 months, although the optimal duration of chemotherapy is not defined. Based on expert opinion, repeated lumbar punctures should be considered to monitor changes in cerebrospinal fluid cell count, glucose, and protein, especially early in the course of therapy. In children with tuberculous meningitis, the American Academy of Pediatrics (AAP) lists an initial 4-drug regimen composed of INH, RIF, PZA, and ethionamide, if possible, or an aminoglycoside, followed by 7–10 months of INH and RIF as the preferred regimen [77]. There are no data from controlled trials to guide the selection of EMB vs an injectable or ethionamide as the fourth drug for tuberculosis meningitis [78]. Most societies and experts recommend the use of either an injectable or EMB. For adults, based on expert opinion, our guideline committee prefers using EMB as the fourth drug in the regimen for tuberculous meningitis.

The role of adjunctive corticosteroid therapy in the treatment of tuberculous meningitis has been reported by numerous studies [79–91], and our updated systematic review found a mortality benefit from the use of adjuvant corticosteroids. Therefore, we recommend adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks for patients with tuberculous meningitis (see PICO Question 8 and Supplementary Appendix B, Evidence Profile 15).

PICO Question 8: Does the use of adjuvant corticosteroids in tuberculous meningitis provide mortality and morbidity benefits?

Recommendation 8: We recommend initial adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks for patients with tuberculous meningitis *(strong recommendation; moderate certainty in the evidence).*

Culture-Negative Pulmonary Tuberculosis in Adults

Failure to isolate *M. tuberculosis* from appropriately collected sputum specimens in persons who, because of clinical or radiographic findings, are suspected of having pulmonary tuberculosis does not exclude a diagnosis of active tuberculosis. Some causes of failure to isolate organisms include low bacillary populations, inadequate sputum specimens, temporal variations in the number of expelled bacilli, overgrowth of cultures with other microorganisms, and errors in specimen processing [92]. Alternative diagnoses must be considered and appropriate diagnostic studies undertaken in patients who appear to have culture-negative tuberculosis. At a minimum, patients suspected of having pulmonary tuberculosis have 2 sputum specimens (using sputum induction with hypertonic saline if necessary) for AFB smears and cultures for mycobacteria or for rapid molecular testing for *M. tuberculosis* as part of the diagnostic evaluation. Other diagnostic procedures, such as bronchoscopy with bronchoalveolar lavage and biopsy, are considered before making a presumptive diagnosis of culture-negative tuberculosis.

Patients who, on the basis of careful clinical and radiographic evaluation, are thought to have pulmonary tuberculosis should have treatment initiated with INH, RIF, PZA, and EMB even when the initial sputum smears are negative. If *M. tuberculosis* is isolated in culture or a rapid molecular test is positive, treatment for active disease is continued for a full, standard 6-month course (Table 2), if appropriate based on drug susceptibility test results. Patients who have negative cultures but who still are presumed to have pulmonary tuberculosis should have thorough clinical and radiographic follow-up after 2–3 months of therapy [93]. If there is clinical or radiographic improvement and no other etiology is identified, treatment should be continued.

The optimum treatment regimens and duration for smear-negative, culture-negative tuberculosis have not been convincingly established. We performed a systematic review that evaluated treatment regimens of varying durations in adult patients with

culture-negative, paucibacillary tuberculosis, and we suggest that a 4-month treatment regimen is adequate for smear-negative, culture-negative pulmonary tuberculosis (see PICO Question 9 and Supplementary Appendix B, Evidence Profile 16). Operationally, treatment is initiated with an intensive phase of INH, RIF, PZA, and EMB daily and continued even when the initial bacteriologic studies are negative. If all cultures on adequate samples are negative (defining culture-negative tuberculosis) and there is clinical or radiographic response after 2 months of intensive phase therapy, the continuation phase with INH and RIF can be shortened to 2 months. Alternatively, if there is concern about the adequacy of workup or the accuracy of the microbiologic evaluations, a standard 6-month regimen remains preferred (see Table 2 and "Culture-Negative Pulmonary Tuberculosis" in the full-text version of the guideline) [14, 15].

PICO Question 9: Does a shorter duration of treatment have similar outcomes compared to the standard 6-month treatment duration among HIV-uninfected patients with paucibacillary tuberculosis (ie, smear negative, culture negative)?

Recommendation 9: We suggest that a 4-month treatment regimen is adequate for treatment of HIV-uninfected adult patients with AFB smear- and culture-negative pulmonary tuberculosis *(conditional recommendation; very low certainty in the evidence)*.

CONCLUSIONS

Treatment of tuberculosis is focused on both curing the individual patient and minimizing the transmission of *M. tuberculosis* to other persons, thus, successful treatment of tuberculosis has benefits both for the individual patient and the community in which the patient resides. A 4-drug regimen of INH, RIF, PZA, and EMB remains the preferred initial treatment for drug-susceptible pulmonary tuberculosis. Treatment is initiated promptly even before AFB smear microscopy, molecular tests, and mycobacterial culture results are known in patients with high likelihood of having tuberculosis or those seriously ill with a disorder suspicious for tuberculosis. Initiation of treatment should not be delayed because of negative AFB smears for patients in whom tuberculosis is suspected and who have a life-threatening condition. There are variations of the preferred regimen that are appropriate in certain public health situations or in special clinical situations. Additional detailed and extensively referenced information on treatment of tuberculosis in special situations (patients with renal disease or hepatic disease, those of advanced age, etc), the use of case management strategies (including DOT), regimen and dosing selection in adults and children (daily vs intermittent), the role of TDM, treatment of tuberculosis in the presence of HIV infection (duration of tuberculosis treatment and timing of initiation of ART), treatment of tuberculosis in children, treatment of tuberculosis during pregnancy, and treatment of extrapulmonary tuberculosis, as well as key research priorities, are provided in the full-text version of this practice guideline.

BACKGROUND

The ATS, the CDC, and the IDSA have jointly developed this guideline for the treatment of drug-susceptible tuberculosis. This document provides guidance on the clinical and public health management of tuberculosis in low-incidence countries.

The current document differs from its predecessor, published in 2003 [94], in 3 important areas. First, the process by which the recommendations were developed was substantially modified. For the first time, the Guideline Writing Committee based its recommendations on the certainty in the evidence (also known as the quality of evidence) assessed according to the GRADE methodology (see Supplementary Appendix A: Methods), which incorporates patient values and costs as well as judgments about trade-offs between benefits and harms [1, 2]. A carefully selected panel of experts, screened for conflicts of interest, including specialists in pulmonary medicine, infectious diseases, pharmacokinetics, pediatrics, primary care, public health, and systematic review methodology were assembled to assess the evidence supporting each recommendation. The GRADE method was used to assess the certainty in the evidence and to rate the strength of the recommendations. Second, the ERS has become an endorser of the statement, along with the US NTCA. Representatives from the AAP, the Canadian Thoracic Society, the International Union Against Tuberculosis and Lung Disease, and the WHO also participated in the development of this guideline. Together, these committee members served to provide broader input, thereby expanding the applicability of the guidance beyond North America to include Europe and other low-incidence settings. Last, practice guidelines for the treatment of drug-resistant tuberculosis (including INH monoresistance) are no longer included in this statement and are now covered in a separate practice guideline under development by the ATS, CDC, ERS, and IDSA.

Whereas significant changes have been made, the current document also retains many of the basic principles of tuberculosis care described in the 2003 version. As before, a fundamental aspect of tuberculosis care, regardless of the treatment selected, is ensuring patient adherence to the drug regimen and successful completion of therapy. The responsibility for successful treatment of tuberculosis is placed primarily on the provider or program initiating therapy rather than on the patient. It is well established that appropriate treatment of tuberculosis rapidly renders the patient noninfectious, prevents drug resistance, minimizes the risk of disability or death from tuberculosis, and nearly eliminates the possibility of relapse [95]. Provider responsibility is a central concept in treating patients with tuberculosis, no matter what the source of their care.

The recommendations in this statement are not applicable under all epidemiological circumstances or across all levels of resources that are available to tuberculosis control programs worldwide. It should be emphasized that these guidelines are intended for areas in which mycobacterial cultures, molecular and

phenotypic drug susceptibility tests, and radiographic facilities are available on a routine basis—typically low-incidence (<100 tuberculosis cases per million population), well-resourced countries, where in some settings tuberculosis epidemiology is at or nearing preelimination levels (<10 cases per million) [96, 97]. The WHO has developed tuberculosis practice guidelines (currently under revision) specifically for high-incidence, resource-limited areas of the world [98].

OBJECTIVES OF ANTITUBERCULOSIS THERAPY

Treatment of tuberculosis is focused on both curing the individual patient and minimizing the transmission of *Mycobacterium tuberculosis* to other persons; successful treatment of tuberculosis has benefits both for the individual patient and the community in which the patient resides.

The objectives of tuberculosis therapy are:

1. To reduce the bacillary population rapidly thereby decreasing severity of the disease, preventing death and halting transmission of *M. tuberculosis*;
2. To eradicate persisting bacilli in order to achieve durable cure (prevent relapse) after completion of therapy; and
3. To prevent acquisition of drug resistance during therapy.

Sixty-five years of investigation, including many clinical trials, have consistently supported the requirement for treatment with multiple drugs to achieve these objectives, minimize drug toxicity, and maximize the likelihood of treatment completion [3, 4]. The most effective agents to curtail rapid multiplication of tuberculous bacilli are INH and the fluoroquinolones. Persisting bacilli appear to curtail their metabolic activity; drugs known to be effective against such persisters include the rifamycins and PZA, the latter with activity believed limited to special microenvironments of relatively increased acidity [99].

Objective 1: Rapid killing of multiplying bacilli ("bactericidal effect"): Rapid reduction in the number of replicating bacilli reduces mortality risk [100, 101], and appears to diminish infectiousness, but even optimal therapy on average requires 4–5 weeks to render sputum cultures negative [102–105]. Studies of early bactericidal activity (EBA) measure the rate of decline in bacillary numbers in sputum during the initial 1–2 weeks of treatment; EBA studies have been used in the initial evaluation of virtually every new tuberculosis drug since 1980 [106, 107]. However, the relationship of a drug or regimen's EBA to its ability to achieve durable cure is still uncertain [108]. For example, INH has a remarkable EBA but acts only slowly on persisting bacilli; RIF at the dose currently used (10 mg/kg) has moderate EBA but potent activity against persisters; and PZA has almost no measurable EBA, but acts potently to assist in achieving durable cure [99, 109].

Objective 2: Achievement of relapse-free cure ("sterilizing effect"): Demonstration of relapse-free cure requires lengthy clinical trials. Among the few drugs effective in preventing relapse, the most prominent have been the rifamycins. Rapid and reliable measurement of the sterilizing effect of antituberculous agents remains elusive. In vitro models are not entirely predictive [110, 111]. The most commonly used animal model is the murine model, which has reliably reproduced the results of standard short-course chemotherapy [112]; however, the murine model has been criticized because mice do not develop cavities and caseous necrosis, pathologic hallmarks of human tuberculosis [113]. Other animal models have been proposed, but none fully replicates the human response to *M. tuberculosis* [114]. Recent evidence suggests that extracellular bacilli in necrotic material within cavities may be the major challenge to prevention of relapse after therapy. Studies using sensitive analytic tools such as positron emission tomography–computed tomography scanning and matrix-assisted laser desorption/ionization mass spectrometry imaging in experimental animals and in patients undergoing pulmonary resection have provided evidence of the marked differences in the ability of key drugs (RIF, PZA, levofloxacin, moxifloxacin) to penetrate into pulmonary tissue, into the cellular granuloma, and into caseous material within cavities [115–119]. However, the pathologic sites from which relapses arise remain unclear.

Objective 3: Protection against acquisition of drug resistance (through use of multidrug therapy): The basic biology underlying the acquisition of drug resistance is well understood, though the details involving some individual agents are still uncertain. As a rule, genetic mutations conferring substantial resistance to individual antituberculous agents occur at constant low rates. For example, rifamycins act primarily by inhibiting the action of bacterial RNA polymerase in the translation of DNA to RNA, by binding to and obstructing access to a subunit of the bacterial RNA polymerase. Mutations in a relatively limited (81 base pairs [bp]) genomic segment encoding for this subunit lead to obstruction of rifamycin binding to the polymerase β subunit (*rpoB*); more than half a dozen amino acid substitutions conferring RIF resistance have been well described. In the case of PZA, resistance is most often conferred by mutations in the *pncA* gene, which encodes for an amidase that is required to convert PZA, a prodrug, into its active form, pyrazinoic acid. The *pncA* mutations occur throughout the 350-bp gene, with no notable preference for specific mutations yet described. INH is also a prodrug requiring activation by a bacterial catalase-peroxidase enzyme (encoded by *katG*), coupling with NADH, and binding to an acyl carrier protein reductase (encoded by *inhA*); the process inhibits the synthesis of mycolic acid needed for the mycobacterial cell wall. Resistance to INH arises through multiple mechanisms, including loss of the *katG*-encoded catalase peroxidase activity, and overexpression or alterations in the *inhA*-encoded reductase [120].

The frequency of mutation engendering resistance to specific agents was estimated some 40 years ago; the highest proportion of resistant mutants expected in an unselected bacterial population were 3.5×10^{-6} for INH and 3.1×10^{-8} for RIF [4, 121].

Because these mutations generally occur independently, the likelihood of simultaneous resistance mutations to both INH and RIF is in the range of 11×10^{-14}. Thus, in patients with very high bacillary burdens, the occurrence of mutations conferring resistance to a single drug is likely, to 2 drugs is possible, but to 3 drugs is highly unlikely [10]. Acquisition of drug resistance might occur more readily if there is irregular or sporadic drug taking, inadequate drug absorption, inadequate drug dosing, or ill-informed use of single drug treatment (either by error, or because tuberculosis has not been recognized or considered). If resistance to a specific drug occurs, then the resistant clone will possess an advantage relative to susceptible strains when confronted with that drug, and will have no advantage (or possibly a modest disadvantage, if the mutation confers some biologic "cost") if the drug is not used. In the situation of the standard 3-drug regimen (INH, RIF, PZA), 3 circumstances must likely be present for resistance to RIF to emerge: (1) some mutant bacilli resistant to RIF must be present or appear; (2) the bacilli must be exposed to RIF to favor multiplication of the resistant bacteria; and (3) INH and PZA must not be present in sufficient concentration to offset the survival advantage enjoyed by the RIF-resistant clones; this could occur because they are not employed at all (ie, single drug therapy), or because some combination of circumstances affects the other drugs (eg, a nonacidic compartment is involved thereby disadvantaging PZA, and INH happens to be rapidly metabolized [so-called rapid acetylation due to genetic polymorphisms affecting *N*-acetyl transferase], so that INH is not present in adequate concentration) [59].

Multiple Factors Influence the Outcome of Tuberculosis Treatment

Multiple interrelated factors have been associated with the outcome of tuberculosis therapy. These include:

- Patient factors, such as age, comorbid conditions, immunologic competence, nutritional status, alcohol abuse;
- Radiographic features, such as extent of disease, presence and size of cavities;
- Microbiologic factors, such as baseline colony count, culture positivity at 2 or 3 months;
- Genetic factors, including individual genetic features of drug absorption and metabolism, individual vulnerability to toxicities, immunologic characteristics;
- Programmatic factors, including adherence support interventions (enhancers, enablers, monitoring, supervision/DOT), dosing frequency;
- Pharmacokinetic factors, such as absorption, metabolism, protein binding, drug clearance, total drug quantities administered;
- Bacillary factors, such as drug tolerance, strain susceptibilities to drugs in the regimen; and
- Regimen factors, such as number of active drugs, bactericidal and sterilizing potency, synergy or antagonism, and duration of therapy in relation to drugs employed.

The success of therapy depends upon many diverse elements, only some of which are presently predictable, identifiable, or modifiable. Numerous studies have found an increased risk of relapse among patients with signs of more extensive disease (ie, cavitation or more extensive disease on chest radiograph) [5–9], and/or slower response to treatment (ie, culture status at 2 or 3 months) [4,6,10,11]. Better understanding of the causal pathways through which these elements exert their effect, and greater ability to identify and quantify each of these, should lead to increased therapeutic success, and will inform efforts to develop shorter, less toxic, and better-tolerated treatment regimens in the future [122].

ORGANIZATION AND SUPERVISION OF TREATMENT

PICO Question 1: Does adding case management interventions to curative therapy improve outcomes compared to curative therapy alone among patients with tuberculosis?
(Case management is defined as patient education/counseling, field/home visits, integration/coordination of care with specialists and medical home, patient reminders, incentives/enablers).

Recommendation 1: We suggest using case management interventions during treatment of patients with tuberculosis *(conditional recommendation; low certainty in the evidence).*

PICO Question 2: Does self-administered therapy (SAT) have similar outcomes compared to directly observed therapy (DOT) in patients with various forms of tuberculosis?

Recommendation 2: We suggest using DOT rather than SAT for routine treatment of patients with all forms of tuberculosis *(conditional recommendation; low certainty in the evidence).*

Role of Health Department

Due to the public health implications of prompt diagnosis and effective treatment of tuberculosis, most low-incidence countries designate a government public health agency as having legal authority for controlling tuberculosis [12, 13]. To effectively carry out this charge, the public health agency conducts ongoing epidemiologic surveillance of tuberculosis, ensures access to quality-assured microbiological laboratory services, maintains an uninterrupted supply of antituberculosis medications, and monitors and reports treatment outcomes [13]. The public health agency may also have the authority to apply legal measures in situations of nonadherence as a last resort where other interventions have been pursued without effect. In some jurisdictions diagnostic and treatment services are provided directly by the public health agency, whereas in others, these services are provided by the private sector or by a combination of public and private providers.

Patient-Centered Care and Case Management

Patient-centered care respects an individual's right to participate actively as an informed partner in decisions and activities related to tuberculosis diagnosis and treatment [123, 124]. The Institute of Medicine defines patient-centered care as "providing care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values

guide all clinical decisions" [125]. Given that tuberculosis treatment requires multiple drugs be given for several months, it is crucial that the patient be involved in a meaningful way in making decisions concerning treatment supervision and overall care. International standards have been developed that also support using patient-centered approaches to the management of tuberculosis [14–16].

The optimal organization of tuberculosis treatment often requires the coordination not only of primary and specialty clinical care services, but also community-based organizations and agencies in the public and private sectors [14–16]. The inherent complexities of the healthcare delivery system combined with the diversity of characteristics of patients are best addressed by providing individualized patient-centered case management [13]. In most settings, a patient is assigned a case manager who assesses needs and barriers that may interfere with treatment adherence [17]. With active input from the patient and healthcare providers, the case manager, together with the patient, develops an individualized case management plan with interventions to address the identified needs and barriers [18–20]. The plan is reviewed periodically and revised as needed with the patient and medical team to evaluate the clinical response to therapy, monitor potential drug toxicities, and address any challenges identified with adherence. The spectrum of interventions for achieving adherence may range from routine monthly monitoring to legal confinement [126, 127], with confinement being used only as a last resort. The least restrictive public health interventions that are effective are used to achieve adherence.

Key considerations when developing a case management plan include (1) improving "treatment literacy" by educating the patient about tuberculosis and its treatment, including possible adverse effects [21, 22]; (2) discussing expected outcomes of treatment, specifically the ability to cure the patient of the disease; (3) reviewing methods of supervision and assessing response to therapy; and (4) discussing infectiousness and infection control measures using terminology that is appropriate to the culture, language, age, and reading level of the patient [23]. For non-English-speaking patients, the use of medical interpreter services is preferred over using family or friends as interpreters [24]. Relevant information should be reinforced at each visit. Other components of the patient-centered case management plan include, but are not limited to, setting up patient reminders and systems to follow-up missed appointments [23, 28, 29], use of incentives and enablers [25–27, 30, 31], field and home visits [32], integration and coordination of tuberculosis care with the patient's primary and specialty care, and legal interventions when indicated (Table 4). Overall, the quality of evidence is variable in the few studies examining the impact of case management interventions on outcomes such as treatment success; however, these studies suggest that for the most part, patient-centered case management interventions are helpful with little evidence of harm to patients [128] (see Supplementary Appendix B, Evidence Profiles 1–3). For these reasons, we suggest using case management interventions during treatment of patients with tuberculosis (Recommendation 1: *conditional recommendation; very low certainty in the evidence*).

Approaches to Ensuring Adherence and Treatment Success

Given the critical importance of chemotherapy, both to the patient and to the public, approaches to ensuring adherence to the treatment regimen are a major focus of the overall management plan. To maximize completion of therapy, management strategies should utilize a broad range of approaches. Among these, DOT, the practice of observing the patient swallow her or his antituberculosis medications, has been widely used and deserves special emphasis. To be consistent with the principles of patient-centered care, decisions regarding the use of DOT must be made in concert with the patient [14–16]. For example, DOT can be provided in the office, clinic, or in the "field" (patient's home, place of employment, school, or any other site that is mutually agreeable) by appropriately trained personnel [32]. DOT enables early identification of adverse drug reactions, clinical worsening of tuberculosis, and nonadherence [33]. Moreover, frequent contact with the patient allows providers to facilitate linkage to other medical care and services.

However, the implementation of DOT may not be readily feasible when resources are limited [129]. In such circumstances, patients who are more likely to present a transmission risk to others or are more likely to have difficulty with adherence are prioritized for DOT [17]. In addition, experts advise that DOT must be used with regimens that use intermittent drug administration because of the potential serious consequences of missed doses. Careful attention is needed to ensure that ingestion of the medication is, in fact, observed, as the use of DOT does not guarantee ingestion of all doses of every medication [130]. Patients may miss appointments, may not actually swallow the tablets or capsules, or may deliberately regurgitate the medications. Consequently, the use of DOT does not mitigate the continued need for monitoring for signs of treatment failure. DOT is also advised for all patients residing in institutional settings such as hospitals, nursing homes, opiate replacement clinics, or correctional facilities. In special populations such as individuals with treatment failure, recurrence, or at risk for disseminated tuberculosis (eg, HIV coinfected), experts recommend against the use of SAT given the risks involved in developing drug resistance (Table 5). In recent years, DOT has expanded to other modalities such as web-based video and mobile phones, which have been well received by both patients and health department staff [131–133]. Special attention to maintaining patient privacy is needed when web-based and wireless modalities are used for monitoring.

Systematic reviews of studies conducted in countries with high, medium, and low burdens of tuberculosis have not shown improvement in cure or treatment completion in

patients receiving their antituberculosis treatment by DOT compared with SAT [134–136]. The systematic review conducted to obtain evidence in support of this practice guideline also did not find any significant differences between SAT and DOT when assessing several outcomes of interest, including mortality, treatment completion, and relapse (see Supplementary Appendix B, Evidence Profile 4). However, DOT was significantly associated with improved treatment success (the sum of patients cured and patients completing treatment) and with increased sputum smear conversion during treatment, as compared to SAT. Because DOT is a multifaceted public health intervention that is not amenable to the conventional clinical trials approaches to assessing benefits, and because participation in DOT can be advantageous for early recognition of adverse drug reactions and treatment irregularities, for allowing providers to establish rapport with the patient and for addressing treatment complications expeditiously, DOT remains the standard of practice in the majority of tuberculosis programs in the United States [33–35] and Europe [15]. Population-based studies (representing a low quality of evidence) have suggested that tuberculosis treatment by DOT in comparison to SAT is associated with a reduction in the acquisition and transmission of drug-resistant *M. tuberculosis* (Texas), increased treatment success in HIV-infected patients receiving RFB-containing regimens, shorter duration for completion of treatment (New York City), higher treatment completion rates in incarcerated patients transitioning to the community (Chicago), and a reduction in mortality and loss to follow-up (Brazil) [34, 137–140]. Consequently, we suggest using DOT rather than SAT for routine treatment of patients for all forms of tuberculosis (Recommendation 2: *conditional recommendation; low certainty in the evidence*).

Transfers Between Jurisdictions

Patients being treated for tuberculosis who move from one jurisdiction to another before completion of therapy are more likely to be lost to follow-up than patients who do not move [141]. In the United States, health departments track patients via interjurisdictional referrals, and can use other patient tracking mechanisms (eg, TBNet at http://www.migrantclinician.org/services/network/tbnet.html) for patients who travel internationally) [142–144].

Legal Interventions to Protect Public Health

In extreme circumstances, nonadherent patients may be subject to legal intervention in the form of court-ordered medical examination, DOT, completion of therapy, or civil or criminal detention for completion of tuberculosis treatment when less restrictive measures have been tried and shown to fail [126, 127, 145]. These situations involve special circumstances such as drug resistance, evidence of treatment failure or relapse, and continued concern for transmission in the community, thereby justifying the temporary restriction of individual rights to protect the public's health and safety. Public health laws exist in most jurisdictions that allow these legal interventions, at least for patients who remain infectious, but they should be pursued as a plan of last resort. In the United States, health departments have the sole authority to initiate legal action, and generally the interventions produce good outcomes with treatment completion rates >95% [126, 127]. Outside the United States, legal authority to enforce tuberculosis adherence may originate in other government agencies outside the health department [146].

RECOMMENDED TREATMENT REGIMENS

PICO Question 3: Does intermittent dosing in the intensive phase have similar outcomes compared to daily dosing in the intensive phase for treatment of drug-susceptible pulmonary tuberculosis?

Recommendation 3a: We recommend the use of daily rather than intermittent dosing in the intensive phase of therapy for drug-susceptible pulmonary tuberculosis *(strong recommendation; moderate certainty in the evidence)*.

Recommendation 3b: Use of thrice-weekly therapy in the intensive phase (with or without an initial 2 weeks of daily therapy) may be considered in patients who are not HIV-infected and are also at low risk of relapse (pulmonary tuberculosis caused by drug-susceptible organisms, that at the start of treatment is noncavitary and/or smear negative) *(conditional recommendation; low certainty in the evidence)*.

Recommendation 3c: In situations where daily or thrice-weekly DOT therapy is difficult to achieve, use of twice-weekly therapy after an initial 2 weeks of daily therapy may be considered for patients who are not HIV-infected and are also at low risk of relapse (pulmonary tuberculosis caused by drug-susceptible organisms, that at the start of treatment is noncavitary and/or smear negative) *(conditional recommendation; very low certainty in the evidence)*. Note: If doses are missed in a regimen using twice-weekly dosing then therapy is equivalent to once weekly, which is inferior (see PICO Question 4).

PICO Question 4: Does intermittent dosing in the continuation phase have similar outcomes compared to daily dosing in the continuation phase in patients with drug-susceptible pulmonary tuberculosis patients?

Recommendation 4a: We recommend the use of daily or thrice-weekly dosing in the continuation phase of therapy for drug-susceptible pulmonary tuberculosis *(strong recommendation; moderate certainty in the evidence)*.

Recommendation 4b: If intermittent therapy is to be administered in the continuation phase, then we suggest use of thrice-weekly instead of twice-weekly therapy *(conditional recommendation; low certainty in the evidence)*. This recommendation allows for the possibility of some doses being missed; with twice-weekly therapy, if doses are missed then therapy is equivalent to once weekly, which is inferior.

Recommendation 4c: We recommend against use of once-weekly therapy with INH 900 mg and rifapentine (RPT) 600 mg in the continuation phase *(strong recommendation; high certainty in the evidence)*. In uncommon situations where more than once-weekly DOT is difficult to achieve, once-weekly continuation phase therapy with INH 900 mg plus RPT 600 mg may be considered for use only in HIV-uninfected persons without cavitation on chest radiography.

Deciding to Initiate Treatment

Empiric treatment with a 4-drug regimen is initiated promptly in patients (children and adults) with high likelihood of having tuberculosis or those seriously ill with a disorder suspicious for tuberculosis, even before AFB smear microscopy, molecular tests, and mycobacterial culture results are known. Initiation of treatment is not delayed because of negative AFB smears for patients in whom tuberculosis is suspected and who have

a life-threatening condition. The decision to initiate combination chemotherapy for tuberculosis is based on multiple factors including clinical, radiographic, laboratory, patient, and public health factors (Figure 1). Clinical judgment and index of suspicion also play a critical role in deciding to initiate treatment. In addition to smear microscopy and mycobacterial culture, CDC recommends the use of a rapid molecular test on at least one specimen from each patient with signs and symptoms of pulmonary tuberculosis for whom a diagnosis of tuberculosis is being considered but has not been established, and for whom the test result would alter case management or tuberculosis control activities [147]. Use of molecular tests directly on clinical samples has been shown to shorten time to diagnosis, and some tests have the additional ability to provide information on drug susceptibility [147, 148].

In the presence of a clinical syndrome compatible with tuberculosis, a positive AFB smear provides strong inferential evidence for the diagnosis of tuberculosis. If the diagnosis is confirmed by isolation of *M. tuberculosis* or a positive rapid molecular test, or is strongly inferred from clinical or radiographic improvement consistent with a response to tuberculosis treatment, the regimen is continued to complete a standard course of therapy. In patients with a positive AFB smear, but a negative rapid molecular test (including an assessment for polymerase chain reaction inhibitors, reported to be present in 2%–5% of respiratory specimens tested by nucleic acid amplification tests [149, 150]), it is unlikely that the positive smear is due to *M. tuberculosis*, particularly when molecular testing of a second smear-positive specimen is also negative [147]. If empiric treatment is started, cultures throughout are negative, and there is no response to treatment, yet the interferon-γ release assay (IGRA) or purified protein derivative (PPD)–tuberculin skin test (TST) is positive, consideration is given to treatment of latent tuberculosis infection using the following options: (1) stop treatment if RIF and PZA were included in the initial empiric 4-drug therapy, administered for at least 2 months [151]; (2) continue treatment with RIF, with or without INH, for a total of 4 months; (3) give 12 weekly doses of INH/RPT by DOT [152]; or (4) continue treatment with INH for a total of 9 months [83, 153, 154]. In patients in whom there is a low suspicion for active tuberculosis (not initially treated), if cultures remain negative, the IGRA or PPD-TST is positive (≥5 mm), and the abnormal chest radiograph is unchanged after 2 months (ATS/CDC class 4), treatment for latent tuberculosis infection is indicated [155]. If not previously treated, these patients are at increased risk for development of active tuberculosis with case rates 2.5–19 times higher than those of persons infected by *M. tuberculosis* with normal chest radiographs [156–159]. These patients are high-priority candidates for treatment of latent tuberculosis infection.

If clinical suspicion for active tuberculosis is low, the options are to begin treatment with combination chemotherapy or to defer treatment until additional data have been obtained to clarify the situation (usually within 2 months). An advantage of the early use of combination chemotherapy is that once active disease is excluded by negative cultures and lack of clinical or radiographic response to treatment, the patient will have completed 2 months of combination treatment that can be applied to the total duration of treatment for latent tuberculosis infection. Even when the suspicion for active tuberculosis is low, treatment for latent tuberculosis infection with a single drug is *not* initiated until active tuberculosis has been excluded, usually by negative cultures.

In general, for complicated diagnostic or management situations, consultation with local and state health departments is advised. In the United States, the CDC's Division of Tuberculosis Elimination funds tuberculosis regional training and medical consultation centers (http://www.cdc.gov/tb/education/rtmc/), which provide medical consultation to programs and health providers on management of tuberculosis. In Europe, the WHO and ERS Tuberculosis Consilium (https://www.tbconsilium.org) provides similar consultation services regarding the diagnosis and treatment of tuberculosis.

Regimens

The preferred regimen and other choices are listed in Table 2. Patient factors should be considered when selecting administration schedule (intermittency), and in some instances regimen composition. Feasibility of DOT is sometimes an additional consideration when selecting frequency of administration. Regimens for adults and children are identical except in uncommon circumstances where it may be acceptable to omit EMB from the initial treatment regimen for young children (see "Children"). For all regimens, patients are treated until they have received the specified total number of doses for the treatment regimen (ie, not solely based on duration of treatment).

Preferred Regimen

The preferred regimen for treating adults with tuberculosis caused by organisms that are not known or suspected to be drug resistant is a regimen consisting of an intensive phase of 2 months of INH, RIF, PZA, and EMB followed by a continuation phase of 4 months of INH and RIF [3, 36, 37]. To reduce the risk of relapse, the continuation phase of treatment is extended for an additional 3 months for patients who had cavitation on the initial (or follow-up) chest radiograph and, in addition, are culture positive at the time of completion of the intensive phase of treatment.

The intensive phase of treatment consists of 4 drugs (INH, RIF, PZA, EMB) because of the current proportion of new tuberculosis cases worldwide caused by organisms that are resistant to INH [38–41]; however, if therapy is being initiated after drug susceptibility test results are known and the patient's isolate is susceptible to both INH and RIF, EMB is not necessary, and the intensive phase can consist of INH, RIF, and PZA only. EMB can be discontinued as soon as the results of drug

susceptibility studies demonstrate that the isolate is susceptible to INH and RIF.

With respect to administration schedule, the preferred frequency is once daily for both the intensive and continuation phases. Based on systematic reviews conducted to obtain evidence in support of this guideline (see Supplementary Appendix B, Evidence Profiles 5–10), we recommend the use of daily rather than intermittent dosing in the intensive phase of therapy for drug-susceptible pulmonary tuberculosis (Recommendation 3a: *strong recommendation; moderate certainty in the evidence*). For the continuation phase, based on systematic reviews conducted to obtain evidence in support of this guideline (see Supplementary Appendix B, Evidence Profiles 5–10), we recommend use of daily or thrice-weekly dosing for the continuation phase of therapy (Recommendation 4a: *strong recommendation; moderate certainty in the evidence*). Although administration of antituberculosis drugs using DOT 5 days a week has been reported in a large number of studies, it has not been compared with 7-day administration in a clinical trial. Nonetheless, on the basis of substantial clinical experience, experts believe that 5-days-a-week drug administration by DOT is an acceptable alternative to 7-days-a-week administration, and either approach may be considered as meeting the definition of "daily" dosing. Patient-centered care, case management, and DOT are discussed in the "Organization and Supervision of Treatment" section of this guideline.

Other Regimens

There are alternative regimens that are variations of the preferred regimen. As described below, alternative regimens may be acceptable in certain clinical and/or public health situations (see "Treatment in Special Situations"). An administration frequency of less than daily in the intensive phase of treatment is generally not preferred.

Thrice-Weekly Dosing Throughout

In HIV-uninfected patients with noncavitary disease caused by drug-susceptible organisms, thrice-weekly (ie, 3 times per week) dosing throughout both intensive and continuation phases of treatment by DOT may be considered when daily treatment is not feasible or poorly tolerated. Thrice-weekly dosing has been associated with higher rates of treatment failure, relapse, and acquired drug resistance in high-quality systematic reviews [36, 160]. The risks for these poor outcomes of treatment were higher in HIV-infected patients (especially if not treated with antiretrovirals), and patients with cavitary disease or baseline drug resistance. Based on evidence supporting the recommendations obtained through systematic reviews (see Supplementary Appendix B, Evidence Profiles 5,6,8–10), use of thrice-weekly therapy in the intensive phase (with or without an initial 2 weeks of daily therapy) may be considered in patients who are not HIV-infected and are also at low risk of relapse (pulmonary tuberculosis caused by drug-susceptible organisms, that at the start of treatment is noncavitary and/or smear negative) (Recommendation 3b: *conditional recommendation; low certainty in the evidence*).

Twice-Weekly Dosing Throughout or Twice-Weekly Dosing After 2–3 Weeks of Daily Dosing

Twice-weekly dosing (ie, 2 times per week) either throughout treatment or after an initial period of 2–3 weeks of daily therapy is not generally recommended because of a lack of high-quality evidence to support its use, and because in twice-weekly therapy, if doses are missed then therapy is equivalent to once weekly, which is inferior (see "Once-Weekly Continuation Phase," below). However, some tuberculosis programs have reported longstanding programmatic treatment success with an initial daily regimen followed by twice-weekly therapy [161], and this regimen remains in use by some public health programs in the United States. In situations where daily or thrice-weekly DOT therapy is difficult to achieve, use of twice-weekly therapy after an initial 2 weeks of daily therapy may be considered for patients who are not HIV infected and are also at low risk of relapse (pulmonary tuberculosis caused by drug-susceptible organisms, that at the start of treatment is noncavitary and/or smear negative) (Recommendation 3c: *conditional recommendation; very low certainty in the evidence*) (see Supplementary Appendix B, Evidence Profile 7).

Twice-Weekly Continuation Phase

Twice weekly treatment in the continuation phase has been studied in clinical trials [36], and is used by US tuberculosis control programs. Based on our systematic review, if intermittent therapy during the continuation phase is considered, then we suggest use of thrice-weekly instead of twice-weekly therapy. (Recommendation 4b: *conditional recommendation; low certainty in the evidence*) (see Supplementary Appendix B, Evidence Profiles 5–8). As noted above for twice-weekly regimens, an advantage of a thrice-weekly regimen is that it allows for the possibility of some doses being missed; with twice-weekly therapy, if doses are missed then therapy is equivalent to once weekly, which is inferior (see "Once-Weekly Continuation Phase," below).

Once-Weekly Continuation Phase

In clinical trials, once-weekly treatment with INH plus RPT 600 mg was less active than standard RIF-based treatment [9, 162]. In the Tuberculosis Trials Consortium (TBTC) Study 22, characteristics independently associated with increased risk of failure or relapse were sputum culture positivity at the end of intensive phase, cavitation on chest radiograph, being underweight, bilateral pulmonary involvement, and being a non-Hispanic white person [9]. Furthermore, relapse with rifamycin-monoresistant tuberculosis occurred among HIV-infected tuberculosis patients treated with the once-weekly INH/RPT continuation phase regimen [59]. In uncommon situations where more than once-weekly DOT is difficult to achieve, once-weekly continuation phase therapy with INH 900 mg plus RPT 600 mg

may be considered for use only in HIV-uninfected persons without cavitation on chest radiography. Otherwise, we recommend against use of once-weekly therapy with INH 900 mg plus RPT 600 mg (Recommendation 4c: *strong recommendation; high certainty in the evidence*) (see Supplementary Appendix B, Evidence Profile 11).

Alternative Regimen Composition

In some cases, either because of intolerance to first-line drugs or the presence of monoresistance, an alternative regimen may be required. If PZA cannot be included in the initial regimen, or the isolate is determined to be resistant to PZA (an unusual circumstance, except for *M. bovis* and *M. bovis* var BCG), experts recommend a regimen consisting of INH, RIF, and EMB for the initial 2 months followed by INH and RIF for 7 months given either daily or thrice weekly.

Fluoroquinolones (Moxifloxacin and Levofloxacin)

In scenarios in which EMB or INH cannot be used, the role of moxifloxacin or levofloxacin has not been established through clinical trials. Experts on occasion use moxifloxacin or levofloxacin in place of EMB during intensive phase in adults in whom EMB cannot be used, or in place of INH throughout treatment in adults in whom INH cannot be used (see Supplementary Appendix C: Drugs in Current Use for details on adverse effects of fluoroquinolones, including QT prolongation).

There is no evidence that moxifloxacin or levofloxacin can be used in place of a rifamycin or PZA while maintaining a 6-month treatment duration. If a rifamycin cannot be included in the initial regimen due to resistance or intolerance, then a regimen based on the principles described for treating drug-resistant tuberculosis is used. In situations in which several of the first-line agents cannot be used because of intolerance, regimens based on the principles described for treating drug-resistant tuberculosis are used.

Importantly, all alternative regimens using fluoroquinolones in place of EMB or INH are 6 months or longer in duration. There is definitive clinical trial evidence that 4-month daily regimens that substitute moxifloxacin or gatifloxacin for EMB, or moxifloxacin for INH, are significantly less effective than the preferred, standard daily 6-month treatment for drug-susceptible pulmonary tuberculosis [5, 163, 164]. Therefore we recommend against the routine use of 4-month fluoroquinolone-containing regimens for treatment of drug-susceptible pulmonary tuberculosis.

A single randomized trial showed that a regimen of daily moxifloxacin/RIF/PZA/EMB for 2 months followed by once-weekly 1200 mg RPT + 400 mg moxifloxacin for 4 continuation phase months had relapse rates similar to the standard 6-month regimen given daily [164]. Use of this regimen (including a daily moxifloxacin-containing intensive phase) may be considered. It is important to note that each dose of RPT was preceded by a meal of 2 boiled eggs and slices of bread, provided to increase the absorption of RPT. If this regimen is used, it is ideally implemented within the context of program-based operational research with suitable monitoring [165]. Of note, there is no evidence that a once-weekly continuation phase comprised of 1200 mg RPT + 400 mg moxifloxacin after 2 months of intensive phase INH/RIF/PZA/EMB (ie, without moxifloxacin in place of EMB in the intensive phase), would achieve similar outcomes.

Baseline and Follow-up Evaluations

Recommended baseline and follow-up evaluations for patients suspected of having tuberculosis and treated with first-line medications are summarized in Figure 2. At baseline, patients in whom pulmonary tuberculosis is suspected have 3 appropriate sputum specimens collected for microscopic examination and mycobacterial culture, and at least one specimen is tested with a rapid molecular test. When the lung is the site of disease, 3 sputum specimens are obtained 8–24 hours apart [166, 167]. In patients who are not producing sputum spontaneously, induction of sputum using aerosolized hypertonic saline or bronchoscopy (performed under appropriate infection-control procedures) may be necessary to obtain specimens. Susceptibility testing for INH, RIF, EMB, and PZA is performed on an initial positive culture, regardless of the source. A rapid molecular test for drug resistance is performed in patients at risk for drug-resistant tuberculosis, and when resources permit, may be performed in all patients [15, 168]. Second-line drug susceptibility testing should be done only in reference laboratories and is limited to specimens from patients who have had prior therapy, have been in contact with a patient with known multidrug or extensively drug-resistant tuberculosis, have suspected or demonstrated resistance to RIF and/or other first-line drugs, are unable to tolerate RIF, or who have positive cultures after >3 months of treatment [15, 168].

During treatment of patients with pulmonary tuberculosis, at a minimum, a sputum specimen for AFB smear and culture are obtained at monthly intervals until 2 consecutive specimens are negative on culture. Duration of the continuation phase regimen hinges on the microbiological status at the end of the intensive phase of treatment, thus, obtaining sputum specimens at the time of completion of 2 months of treatment is critical if sputum culture conversion to negative has not already been documented. For patients who had positive AFB smears at the time of diagnosis, follow-up smears may be obtained at more frequent intervals (for example, every 2 weeks until 2 consecutive specimens are negative) to provide an early assessment of the response to treatment, especially for patients in situations with high risk of transmission. On occasion, AFB-positive sputa are culture-negative; this occurs most frequently among patients with far-advanced cavitary tuberculosis after the first few months of treatment. It is thought that AFB smear positive (but culture-negative) sputa contain organisms that are dead and that their presence is not a sign of treatment failure, even when noted later in treatment. Dead organisms also can cause

a positive result on molecular tests; routine performance of molecular tests on follow-up sputum samples, after an initial positive test, is not useful.

Drug susceptibility tests are repeated on *M. tuberculosis* isolated in culture from sputum obtained after a patient has been on treatment for ≥3 months. As described in the "Treatment Failure" section, patients who have *M. tuberculosis* isolated in culture from sputum obtained after 4 months of treatment are considered as having failed treatment and managed accordingly.

For patients with positive cultures at diagnosis, a repeat chest radiograph at completion of 2 months of treatment may be useful but is not essential. Tuberculosis programs often conduct a chest radiograph at completion of therapy as it provides a baseline against which subsequent examinations can be compared, but, as with the 2-month examination, it is not essential. When the initial sputum cultures are negative, a presumptive diagnosis can be made if radiographic improvement is noted, generally by the time 2–3 months of treatment have been completed [93]. Thus, based on expert opinion, in patients with negative initial cultures, a chest radiograph is recommended after 2–3 months of treatment and at the completion of treatment to document response to therapy. Generally, systematic follow-up after completion of therapy is not necessary.

In addition to the microbiological and imaging examinations discussed here, other appropriate assessments and laboratory tests are summarized in Figure 2. For patients with extrapulmonary tuberculosis, the frequency and kinds of evaluations will depend on the sites involved and the ease with which specimens can be obtained. Monitoring assessments for patients treated with second-line drugs are listed by drug in Supplementary Appendix C: Drugs in Current Use.

Identification and Management of Patients at Increased Risk of Relapse

The culture result of a sputum specimen obtained at the completion of the intensive phase of treatment (2 months) has been shown to correlate with the likelihood of relapse after completion of treatment for pulmonary tuberculosis, albeit with low sensitivity [9, 44–46]. Cavitation on the initial chest radiograph has also been shown to be a risk factor for relapse [9, 47]. In patients treated for 6 months, having both cavitation and a positive culture at completion of 2 months of therapy has been associated with rates of relapse of approximately 20% compared with 2% among patients with neither factor [9, 45].

The most effective means of decreasing the likelihood of relapse for patients at risk has not yet been determined by clinical trials; however, indirect evidence from a controlled clinical trial and an observational study among patients with pulmonary tuberculosis in Hong Kong showed that prolonging treatment decreased the rate of relapse [47, 169]. It has also been reported that for patients at high risk of relapse, prolongation of the once-weekly INH/RPT continuation phase from 4 to 7 months resulted in a decreased rate of relapse [170].

In view of this evidence, for patients who have cavitation on the initial chest radiograph and who have positive cultures at completion of 2 months of therapy, expert opinion is to extend the continuation phase with INH and RIF for an additional 3 months (ie, a continuation phase of 7 months in duration, corresponding to a total of 9 months of therapy).

Because patients who had either cavitation on the initial chest radiograph or a positive culture at 2 months had an increased rate of relapse [9, 45], patients with one or the other of these risk factors are followed more closely and consideration given to extending treatment duration if there are suggestions of a poor response. Additional factors to be considered in deciding to prolong treatment in patients with either cavitation or a positive culture at 2 months (but not both) might include being >10% below ideal body weight; being a smoker; having diabetes, HIV infection, or other immunosuppressing condition; or having extensive disease on chest radiograph [46, 48–52].

Interruptions in Therapy

Interruptions in therapy are common in the treatment of tuberculosis. When interruptions occur, the person responsible for supervision must decide whether to restart a complete course of treatment or simply to continue as intended originally. In general, the earlier the break in therapy and the longer its duration, the more serious the effect and the greater the need to restart treatment from the beginning. Continuous treatment is more important in the intensive phase of therapy when the bacillary population is highest and the chance of developing drug resistance greatest. During the continuation phase, the number of bacilli is much smaller and the goal of therapy is to kill the persisting organisms. The duration of the interruption and the bacteriologic status of the patient prior to and after the interruption are also important considerations.

There is no evidence upon which to base detailed recommendations for managing interruptions in treatment, and no recommendations will cover all of the situations that may arise. The approach summarized in Table 6 (modified from the New York City Bureau of Tuberculosis Control [171]) is presented as an example.

When interruptions are due to an interim loss of follow-up, at the time the patient is returned to treatment, additional sputum are obtained for repeat culture and drug susceptibility testing. If the cultures are still positive, the treatment regimen is restarted. If sputum cultures are negative, the patient could be treated as having culture-negative tuberculosis and given an additional 4 months of INH and RIF chemotherapy, as long as the original specimen was drug susceptible and the original intensive phase regimen included INH, RIF, and PZA. Regardless of the timing and duration of the interruption, DOT is used subsequently. If the patient was already being managed with DOT, additional measures will be necessary to ensure completion of therapy. Consultation with an expert is advised to assist in managing treatment interruptions.

Definition of Completion of Therapy

The determination of whether or not treatment has been completed is based on the total number of doses taken—not solely on the duration of therapy (Table 2). Tuberculosis control program practice in the United States and in several European countries is to administer all of the specified number of doses for the intensive phase within 3 months and those for the 4-month continuation phase within 6 months, so that the 6-month regimen is completed within 9 months. If these targets are not met, the patient must be considered to have interrupted therapy and be managed as described above (Table 6).

PRACTICAL ASPECTS OF TREATMENT

Drug Administration

In general, tuberculosis drugs are administered together, at one dosing so as to achieve maximal peak serum concentrations and to facilitate DOT. Bioavailability of all of the drugs (except for RPT) is greatest when taken on an empty stomach. The exception is RPT, for which bioavailability increases by up to 86% with high-fat meals [172]. If medications need to be combined with food or liquid for dosing, keep in mind that INH absorption decreases when combined with glucose or lactose; crushed INH tablets in foods containing low glucose, such as sugar-free pudding, are stable. However, crushed tablets mixed with food should not be stored for later use [173]. The commercially prepared INH elixir uses sorbitol as the vehicle; sorbitol may also cause diarrhea, thereby limiting its use.

Parenteral drug administration is indicated for severely ill patients who cannot take oral therapy, and may be useful for the uncommon patient with suspected or documented malabsorption. Of the first-line drugs, parenteral preparations of INH and RIF, as well as most fluoroquinolones, are available.

Fixed-Dose Combination Preparations

Clinical trials and a recent systematic review have concluded that overall, there is no significant difference between fixed-dose combinations (FDCs) and single-drug combinations for key outcomes, including sputum smear or culture conversion, failure, relapse, death, serious adverse events, or adverse events that lead to discontinuation of therapy [174–178]. The patient-specific advantages to using FDC drugs include ease of administration and the potential for reducing medication errors. The key program and clinician-specific advantage of FDC formulations is the simplification of drug supply management (procurement, storage, and distribution) and simpler prescription writing. If FDCs are used, clinicians should be aware that FDC and non-FDC products have similar commercial names with different drug compositions, including Rifadin (RIF only), Rifamate (INH and RIF), and Rifater (INH, RIF, and PZA) (see Supplementary Appendix C).

Management of Common Adverse Effects

Mild adverse effects usually can be managed with treatment directed at controlling the symptoms; severe effects usually require the offending drug(s) to be discontinued. If a drug is permanently discontinued, then a replacement drug, typically from a different drug class, is included in the regimen. Patients with severe tuberculosis often require the initiation of an alternate regimen during the time the offending drug(s) are held. Management of serious adverse effects often requires expert consultation. The suggested practices listed below for handling common adverse effects during treatment (ordered from most to least common) are based on expert opinion.

Gastrointestinal Upset; Nausea, Vomiting, Poor Appetite, Abdominal Pain

Gastrointestinal reactions are common, especially early in therapy [53]. The optimum approach to management of epigastric distress or nausea with tuberculosis drugs is not clear. To minimize symptoms, patients receiving SAT may take the medications at bedtime. Gastrointestinal intolerance not associated with hepatotoxicity can be treated with antacids, which have less impact on absorption or peak concentration of first-line drugs than administration with food [54]. Some experts report success with proton pump inhibitors for reducing gastrointestinal upset. Any combination of otherwise unexplained nausea, vomiting, and abdominal pain is evaluated with a physical examination and liver function tests, including ALT, AST, bilirubin, and alkaline phosphatase to assess for possible hepatotoxicity [55]. Alternatively, a light snack (low-fat food) such as a cracker might suffice for some patients. Either option is preferable to splitting a dose or changing to a second-line drug. It is important to note that divalent cations (calcium, iron, zinc) as occur in some antacids and nutritional supplements are not coadministered with fluoroquinolones because they decrease absorption of the drug, possibly leading to treatment failure [179].

Rash

All antituberculosis drugs can cause a rash, the severity of which determines management [180]. If the rash is mainly itchy without mucous membrane involvement or systemic signs such as fever, treatment is symptomatic with antihistamines, and all antituberculosis medications can be continued. A petechial rash is more concerning and suggests thrombocytopenia from a rifamycin (ie, RIF, RFB, RPT) hypersensitivity [181]. If the platelet count is low, the rifamycin is permanently stopped and the platelet count closely monitored until definite improvement is noted. Drugs are also stopped if the patient has a generalized erythematous rash. Fever and/or mucous membrane involvement suggests Stevens-Johnson syndrome, toxic epidermal necrosis, or drug reaction with eosinophilia and systemic symptoms syndrome or drug hypersensitivity syndrome. Hypersensitive reactions to multiple antituberculosis drugs have been noted, particularly in persons with HIV infection [180].

Some experts manage severe systemic reactions in the inpatient setting, using an interval of several days between drug rechallenges, closely monitoring markers of hypersensitivity (such as rash, fever, transaminitis, eosinophilia, pruritus, etc). If any of these markers develop, then the drug is stopped and identified as the offender, eliminating it from the regimen. Systemic corticosteroids may be used to treat severe systemic reactions. Using steroids to treat systemic reactions, even in the setting of severe tuberculosis, has not worsened outcomes [182].

When the rash has substantially improved, medications can be restarted individually at intervals of 2–3 days. RIF is restarted first (the most potent drug), followed by INH, then EMB or PZA. If the rash recurs, the last drug added is stopped. If the first 3 drugs have been restarted without a rash, the fourth drug is not restarted unless the rash was mild and that drug essential. Research evaluating drug provocation tests or drug desensitization strategies is needed [180].

Drug Fever

Drug fever is essentially a diagnosis of exclusion. Other causes of fever such as tuberculosis (fever may persist 2 months or longer into treatment) [183, 184]; paradoxical reaction, especially in HIV-infected patients (See "HIV Infection") [185–187]; and superinfection must be excluded. Patients with drug fever generally feel well despite body temperatures ≥39°C. Drug fever does not follow a specific pattern and eosinophilia need not be present. Stopping drugs usually resolves the fever within 24 hours. Once afebrile, the patient should restart drugs individually every 2–3 days, similar to the approach to drug rechallenge for rash.

Hepatotoxicity

Drug-induced hepatitis is the most frequent serious adverse reaction to the first-line drugs (see "Hepatic Disease" and Supplementary Appendix C). INH, RIF, and PZA can cause drug-induced liver injury, which is suspected when the ALT level is ≥3 times the upper limit of normal in the presence of hepatitis symptoms, or ≥5 times the upper limit of normal in the absence of symptoms [56]. If the ALT level is <5 times the upper limit of normal, toxicity can be considered mild, an ALT level 5–10 times normal defines moderate toxicity, and an ALT level >10 times normal (ie, >500 IU) is severe.

An asymptomatic increase in ALT concentration occurs in nearly 20% of patients treated with the standard 4-drug regimen [188, 189]. In the absence of symptoms, therapy should not be altered because of modest asymptomatic elevations of ALT, but the frequency of clinical and laboratory monitoring should be increased. In most patients, asymptomatic ALT elevations resolve spontaneously. However, if ALT levels are ≥5 times the upper limit of normal (with or without symptoms) or ≥3 times normal in the presence of symptoms, hepatotoxic drugs are stopped immediately and the patient is evaluated carefully. Similarly, a significant increase in bilirubin and/or alkaline phosphatase is cause for a prompt evaluation; disproportionate increases in bilirubin and alkaline phosphatase (as compared to increases in serum ALT) may be seen with RIF hepatotoxicity [56].

Other causes of abnormal liver tests must be excluded before diagnosing drug-induced hepatitis (Table 7). If ALT levels are consistent with hepatotoxicity, all hepatotoxic drugs must be stopped and serum ALT and prothrombin time or international normalized ratio (INR) levels followed until levels return to baseline. Consult a liver specialist if the patient's clinical or laboratory status continues to worsen.

Once the ALT concentration returns to <2 times the upper limit of normal, antituberculosis medications are restarted individually (see [56] for additional details). In patients with elevated baseline ALT from preexisting liver disease, drugs are restarted when the ALT returns to near-baseline levels. The optimal approach to reintroducing tuberculosis treatment after hepatotoxicity is not known [57, 58]; however, most tuberculosis programs use sequential reintroduction of drugs. Because RIF is much less likely to cause hepatotoxicity than INH or PZA, it is restarted first. If there is no increase in ALT after approximately 1 week, INH may be restarted. PZA can be started 1 week after INH if ALT does not increase. If symptoms recur or ALT increases, the last drug added should be stopped. If RIF and INH are tolerated and hepatitis was severe, PZA can be assumed to be responsible and is discontinued. In this last circumstance, depending on the number of doses of PZA taken, severity of disease, and bacteriological status, the total duration of therapy might be extended to 9 months.

Optic Neuritis

EMB-related visual impairment during treatment of active tuberculosis has been estimated to occur in 22.5 per 1000 persons (2.25%) receiving EMB at standard doses [190] (see Supplementary Appendix C). The onset of optic neuritis is usually >1 month after treatment initiation but can occur within days [191, 192]. The opinion of experts is that baseline visual acuity (Snellen test) and color discrimination tests followed by monthly color discrimination tests are performed during EMB use. To avoid permanent deficits, EMB is promptly discontinued if visual abnormalities are found. If vision does not improve with cessation of EMB, experts recommend stopping INH as well, as it is also a rare cause of optic neuritis [193].

Drug–Drug Interactions

Interactions Affecting Antituberculosis Drugs

Drug–drug interactions can change the concentrations of the drugs involved. Relatively few interactions substantially change antituberculosis drug concentrations; much more often, the antituberculosis drugs cause clinically relevant changes in the concentrations of other drugs. The exceptions to this general rule are RFB and the fluoroquinolones.

- Inhibitors of CYP3A increase the serum concentrations of RFB and one of its metabolites (25-O-desacetyl-rifabutin),

sometimes producing toxicities. For example, administering ritonavir, a very potent CYP3A inhibitor, with the standard daily dose of RFB (300 mg) increases the serum concentrations of RFB (4-fold) and 25-O-desacetyl-rifabutin (35-fold) [194] and is associated with increased rates of leukopenia, arthralgias, skin discoloration, and anterior uveitis [195, 196]. Conversely, administering RFB with a CYP3A inducer such as efavirenz or phenytoin may decrease RFB concentrations [197], and this may lead to clinical failures and the selection of rifamycin-resistant *M. tuberculosis*. Recommendations for RFB dose adjustments are available at AIDSinfo, and at the CDC website (http://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/default.htm). Because interactions are complex and given the rapid emergence of new data on antiretroviral therapy (ART), the management of HIV-related tuberculosis cases should involve a physician with experience in this field.

- Absorption of the fluoroquinolones is markedly decreased by ingestion of medications containing divalent cations (calcium, iron, zinc) including antacids [198, 199]; supplements or vitamins containing calcium, iron, or zinc [200]; sucralfate [201]; and the chewable tablet formulation of didanosine [202]. These drug interactions can be avoided by ingesting medications containing divalent cations at least 2 hours apart from fluoroquinolones [203]. In addition, moxifloxacin serum concentrations are decreased by 25%–30% in the presence of RIF due to the induction of phase II metabolic enzymes (sulfation and glucuronidation) [204]. RPT and RFB also may decrease moxifloxacin serum concentrations, though the clinical significance of these drug–drug interactions in individual patients is uncertain.

Antituberculosis Drugs Affecting Other Drugs

Drug Interactions Due to Rifamycins

Most of the clinically relevant drug–drug interactions involving the antituberculosis drugs are due to the effect of the rifamycins (RIF, RFB, and RPT) on the metabolism of other drugs [205]. All of the rifamycins are inducers of a variety of metabolic pathways, particularly those involving the various isozymes of the cytochrome P450 (CYP) system [206]. By inducing the activity of metabolic enzymes, rifamycins decrease the serum concentrations of many drugs, sometimes to subtherapeutic levels [207]. RIF is the most potent enzyme inducer and RFB the least, while RPT's potency depends on its frequency of administration [208, 209]. Daily RPT is at least as potent as daily RIF, while once-weekly RPT (as used in combination with INH for latent tuberculosis infection [210]) has limited effects on other drugs.

The well-described, clinically relevant, drug–drug interactions involving the rifamycins are presented in Table 8 [206, 211]; however, many possible interactions involving the rifamycins have not been fully investigated and additional clinically relevant interactions undoubtedly will be described. Therefore, it is important to check all concomitant medications for possible, as well as confirmed, drug–drug interactions with rifamycins.

Rifamycin inductive effects typically take approximately 1–2 weeks to reach steady state after the rifamycin is started, and inductive effects typically resolve over approximately 2 weeks after the rifamycin is discontinued [209]. If the dose of a medication is increased to compensate for the effect of a rifamycin, it is critical to reduce the dose within 2 weeks after the rifamycin is discontinued and its inductive effect resolves.

RFB can be used in place of RIF if there is an unacceptable drug–drug interaction between RIF and another drug such as cyclosporine [212, 213] and most of the HIV-1 protease inhibitors [208, 214, 215]. All the rifamycins may cause unacceptable decreases in the serum concentrations of certain drugs such as itraconazole [216–218].

Drug Interactions Due to INH

INH is a relatively potent inhibitor of several CYP isozymes [219, 220] and increases concentrations of some drugs to the point of toxicity such as the anticonvulsants phenytoin [221, 222] and carbamazepine [223, 224]. INH also increases concentrations of benzodiazepines metabolized by oxidation, such as diazepam [225] and triazolam, but not those metabolized by conjugation, such as oxazepam [226]. Of note, the inductive effect of RIF on CYP isozymes outweighs the inhibitory effect of INH, so that the overall effect of combined therapy with RIF and INH is a decrease in the concentrations of drugs such as phenytoin [227] and diazepam [225].

INH may increase toxicity of other drugs—acetaminophen [228], valproate [229], serotonergic antidepressants [230], warfarin [231], and theophylline [232]—but these potential interactions have not been well studied. A possible interaction between INH and disulfiram was initially described [233]; however, a retrospective study found that disulfiram was safe when added to intermittent, directly observed INH-containing tuberculosis treatment [234].

Drug Interactions Due to the Fluoroquinolones

Ciprofloxacin [235] inhibits the metabolism of theophylline and can cause clinical theophylline toxicity [236]; however, levofloxacin [237], gatifloxacin [238], and moxifloxacin [239] do not affect theophylline metabolism.

Useful Websites Regarding Drug Interactions

Useful websites regarding drug interactions (tuberculosis/HIV and other) are available through the following hyperlinks: AIDSinfo, Centers for Disease Control and Prevention, University of California San Francisco, University of Liverpool, Indiana University, and University of Maryland.

Therapeutic Drug Monitoring

TDM generally consists of measurements of drug concentrations in serum specimens typically collected at 2 and 6 hours after a dose of the drug, or drugs, in question. Other sampling times may be used for selected situations. Blood samples are centrifuged; the serum is harvested and frozen, and then

shipped frozen to a reference laboratory. Quality-assured laboratories in the United States and in Europe offer assays for some or all of the antituberculosis drugs [240, 241]. There are no prospective randomized trials that clearly define the role of TDM for antituberculosis drugs. As such, opinions vary regarding the utility of TDM. Experts generally use TDM as a specialized tool, providing insight into the adequacy of drug dosing [242]. For example, serum concentrations of tuberculosis drugs among children and HIV-infected patients with tuberculosis are frequently lower than those in healthy volunteers, at the same (mg/kg body weight) dose [243–246]. In some reports, lower concentrations did not have an impact on treatment response or cure [247–249]. Other reports have found an association between low drug exposure and failure, relapse, and acquired rifamycin resistance [250–252]. TDM cannot predict who will be cured, fail, or relapse; however, it does allow for timely, informed decisions regarding the need for dose adjustment when necessary. Experts suggest that TDM may be particularly helpful in situations in which drug malabsorption, drug underdosing, or clinically important drug–drug interactions are suspected (Table 9). Examples of situations in which TDM may be useful include (1) patients with delayed sputum conversion or treatment failure not explained by nonadherence or drug resistance; (2) patients with medical conditions (eg, reduced renal function) that are suspected of leading to subtherapeutic or toxic drug concentrations; and (3) patients undergoing treatment for drug-resistant tuberculosis.

Table 9. Conditions or Situations in Which Therapeutic Drug Monitoring May Be Helpful

Poor response to tuberculosis treatment despite adherence and fully drug-susceptible *Mycobacterium tuberculosis* strain
Severe gastrointestinal abnormalities: severe gastroparesis, short bowel syndrome, chronic diarrhea with malabsorption
Drug–drug interactions
Impaired renal clearance: renal insufficiency, peritoneal dialysis, critically ill patients on continuous renal replacement
HIV infection
Diabetes mellitus
Treatment using second-line drugs

Abbreviation: HIV, human immunodeficiency virus.

TREATMENT IN SPECIAL SITUATIONS

HIV Infection

PICO Question 5: Does extending treatment beyond 6 months improve outcomes compared to the standard 6-month treatment regimen among pulmonary tuberculosis patients coinfected with HIV?

Recommendation 5a: For HIV-infected patients receiving ART, we suggest using the standard 6-month daily regimen consisting of an intensive phase of 2 months of INH, RIF, PZA, and EMB followed by a continuation phase of 4 months of INH and RIF for the treatment of drug-susceptible pulmonary tuberculosis *(conditional recommendation; very low certainty in the evidence)*.
Recommendation 5b: In uncommon situations in which HIV-infected patients do NOT receive ART during tuberculosis treatment, we suggest extending the continuation phase with INH and RIF for an additional 3 months (ie, a continuation phase of 7 months in duration, corresponding to a total of 9 months of therapy) for treatment of drug-susceptible pulmonary tuberculosis *(conditional recommendation; very low certainty in the evidence)*.

PICO Question 6: Does initiation of ART during tuberculosis treatment compared to at the end of tuberculosis treatment improve outcomes among tuberculosis patients coinfected with HIV?

Recommendation 6: We recommend initiating ART during tuberculosis treatment. Antiretroviral therapy should ideally be initiated within the first 2 weeks of tuberculosis treatment for patients with CD4 counts <50 cells/μL and by 8–12 weeks of tuberculosis treatment initiation for patients with CD4 counts ≥50 cells/μL *(strong recommendation; high certainty in the evidence)*. Note: an exception is patients with HIV infection and tuberculous meningitis (see Immune Reconstitution Inflammatory Syndrome).

Both the CDC and WHO recommend routine HIV testing and counseling to all patients with presumptive and diagnosed tuberculosis [253, 254]. Treatment of tuberculosis in patients with HIV infection has several important differences compared with treatment of patients who do not have HIV infection. These differences include the need for ART, the potential for drug–drug interactions, especially between the rifamycins and antiretroviral agents, paradoxical reactions that may be interpreted as clinical worsening, and the potential for developing resistance to rifamycins when using intermittent tuberculosis therapy. Because of the strong epidemiological association between HIV and tuberculosis infections and the clinical considerations discussed below, all individuals diagnosed with tuberculosis are tested for HIV infection.

Clinical Trials of Treatment for Tuberculosis in HIV-Infected Patients

There have been a number of prospective studies, including 4 randomized controlled trials, of 6-month regimens for the treatment of pulmonary tuberculosis in patients with HIV infection for which recurrence data were reported [59, 247, 248, 255–257]. All reported a good early clinical response to tuberculosis therapy. The time required for sputum culture conversion from positive to negative and tuberculosis treatment failure rates were similar to these indices of treatment efficacy in patients without HIV infection. Recurrence of tuberculosis after treatment completion may be due to relapse or reinfection. Relapse of tuberculosis in HIV-infected individuals is associated with nonadherence to treatment, use of intermittent regimens, and with low plasma drug concentrations, all of which also contribute to the emergence of rifamycin resistance [9, 59–62, 250]. Reinfection with a new strain of *M. tuberculosis* is well documented in patients with HIV infection and occurs in settings where transmission is more common, such as in countries with high rates of tuberculosis or congregate living facilities (eg, prisons or hospitals) where infection control is inadequate. A study in Democratic Republic of the Congo (formerly Zaire) found that extending treatment from 6 to 12 months reduced the recurrence rate from 9% to 3% [255]. A randomized trial in Haiti found that 6-month treatment with a standard regimen

Table 10. Suggested Pyrazinamide Doses, Using Whole Tablets, for Adults Weighing 40–90 kg[a]

	Weight, kg[b,c]		
Regimen	40–55	56–75	76–90
Daily (mg/kg)	1000 mg (18.2–25.0)	1500 mg (20.0–26.8)	2000 mg (22.2–26.3)
Thrice weekly (mg/kg)	1500 mg (27.3–37.5)	2500 mg (33.3–44.6)	3000 mg (33.3–39.5)
Twice weekly (mg/kg)	2000 mg (36.4–50.0)	3000 mg (40.0–53.6)	4000 mg (44.4–52.6)

[a] With normal renal function.

[b] Based on estimated lean body weight. Optimal doses for obese patients are not established.

[c] Numbers in parentheses are the calculated mg/kg doses for patients at the highest and lowest body weights in the weight band.

followed by 12 months of INH preventive therapy reduced recurrences from 7.8 per 100 person-years to 1.4 per 100 person-years [258]. Therefore, in areas where reinfection is likely, the opinion of experts is that secondary preventive therapy with INH may be justified.

In regard to duration of treatment for drug-susceptible pulmonary tuberculosis in the presence of HIV infection, the standard regimen currently used worldwide is the 6-month regimen consisting of an intensive phase of 2 months of INH, RIF, PZA, and EMB followed by a continuation phase of 4 months of INH and RIF [10, 67, 98]. There is, however, a paucity of data on the optimal duration of tuberculosis treatment for HIV-infected patients receiving highly active antiretroviral therapy (HAART), though it is widely believed that the standard 6-month regimen is effective and achieves tuberculosis cure rates comparable to those reported for HIV-uninfected patients. In the TB-HAART (Early Versus Delayed Initiation of HAART for HIV-Infected Adults With Newly Diagnosed Pulmonary Tuberculosis) trial, patients with CD4 counts ≥220 cells/μL were randomized on timing of ART initiation [259]. All patients were treated with the standard 6-month regimen for tuberculosis and were followed for 12 months. Among patients who completed treatment, recurrence of tuberculosis occurred in 2.0%, providing indirect but supportive evidence that a 6-month regimen is effective in HIV-infected patients receiving ART. In our updated systematic review of randomized trials and cohort studies comparing various durations of tuberculosis therapy (6 months vs 8 months or longer), most of which were conducted prior to the era of HAART, we found that the risk of recurrence is lower when the continuation phase of treatment is extended. However, it is important to note that the majority of these studies were reports on nonrandomized cohorts, most were completed prior to the era of routine antiretroviral use, many tested intermittent regimens, and few distinguished between reinfection and relapse (see Supplementary Appendix B). As discussed below, based on data that show significant reductions in mortality and AIDS-defining illnesses, patients with HIV infection and tuberculosis should receive ART in conjunction with daily antituberculosis medications. For HIV-infected patients receiving ART, we suggest using the standard 6-month daily regimen consisting of an intensive phase of 2 months of INH, RIF, PZA, and EMB followed by a continuation phase of 4 months of INH and RIF for the treatment of drug-susceptible pulmonary tuberculosis (Recommendation 5a: *conditional recommendation; very low certainty in the evidence*) (see Supplementary Appendix B, Evidence Profile 12). In the uncommon situation in which an HIV-infected patient does NOT receive ART during tuberculosis treatment, we suggest extending the continuation phase with INH and RIF for an additional 3 months (ie, a continuation phase of 7 months in duration, corresponding to a total of 9 months of therapy) for treatment of drug-susceptible pulmonary tuberculosis (Recommendation 5b: *conditional recommendation; very low certainty in the evidence*). As is noted for drug-susceptible pulmonary tuberculosis in patients without HIV coinfection, the continuation phase is extended in specific situations that are known to increase risk for relapse (see "Identification and Management of Patients at Increased Risk of Relapse"), as well as for selected extrapulmonary sites of disease, namely tuberculous meningitis, and bone, joint, and spinal tuberculosis (see "Extrapulmonary Tuberculosis").

Table 11. Suggested Ethambutol Dosages, Using Whole Tablets, for Adults Weighing 40–90 kg[a]

	Weight, kg[b,c]		
Regimen	40–55	56–75	76–90
Daily (mg/kg)	800 mg (14.5–20.0)	1200 mg (16.0–21.4)	1600 mg (17.8–21.1)
Thrice weekly (mg/kg)	1200 mg (21.8–30.0)	2000 mg (26.7–35.7)	2400 mg (26.7–31.6)
Twice weekly (mg/kg)	2000 mg (36.4–50.0)	2800 mg (37.3–50.0)	4000 mg (44.4–52.6)

[a] With normal renal function.

[b] Based on estimated lean body weight. Optimal doses for obese patients are not established.

[c] Numbers in parentheses are the calculated mg/kg doses for patients at the highest and lowest body weights in the weight band.

Use of intermittent tuberculosis treatment regimens in HIV-infected patients has been associated with high rates of relapse and the emergence of drug resistance. In TBTC Study 22, patients with HIV infection who received once-weekly RPT and INH or twice-weekly RIF and INH in the continuation phase had an unacceptably high rate of relapse: 5 of 30 (16.7%) in the former and 3/31 (9.8%) in the latter group [9]. In addition, for those receiving weekly therapy, 4 patients relapsing had acquired rifamycin resistance, which was associated with low serum concentrations of INH and was presumably the result of unopposed rifamycin exposure [59]. In a trial of RFB-based antituberculosis therapy in combination with antiretroviral drugs, patients treated with twice-weekly RFB had a relapse rate of 5.3%, but 8 of 9 relapses had acquired rifamycin resistance [60]. Relapse and resistance were associated with low CD4 lymphocyte counts, as all recurrences occurred in patients with baseline CD4 lymphocyte counts <100 cells/μL. In the pharmacokinetic substudy of the trial, lower plasma concentrations of RFB and INH were identified as key risk factors for acquiring rifamycin resistance [250]. More recently, the use of a thrice-weekly RIF-based regimen during the intensive and continuation phases of treatment was associated with a higher rate of relapse and emergence of rifamycin resistance in HIV-infected individuals not receiving antiretrovirals compared with HIV-infected patients also receiving antiretrovirals or HIV-uninfected patients [62]. Based in part on systematic reviews conducted to obtain evidence in support of this guideline, our expert opinion is that treatment of HIV-related tuberculosis be given daily in both the intensive and continuation phases to avoid recurrent disease and the emergence of rifamycin resistance (see "Recommended Treatment Regimens").

Mortality among patients with HIV and tuberculosis is high, principally due to complications of immunosuppression and occurrence of other HIV-related opportunistic diseases. In this regard, the value of co-trimoxazole (trimethoprim-sulfamethoxazole) prophylaxis in reducing morbidity and mortality in HIV-infected patients with newly diagnosed tuberculosis is well established [63–65]. Whereas the WHO recommends routine co-trimoxazole prophylaxis for all HIV-infected people with active tuberculosis disease regardless of the CD4 cell count [66], in high-income countries, co-trimoxazole prophylaxis is primarily used in tuberculosis patients coinfected with HIV with CD4 counts <200 cells/μL [67]. The use of ART during tuberculosis treatment in persons with HIV infection also reduces mortality rates significantly for those with advanced HIV disease and decreases the risk of developing AIDS-related conditions. The Starting Antiretroviral therapy at Three Points in Tuberculosis (SAPiT) trial randomized patients with tuberculosis and HIV with CD4 lymphocyte counts <500 cells/μL to initiate ART after 2 weeks (immediate), 8 weeks (early), or 6 months (deferred) of tuberculosis treatment [260]. Patients receiving immediate or early ART had a 56% reduction in the relative risk of death compared with patients receiving deferred ART (5.6 per 100 person-years vs 12.1 per 100 person-years). The benefit of ART given immediately or early was seen in patients with CD4 lymphocyte counts <200 cells/μL and 200–500 cells/μL. Subsequently, the Cambodian Early Versus Late Introduction of Antiretrovirals trial showed that initiation of ART within 2 weeks of starting antituberculosis treatment reduced mortality rate by 34% compared to starting after 8 weeks, in a population of HIV-infected individuals with very low CD4 cell counts (median, 25 cells/μL) [261]. The Immediate vs Deferred Start of Anti-HIV Therapy in HIV-Infected Adults Being Treated for Tuberculosis (STRIDE) trial and the second phase of the SAPiT study, both of which compared immediate (2 weeks) with early (8–12 weeks) ART for HIV-infected patients beginning antituberculosis treatment, showed that immediate therapy was associated with significantly lower rates of progression of HIV disease to new AIDS-defining conditions or death compared to early therapy for patients with CD4 counts <50 cells/μL, but starting ART within 2 weeks was not superior to starting at 8 weeks for individuals with CD4 counts >50 cells/μL [262, 263]. All of these studies also showed that immediate ART was associated with significantly greater rates of IRIS, most of which was not severe.

More recently, the TB-HAART trial found that among patients with HIV and CD4 counts >220 cells/μL, immediate initiation of ART did not reduce mortality compared with waiting until completion of 6 months of antituberculosis treatment to start ART [259]. Unlike the SAPiT and STRIDE trials, however, TB-HAART did not assess progression of HIV disease as a study endpoint. Although the study did not find a survival benefit in patients with HIV-related tuberculosis and higher CD4 lymphocyte counts, it did confirm the safety of co-treatment of tuberculosis and HIV infection and documented good outcomes of tuberculosis treatment in those patients receiving dual therapy.

We performed a systematic review and meta-analysis to obtain evidence in support of this guideline, which included the 4 trials above and 4 additional studies (see Supplementary Appendix B, Evidence Profile 13) [259–266]. We found that the overall reduction in mortality with ART initiated during treatment of tuberculosis was 24% (risk ratio, 0.76; 95% confidence interval [CI], .57–1.01). The overall risk of HIV disease progression was reduced by 34% with early or immediate ART (4 studies: risk ratio, 0.66; 95% CI, .47–.91). Initiation of ART during antituberculosis therapy was associated with an increased risk of IRIS (8 studies: risk ratio, 1.88; 95% CI, 1.31–2.69). Our meta-analysis identified no increase in the risk of other adverse events or poor outcome of tuberculosis therapy. Consequently, on the basis of high certainty in the evidence that the benefits outweigh the harms, we recommend that patients with tuberculosis and HIV infection receive ART during antituberculosis treatment. Antiretroviral therapy should ideally be started within 2 weeks for those patients with a CD4 count <50 cells/μL and by 8–12

weeks for those with a CD4 count ≥50 cells/μL (Recommendation 6: *strong recommendation; high certainty in the evidence*). An important exception is HIV-infected patients with tuberculous meningitis, in whom ART should not be initiated in the first 8 weeks of antituberculosis therapy (see "Immune Reconstitution Inflammatory Syndrome").

Concurrent Administration of Antiretrovirals and Rifamycins

Interaction of RIF with antiretroviral agents is a major treatment concern (see "Drug–Drug Interactions"). RIF is a potent inducer of drug metabolizing enzymes in the CYP family and drug transporters such as P-glycoprotein [206]. Coadministration of RIF with drugs metabolized or transported by these compounds may lead to reductions in exposure and loss of efficacy [207]. HIV protease inhibitors are metabolized by CYP3A4, and their concomitant administration with RIF leads to >80% reductions in serum concentrations of the protease inhibitors and loss of therapeutic benefit. RIF also increases the metabolism of nonnucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs), and CCR-5 inhibitors. Detailed recommendations for coadministration of rifamycins and antiretroviral drugs have been published by the CDC, and we support these guidelines [215].

The NNRTI efavirenz is the most widely used antiretroviral drug and is the preferred initial treatment for HIV (in combination with other antiretroviral drugs) in many countries. Coadministration of RIF-containing antituberculosis regimens with efavirenz results in satisfactory antiviral efficacy, despite reductions in trough efavirenz concentrations [267, 268]. INH is an inhibitor of an alternative, minor CYP pathway involved in efavirenz metabolism. Thus, when INH and RIF are given to individuals with genetic polymorphisms associated with slow efavirenz clearance, efavirenz serum concentrations may reach supratherapeutic levels. The US Food and Drug Administration (FDA) recommends that the dosage of efavirenz be increased from 600 mg/day to 800 mg/day for patients weighing >60 kg on the basis of pharmacokinetic modeling of data from healthy volunteers; however, data from clinical studies, including the STRIDE study, do not support this advice [267, 268], and many other experts believe that efavirenz should be administered at the standard dose of 600 mg/day in patients receiving standard dose RIF-containing regimens. A treatment-shortening trial evaluating high-dose daily RPT used in combination with efavirenz-based ART for HIV-infected patients is under way (ClinicalTrials.gov identifier: NCT02410772).

The NNRTI nevirapine has also been studied as an alternative treatment for HIV-infected patients with tuberculosis [269]. However, RIF also reduces concentrations of nevirapine, a drug that induces its own metabolism [270]. Due to this autoinduction, nevirapine is initially given at a dosage of 200 mg/day for 2 weeks and then increased to 200 mg/twice daily or 400 mg/once daily. When nevirapine is started during antituberculosis treatment, use of the 200 mg daily lead-in dose can lead to subtherapeutic concentrations, loss of antiviral efficacy, and emergence of drug resistance [271–273]. Therefore, expert opinion is that if nevirapine is used during treatment with RIF, the initiation dose should be at the full 400-mg daily dosage (200 mg twice daily or 400 mg daily).

The INSTIs are now considered first-line agents for HIV infection in the United States and in Europe. Raltegravir and dolutegravir are metabolized mainly by uridine 5′-diphosphoglucuronosyltransferase 1A1 [274, 275], and concomitant use of RIF reduces trough concentrations significantly. The "Raltegravir for the treatment of patients co-infected with HIV and tuberculosis" (Reflate TB) trial showed that coadministration of RIF-based antituberculosis treatment and raltegravir at 400 mg/twice daily was associated with similar antiviral effectiveness compared to coadministration of RIF-based antituberculosis treatment and raltegravir 800 mg twice daily; both were somewhat more effective than efavirenz 600 mg daily [274]. However, pharmacokinetic data favor increasing the dose to 800 mg twice daily, and expert opinion in the United States favors this strategy [276]. Pharmacokinetic studies demonstrate that coadministration of RIF and dolutegravir at a dosage of 50 mg given twice daily results in adequate trough concentrations of dolutegravir [275]. A clinical study of patients with active tuberculosis given RIF and dolutegravir is under way (ClinicalTrials.gov identifier: NCT02178592).

RFB is less potent an inducer of CYP isoenzymes and may be used in patients receiving ART; however, RFB itself is metabolized by CYP3A enzymes, and the antiretroviral agent ritonavir (used to boost protease inhibitor levels) inhibits CYP3A enzymes, which increases concentrations of RFB. High concentrations of RFB are associated with an increased risk of uveitis and other toxicities, so dose adjustment of the standard RFB dosage of 300 mg daily is necessary [215].

Expert opinion is to use RFB at a dose of 150 mg/day or 300 mg every other day as part of a combination antituberculosis regimen for patients receiving ritonavir-boosted protease inhibitors [214]. In patients receiving dose-adjusted RFB because of concomitant protease inhibitor use, frequent assessment of adherence to both medicines is prudent, as discontinuation of the protease inhibitor while continuing dose-adjusted RFB (ie, in the context of DOT tuberculosis therapy but self-administered antiretrovirals) would be expected to result in subtherapeutic concentrations of the rifamycin, possibly with consequent poor treatment outcome and acquired rifamycin resistance. Efavirenz is also a CYP3A inducer, and when RFB is coadministered with this agent the RFB dosage needs to be increased to 600 mg/day; however, indications to use RFB instead of RIF in patients receiving efavirenz are rare.

When RFB is not available and treatment with a protease inhibitor is required because of resistance to NNRTIs and/or INSTIs, use of RIF with a lopinavir/ritonavir regimen may be attempted. For adults, this generally entails increasing the

dosage of lopinavir/ritonavir from 400 mg/100 mg twice daily to 800 mg/200 mg twice daily over 2 weeks. This so-called "double dosing" of boosted lopinavir may result in hepatotoxicity and careful clinical monitoring is necessary [215]. Alternatively, "super boosting" of lopinavir, though poorly tolerated in adults, is sometimes effective, especially in children. In this instance, the dosage of lopinavir is maintained at 400 mg twice daily, but ritonavir dosage is increased from 100 mg twice daily to 400 mg twice daily. Super boosting of ritonavir is poorly tolerated in adults, however, and the double-dosing strategy is preferred. These complicated interactions underscore the importance of expert consultation in treating individuals with concurrent HIV and tuberculosis infections. For situations involving complex drug–drug interactions, some clinicians prefer to measure the concentrations of the interacting drugs, and to dose these drugs based upon individualized data [242].

Immune Reconstitution Inflammatory Syndrome

Transient worsening of tuberculosis symptoms and lesions in response to antituberculous therapy has previously been reported in HIV-uninfected patients [277]. Patients with HIV infection and tuberculosis are at an increased risk of developing paradoxical worsening of symptoms, signs, or clinical manifestations of tuberculosis after beginning antituberculosis and antiretroviral treatments. These reactions develop as a consequence of reconstitution of immune responsiveness brought about by ART, and are designated as the IRIS. Tuberculosis IRIS has been noted to be more common in participants with earlier ART initiation and $CD4^+$ lymphocyte counts <50 cells/μL. In the STRIDE study, IRIS occurrence was infrequent at 7.6%. When tuberculosis IRIS occurred, the majority (69%) of cases were mild to moderate in severity; however, 31% were hospitalized with tuberculosis IRIS and more than half received corticosteroids [68]. Signs of IRIS may include high fevers, worsening respiratory symptoms, increase in size and inflammation of involved lymph nodes, new lymphadenopathy, expanding central nervous system (CNS) lesions, worsening of pulmonary parenchymal infiltrations, new or increasing pleural effusions, and development of intra-abdominal or retroperitoneal abscesses [69]. Such findings are attributed to IRIS only after excluding other possible causes, especially tuberculosis treatment failure from drug-resistant tuberculosis or another opportunistic disease, such as non-Hodgkin lymphoma or infection. Antiretroviral treatment of patients with incubating, subclinical tuberculosis may also result in what is called "unmasking IRIS," where tuberculosis symptoms and clinical manifestations become more pronounced, though whether this represents normal progression of untreated tuberculosis is not known [187].

The relative risk of developing IRIS for patients who receive ART during therapy for tuberculosis is 1.88 (95% CI, 1.31–2.69), and those who start ART within 2 weeks after starting tuberculosis therapy have higher rates than those who start between 8–12 weeks [261–263]. In general, development of IRIS does not worsen treatment outcomes for either tuberculosis or HIV infection, and most episodes can be managed symptomatically. An exception to this is the development of IRIS in patients with CNS tuberculosis, where IRIS may cause severe or fatal neurological complications. In a study of patients with tuberculosis meningitis and HIV infection, early initiation of ART (within 2 weeks) was associated with increased rates of adverse events and higher mortality [278]. Thus, ART is not initiated in the first 8 weeks of antituberculosis therapy for patients with HIV infection and tuberculous meningitis (or other CNS tuberculosis), even for patients with CD4 cell counts <50 cells/μL.

Management of IRIS is symptomatic. Based on expert opinion, for most patients with mild IRIS, tuberculosis and antiretroviral therapies can be continued with the addition of anti-inflammatory agents such as ibuprofen. For patients with worsening pleural effusions or abscesses, drainage may be necessary. For more severe cases of IRIS, treatment with corticosteroids is effective. In a placebo-controlled trial of prednisone for patients with moderate IRIS, prednisone 1.25 mg/kg/day significantly reduced the need for hospitalization or surgical procedures [70]. For patients who develop IRIS, prednisone may be given at a dose of 1.25 mg/kg/day (50–80 mg/day) for 2–4 weeks, with tapering over a period of 6–12 weeks or longer. Controlled trials investigating whether treatment with nonsteroidal anti-inflammatory agents or corticosteroids can prevent the development of IRIS are under way or in development.

Children

Children commonly develop tuberculosis as a complication of the initial infection with *M. tuberculosis* (primary tuberculosis). The radiographic presentation of primary tuberculosis in children is characterized by intrathoracic lymphadenopathy with or without lung opacities, occasionally presenting with lymph node enlargement to a degree that there is compression of airways with or without hyperinflation or collapse of lobe or lung; breakthrough of node(s) in the airways can manifest with lobar or segmental infiltration, and a miliary pattern [279, 280]. The diagnosis of tuberculosis in children is challenging, especially in young children (<5 years) due to the paucibacillary nature of the disease. Depending on the setting and resources, diagnosis is microbiologically confirmed in only 15%–50% of pediatric cases, and clinical case definitions for tuberculosis in children have recently been updated [281]. Children, rarely, and adolescents, more frequently, can also develop adult-type tuberculosis (upper lobe opacities and cavitation associated with sputum production). The lesions of primary tuberculosis have fewer *M. tuberculosis* organisms than those of adult-type pulmonary tuberculosis; thus, treatment failure, relapse, and development of secondary resistance are less common events among children when standard treatment regimens are initiated in a timely

manner. However, it is often more difficult to isolate *M. tuberculosis* from a child with pulmonary tuberculosis than from an adult. Therefore, choosing appropriate treatment drugs often requires the results of specimen culture and drug susceptibility tests from the person presumed to be the source of the child's infection. Based on expert opinion, when drug resistance is suspected or no source-case isolate is available, attempts to isolate organisms are critical; approaches including obtaining 3 early morning gastric aspirations (optimally during hospitalization), sputum induction [282], bronchoalveolar lavage [283], or tissue biopsy must be considered. Any information gained from molecular and phenotypic tests conducted on these samples is used to select an individualized regimen for the patient. Because tuberculosis in infants and children <4 years of age is more likely to disseminate and result in subsequent morbidity and mortality, empiric treatment is started as soon as the diagnosis is suspected, and particular care is given to drug dosage selection as an important component of achieving adequate concentrations of bactericidal drugs in body fluids, including the cerebrospinal fluid [284].

Several controlled and many observational trials of 6-month therapy in children with known or presumed drug-susceptible pulmonary tuberculosis have been published [285]. Based on systematic reviews of the literature, both the AAP [77] and the WHO [286, 287], list a 4-drug regimen (INH, RIF, PZA, and EMB) for 2 months followed by a 2-drug (INH and RIF) regimen for 4 months as the preferred regimen for children with suspected or confirmed pulmonary tuberculosis. The AAP Red Book also states that children who are receiving EMB should be monitored monthly for visual acuity and red-green color discrimination if they are old enough to cooperate. The AAP further notes that the use of EMB in young children whose visual acuity cannot be monitored requires consideration of risks and benefits, but it can be used routinely to treat tuberculosis disease in infants and children unless otherwise contraindicated [77]. As an approach to avoiding EMB ocular toxicity, some clinicians use a 3-drug regimen (INH, RIF, and PZA) in the initial 2 months of treatment for children who are HIV uninfected, have no prior tuberculosis treatment history, are living in an area of low prevalence of drug-resistant tuberculosis, and have no exposure to an individual from an area of high prevalence of drug-resistant tuberculosis. However, because the prevalence of and risk for drug-resistant tuberculosis can be difficult to ascertain, the AAP and most experts include EMB as part of the intensive phase regimen for children with tuberculosis. Pyridoxine, 25–50 mg/day, is given to infants, children, and adolescents undergoing INH treatment if they have nutritional deficiencies, symptomatic HIV infection, or are breastfeeding. Pyridoxine is also given to breastfeeding infants of mothers who are receiving INH [42, 77, 288, 289]. The lack of approved pediatric dosage forms for most antituberculosis medications has resulted in the creation and use of improvised formulations. This has entailed crushing tablets or opening capsules to access the drug, followed by weighing or proportioning of the contents that are in turn admixed with food or prepared into a suspension. With the recent development of child-friendly antituberculosis formulations meeting the dosage guidelines set by the WHO, procedures for making such improvised formulations should no longer be needed [290].

In the United States, DOT has become the default programmatic approach to treating children with tuberculosis [17]. Based on expert opinion, parents should not supervise DOT for their children. Even when drugs are administered under DOT, tolerance of the medications must be monitored closely. When feasible, daily dosing is preferred by experts [77, 279, 287]; however, twice- or thrice-weekly dosing has also been endorsed during the continuation phase of treatment for HIV-uninfected children in settings where DOT is well established [77] (see Supplementary Appendix C and Table 3 for dosing of antituberculosis drugs in children).

Monitoring response to treatment in children can be challenging because of the difficulties in demonstrating *M. tuberculosis* in children. Clinical and radiographic worsening may not be accompanied by positive AFB smears or mycobacterial cultures. According to experts, continued child growth and development while on treatment for tuberculosis usually predicts a positive outcome of treatment. A decision to modify the drug regimen should be undertaken with caution. Changes to the regimen are usually based on clinical and radiographic grounds. However, experts note that hilar adenopathy and resultant atelectasis in children on occasion can require 1–2 years to resolve; thus, an improving but persistent abnormality on a chest radiograph in an asymptomatic child is not believed to justify an extension of therapy. If there is concern that poor treatment response may be due to possible drug-resistant tuberculosis, expert opinion is that the child should be fully reinvestigated, verifying contact history and source case drug susceptibility test results, as well as obtaining additional specimens for cultures and drug susceptibility testing.

According to expert opinion, most forms of extrapulmonary tuberculosis in children can be treated with the same regimens as pulmonary disease [77, 286]; however, for children with confirmed or suspected tuberculous meningitis or osteoarticular tuberculosis caused by a drug-susceptible organism, expert opinion is that the duration of the continuation phase should be extended (See "Tuberculous Meningitis"). For tuberculous meningitis, the AAP lists an initial 4-drug regimen of INH, RIF, PZA, and an aminoglycoside or ethionamide for 2 months, followed by 7–10 months of INH and RIF. For patients who may have acquired tuberculosis in geographic areas where resistance to streptomycin is common, kanamycin, amikacin, or capreomycin is used instead of streptomycin [77]. Fluoroquinolones have been studied in adults with tuberculous meningitis [291], and these studies provide some evidence in support of their use; however, there have been no published trials of their use for tuberculous meningitis in children.

Extrapulmonary Tuberculosis

PICO Question 7: Does the use of adjuvant corticosteroids in tuberculous pericarditis provide mortality and morbidity benefits?

Recommendation 7: We suggest initial adjunctive corticosteroid therapy not be routinely used in patients with tuberculous pericarditis *(conditional recommendation; very low certainty in the evidence)*.

PICO Question 8: Does the use of adjuvant corticosteroids in tuberculous meningitis provide mortality and morbidity benefits?

Recommendation 8: We recommend initial adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks for patients with tuberculous meningitis *(strong recommendation; moderate certainty in the evidence)*.

Tuberculosis can involve virtually any organ or tissue in the body. The principles underlying the treatment of pulmonary tuberculosis also apply to extrapulmonary disease. Chemotherapy for extrapulmonary tuberculosis is initiated with INH, RIF, PZA, and EMB in an initial 2-month phase. After 2 months of 4-drug therapy, for extrapulmonary tuberculosis known or presumed to be caused by susceptible strains, PZA and EMB may be discontinued, and INH and RIF continued during a continuation phase. Increasing evidence, including randomized controlled trials, suggests that 6–9 month INH and RIF-containing regimens are effective for the majority of extrapulmonary sites of disease. The exception is tuberculous meningitis where the optimal duration of therapy has not been established through randomized controlled trials, but most experts and society guidelines prescribe 12 months of treatment [78, 292]. The opinion of experts is that the preferred frequency of dosing for extrapulmonary tuberculosis is once daily for both the intensive and continuation phases. No randomized controlled trials have studied intermittent drug administration for extrapulmonary tuberculosis. If intermittent regimens are used, experts believe that highly intermittent, once-weekly regimens should be avoided because of insufficient experience with this regimen in extrapulmonary tuberculosis. In regard to treatment monitoring, bacteriologic evaluation is often limited by the difficulty in obtaining follow-up specimens. Sputum specimens are obtained when there is concurrent pulmonary involvement, otherwise, response to treatment in extrapulmonary diseases is often judged on the basis of clinical and radiographic findings.

Lymph Node Tuberculosis

We believe a 6-month regimen is adequate for initial treatment of all patients with drug-susceptible tuberculous lymphadenitis [293–298]. Affected lymph nodes may enlarge and new nodes can appear during or after therapy without any evidence of bacteriological relapse [293, 295, 296, 299]. Therapeutic lymph node excision is not indicated except in unusual circumstances. For large lymph nodes that are fluctuant and appear to be about to drain spontaneously, aspiration has been reported by some experts to be beneficial, although this approach has not been examined systematically. Incision and drainage techniques applied to cervical lymphadenitis, however, have been reported to be associated with prolonged wound discharge and scarring [300]. Of note, the majority of lymphatic cases of mycobacterial disease in US children are caused by nontuberculous mycobacteria [301].

Bone, Joint, and Spinal Tuberculosis

Six- to 9-month regimens containing RIF for treatment of bone, joint, and spinal tuberculosis are at least as effective as 18-month regimens that do not contain RIF [302–304]. Because of the difficulties in assessing response, however, some experts tend to favor the 9-month duration, and in the setting of extensive orthopedic hardware, some experts extend the duration of treatment further to 12 months. Several trials found no additional benefit of surgical debridement in combination with chemotherapy compared with chemotherapy alone for spinal tuberculosis [80, 303–306]. As such, uncomplicated cases of spinal tuberculosis are managed with medical rather than surgical treatment. However, based on expert opinion, surgery can be considered in situations in which (1) there is poor response to chemotherapy with evidence of ongoing infection or ongoing deterioration; (2) relief of cord compression is needed in patients with persistence or recurrence of neurologic deficits; or (3) there is instability of the spine [307]. Spinal tuberculosis with evidence of meningitis is managed as tuberculous meningitis, including consideration of adjunctive corticosteroids (see Tuberculous Meningitis).

Pericardial Tuberculosis

A 6-month regimen is adequate for patients with pericardial tuberculosis. Based on small studies that have shown mortality and morbidity benefits [71–73], corticosteroids have previously been universally recommended as adjunctive therapy for tuberculous pericarditis, however, a recent placebo-controlled randomized clinical trial with 1400 participants did not find a difference in the combined primary endpoint of the trial, which included mortality, cardiac tamponade, or constrictive pericarditis, between patients treated with adjunctive corticosteroids vs placebo [74]. A subgroup analysis, however, did suggest a benefit in preventing constrictive pericarditis. Similarly, a systematic review conducted to obtain evidence in support of this guideline did not find a statistically significant benefit in terms of mortality or constrictive pericarditis from the use of corticosteroids (see Supplementary Appendix B, Evidence Profile 14) [71–75]. Therefore, we suggest that adjunctive corticosteroids should not be used routinely in the treatment of patients with pericardial tuberculosis (Recommendation 7: *conditional recommendation; very low certainty in the evidence*). However, selective use of glucocorticoids in patients who are at the highest risk for inflammatory complications might be appropriate. Such patients might include those with large pericardial effusions, those with high levels of inflammatory cells or markers in pericardial fluid, or those with early signs of constriction [76].

Pleural Tuberculosis

A standard 6-month regimen (Table 2) is also adequate for treating pleural tuberculosis. Some clinicians consider using

adjunctive corticosteroid therapy for tuberculous pleural effusions, and a number of studies have examined the risks and benefits of this approach [308]. Four have been prospective, double blind, and randomized [309–311], one of which was conducted in patients with HIV infection [312]. In all 4 studies, prednisone (or prednisolone) administration did not confer a beneficial effect on residual pleural thickening or prevention of other long-term pleural sequelae. In one study, an increased risk for Kaposi sarcoma was noted with the use of prednisolone in HIV-associated tuberculous pleurisy [312]. Based on these randomized clinical trials and a systematic review, there is no evidence to support the routine use of adjunctive corticosteroids in patients with tuberculous pleurisy.

Tuberculous empyema, a chronic, active infection of the pleural space containing a large number of tubercle bacilli, usually occurs when a cavity ruptures into the pleural space. Treatment consists of drainage (often requiring a surgical procedure) and antituberculous chemotherapy [313]. The optimum duration of treatment for this unusual form of tuberculosis has not been established.

Tuberculous Meningitis

Tuberculous meningitis remains a potentially devastating disease associated with a high morbidity and mortality in children and adults, despite prompt initiation of adequate chemotherapy [314]. HIV-infected individuals appear to be at increased risk for developing tuberculous meningitis, but the clinical features of the disease are similar to those in tuberculous meningitis patients without HIV infection [315–317]. High short-term morbidity and mortality is reported regardless of HIV serostatus [315–317]; however, 9-month survival was further decreased in HIV-infected patients compared with HIV-uninfected patients in one cohort study [318].

Chemotherapy for tuberculous meningitis is initiated with INH, RIF, PZA, and EMB in an initial 2-month phase. After 2 months of 4-drug therapy, for meningitis known or presumed to be caused by susceptible strains, PZA and EMB may be discontinued, and INH and RIF continued for an additional 7–10 months, although the optimal duration of chemotherapy is not defined. Based on expert opinion, repeated lumbar punctures should be considered to monitor changes in cerebrospinal fluid cell count, glucose, and protein, especially early in the course of therapy. In children with tuberculous meningitis, the AAP lists an initial 4-drug regimen of INH, RIF, PZA, and ethionamide or an aminoglycoside for 2 months (in place of EMB), followed by 7–10 months of INH and RIF [77]. There are no data from controlled trials to guide the selection of EMB vs an injectable or ethionamide as the fourth drug for tuberculosis meningitis [78]. Most societies and experts recommend the use of either an injectable or EMB. For adults, based on expert opinion, our writing committee prefers using EMB as the fourth drug. Fluoroquinolones, as well as higher doses of intravenous RIF, are being evaluated in adults with tuberculous meningitis [291, 319]; a large randomized controlled trial (ISRCTN61649292) is under way to evaluate the impact on reducing mortality of levofloxacin combined with higher-dose rifampicin during the intensive phase of treatment [320]. Selected complications of tuberculous meningitis warranting neurosurgical referral include hydrocephalus, tuberculous cerebral abscess, and clinical situations in which there is paraparesis [78].

A number of studies have examined the role of adjunctive corticosteroid therapy in the treatment of tuberculous meningitis [79–91]. Our updated systematic review found a mortality benefit from the use of adjuvant corticosteroids (See Supplementary Appendix B, Evidence Profile 15). Therefore, we recommend adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks for patients with tuberculous meningitis (Recommendation 8: *strong recommendation; moderate certainty in the evidence*).

Disseminated Tuberculosis

Based on expert opinion, a standard daily 6-month regimen (Table 2) is adequate for tuberculosis at multiple sites and for miliary tuberculosis; however, supporting data from controlled clinical trials are limited. Some experts believe concurrent corticosteroid therapy is indicated for treating severe respiratory failure or adrenal insufficiency caused by disseminated tuberculosis [321–323], though the role of adjunct corticosteroid treatment in patients with miliary tuberculosis remains unclear [324]. Patients with disseminated tuberculosis may have concomitant neurologic complications, with indolent symptoms of CNS involvement, which should be appropriately worked up [325]. Treatment recommendations for tuberculous meningitis are followed when there is CNS involvement.

Genitourinary Tuberculosis

Renal tuberculosis is treated primarily with medical rather than surgical therapy, and expert opinion is that a standard daily 6-month regimen (Table 2) is adequate [326–329]. If ureteral obstruction occurs, procedures to relieve the obstruction are indicated. In cases of hydronephrosis and progressive renal insufficiency due to obstruction, renal drainage by stenting or nephrostomy is advised by experts [330]. Nephrectomy is considered when there is a nonfunctioning or poorly functioning kidney, particularly if hypertension or continuous flank pain is present. Dose adjustment is required in patients with coexistent renal failure. Tuberculosis of the female or male genital tract responds well to standard chemotherapy, although surgery may be indicated for residual, large, tubo-ovarian abscesses.

A positive urine culture for *M. tuberculosis* is a component of the diagnostic assessment of genitourinary tuberculosis [331]. A positive urine culture for *M. tuberculosis* is also sometimes seen in tuberculosis patients with advanced HIV infection, and may reflect disseminated disease and/or occult genitourinary tract involvement. Rarely, a positive culture may occur in the

absence of any abnormalities on urinalysis and does not necessarily represent invasive genitourinary tract involvement [332].

Abdominal Tuberculosis

Expert opinion is that a 6-month regimen is adequate for patients with peritoneal or intestinal tuberculosis [333–335]. The nonspecific presentation of abdominal tuberculosis means that a high index of suspicion is an important factor in early diagnosis and initiation of treatment [336, 337]. Data on adjunctive corticosteroid therapy in the treatment of tuberculous peritonitis are limited [338]; thus, experts believe it should not be prescribed routinely.

Other Sites of Involvement

As noted above, tuberculosis can involve any organ or tissue. When treating tuberculosis in sites other than those mentioned, the basic principles of therapy apply, but experts should be consulted.

Culture-Negative Pulmonary Tuberculosis in Adults

PICO Question 9: Does a shorter duration of treatment have similar outcomes compared to the standard 6-month treatment duration among HIV-uninfected patients with paucibacillary tuberculosis (ie, smear negative, culture negative)?

Recommendation 9: We suggest that a 4-month treatment regimen is adequate for treatment of HIV-uninfected adult patients with AFB smear- and culture-negative pulmonary tuberculosis *(conditional recommendation; very low certainty in the evidence)*.

Failure to isolate *M. tuberculosis* from appropriately collected sputum specimens in persons who, because of clinical or radiographic findings, are suspected of having pulmonary tuberculosis does not exclude a diagnosis of active pulmonary tuberculosis. Some causes of failure to isolate organisms include the recent use of antibiotics with bactericidal activity against *M. tuberculosis* (eg, fluoroquinolones), low bacillary populations, inadequate sputum specimens, temporal variations in the number of expelled bacilli, overgrowth of cultures with other microorganisms, and errors in specimen processing [92]. Alternative diagnoses must be considered and appropriate diagnostic studies undertaken in patients who appear to have culture-negative tuberculosis. At a minimum, patients suspected of having pulmonary tuberculosis have 2 sputum specimens (using sputum induction with hypertonic saline if necessary) for AFB smears and cultures for mycobacteria or for rapid molecular testing for *M. tuberculosis* as part of the diagnostic evaluation. Other diagnostic procedures, such as bronchoscopy with bronchoalveolar lavage and biopsy, are considered before making a presumptive diagnosis of culture-negative tuberculosis.

Patients who, on the basis of careful clinical and radiographic evaluation, are thought to have pulmonary tuberculosis should have treatment initiated with INH, RIF, PZA, and EMB even when the initial sputum smears are negative. If *M. tuberculosis* is isolated in culture or a rapid molecular test is positive, treatment for active disease is continued for a full, standard 6-month course (Table 2), if appropriate based on drug susceptibility test results. Patients who have negative cultures but who still are presumed to have pulmonary tuberculosis should have thorough clinical and radiographic follow-up after 2 months of therapy. If there is clinical or radiographic improvement and no other etiology is identified, treatment should be continued.

The optimum treatment regimens and duration for culture-negative tuberculosis have not been convincingly established. We performed a systematic review that evaluated 4- and 6-month treatment regimens using available clinical trials data in adult (>15 years of age) patients. No clinical trials data on shortened treatments in children were available. A study from Hong Kong demonstrated that for adults with smear-negative, culture-positive, and culture-negative pulmonary tuberculosis, a 4-month regimen of INH, RIF, streptomycin, and PZA given either daily or thrice weekly was highly successful [339]. In Arkansas, a 4-month INH and RIF regimen for culture-negative tuberculosis was successful with only 1.2% relapses during an average follow-up of 44 months [340]. In Singapore, a study of a small number of patients with smear-negative and either culture-positive or culture-negative tuberculosis treated with INH, RIF, and PZA daily for 2 months followed by INH and RIF either daily or thrice weekly for 2 months showed a high degree of success in both groups [341]. Overall, these 3 studies report a proportion relapsing of only 1.9% among a total of 940 patients treated for 4 months, all of whom had at least 3 negative smears/cultures prior to starting therapy. Our systematic review of available clinical trials data in adult (>15 years of age) patients did not identify a significant difference in the risk of relapse in culture-negative tuberculosis treated for either 4 or 6 months (see Supplementary Appendix B, Evidence Profile 16). Consequently, we suggest that a 4-month treatment regimen is adequate for HIV-uninfected adults with culture-negative pulmonary tuberculosis (*conditional recommendation; very low certainty in the evidence*). Operationally, treatment is initiated with an intensive phase of INH, RIF, PZA, and EMB daily and continued in all patients suspected of having pulmonary tuberculosis even when the initial bacteriologic studies are negative. If all cultures on samples deemed to be adequate are negative and there is clinical or radiographic response after 2 months of intensive phase therapy, the continuation phase with INH and RIF can be shortened to 2 months. Clinical and radiographic response, assessed at the end of treatment, is used to determine whether an extension in treatment to a full standard 6-month regimen is needed. Alternatively, if there is concern about the adequacy of workup or the accuracy of the microbiologic evaluations, a standard 6-month regimen remains preferred (Table 2) [14, 15].

On occasion, patients who are being evaluated for pulmonary tuberculosis will be found to have positive AFB smears but negative cultures. Potential causes include the possibilities that the

acid-fast organisms are fastidious mycobacteria other than *M. tuberculosis* complex, that they are nonviable *M. tuberculosis*, or that the results are due to laboratory error (false-positive smear, or false-negative culture). The approach in such cases is individualized on the basis of clinical and radiographic findings, as well as the results of rapid molecular diagnostic studies; discussion with the microbiologist performing the cultures is prudent. If clinical suspicion of tuberculosis is high, particularly if there is clinical and radiologic improvement since the start of therapy, then therapy is continued for a minimum of 6 months as for culture-positive pulmonary tuberculosis.

Pregnancy and Breastfeeding

Treatment for tuberculosis is initiated whenever the probability of maternal disease is moderate to high because of the risk of untreated tuberculosis to a pregnant woman and her fetus [342–345]. Although antituberculosis drugs cross the placenta, they do not appear to have teratogenic effects in humans [346–349]. However, the inclusion of PZA in the treatment regimen for pregnant women is controversial in the United States. The FDA previously classified all 4 first-line drugs, INH, RIF, PZA, and EMB, as having equal potential for teratogenicity (all assigned to category C according to the previous FDA letter-based classification system, which is currently being revised [350]). We suggest that clinicians evaluate the risks and benefits of prescribing PZA on a case-by-case basis, allowing the patient to make an informed and educated decision, recognizing that for all first-line drugs, risk cannot be ruled out as there are no adequate and well-controlled studies in humans, but potential benefits warrant use of the drug in pregnant women despite potential risks. It is also important to recognize that PZA has been used extensively in high-burden countries for many years, and is recommended by the WHO for tuberculosis in pregnancy, as part of the standard treatment regimen [98]. Expert opinion is that in pregnant women with tuberculosis and HIV, extrapulmonary or severe tuberculosis, it is more beneficial to include PZA in the treatment regimen than to not include PZA. If a decision is made to exclude PZA from the regimen, a minimum of 9 months of INH, RIF, and EMB is used for most pregnant women with drug-susceptible tuberculosis. Expert consultation should be sought when first-line drugs cannot be used due to adverse effects or antibiotic resistance, when there is extensive disease and/or a risk of noncompliance. Although the fetal effects of many second-line drugs are not well established, small case series of pregnant women treated with second-line drugs (from studies in drug-resistant tuberculosis) suggest that good outcomes are achievable and that termination of the pregnancy is not necessary [351–354]. Overall, the absence of high-quality studies combined with estimates of >200 000 cases of tuberculosis in pregnant women each year highlight the need for additional research in this area [355, 356].

Breastfeeding is encouraged for women who are deemed noninfectious and are being treated with first-line agents. The small concentrations of antituberculosis drugs measured in breast milk have not been reported to produce toxic effects in the nursing infant [77]. Conversely, drugs in breast milk should not be considered to serve as effective treatment for active tuberculosis or latent tuberculosis infection in a nursing infant. Whenever INH is given to a pregnant or nursing woman, supplementary pyridoxine, 25–50 mg/day, is prescribed [42, 43, 357, 358]. According to the AAP, supplementary pyridoxine (1–2 mg/kg/day) is also prescribed to exclusively breastfed infants, even those not receiving INH [77, 289].

Renal Disease

Patients with renal insufficiency or end-stage renal disease (ESRD) are immunocompromised [359]. Tuberculosis patients with chronic renal failure have worse clinical outcomes than those without renal failure, and, thus, experts recommend close monitoring during tuberculosis treatment [360]. The pharmacokinetics of antituberculosis drugs are altered as some are cleared by the kidneys and/or removed via hemodialysis [361, 362]. Therefore, dose adjustment in patients with renal insufficiency or ESRD may be required (Table 3 and Table 12). Decreasing the dose lowers peak serum drug concentrations and can compromise treatment efficacy. Based on expert opinion, the interval between drug doses in patients with a creatinine clearance of <30 mL/minute and those receiving hemodialysis should be increased instead. In patients with borderline renal function, a 24-hour urine collection may be needed to more accurately define the degree of renal insufficiency prior to making regimen changes [242, 363]. Insufficient data exist to guide dosing recommendations for patients with a reduced but >30 mL/min creatinine clearance. In such patients, standard doses are used by experts, but measurement of serum concentrations 2 and 6 hours after timed administration can be used to assist with optimizing drug dosages.

RIF and INH are metabolized by the liver, and conventional dosing can be used in the setting of renal insufficiency. Although PZA is metabolized by the liver, its metabolites (pyrazinoic acid and 5-hydroxy-pyrazinoic acid) may accumulate in patients with renal insufficiency. EMB is approximately 80% cleared by the kidneys and may accumulate in patients with renal insufficiency. Experts suggest a longer interval between doses (ie, thrice weekly) for PZA and EMB [242, 363]. With hemodialysis, PZA and, presumably, its metabolites are cleared to a significant degree, INH and EMB are cleared to some degree, and RIF is not cleared by hemodialysis [361]. The fluoroquinolones are also cleared variably by the kidneys. Levofloxacin undergoes greater renal clearance than moxifloxacin [179]. Postdialysis administration of all antituberculosis medications is preferred to facilitate DOT and to avoid premature clearance of drugs such as PZA. Monitoring serum drug concentrations, along with careful clinical and pharmacological assessment, in patients with ESRD, may be necessary. ESRD patients are often taking other medications that interact with antituberculosis drugs or have comorbid clinical

Table 12. Dosing Recommendations for Adult Patients With Reduced Renal Function[a]

Drug	Change in Frequency?	Recommended Dose and Frequency for Patients With Creatinine Clearance <30 mL/min, or Patients Receiving Hemodialysis
Isoniazid	No	300 mg once daily, or 900 mg 3 times/wk
Rifampin	No	600 mg once daily, or 600 mg 3 times/wk
Pyrazinamide	Yes	25–35 mg/kg/dose 3 times/wk (not daily)
Ethambutol	Yes	20–25 mg/kg/dose 3 times/wk (not daily)
Levofloxacin	Yes	750–1000 mg/dose 3 times/wk (not daily)
Moxifloxacin	No	400 mg once daily
Cycloserine	Yes	250 mg once daily, or 500 mg/dose 3 times/wk[b]
Ethionamide	No	250–500 mg/dose daily
Para-amino salicylic acid	No	4 g/dose twice daily
Streptomycin	Yes	15 mg/kg/dose 2-3 times/wk (not daily)
Capreomycin	Yes	15 mg/kg/dose 2-3 times/wk (not daily)
Kanamycin	Yes	15 mg/kg/dose 2-3 times/wk (not daily)
Amikacin	Yes	15 mg/kg/dose 2-3 times/wk (not daily)

- Standard doses are given unless there is intolerance.
- The medications should be given after hemodialysis on the day of hemodialysis.
- Monitoring of serum drug concentrations should be considered to ensure adequate drug absorption, without excessive accumulation, and to assist in avoiding toxicity.
- Data currently are not available for patients receiving peritoneal dialysis. Until data become available, begin with doses recommended for patients receiving hemodialysis and verify adequacy of dosing using serum concentration monitoring.
- In patients with 30–50 mL/min creatinine clearance, standard doses are used by experts, but measurement of serum concentrations 2 and 6 hours after timed administration can be used to assist with optimizing drug dosages.

[a] Including adult patients receiving hemodialysis.

[b] The appropriateness of 250-mg daily doses has not been established. There should be careful monitoring for evidence of neurotoxicity.

conditions that could affect drug absorption, such as diabetes mellitus with gastroparesis. For patients receiving peritoneal dialysis, there is currently a paucity of pharmacokinetic and dosing data, and the dosages in Table 12 may not apply to patients receiving peritoneal dialysis. Such patients may require close monitoring for toxicity, and measurements of the serum concentrations of antituberculosis drugs before and after peritoneal dialysis should be considered.

Hepatic Disease

Tuberculosis treatment in patients with preexisting advanced liver disease poses significant challenges. The likelihood of drug-induced hepatitis is increased with prior advanced liver disease [364], liver transplant [365], or hepatitis C infection [366, 367]. Abnormal baseline aminotransferases alone are an independent risk factor for DILI [364, 368]. Experts recommend that patients with a history of injection drug use, birth in Asia or Africa (or other hepatitis virus endemic regions), or HIV infection have hepatitis B and C virus screening at baseline (Table 7). For patients with marginal hepatic reserve, superimposed DILI [56] may be severe, even life-threatening [369]. Fluctuations of serum aminotransferases and total bilirubin from preexisting liver disease can confound monitoring for DILI. Hepatic tuberculosis may also cause elevated aminotransferases, which improve with effective tuberculosis treatment.

Regimens with fewer potentially hepatotoxic agents are selected in patients with advanced liver disease or whose serum ALT is >3 times the upper limit of normal at baseline (and not thought to be caused by tuberculosis). The crucial efficacy of INH and particularly RIF warrant their use and retention, if at all possible, even in the face of preexisting liver disease. Expert consultation is advisable. Adjustments during treatment may be necessary. Drug susceptibility testing to fluoroquinolones and injectables is indicated if use of these drugs is being considered.

Alternative regimens for use in patients with hepatic disease include:

- Treatment without PZA: PZA has often been implicated in DILI. A potential regimen could be INH, RIF, and EMB for 2 months, followed by 7 months of INH and RIF [370, 371].
- Treatment without INH and PZA: For advanced liver disease patients, RIF and EMB with a fluoroquinolone, injectable, or cycloserine for 12–18 months, depending on the extent of the disease and response could be considered [372].
- Treatment without INH: Based on outcomes of studies on INH-resistant tuberculosis, a regimen of RIF, PZA, and EMB with or without a fluoroquinolone could be considered for a total duration of at least 6 months [373]. Although this regimen has 2 potentially hepatotoxic medications, it has the advantage of retaining a treatment duration of 6 months.
- Regimens with little or no potential hepatotoxicity: For patients with severe, unstable liver disease, EMB combined with a fluoroquinolone, cycloserine, and second-line injectable for 18–24 months (similar to an multidrug-resistant tuberculosis regimen) can be considered [374]. Some experts avoid aminoglycosides in patients with severe, unstable liver disease due to concerns about renal insufficiency or bleeding from the site of injected medication due to thrombocytopenia and/or coagulopathy.

Monitoring of Treatment in Hepatic Disease

Data to guide the monitoring of patients with preexisting severe liver disease are scarce. Clinical monitoring and patient education for manifestations of liver injury is warranted for all patients [56]. Experts in the field recommend measuring serum aminotransferases and total bilirubin concentrations every 1–4 weeks for at least the first 2–3 months of treatment. The INR may also be periodically followed for patients with severe hepatic impairment [56, 375, 376]. An increase in serum ALT is more specific for hepatocellular injury than an increase in AST, which can also signify abnormalities in muscle, heart, or kidney [56, 377]. In patients with more advanced preexisting disease, such as those with cirrhosis or encephalopathy, the ALT thresholds for treatment interruption have not been defined. Some experts recommend, in addition to weekly or twice-weekly ALT monitoring, interrupting treatment for only a 3-fold elevation of ALT, even if asymptomatic [375, 376]. Reintroduction of antituberculous treatment may entail rechallenge and/or substitution of agents, while trying to retain the most effective medications [56]. Whenever feasible, management of tuberculosis in the setting of severe hepatic disease is undertaken in consultation with experts.

Advanced Age

The risk of drug-induced hepatitis and other serious adverse effects increases with advancing age because of less efficient drug elimination due to reduced renal and hepatic clearance [56]. Because PZA is the most common culprit [378, 379], the benefits of including PZA in the initial regimen for elderly patients with modest disease and low risk of drug resistance may be outweighed by the risk of serious adverse events. Consequently, some experts avoid the use of PZA during the intensive phase among patients >75 years of age. In such cases, the initial regimen consists of INH, RIF, and EMB. If PZA is not used during the intensive phase, then the total duration of tuberculosis treatment should be extended to at least 9 months. When the elderly patient has active tuberculosis with high bacillary burden (ie, bilateral cavitation) and, thus, treatment failure or the development of drug resistance is a concern, benefits and risks of adding PZA or a fluoroquinolone (eg, levofloxacin, moxifloxacin) vs no fourth drug should be carefully considered. The risk of drug interaction is increased in the elderly and consideration may need to be given to dose adjustments or use of alternative regimens. Careful clinical monitoring to detect intolerance and adverse reactions is warranted.

Other Comorbid Conditions

As noted previously, the CDC and WHO recommend routine HIV testing and counseling to all patients with presumptive and diagnosed tuberculosis [253, 254]. Experts also recommend that patients with a history of injection drug use, HIV infection, or birth in Asia or Africa (or other hepatitis virus endemic regions) undergo hepatitis B and C virus screening at baseline. Based on limited data, some experts also suggest screening for helminthic infections, including malaria, strongyloides, and schistosomiasis in patients originating from regions hyperendemic for these diseases. In general, tuberculosis treatment for patients with diseases or conditions that alter immune responsiveness, including HIV infection, parasitic and helminthic infections, hematologic or reticuloendothelial malignancies, immunosuppressive therapy (eg, TNF-α inhibitors) [380], chronic renal failure [381], diabetes mellitus, and malnutrition is based on the standard, daily 6-month regimen (Table 2). Nonetheless, decisions regarding treatment of comorbidities and the duration of tuberculosis treatment can be individualized, taking into account disease severity, organs involved, and response to treatment. For example, based on increased rates of tuberculosis recurrence, some experts suggest extending the total duration of tuberculosis treatment to 9 months in poorly controlled diabetes mellitus [49, 50, 382, 383]. Similarly, for patients with silicotuberculosis, data demonstrate that cure rate is improved if the continuation phase is extended by at least 2 months [169, 384]. Based on data suggesting increased mortality with shorter durations of treatment, some experts also suggest extending the total duration of tuberculosis treatment to at least 9 months for all solid organ transplant recipients [385].

The management of immunosuppressive therapy in patients who develop active tuberculosis varies based on the comorbid condition. If possible, steps are taken to correct immunodeficiency. In patients with rheumatologic disease, expert opinion is that TNF-α inhibitor therapy is held if clinically feasible, when active tuberculosis is suspected or confirmed. There is no consensus on when TNF-α inhibitor therapy can be resumed. However, small case series suggest that it is safe to resume TNF-α inhibitor therapy in patients who complete at least 2 months of antituberculosis treatment and have a good clinical response [380, 386, 387]. The decision to restart TNF-α inhibitor treatment should be individualized, taking into account the clinical need for immunosuppressive therapy, the extent of tuberculosis disease, and clinical response to antituberculosis treatment. Of note, severe IRIS-like reactions in the setting of holding TNF-α inhibitor treatment have been reported [388]. In solid organ transplant recipients, significant pharmacological interactions can occur between rifamycin-based antituberculosis regimens (particularly RIF) and calcineurin inhibitors or rapamycin; on this basis, strict monitoring of serum drug concentrations is needed to prevent rejection [389].

RECURRENT TUBERCULOSIS, TREATMENT FAILURE, AND DRUG RESISTANCE

Recurrent Tuberculosis

Recurrence refers to the circumstance in which a patient whose sputa had become and remained culture negative while

receiving antituberculosis drugs becomes culture positive or experiences clinical or radiographic deterioration consistent with active tuberculosis after completion of therapy. In such patients, vigorous efforts are made to establish a diagnosis and to obtain microbiologic confirmation of the relapse to enable testing for drug resistance. True relapses, defined as recurrent tuberculosis caused by the same strain as was identified at baseline, are thought to be due to failure of chemotherapy to sterilize the host tissues, thereby enabling endogenous recrudescence of the original infection. In high-incidence settings or where infection control is poor, however, exogenous reinfection with a new strain of *M. tuberculosis* may be responsible for the apparent recurrence (in this context, not referred to as relapse) [390, 391].

Patients at risk for relapses are those with extensive disease at baseline and whose sputum cultures remain positive after completion of the intensive phase of treatment [9, 392]. However, the sensitivity of culture-positive status at 2 months for predicting relapse is low [46]. Most relapses occur within the first 6–12 months after completion of therapy [393]. In the majority of patients with tuberculosis caused by drug-susceptible organisms who were treated by DOT with rifamycin-containing regimens, relapses occur with susceptible organisms [394, 395]. However, the risk of acquired drug resistance is substantial in patients who have a relapse after receiving SAT, a highly intermittent regimen in the setting of HIV infection, a non-rifamycin-containing regimen (including receiving only INH and EMB in the continuation phase of treatment), or a second-course of a first-line regimen reinforced by streptomycin [59, 60, 396–400]. In addition, if initial drug susceptibility testing was not performed and the patient fails or relapses with a rifamycin-containing regimen using DOT, a high likelihood exists that the organisms were resistant from the outset [399, 401, 402]. To help guide regimen selection, rapid molecular tests have been used at the time of suspected recurrence as an approach to rapidly identifying the presence of resistance-conferring mutations; however, the detection of *M. tuberculosis* DNA and RIF resistance have been reported as being false positive [403]. Experts suggest caution in interpreting results from molecular tests used at the time of suspected recurrence.

The selection of empiric treatment regimens for patients with relapses is based on the prior treatment scheme. For patients with relapse who were treated for drug-susceptible tuberculosis using DOT, experts recommend retreatment using the standard intensive phase regimen until the results of susceptibility tests are known. For patients who did not receive DOT or had irregular treatment, it is prudent to infer a higher risk of acquired drug resistance. Whenever feasible, rapid molecular and phenotypic diagnostics for detection of drug resistance should be used to inform regimen selection. When immediate treatment initiation is necessary, consider the use of an expanded empiric regimen in consultation with experts in the treatment of drug-resistant disease. If started, an expanded empiric regimen is administered until the results of susceptibility tests are known and commonly consists of the standard intensive phase regimen of daily INH, RIF, PZA, and EMB, plus a later-generation fluoroquinolone, an injectable, and depending on the severity of disease or the anticipated extensiveness of resistance, an additional second-line drug [404]. All drugs are administered using DOT. An expanded regimen is indicated especially in patients with impaired immunity, limited respiratory reserve, CNS involvement, other life-threatening circumstances, or any other situation in which treatment with an inadequate regimen could have severe consequences to the individual or the community.

When epidemiological circumstances render exogenous reinfection the most likely cause of apparent relapse, the regimen choice is influenced by the drug susceptibility pattern of the presumed source case and/or drug-resistance testing. If the presumed source case is known to have drug-resistant organisms, an expanded empiric regimen based on the resistance profile of the putative source case may be suitable.

Poor Treatment Response and Treatment Failure

In the United States, treatment failure is defined as continuously or recurrently positive cultures after 4 months (5 months in Europe and WHO guidelines [98]) of treatment in a patient receiving appropriate chemotherapy. Among patients with drug-susceptible pulmonary tuberculosis, even with extensive lung cavitation, 90%–95% will be culture negative after 3 months of treatment with a regimen that contains INH and RIF. During this time, the vast majority of patients show clinical improvement, including reduced fever, reduced cough, and weight gain. Thus, patients with persistently positive cultures after 3 months of chemotherapy, with or without ongoing symptoms, are evaluated carefully to identify the cause of delayed response.

Multiple reasons for poor treatment response and treatment failure exist. For patients not receiving DOT, one explanation may be nonadherence to the treatment regimen. Among patients receiving DOT, cryptic nonadherence (spitting out or deliberately regurgitating tablets or capsules) or failure of the healthcare system to reliably deliver the drugs may be a cause. Other potential reasons include unrecognized drug resistance (drug susceptibility testing not done, misreported, or misinterpreted; reinfection with a drug-resistant strain), malabsorption (diarrhea, or prior resection surgery of the stomach or small intestine, or taking tuberculosis medications with antacids or other drugs/substances that might bind or interfere with drug absorption), or diabetes mellitus with or without gastroparesis [198, 199, 201, 405–410]. Some experts use TDM to evaluate poor drug exposure as a contributing factor to treatment failure [242]. Laboratory error (eg, cross-contamination or mislabeling of specimens) is also a possible reason for a positive culture in a patient who is doing well clinically [411].

Clinicians should be alert, as well, to the possibility of transient clinical or radiographic worsening (paradoxical reactions), despite appropriate therapy that would eventually result in cure.

Examples of this include ongoing inflammation at sites of lymphadenitis, worsened abnormalities on chest radiographs after several months of treatment, or the new appearance of pleural effusions during therapy for pulmonary tuberculosis. Such paradoxical worsening during treatment can occur in HIV-uninfected patients, as well as in HIV-infected patients (see "Immune Reconstitution Inflammatory Syndrome"). The diagnosis of a paradoxical reaction is made only after a thorough evaluation has excluded other etiologies, particularly tuberculosis treatment failure and drug resistance.

For patients who meet criteria for treatment failure, the possible reasons listed above should be addressed promptly. Recent mycobacterial isolates should be sent to a reference laboratory for susceptibility testing to both first-and second-line drugs. If clinicians are not familiar with the management of drug-resistant tuberculosis, immediate referral to, or consultation with a specialty center is indicated. If treatment failure is presumably due to drug resistance and the patient is seriously ill or has a positive sputum AFB smear, an empiric regimen is started immediately and continued until susceptibility tests are available to guide therapy; however, if the patient's clinical presentation is not severe, one may either initiate an empiric retreatment regimen or wait for drug susceptibility results from a recent isolate. Of note, patients who are not on the correct regimen remain infectious [102, 412].

A single new drug is never to be added to a failing regimen as it can lead to amplification of drug resistance, including acquired resistance to the newly added drug [413]. To lessen the likelihood of increasing resistance, it is generally prudent to add 2–3 new drugs to which susceptibility could logically be inferred (eg, using regional drug-resistance surveillance data and the patient's history of medication use). When drug susceptibility results are available, the regimen is adjusted accordingly.

Tuberculosis Caused by Drug-Resistant Organisms

Mycobacterium tuberculosis bacilli are continually undergoing spontaneous mutations that create resistance to individual antituberculosis drugs; however, the frequency of these mutations is sufficiently low that with appropriate combination chemotherapy that is reliably ingested, clinically significant resistance is very unlikely to develop [121, 414]. Acquired drug resistance can occur, however, when there is a large bacillary population (such as in pulmonary cavities), an inadequate drug regimen, a combined failure of both the patient and the provider to ensure that an adequate regimen is ingested, or malabsorption of one or more antituberculosis drugs [415, 416]. During extended or repeated treatment, amplification of resistance to multiple agents may occur. Patients with acquired drug resistance may transmit their strains to others who, if they develop tuberculosis, will have primary drug resistance. Notable clinical and demographic risk factors for drug-resistant tuberculosis include having a previous episode of tuberculosis treatment (in particular if the regimen was inadequate or adherence to the regimen was low), originating from or living for an extended period in a country with a high prevalence of drug-resistant tuberculosis, and having a history of exposure to an index case with drug-resistant tuberculosis.

Comprehensive guidance on the management of drug-resistant tuberculosis is beyond the scope of this document, though international guidelines exist [404]. An ATS/CDC/ERS/IDSA practice guideline for the management of drug-resistant tuberculosis is also currently under development using GRADE methodology.

RESEARCH AGENDA FOR TUBERCULOSIS TREATMENT

Much progress has been made over the last 10 years in the treatment of tuberculosis [109, 417]. The corpus of knowledge on new drug combinations, drug interaction with antiretrovirals, methods of dosing, and timing of dosing is increasing. Based on the writing of this guideline, however, several priority areas in need of additional research were identified.

New Antituberculosis Drugs and Regimens

Treatment of tuberculosis remains centered around the same 6-month, 4-drug regimen introduced >40 years ago. The identification of more potent drugs and drug regimens that permit shortening the duration of treatment remains a key priority. A number of new drugs and regimens for tuberculosis are currently being investigated in clinical trials. This includes repurposed drugs (eg, daily high-dose RPT and higher dosages of RIF, linezolid and carbapenems) and new drugs (eg, bedaquiline, delamanid, and pretomanid [formerly PA-824]). High-dose, daily RPT is being tested in a treatment-shortening phase 3 clinical trial, with dosage selected based on dose-ranging, drug-exposure optimization studies (ClinicalTrials.gov identifier: NCT02410772) [418]. Pretomanid is being tested as part of a combination regimen including moxifloxacin and PZA for the treatment of both drug-susceptible and drug-resistant tuberculosis (ClinicalTrials.gov identifier: NCT02193776). Bedaquiline, approved by the US FDA for treatment of multidrug-resistant tuberculosis in 2012, is also being investigated in drug-susceptible disease as part of a combination regimen including pretomanid and PZA and/or clofazimine in a phase 2 study (ClinicalTrials.gov identifier: NCT01691534). Broadly, the tuberculosis therapeutics development field would greatly benefit from dose-ranging and drug–drug interaction studies for new and existing drugs so as to identify the drug exposures and optimal combinations necessary to achieve maximal efficacy, while improving safety and tolerability.

Biomarkers of Treatment Effect and Individualization of Therapy

The success of therapy depends upon many diverse factors and only some are presently predictable, identifiable, or modifiable. Inclusion of biomarker substudies that assess both microbial and host biomarkers within phase 3 clinical trials will yield

important knowledge on the factors that impact therapeutic success. Additionally, data on pharmacokinetic/pharmacodynamic properties that influence drug safety and efficacy, data on drug penetration and distribution, and the pursuit of sensitive and specific biomarkers that can reliably predict relapse will be critically important to advancing the tuberculosis therapeutics field [116, 418, 419]. New biomarkers of treatment effect that can be implemented in the field and accurately monitor response to treatment on an individual basis may also allow for the individualization of the duration of treatment [420]. However, a considerable increase in investment in fundamental research is needed to develop and validate biomarkers of durable cure [421].

Treatment of Tuberculosis in Special Situations

Based on the writing of this guideline, the need for additional research was notable for treatment of tuberculosis in special situations. In particular, there is a paucity of high-quality studies on tuberculosis in pregnant women, breastfeeding women, and children. A recent US National Institutes of Health convened workshop examining the inclusion of pregnant and postpartum women in tuberculosis drug trials has provided consensus statements to help accelerate research in this area [422]. The lack of pediatric dosage forms of most antituberculosis medications has up to now necessitated using crushed tablets or opening capsules and creating suspensions to facilitate dosing in young children, and additionally has hampered inclusion of children in drug trials. As a result of key partnerships and concerted investments in pediatric therapeutics research, an affordable, high-quality, child-friendly fixed-dose combination meeting WHO quality assurance metrics is now being produced; however, these products are not yet registered in the United States or Europe [290]. Broadly, to address the paucity of data on the optimal treatment of children with tuberculosis, the drug development field should design trials to be more inclusive of children as study participants across key stages of therapeutics research, from pharmacokinetic studies through to phase 3 clinical trials. Examples of ongoing tuberculosis treatment trials that enroll children and adolescents are the SHINE study (Shorter Treatment for Minimal TB in Children Study; ISRCTN63579542), and TBTC Study 31/ACTG A5349 (Rifapentine-Containing Tuberculosis Treatment Shortening Regimens; NCT02410772) [423].

Implementation Research

Even as new drugs and new regimens are being developed, there remains a critical need to improve the delivery of tuberculosis treatment. DOT has been the dominant mode of treatment delivery, but evidence supporting its use has been weak. Strategies that are more convenient for patients and less resource-intensive for public health programs should be further explored [424]. For example, in low-incidence countries, early studies have shown that video DOT using smartphones is feasible, has high patient uptake, and is associated with similar adherence rates as in-person DOT [131]. Research to improve tuberculosis treatment delivery strategies should be informed by behavioral studies and/or implementation science frameworks, which have been shown to increase the likelihood of identifying successful multifaceted individual behavior change and health system interventions. Finally, research on the optimal introduction of new drugs is needed (even after approval from regulatory bodies) so as to provide data that will facilitate key implementation decisions around programmatic feasibility, cost-effectiveness, and optimal approaches to surveillance of drug resistance and prevention of emergence of new drug resistance [425].

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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