# Chapter 6: Treatment of Tuberculosis Disease

## Contents

# Introduction

## Purpose

The overall goals for treatment of tuberculosis (TB) are to cure the patient and to minimize the transmission of *Mycobacterium tuberculosis* to others. In the 2005 "Controlling Tuberculosis in the United States: Recommendations from the American Thoracic Society, Centers for Disease Control and Prevention, and the Infectious Diseases Society of America," one of the recommended strategies to achieve the goal of reduction of TB morbidity and mortality is the early and accurate detection, diagnosis, and reporting of TB cases, leading to initiation and completion of treatment.[1] Successful treatment of TB has benefits both for the individual patient and for the community in which the patient resides.

Use this section to understand and follow national and Wisconsin guidelines to do the following:

- Follow basic treatment principles for TB disease
- Select appropriate treatment regimens, dosages, and duration
- Monitor patients for side effects and adverse reactions
- Assess patients' response to treatment
- Determine completion of therapy
- Determine the need for post-treatment evaluation
- Provide treatment in special situations, such as when a patient has drug-resistant TB or TB–human immunodeficiency virus (HIV) coinfection
- Hospitalize and coordinate hospital discharges of patients with infectious TB

## Policy

Patients with TB disease in Wisconsin or who move to Wisconsin with reported TB disease should receive and complete treatment in accordance with the national guidelines set forth in CDC guidance and in accordance with Wisconsin laws and regulations. In Wisconsin, local jurisdictions have the responsibility and authority to verify treatment is complete and appropriate. Per Wis. Stat. §250.04(6) the Wisconsin Department of Health Services' Tuberculosis program provides "consultation, technical assistance and training regarding public health to local health departments, community organizations, and others." All guidance and recommendations issued by the State of Wisconsin Tuberculosis program are intended to support best practices and decision-making at the local jurisdictional level with respect to the control of TB and latent tuberculosis infection (LTBI) in Wisconsin.

## Forms

Required and recommended forms are available on the Wisconsin Tuberculosis Program Forms and Publications webpage.

For roles and responsibilities, refer to the "Roles, Responsibilities, and Contact Information" topic in the Introduction.

# Basic treatment principles

Follow the basic treatment principles for TB disease, as outlined below in Table 6.1.

**Table 6.1: Basic treatment principles for tuberculosis disease**

| Phase | Principles |
|---|---|
| **At start of treatment** | **Patient-centered care and directly observed therapy (DOT).** An adherence plan should tailor treatment and supervision to each patient by considering the patient's clinical and social circumstances (patient-centered care), as well as emphasizing DOT. |
| | **Cultural competence.** It is imperative to become culturally competent and guide other health care providers toward culturally competent health care. A culturally competent system acknowledges cultural differences regarding health care and incorporates them into all levels of the health care delivery system, from policy to provider to patient. |
| | **Human immunodeficiency virus (HIV) testing.** HIV testing should be offered to all patients with TB disease. |
| | **Medical supervision.** Patients with confirmed or suspected TB disease must be under the medical supervision of a provider who is licensed to practice medicine in Wisconsin. |
| | **Prompt start.** Start patients with confirmed or suspected TB disease promptly on appropriate treatment. It is not necessary to wait for laboratory confirmation. |
| **Regimen during treatment** | **Multiple drugs.** Treatment regimens must consist of multiple drugs to which the organism is susceptible. The administration of a single drug or the addition of a single drug to a failing regimen can lead to the development of resistance. |
| | **Single doses.** TB medications should be administered together as a single dose rather than in divided doses. A single dose leads to higher, and potentially more effective, peak serum concentrations, and facilitates DOT. Although ingesting the medications with food will delay or moderately decrease the absorption of the medications, the effects are of little clinical significance. |
| | **Pyridoxine to prevent neuropathy.** Pyridoxine (Vitamin B-6, 25-50 mg) is recommended for individuals receiving isoniazid (INH) as part of their treatment regimen to prevent peripheral neuropathy. It should definitely be used in people at |

| | |
|---|---|
| | risk for neuropathy (people who are pregnant or breastfeeding or people who have nutritional deficiency, diabetes, HIV infection, renal failure, or alcohol use disorder). |
| **Persistent positive cultures** | **Evaluation when positive cultures persist.** Monitor for culture conversion and promptly evaluate patients with persistently positive cultures after 2–3 months of therapy to identify the cause. Delayed culture conversion is defined as persistently positive cultures collected after 2 months of treatment. Treatment failure is defined as continued or recurrent positive cultures after 4 months of treatment. |
| **At completion of treatment** | **Completion in terms of the number of doses.** The criteria for treatment completion are based upon the total number of doses taken by DOT and not solely on the duration of therapy. Both duration in number of weeks of therapy and doses ingested via DOT must be met for treatment completion verification. |

# Treatment regimens and dosages

Use this information to do the following:

- Identify the appropriate regimen.
- Determine the appropriate dosage for each drug.
- Determine the duration of treatment.

The information in this topic was developed using guidelines for treating TB that have been developed by the American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC), and Infectious Diseases Society of America (IDSA).

See the “Treatment in Special Situations” topic in this section for information on treatment when there is drug-resistant TB, human immunodeficiency virus (HIV) infection, liver disease, or renal disease; when the patient is taking tumor necrosis factor-alpha (TNF-α) antagonists; where there is culture-negative TB or extrapulmonary TB; when the patient is pregnant or breastfeeding; or when the patient is considered to be of pediatric age.

See the full Executive Summary: Official American Thoracic Society/Centers for Diseases Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis.

For information regarding how to interpret or implement the treatment guidelines for drug susceptible TB, contact the Wisconsin TB Program at 608-261-6319.

As you use this section, remember the abbreviations for first-line drugs, which are listed in Table 6.2 below.

**Table 6.2: Abbreviations for first-line drugs**

| Drug | Abbreviation |
|---|---|
| Ethambutol | EMB |
| Isoniazid | INH |
| Pyrazinamide | PZA |
| Rifabutin | RFB |
| Rifampin | RIF |
| Rifapentine | RPT |

## Regimens

Identify the appropriate regimen for the patient. There are four basic regimens recommended for treating adults with TB caused by organisms that are known or presumed to be susceptible to isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB). The preferred regimen for treating TB disease for most adults consists of an initial two-month (8 week) phase of four drugs: INH, RIF, PZA, and EMB followed by a four-month (18 week) continuation phase of INH and RIF.

Children too young to undergo optical monitoring exams (e.g., Snellen and color discrimination tests) may not be prescribed EMB in the initial phase of a six-month (26 week) regimen, but the regimens are otherwise identical.

If a decision is made to exclude PZA from the regimen for a pregnant person, a minimum of nine months of INH, RIF, and EMB is used for most pregnant people with drug-susceptible tuberculosis. Please see the Pregnancy and Breastfeeding section for more information about PZA use during pregnancy.

Each regimen has an initial phase of two months (8 weeks), followed by a choice of several options for a continuation phase of either four or seven months (18–31 weeks). In Table 3: **Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms**, the initial phase is denoted by a number (1, 2, 3, or 4), and the options for the continuation phase are denoted by the respective number and a letter designation (a, b, or c).

Directly Observed therapy (DOT) is the best practice for active TB disease. The health officer may order treatment to be given by DOT as stated in Wis. Stat. § 252.075(5). The state TB program recommends seven day a week DOT for the first two weeks of therapy, followed by five day a week DOT for the remainder of therapy, for most patients.

The recommended regimens, and the number of doses specified by each regimen, are described on the next pages in Tables 6.3, 6.4, 6.5, 6.6, and 6.7.

For consultation regarding the treatment of TB, contact the Wisconsin TB Program at 608-261-6319.

**Table 6.3: Drug regimens for microbiologically confirmed pulmonary tuberculosis caused by drug-susceptible organisms**

| Regimen | Intensive phase drug(s)[a] | Interval and dose[b] (minimum duration) | Continuation phase drug(s) | Interval and dose[b,c] (minimum duration) | Range of total doses | Comments[c,d] | Regimen effectiveness |
|---|---|---|---|---|---|---|---|
| 1 | INH<br>RIF<br>PZA<br>EMB | 7 d/wk for 56 doses OR<br>5 d/wk for 40 doses<br>(8 weeks total) | INH<br>RIF | 7 d/wk for 126 doses OR<br>5 d/wk for 90 doses (18 weeks total) | 130-182 | This is the preferred regimen for patients with newly diagnosed pulmonary TB. | Greater |
| 2 | INH<br>RIF<br>PZA<br>EMB | 7 d/wk for 56 doses OR 5 d/wk for 40 doses<br>(8 weeks total) | INH<br>RIF | 3 times weekly for 54 doses (18 weeks total) | 94-110 | Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve. | |
| 3 | INH<br>RIF<br>PZA<br>EMB | 3 times weekly for 24 doses (8 weeks total) | INH<br>RIF | 3 times weekly for 54 doses (18 weeks) | 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<br>RIF<br>PZA<br>EMB | 7 d/wk for 14 doses then twice weekly for 12 doses | INH<br>RIF | Twice weekly for 36 doses (18 weeks) | 62 | Do not use twice weekly regimens in HIV-infected individuals 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: DPT, directly observed therapy; EMB, ethambutol; HIV, human immunodeficiency virus; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin.

[a] Other combinations may be appropriate in certain circumstances

[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), 25–60 mg/day, is given with INH to all people at risk of neuropathy (for example, pregnant people; breastfeeding infants; people 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] Alternatively, some U.S. tuberculosis programs have administered intensive-phase regimens 5 days per week for 15 doses (3 weeks), then twice weekly for 12 doses

**Table 6.4: Dosing recommendations for a 4-month rifapentine-moxifloxacin regimen for patients aged 12 years or older with pulmonary tuberculosis caused by drug-susceptible organisms- United States, 2022**

| Medication* | Body weight in kg | Dose |
|---|---|---|
| Rifapentine | ≥40 | 1,200 mg |
| Moxifloxacin | ≥40 | 400 mg |
| Isoniazid† | ≥40 | 300 mg |
| Pyrazinamide | 40- <55<br>≥55- 75<br>>75 | 1,000 mg<br>1,500 mg<br>2,000 mg |

*Medication should be administered with food

†Pyridoxine (vitamin B6), 25-50 mg/day, should be given with isoniazid to all patients.

Source: ATS, CDC, IDSA. Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clinical Infectious Diseases, Volume 63, Issue 7, 1 October 2016, Pages 853–867, https://doi.org/10.1093/cid/ciw566; Carr W, Kurbatova E, Starks A, Goswami N, Allen L, Winston C. Interim Guidance: 4-Month Rifapentine-Moxifloxacin Regimen for the Treatment of Drug-Susceptible Pulmonary Tuberculosis — United States, 2022. MMWR Morb Mortal Wkly Rep 2022;71:285–289. DOI: http://dx.doi.org/10.15585/mmwr.mm710

## Dosages

Once the appropriate regimen has been identified, refer to the following tables for instructions on dosages for each drug. First-line antituberculosis medications should be administered together, split dosing should be avoided.

For information regarding second-line drugs, contact the Wisconsin TB Program at 608-261-6319.

## Table 6.5: Doses of first-line antituberculosis drugs for adults and children

| Drug | Preparation | Adults/children | Doses | | | |
|---|---|---|---|---|---|---|
| | | | Daily | 1x/wk | 2x/wk | 3x/wk |
| INH | Tablets (50 mg, 100 mg, 300 mg); elixir (50 mg/5 ml); aqueous solution (100 mg/ml) for intramuscular injection[¶] | 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] |
| RIF* | 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 | — |

Definitions of abbreviations: EMB = ethambutol; FDA = Food and Drug Administration; INH = isoniazid; PZA = pyrazinamide; RFB = rifabutin; RIF = rifampin; RPT = rifapentine.

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 the 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.

*Rifampin is available in 25mg/ml compounded liquid and Isoniazid is available in 50mg/5ml in liquid form commercially

| Drug | Preparation | Adults/children | Doses | | | |
|---|---|---|---|---|---|---|
| | | | Daily | 1x/wk | 2x/wk | 3x/wk |
| RFB | Capsule (150 mg) | Adults[d] | 5 mg/kg (typically 300 mg) | __ | Not recommended | Not recommended |
| | | Children | Appropriate dosing for children is unknown. Estimated at 5mg/kg. | | | |
| RPT | Tablet (150 mg, film coated) | Adults | __ | 10 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. | | | |
| PZA | Tablet (500 mg, scored) | Adults | See Table 6.6 | __ | See Table 6.6 | See Table 6.6 |
| | | Children | 35 (30-40) mg/kg | __ | 50 mg/kg | __[b] |
| EMB | Tablet (100 mg, 400 mg) | Adults | See Table 6.7 | __ | See Table 6.7 | See Table 6.7 |
| | | Children[f] | 20 (15-25) mg/kg | __ | 50 mg/kg | __[b] |

Definitions of abbreviations: EMB = ethambutol; FDA = Food and Drug Administration; INH = isoniazid; PZA = pyrazinamide; RFB = rifabutin; RIF = rifampin; RPT = rifapentine.

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 the 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.

Source: ATS, CDC, IDSA. Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clinical Infectious Diseases, Volume 63, Issue 7, 1 October 2016, Pages 853–867, https://doi.org/10.1093/cid/ciw566

## Table 6.6: Suggested pyrazinamide doses, using whole tablets, for adults weighing 40 to 90 kilograms[a]

| Interval | Weight (kg)[B, C] 40–55 kg | 56–75 kg | 76–90 kg |
|---|---|---|---|
| Daily, mg (mg/kg) | 1,000 (18.2–25.0) | 1,500 (20.0–26.8) | 2,000 † (22.2–26.3) |
| Thrice weekly, mg (mg/kg) | 1,500 (27.3–37.5) | 2,500 (33.3–44.6) | 3,000 † (33.3–39.5) |
| Twice weekly, mg (mg/kg) | 2,000 (36.4–50.0) | 3,000 (40.0–53.6) | 4,000 † (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.

Source: ATS, CDC, IDSA. Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clinical Infectious Diseases, Volume 63, Issue 7, 1 October 2016, Pages 853–867, https://doi.org/10.1093/cid/ciw566

## Table 6.7: Suggested ethambutol doses, using whole tablets, for adults weighing 40 to 90 kilograms[a2]

| Interval | Weight (kg)[B,C] 40–55 kg | 56–75 kg | 76–90 kg |
|---|---|---|---|
| Daily, mg (mg/kg) | 800 (14.5–20.0) | 1,200 (16.0–21.4) | 1,600 (17.8–21.1) |
| Thrice weekly, mg (mg/kg) | 1,200 (21.8–30.0) | 2,000 (26.7–35.7) | 2,400 (26.7–31.6) |
| Twice weekly, mg (mg/kg) | 2,000 (36.4–50.0) | 2,800 (37.3–50.0) | 4,000 (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.

Source: ATS, CDC, IDSA. Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clinical Infectious Diseases, Volume 63, Issue 7, 1 October 2016, Pages 853–867, https://doi.org/10.1093/cid/ciw566

## Duration of treatment

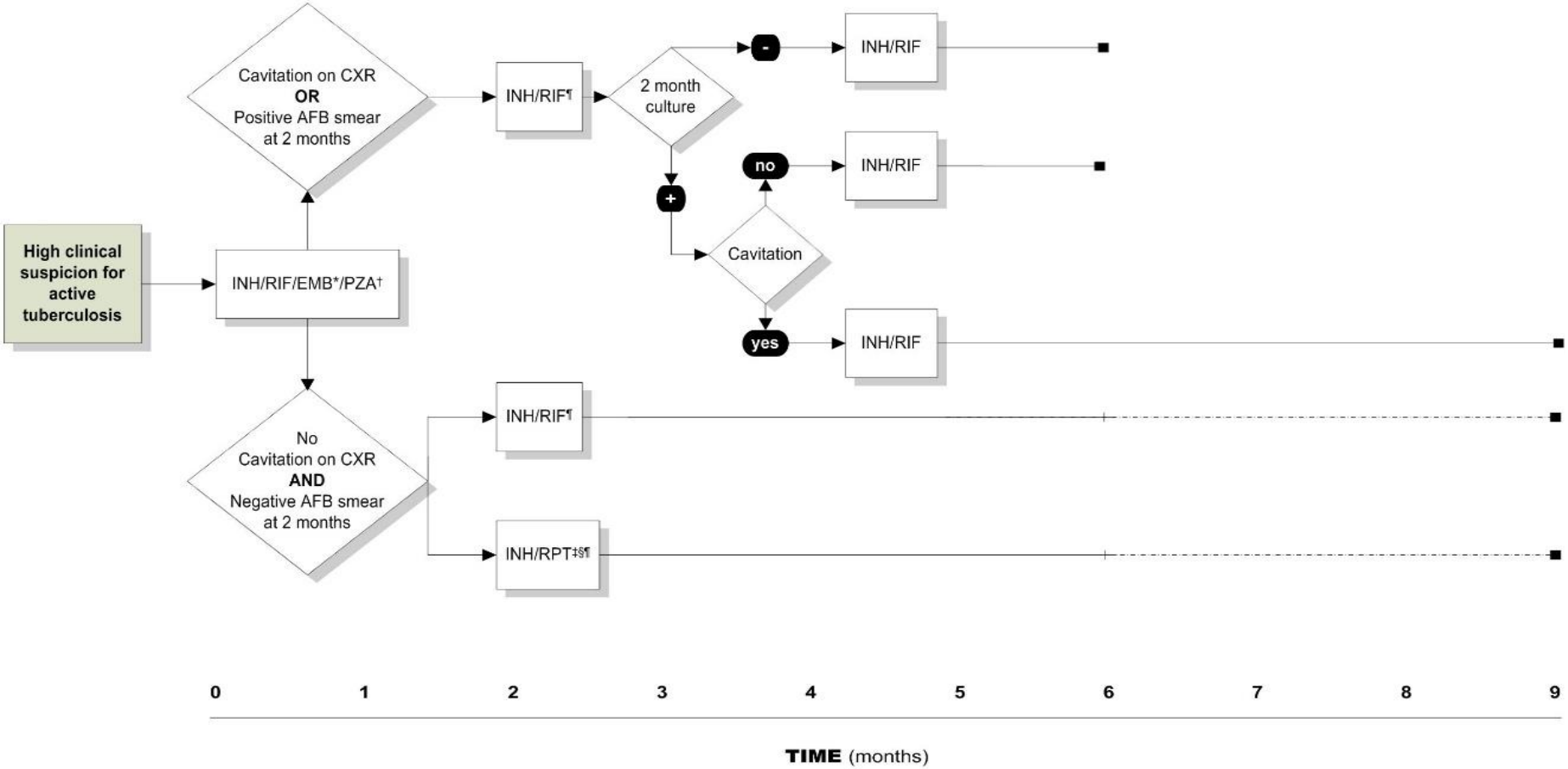
Use the reference tables above and the algorithm below to determine the duration of treatment. The four recommended regimens for treating patients with TB caused by drug-susceptible organisms have a duration of twenty-six (26) weeks to thirty-nine (39) weeks. Each regimen has an initial phase of eight (8) weeks, followed by a continuation phase of either eighteen (18) weeks or thirty-one (31) weeks. In some circumstances, a treatment regimen may need to be extended beyond thirty-one (31) weeks.

The standard duration of treatment for pulmonary TB should be twenty-six (26) weeks, unless **both** cavitation is present **and** the patient is still culture positive after eight (8) weeks, in which case the thirty-nine (39) week regimen is recommended. Note that there are three exceptions to the standard twenty-six (26) week duration of treatment.

For tuberculous 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.

Six- to nine-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. Because of the difficulties in assessing response, however, some experts tend to favor the nine-month duration, and in the setting of extensive orthopedic hardware, some experts extend the duration of treatment further to 12 months. For HIV-infected patients receiving ART, guidelines suggest using the standard six-month daily regimen consisting of an intensive phase of two months of INH, RIF, PZA, and EMB followed by a continuation phase of four months of INH and RIF for the treatment of drug-susceptible pulmonary tuberculosis. 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 three months (that is, a continuation phase of 7 months in duration, corresponding to a total of nine months of therapy) for treatment of drug susceptible pulmonary tuberculosis.

## Treatment algorithm for tuberculosis[3]




Definition of abbreviations: AFB = acid-fast bacilli; CXR = chest radiograph; EMB = ethambutol; HIV = human immunodeficiency virus; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; RPT = rifapentine.

* EMB may be discontinued when results of drug susceptibility testing indicate no drug resistance.

† PZA may be discontinued after it has been taken for 2 months (56 doses).

‡ RPT should not be used in HIV-infected patients with TB or in patients with extrapulmonary TB.

§ Therapy should be extended to 9 months if the 2-month culture is positive.

¶ At 2 months, review drug susceptibility and culture results, if applicable, and review these results regularly throughout treatment if the patient is drug resistant.

Source: ATS, CDC, IDSA. Treatment of tuberculosis. *MMWR* 2003;52(No. RR-11):6.

# Side effects and adverse reactions

The patient should be monitored by a registered nurse, clinician, or case manager at least monthly for signs and symptoms of adverse reactions until treatment is completed. If a patient is symptomatic, the provider should be consulted, and the patient monitored more frequently. Chemistries and complete blood count (CBC), aspartate aminotransferase (AST)/alanine aminotransferase (ALT), or other tests based on specific drugs should be done periodically per physician's orders. See Table 6.9**: Monitoring and Interventions for Side Effects and Adverse Reactions** in this section.

As is true with all medications, combination chemotherapy for tuberculosis is associated with a predictable incidence of adverse effects, some mild, some serious.[4]

Adverse effects are common and often manageable. Although it is important to be attuned to the potential for adverse effects, it is at least equally important that first-line drugs not be stopped without adequate justification.[5] However, adverse reactions can be severe, and thus, it is important to recognize adverse reactions that indicate when a drug should not be used. Mild adverse effects can generally be managed with symptomatic therapy; whereas with more severe effects, the offending drug or drugs must be discontinued.[6] In addition, proper management of more serious adverse reactions often requires expert consultation.[7]

Monitor patients for side effects and adverse reactions following the basic monitoring steps listed below.

See the Wisconsin TB program case management guide for more specific monitoring recommendations from the state program: Nurse Case Management for Active Tuberculosis (TB) Disease

For additional questions about side effects, adverse effects, and monitoring, contact the Wisconsin TB Program at 608-261-6319.

## Basic monitoring steps

1. All health care workers providing treatment for TB disease should be familiar with the American Thoracic Society (ATS) and Centers for Disease Control and Prevention (CDC) guidelines.

    a. All jurisdictions should follow the national monitoring guidelines identified in the current guidelines for treatment of TB, ATS, CDC, IDSA. Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clinical Infectious Diseases, Volume 63, Issue 7, 1 October 2016, Pages 853–867, https://doi.org/10.1093/cid/ciw566.

**b.** It is also important to check for guideline updates posted on the CDC's Division of Tuberculosis Elimination home page and the list of guidelines by date at on the CDC's Clinical Guidelines webpage.

**2.** While on treatment, all patients should be evaluated in person at baseline (before starting treatment) and then at least monthly for side effects and adverse reactions.

**3.** The common side effects of and adverse reactions to drugs used to treat for TB disease are listed below in Table 6.8: **Reporting Reactions to Antituberculosis Medications**. Educate patients to stop the medicine and promptly report any of the symptoms or signs listed in Table 6.8 or any unexplained illness to the prescribing clinic immediately.

**a.** If a patient reports a potentially serious adverse reaction, call the patient's provider immediately and alert the state TB program by calling 608-261-6319.

**b.** If a patient reports a potentially less severe side effect, call the patient's provider immediately and monitor the patient.

**4.** If you suspect that an antituberculosis drug may be causing a particular side effect or adverse reaction:

**a.** Refer to Table 6.9: **Monitoring and Interventions for Side Effects and Adverse Reactions**.

**b.** Consult with the state TB program by calling 608-261-6319.

**5.** If you suspect that an antituberculosis drug may be interacting with other medications that the patient is taking, refer to ATS, CDC, IDSA. Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clinical Infectious Diseases, Volume 63, Issue 7, 1 October 2016, Pages 853–867.

**6.** Document the following patient information:

**a.** Review of symptoms, test results, side effects, and adverse reactions

**b.** Education given

**c.** Refill provided

**d.** Description of any problems encountered, and action taken for that visit

**e.** Next appointment

## Reporting reactions

Table 6.8 below is intended for use by a health care worker who performs case management services. The health care worker should instruct the patient to report to the provider the side effects and adverse reactions listed below in Table 6.8.

**If a patient reports to a health care worker a potentially serious adverse reaction, the health care worker should call 911 for the patient or the patient's medical provider**

**immediately depending on the severity and alert the state TB program by calling 608-261-6319.**

If a patient reports to a health care worker a potentially less severe side effect, the health care worker should call the patient's medical provider immediately and monitor the patient.

**Table 6.8: Reporting reactions to antituberculosis medications[8]**

| Potentially serious adverse reactions* | Less severe signs and symptoms* |
|---|---|
| Immediately report the following signs and symptoms or other abnormalities or unexpected events to the patient's provider. These signs and symptoms suggest side effects, including hepatotoxicity:<br>• Jaundice<br>• Dark urine<br>• Vomiting<br>• Abdominal pain<br>• Fever<br>• Ototoxicity<br>• Visual changes<br>• Vestibular changes<br>• Marked clinical rash<br>In consultation with the provider, instruct the patient to stop TB medications until evaluated by the provider. | Report the following signs and symptoms to the patient's provider within 24 hours:<br>• Anorexia<br>• Nausea<br>• Malaise<br>• Peripheral neuropathy: tingling or burning sensation in hands or feet<br>• Rashes |
| * These lists are not all-inclusive. | |

Source: California Department of Health Services (CDHS)/California Tuberculosis Controllers Association (CTCA). TB case management—core components. *CDHS/CTCA Joint Guidelines* [CTCA Web site]. 2011 update8:9. Available at: https://ctca.org/wp-content/uploads/2018/11/ctca_case_management_5_.pdf

## Monitoring for side effects and adverse reactions by antituberculosis drug

Refer to Table 6.9**: Monitoring and Interventions for Side Effects and Adverse Reactions** to do the following:

- Identify the side effects and adverse reactions associated with antituberculosis drugs.
- Determine how to monitor for side effects and adverse reactions.

See the CDC's *Core Curriculum on Tuberculosis: What the Clinician Should Know* webpage, for full details on drug side effects and reactions.

**Table 6.9: Monitoring and interventions for side effects and adverse reactions**[9,10,11]

| Anti-tuberculosis Drug | Side Effects/ Adverse Reactions | Monitoring | Comments |
|---|---|---|---|
| **Isoniazid (INH)** | Rash<br>Hepatic enzyme elevation<br>Hepatitis<br>Peripheral neuropathy<br>Mild central nervous system effects | Clinical monitoring monthly<br><br>Liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and serum bilirubin) at baseline in selected cases ((human immunodeficiency virus [HIV] infection, history of liver disease, alcoholism, and pregnancy)<br><br>Repeat measurements if:<br>• Baseline results are abnormal.<br>• Patient is pregnant, in the immediate postpartum period, or at high risk for adverse reactions.<br>• Patient has symptoms of adverse reactions. | Hepatitis risk increases with age and alcohol consumption.<br><br>Pyridoxine (vitamin B6, 10–25 mg/d) might prevent peripheral neuropathy and central nervous system effects.<br><br>Serum concentrations of phenytoin, disulfiram (Antabuse), and carbamazepine may be increased in people taking INH. Measure serum concentrations of phenytoin and carbamazepine in patients receiving INH (with or without rifampin)and adjust the dose if necessary. |

| Anti-tuberculosis Drug | Side Effects/ Adverse Reactions | Monitoring | Comments |
|---|---|---|---|
| **Rifampin (RIF)** | Rash<br>Gastrointestinal upset<br>Hepatitis<br>Fever<br>Bleeding problems<br>Thrombocytopenia<br>Renal failure<br>Flu-like symptoms<br>Orange-colored body fluids (secretions, urine, tears) | Complete blood count, platelets, and liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and serum bilirubin) at baseline in selected cases (human immunodeficiency virus [HIV] infection, history of liver disease, alcoholism, and pregnancy)<br><br>Repeat measurements if:<br>• Baseline results are abnormal.<br>• Patient has symptoms of adverse reactions. | There are a number of drug interactions with potentially serious consequences. Significant interactions with methadone, birth control hormones, and many other drugs have been reported.<br><br>Contraindicated or should be used with caution when administered with protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs). Reduces levels of many drugs (for example, PIs, NNRTIs, methadone, dapsone, ketoconazole, coumadin derivatives, hormonal contraceptive, digitalis, sulfonylureas, diazepam, ß-blockers, anticonvulsants, and theophylline).<br><br>For more information, refer to "Section 7: Drug Interactions" on page 45 in "Treatment of Tuberculosis".<br><br>Because information regarding rifamycin drug interactions is evolving rapidly, consult the CDC's Division of Tuberculosis web page to obtain the most up-to-date information.<br><br>Colors body fluids orange.<br><br>May permanently discolor soft contact lenses. |

| Anti-tuberculosis Drug | Side Effects/ Adverse Reactions | Monitoring | Comments |
|---|---|---|---|
| **Rifabutin (RFB)** | Rash<br>Hepatitis<br>Fever<br>Thrombocytopenia<br>Orange-colored body fluids (secretions, urine, tears)<br><br>With increased levels of RFB:<br>Severe arthralgias<br>Uveitis<br>Leukopenia | Complete blood count, platelets, and liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and serum bilirubin) at baseline in selected cases (human immunodeficiency virus [HIV] infection, history of liver disease, alcoholism, and pregnancy)<br><br>Repeat measurements if:<br>• Baseline results are abnormal.<br>• Patient has symptoms of adverse reactions.<br><br>Use adjusted daily dose of RFB and monitor for decreased antiretroviral activity and for RFB toxicity if RFB taken concurrently with protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs). | Although drug interactions are less problematic with RFB, they still occur and close monitoring is required.<br><br>Contraindicated for HIV-infected patients taking hard-gel saquinavir or delavirdine; caution is also advised if RFB is administered with soft-gel saquinavir.<br><br>Similar to rifampin but less potent of an inducer, rifabutin reduces levels of many drugs (for example, PIs, NNRTIs, methadone, dapsone, ketoconazole, coumadin derivatives, hormonal contraceptive, digitalis, sulfonylureas, diazepam, ß-blockers, anticonvulsants, and theophylline).<br><br>When used with efavirenz, the daily dose of RFB should be increased from 300 mg to 450 mg or 600 mg.<br><br>May permanently discolor soft contact lenses. |

| Anti-tuberculosis Drug | Side Effects/ Adverse Reactions | Monitoring | Comments |
|---|---|---|---|
| **Rifapentine (RPT)** | Similar to those associated with rifampin. | Similar to that for rifampin. | Drug interactions involving RPT are being investigated and are likely to be similar to those of rifampin. RPT is an inducer of multiple hepatic enzymes and therefore may increase metabolism of coadministered drugs that are metabolized by these enzymes. For more information, refer to "Section 7: Drug Interactions" on page 45 in "Treatment of Tuberculosis." |
| **Pyrazinamide (PZA)** | Gastrointestinal upset<br>Hepatitis<br>Rash<br>Photosensitive dermatitis<br>Hyperuricemia<br>Joint aches<br>Gout (rare) | Clinical monitoring at weeks 2, 4, and 8<br><br>If the drug is used in patients with underlying liver disease, laboratory and clinical monitoring should be increased.<br><br>Baseline measurements of uric acid<br><br>Liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and serum bilirubin) at baseline in selected cases (human immunodeficiency virus [HIV] infection, history of liver disease, alcoholism, or pregnancy)<br><br>Repeat measurements if:<br>• Baseline results are abnormal.<br>• Patient has symptoms of adverse reactions. | Treat hyperuricemia only if patient has symptoms.<br><br>Might make glucose control more difficult in people with diabetes.<br><br>Serum uric acid measurements are not recommended as routine but may serve as a surrogate marker for compliance. |

| Anti-tuberculosis Drug | Side Effects/ Adverse Reactions | Monitoring | Comments |
|---|---|---|---|
| **Ethambutol (EMB)** | Optic neuritis<br>Rash | Baseline tests of visual acuity (Snellen chart) and color discrimination (Ishihara tests)<br><br>At each monthly visit, patients should be questioned regarding possible visual disturbances, including blurred vision or scotomata.<br><br>Monthly testing of visual acuity and color discrimination is recommended for:<br>• Patients taking doses >15–25 mg/kg.<br>• Patients receiving EMB for >2 months.<br>• Patients with renal insufficiency. | Optic neuritis may be unilateral; check each eye separately.<br><br>Patients should be instructed to contact their physician or public health clinic immediately if they experience a change in vision.<br><br>EMB should be discontinued immediately and permanently if there are any signs of visual toxicity. |
| **Rifamate® (INH and RIF)**<br>**Rifater® (INH, RIF, PZA)** | See comments under individual drugs above | | |

Definitions of abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; EMB = ethambutol; HIV = human immunodeficiency virus; INH = isoniazid;
NNRTIs = nonnucleoside reverse transcriptase inhibitors; PZA = pyrazinamide; PIs = protease inhibitors; RFB = rifabutin; RIF = rifampin; RPT = rifapentine.

Sources: CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49 (No. RR-6):26–29, 38–39; ATS, CDC, IDSA. Treatment of tuberculosis. *MMWR* 2003;52(No. RR-11):19–25; CDC. Update: Adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection—United States. *MMWR* 2003;52(No. 31):735–736; CDC. Table 5: first-line anti-TB medications. In: Chapter 7: treatment of TB disease. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. November 2001. Available at: http://www.cdc.gov/tb/pubs/corecurr/index.htm . Accessed July 3, 2006.

# Response to treatment

For consultation regarding a patient's response to treatment, contact the Wisconsin TB Program at 608-261-6319.

For patients whose sputum cultures are positive before treatment, the best way to measure the effectiveness of therapy is to obtain specimens for culture at least monthly until culture conversion is achieved (at least two consecutive negative cultures with no subsequent positive cultures). Patients with multidrug-resistant tuberculosis (MDR-TB) should have cultures performed monthly for the entire course of treatment.

In some cases, a patient may not be able to produce a sputum specimen after two months of treatment. If the patient has improved clinically and has shown chest radiograph improvement, treatment may be continued as if the patient had a negative sputum specimen at two months.

Radiographic evaluations during treatment are of less importance for those with confirmed TB than sputum evaluation. However, a chest radiograph at completion of treatment provides a baseline for comparison with future films.

Patients whose cultures have not become negative or whose symptoms do not significantly improve or resolve despite two to three months of therapy should be reevaluated for potential drug-resistant disease, potential failure of the regimen for a variety of reasons (therapeutic drug monitoring may be necessary), and DOT adherence. The collection of serum drug levels, timed with drug administration, may be ordered by the treating physician to evaluate for proper drug absorption.

If drug susceptibility results show resistance to any of the first-line drugs or if the patient remains symptomatic or smear- or culture-positive after three months, a TB medical expert should be consulted. Contact the Wisconsin TB Program at 608-261-6319 to set up a consultation with the state TB medical consultant.

In patients with negative sputum cultures before treatment, the major indicators of response to therapy are the chest radiograph and clinical evaluation. The intervals at which chest radiography should be repeated depend on the clinical circumstances and the differential diagnosis that is being considered but usually should be no more than every three months. If the radiograph does not improve after the patient has received three months of treatment, the abnormality may be the result of either previous (not current) TB or another process.[12]

# Completion of therapy

A full course of therapy (completion of treatment) is determined more accurately if the total number of doses ingested is taken into account, as well as the duration of therapy. If there are no interruptions in drug administration, six months (26 weeks) is usually the minimum duration of treatment and accurately indicates the amount of time in which drugs are given. However, in human immunodeficiency virus (HIV)-negative, culture-negative patients, treatment for four months (16 weeks) may be adequate if there is clinical or radiographic improvement and no other etiology identified.[13]

For consultation regarding the treatment of TB in a patient with negative cultures, contact the Wisconsin TB Program at 608-261-6319.

In some cases, either because of drug toxicity or nonadherence to the treatment regimen, the specified number of doses cannot be administered within the targeted period. In such cases, the goal is to deliver the specified number of doses within a recommended maximum timeframe. For example, for a six-month daily regimen, the total doses should be administered within nine months of beginning treatment. If treatment is not completed within this period, the patient should be assessed to determine the appropriate action to take, such as continuing treatment for a longer duration or restarting treatment from the beginning.

Treating a patient for a defined duration, without accounting for the number of doses taken, can result in undertreatment.

Interruptions in treatment may have a significant effect on the duration of therapy. Reinstitution of treatment must take into account the extensiveness of the disease (for example, cavitary versus noncavitary disease on chest radiograph, smears and cultures, immunologic status), the point in time when the interruption occurred, and the duration of the interruption. In general, the earlier in treatment and the longer the duration of the interruption, the more serious the effect and the greater the need to restart therapy from the beginning.[14] See Table 6.10 below for recommendations regarding interruptions in treatment.

For consultation regarding completion of therapy or considerations for re-starting treatment, contact the Wisconsin TB Program at 608-261-6319.

**Table 6.10 Management of treatment interruptions**

| Time point of interruption | Details of interruption | Recommended approach |
|---|---|---|
| During intensive phase | Lapse is < 14 days in duration. | Continue treatment to complete planned total number of doses (as long as all doses are completed in 3 months) |

| | | |
|---|---|---|
| | Lapse is ≥ 14 days in duration | Restart treatment from the beginning |
| During continuation phase | Received ≥ 80% of doses and sputum was AFB smear **negative** on initial testing.<br>Received ≥ 80% of doses and sputum was AFB smear **positive** on initial testing.<br>Received < 80% of doses and accumulative lapse is < 3 months in duration<br>Received < 80% of doses and lapse is ≥ 3 months in duration. | Further therapy may not be necessary.<br>Continue therapy until all doses are completed.<br>Continue therapy until all doses are completed (full course), unless consecutive lapse is > 2 months.<br>If treatment cannot be completed within the recommended time frame for regimen, restart therapy from the beginning (restart intensive phase followed by continuation phase).<br>Restart therapy from the beginning, new intensive and continuation phases. |

# Post-treatment evaluation

Routine follow-up after completion of therapy is not necessary for patients with a satisfactory and prompt bacteriologic response to a six- or nine-month regimen that included both isoniazid and rifampin.

The table below describes the clinician's responsibilities at completion of therapy for cases in which the organisms are drug-susceptible and drug-resistant.

**Table 6.10: Clinician's responsibilities at completion of therapy**

| Drug susceptibility | Clinician's actions |
|---|---|
| **Drug-susceptible organisms** | Instruct the patient to promptly report the development of any symptoms, particularly prolonged cough, fever, or weight loss, or symptoms compatible with their site of disease. |
| **Organisms resistant to isoniazid, rifampin, or both** | Individualize follow-up evaluation.[15] Rifampin-resistant or multi-drug resistant TB is generally followed for two years post therapy. |

For consultation regarding post-treatment evaluation, contact the Wisconsin TB Program at 608-261-6319.

# Treatment in special situations

Treatment of TB in the following situations requires a high level of expertise or close consultation with an expert to provide appropriate management:

- Drug-resistant TB
- Human immunodeficiency virus (HIV) infection
- Alcohol use disorder or excessive alcohol consumption
- Liver disease
- Renal insufficiency and end-stage renal disease
- TB associated with tumor necrosis factor-alpha (TNF-α) antagonists
- Culture-negative pulmonary TB
- Extrapulmonary TB
- Pregnancy and breastfeeding
- TB in children

For consultation regarding treatment in the following situations, contact the Wisconsin TB Program at 608-261-6319.

## Drug-resistant tuberculosis

Treatment of TB caused by drug-resistant organisms should be provided by, or in close consultation with, an expert in the management of these difficult situations. Second-line regimens often represent the patient's last hope for being cured, and inappropriate management can have life-threatening consequences.[16]

Drug resistance is proven only by drug-susceptibility testing performed in a competent laboratory. A patient with a strain of *Mycobacterium tuberculosis* resistant to both isoniazid (INH) and rifampin (RIF) has multidrug-resistant TB (MDR-TB). Refer MDR-TB patients immediately to a specialist or seek consultation with a specialized treatment center.[17]

Acquired drug resistance usually develops when an inadequate drug regimen is prescribed (for example, inappropriate drugs or insufficient dosage) or when there is a combined failure of both the patient and the provider to ensure that an adequate regimen is taken. A patient with acquired drug resistance may transmit his or her strain to others, who may then develop primary drug-resistant TB.[18]

For consultation about the treatment of drug-resistant TB and available treatment regimens and how to acquire specialized medications (for example, BPaL regimen), contact the Wisconsin TB Program at 608-261-6319.

**Resources**

- ATS, CDC, IDSA. Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clinical Infectious Diseases, Volume 63, Issue 7, 1 October 2016, Pages 853–867, Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 3rd edition/2022 Updates, Curry International Tuberculosis Center
- CDC. Clinical Overview of Drug-Resistant Tuberculosis Disease
- CDC. Extensively Drug Resistant Tuberculosis Human Immunodeficiency Virus Infection

## Human immunodeficiency virus infection

Management of human immunodeficiency virus (HIV)-related TB is complex and requires expertise in the management of both HIV disease and TB. Because HIV-infected patients often take numerous medications, some of which interact with antituberculosis medications, clinicians are strongly encouraged to consult with experts who treat HIV-related TB.

It is especially important to use directly observed therapy (DOT) and other adherence-promoting strategies with patients with HIV-related TB.

The following are contraindicated in HIV-infected patients:

- Patients with potential for severe or unmanageable drug interactions, including people living with HIV or AIDS on certain antiretroviral therapy regimens (rifabutin (RFB) may be suggested in place of rifampin for those on antiretroviral therapy with rifampin drug-drug interaction). Twice-weekly rifampin (RIF)- or rifabutin (RFB)-based regimens in patients with CD4+ cell counts of less than 100 per microliter [19]
    - 4-month HPMZ (Isoniazid, Rifapentine, Moxifloxacin, and Pyrazinimide) is contraindicated in the following situations:
        - Patients taking phenytoin and disulfiram.
        - Rifapentine may decrease blood levels of oral or implanted hormonal contraceptives, warfarin, sulfonylureas, methadone, suboxone, some anti-hypertensives, and steroids.
        - Some cardiac medications and certain antiretroviral drugs may have serious drug-drug interactions.
        - Moxifloxacin interacts with other medications that are QTc prolonging.
    - Providers should check carefully for drug-drug interactions before starting a patient on 4-month HPMZ.

Patients with HIV-related TB may experience a temporary exacerbation of symptoms, signs, or radiographic manifestations (paradoxical reactions or TB-immune reconstitution inflammatory syndrome (IRIS)) of TB while receiving antituberculosis treatment.[20]

**Resources**

- ATS, CDC, IDSA. Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clinical Infectious Diseases, Volume 63, Issue 7, 1 October 2016, Pages 853–867, ,
- ATS, CDC. "Notice to Readers: Updated Guidelines for the Use of Rifamycins for the Treatment of Tuberculosis among HIV-infected Patients Taking Protease Inhibitors or Nonnucleoside Reverse Transcriptase Inhibitors" (*MMWR* 2004;53[No. 2]:37). Available at:
- CDC. *Self-Study Modules on Tuberculosis* (Division of Tuberculosis Elimination Web site). Available at: Self-Study Modules on Tuberculosis | Tuberculosis (TB) | CDC
- CDC. "TB Treatment for People with HIV". Available at: TB Treatment for People with HIV | TB | CDC
- CDC. "Treating Opportunistic Infections Among HIV-exposed and Infected Children" (*MMWR* 2004;53[No. RR-14]). Available at: .
- NTCA "A 4-Month Regimen to Treat Pulmonary Tuberculosis: Isoniazid, Rifapentine, Moxifloxacin, and Pryazinamide (HPMZ)". Alcohol use disorder and excessive alcohol consumption

## Alcohol-related treatment complications

Risk of drug-induced liver injury and nonadherence complicate health interventions for patients who are diagnosed with TB disease or LTBI and who also are known or suspected to have an alcohol use disorder, who drink heavily, or who regularly consume alcohol.

In several important ways related to tuberculosis and its treatment, alcohol consumption increases health risks and can complicate the treatment of patients.

**Immunosuppression:** People who use alcohol may be at increased risk for acquiring or developing TB, but given the many other potential risk factors that commonly occur among such people, alcohol use has been difficult to identify as a separate risk factor for TB.[21] However, studies have shown that "alcohol consumption is a major risk factor for infection with opportunistic bacterial, viral, fungal, and parasitic pathogens."[22]

**Liver injury and death**: Drug-induced liver injury (DILI) "may occur with all currently recommended regimens for the treatment of …LTBI".[23] In the treatment of TB disease, "the crucial efficacy of isoniazid, and particularly rifampin, warrants their use and retention, if at all possible, even in the face of preexisting liver disease."[24] However, it is not fully understood yet how antituberculosis medications cause drug-induced liver injury.[25] For people taking isoniazid, an association of hepatitis was found with alcohol consumption, with rates being fourfold higher among people consuming alcohol daily than among those who did not drink alcohol.[26] When a

patient has hepatic disease, the risk of drug accumulation and drug-induced hepatitis is increased. However, with more frequent laboratory and clinical monitoring, isoniazid may be used in patients with stable hepatic disease. Transient asymptomatic hyperbilirubinemia may occur in patients taking rifampin or rifapentine, and more severe clinical hepatitis may also occur. Hepatitis is more common when rifampin is given with isoniazid than when rifampin is given alone or with drugs other than isoniazid.[27,28] Pyrazinamide has slightly lower rates of hepatotoxicity than isoniazid or rifampin, but pyrazinamide can cause liver injury that may be severe and prolonged.[29]

To prevent and manage drug-induced liver injury, the American Thoracic Society recommends the following systematic steps: consideration of benefits and risks in selecting patients and regimens, careful and thorough staff and patient education, ready access to care, good communication between providers, and clinical and biochemical monitoring.[30]

**Nonadherence to treatment:** Patients who do not complete LTBI treatment risk progression to TB disease, and those who do not complete treatment for TB disease risk relapse, development of drug-resistant TB, serious illness, and possible death. Barriers to adherence may be patient related, such as conflicting health beliefs, alcohol or drug dependence, or mental illness, or they may be system related, such as lack of transportation, inconvenient clinic hours, and lack of interpreters.[31] It is more difficult for patients who have an alcohol use disorder to adhere to therapy. In a prospective study of 224 patients, "noncompliance was significantly associated with homelessness and alcoholism."[32] In a study of 237 patients in the Russian Federation undergoing DOTS treatment for TB disease, "substance abuse was identified as the only factor that was strongly associated with non-adherence…These results suggest that DOTS programmes [sic] might be more likely to achieve TB control targets if they include interventions aimed at improving adherence by diagnosing and treating substance abuse concurrently with standard TB therapy."[33] DOTS programs that have explicitly offered substance abuse treatment have reported better outcomes that those that have not.[34] In South Carolina, joint treatment programs to treat patients with TB who have alcohol and substance abuse problems were used in conjunction with incentives, enablers, and a process of increasing restrictions (health department warnings, then court-ordered directly observed therapy, then involuntary confinement) as needed to address noncompliance. This combination of strategies was associated with an increase in overall completion of antituberculosis therapy and a decrease in new cases between 1986-1991.[35]

## Safe treatment guidelines

In 2006, the American Thoracic Society (ATS) issued "An Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy." Pages 943-947 provide guidance in the following areas for the safe treatment of LTBI and TB Disease:

- **Program Infrastructure**
  Adopt these standardized approaches to develop safe treatment of LTBI and TB disease.
- **Provider Education and Resources**
  Develop these written resources, educational programs, and referral mechanisms to

assure that health care providers have the skills, knowledge, and resources to safely diagnose and treat patients with TB disease and LTBI.

- **Pretreatment Clinical Evaluation**
  Refer here for a list of what to include in the pretreatment clinical evaluation and the initial physical examination and when to screen for viral hepatitis.
- **Patient Education**
  Follow these suggestions to improve patients' awareness of and communication about their symptoms of liver disorders. Communicate with patients in their preferred language[36] and carefully confirm that they understand the educational points being made.
- **Medication Administration and Pharmacy**
  Use these tips to distribute antituberculosis medications in ways that encourage and reinforce prompt reporting by patients of adverse effects.
- **Treatment of LTBI and Treatment of TB Disease**
  Use these recommendations to guide treatment decisions and monitoring activities. Numbered lists of recommendations provide detailed information. Three flowcharts show key data and decisions in the following areas: LTBI pretreatment clinical evaluation and counseling, monitoring for hepatotoxicity during LTBI treatment, and monitoring for hepatotoxicity during treatment of TB disease.[37]

## Liver disease

Management of TB in patients with unstable or advanced liver disease is difficult. The likelihood of drug-induced hepatitis may be greater in these patients. The implications of drug-induced hepatitis for patients with marginal hepatic reserve are potentially serious, even life-threatening. Also, fluctuations in the biochemical indicators of liver function (with/without symptoms) related to the preexisting liver disease confound monitoring for drug-induced hepatitis.[38] Clients at higher risk for hepatitis and liver disease should receive a hepatitis B and hepatitis C screening panel prior to initiating treatment.

For all patients with preexisting liver disease, frequent clinical and laboratory monitoring should be performed to detect drug-induced hepatic injury.[39]

**Resources**

- ATS, CDC, IDSA. Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clinical Infectious Diseases, Volume 63, Issue 7, 1 October 2016, Pages 853–867,.
- An Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy." Consult these recommendations at An Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy | American Journal of Respiratory and Critical Care Medicine (atsjournals.org)

For consultation regarding patients with preexisting liver disease, contact the Wisconsin TB Program at 608-261-6319.

## Renal insufficiency and end-stage renal disease

### Treatment complications

Renal insufficiency complicates the management of TB because some antituberculosis medications are cleared by the kidneys. Management may be further complicated by the removal of some antituberculosis agents via hemodialysis. Thus, some alteration in dosing antituberculosis medications is commonly necessary in patients with renal insufficiency and end-stage renal disease (ESRD) receiving hemodialysis.

### Creatinine clearance

Dosing recommendations are based on patients' creatinine clearance.

Administration of drugs that are cleared by the kidneys is managed in the same manner, with an increase in dosing interval for patients having a creatinine clearance of less than 30 ml/minute or for patients receiving hemodialysis.

In patients having a reduced creatinine clearance (but not less than 30 ml/minute), standard doses should be used, but measurement of serum concentrations should be considered to avoid toxicity. [40]

### Dosing recommendations

For patients having a creatinine clearance of less than 30 ml/minute or for patients receiving hemodialysis, the following adjustments to conventional dosing are recommended.

**Table 6.11:** Dosing recommendations for adult patients with reduced renal function and for adult patients receiving hemodialysis[41]

| Drug | Change in frequency? | Recommended dose and frequency for patients with creatinine clearance <30 ml/min or for patients receiving hemodialysis |
|---|---|---|
| Isoniazid | No change | 300 mg once daily, or 900 mg 3 times per week |
| Rifampin | No change | 600 mg once daily, or 600 mg 3 times per week |
| Pyrazinamide | Yes | 25–35 mg/kg per dose 3 times per week (not daily) |

| Drug | Change in frequency? | Recommended dose and frequency for patients with creatinine clearance <30 ml/min or for patients receiving hemodialysis |
|---|---|---|
| Ethambutol | Yes | 20–25 mg/kg per dose 3 times per week (not daily) |
| Moxifloxacin | No | 400 mg/dose daily |
| Levofloxacin | Yes | 750–1,000 mg per dose 3 times per week (not daily) |
| Cycloserine | Yes | 250 mg once daily, or 500 mg/dose 3 times per week* |
| Ethionamide | No change | 250–500 mg/dose daily |
| p-Aminosalicylic acid | No change | 4 g/dose, twice daily |
| Streptomycin | Yes | 15 mg/kg per dose 2 to 3 times per week (not daily) |
| Capreomycin | Yes | 15 mg/kg per dose 2 to 3 times per week (not daily) |
| Kanamycin | Yes | 15 mg/kg per dose 2 to 3 times per week (not daily) |
| Amikacin | Yes | 15 mg/kg per dose 2 to 3 times per week (not daily) |

* The appropriateness of 250-mg daily doses has not been established. There should be careful monitoring for evidence of neurotoxicity. (See Section 3 of the "Treatment of Tuberculosis" guidelines.)

- 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.

Source: \ ATS, CDC, IDSA. Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clinical Infectious Diseases, Volume 63, Issue 7, 1 October 2016, Pages 853–867, https://doi.org/10.1093/cid/ciw566

**Rifampin** and **isoniazid** are metabolized by the liver, so conventional dosing may be used in the setting of renal insufficiency. Supplemental dosing is not necessary for isoniazid, rifampin, or ethambutol. If pyrazinamide is given after hemodialysis, supplemental dosing is not required.

Although PZA is metabolized by the liver, its metabolites (pyrazinoic acid and 5-hydroxy-pyrazinoic acid) may accumulate in patients with renal insufficiency.

A longer interval between doses with three times a week administration is recommended for **pyrazinamide** and **ethambutol**.

Doses of **streptomycin, kanamycin, amikacin,** and **capreomycin** must be adjusted in patients with renal failure, and the dosing interval should be increased. In general, the dose should not be reduced because the drugs exhibit concentration dependent bactericidal action, and smaller doses may reduce drug efficacy.

**Ethionamide** requires no dose adjustment.

Twice daily dosing (4 g) of **p-Aminosalicylic acid (PAS)** should be adequate if the granule formulation is used. Its metabolite, acetyl-PAS, is substantially removed by hemodialysis.

**Cycloserine** requires an increase in the dosing interval to avoid accumulation between hemodialysis sessions, and the drug should be given after hemodialysis to avoid underdosing. The **fluoroquinolones** are also cleared variably by the kidneys. Levofloxacin undergoes greater renal clearance than moxifloxacin.

**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.**

### Administration of drugs immediately after hemodialysis

Administration of all antituberculosis drugs immediately after hemodialysis will facilitate DOT (three times per week) and avoid premature removal of the drugs.

### Monitoring of serum drug concentrations

It is important to monitor serum drug concentrations in people with renal insufficiency who are taking cycloserine, ethambutol, or any of the injectable agents to minimize dose-related toxicity, while providing effective doses.

Clinicians also should be aware that patients with end-stage renal disease may have additional clinical conditions, such as diabetes mellitus with gastroparesis, that may affect the absorption of the antituberculosis drugs, or they may be taking concurrent medications that interact with these drugs. Under these circumstances a careful clinical and pharmacologic assessment is necessary, and, in selected cases, serum drug concentration measurements may be used to assist in determining the optimum dose of the antituberculosis drugs.

Finally, data currently do not exist for patients receiving peritoneal dialysis. Because the drug removal mechanisms differ between hemodialysis and peritoneal dialysis, it cannot be assumed that all of the recommendations in Table 1 will apply to peritoneal dialysis. Such patients may require close monitoring, including measurements of the serum concentrations of the antituberculosis drugs.[42]

## Tuberculosis associated with tumor Necrosis Factor-Alpha Antagonists

TB is a potential consequence of treatment with tumor Necrosis Factor-Alpha (TNF-α) antagonists such as the following:

- Infliximab (Remicade®)
- Etanercept (Enbrel®)
- Adalimumab (Humira®)

These drugs work by blocking TNF-α, an inflammatory cytokine, and are approved for treating rheumatoid arthritis and other selected autoimmune diseases. Blocking TNF-α can allow TB disease to emerge from LTBI. Health care providers should take steps to prevent TB in immunocompromised patients and remain vigilant for TB as a cause of unexplained febrile illness.[43]

Patients should be screened for risk factors for *M. tuberculosis* infection and tested for infection before initiating immunosuppressive therapies, including TNF-α antagonists.[44]

**Resources**

- CDC. "Tuberculosis Associated with Blocking Agents against Tumor Necrosis Factor-Alpha—California, 2002–2003" (*MMWR* 2004;53[No. 30]:83–686). Available at: Culture-Negative Pulmonary Tuberculosis

## Culture-negative pulmonary tuberculosis

A diagnosis of TB should not be ruled out if *M. tuberculosis* cannot be isolated from people suspected of having pulmonary TB on the basis of clinical features and chest radiographic examination. Alternative diagnoses should be carefully considered and further appropriate diagnostic studies undertaken in people with apparent culture-negative TB.[45]

A diagnosis of culture-negative pulmonary TB can be made if all the following conditions are met:

- Initial acid-fast bacilli (AFB) smears and cultures are negative.
- Clinical or radiographic response occurs within two months of initiation of therapy.
- No other diagnosis has been established.[46]

After the initial phase (first two months) is complete in adult patients, continue treatment with an additional two months of isoniazid and rifampin during the continuation phase to complete a total of four months of treatment.[47] However, HIV-infected patients with culture-negative pulmonary TB should be treated for a minimum of six months (26 weeks).[48]

For consultation regarding the treatment of TB in a patient with negative cultures, contact the Wisconsin TB Program at 608-261-6319.

## Extrapulmonary tuberculosis

The basic principles for treating pulmonary TB also apply to extrapulmonary forms of the disease. Guidelines suggest that adjunctive corticosteroids should not be used routinely in the treatment of patients with pericardial tuberculosis. However, selective use of corticosteroids in patients who are at the highest risk for inflammatory complications might be appropriate. Guidelines recommend initial adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks for patients with tuberculous meningitis. Recommendations concerning duration of therapy are as follows:

Use a six-month course of therapy for TB involving any site.[49] **Exceptions:**

- For bone or joint TB, because of the difficulties in assessing response, however, some experts tend to favor the nine-month duration, and in the setting of extensive orthopedic hardware, some experts extend the duration of treatment further to 12 months.
- For TB meningitis the optimal duration of therapy has not been established through randomized controlled trials, but most experts and society guidelines prescribe 12 months of treatment. Consider prolonging therapy for patients with TB in any site that is slow to respond or for patients for whom PZA was either not included in the entire first 8 weeks or was not effective in the regimen (resistant).[50]

**Note:** Affected lymph nodes may enlarge while patients are receiving appropriate therapy or after treatment has ended without any evidence of bacteriologic relapse. On occasion, new nodes can appear during or after treatment as well.[51]

For consultation to discuss length of treatment, contact the Wisconsin TB Program at 608-261-6319.

**Resources**

- ATS, CDC, IDSA. Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clinical Infectious Diseases, Volume 63, Issue 7, 1 October 2016, Pages 853–867,
- Division of Tuberculosis Elimination. *Fact Sheets* (Division of Tuberculosis Elimination Web site; accessed February 2007). Available at: General Public Communication and Education Resources | Tuberculosis (TB) | CDC
- CDC. *Self-Study Modules on Tuberculosis* (Division of Tuberculosis Elimination Web site; 1999). Available at: Self-Study Modules on Tuberculosis | Tuberculosis (TB) | CDC

## Pregnancy and breastfeeding

Because of the risk of TB to the fetus, treatment in pregnant women should be initiated whenever the probability of maternal disease is moderate to high. The initial treatment regimen should consist of isoniazid (INH), rifampin (RIF), and ethambutol (EMB).

Guidelines 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. 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. Although these drugs cross the placenta, they do not appear to have teratogenic effects.

Breastfeeding is encouraged for women who are deemed noninfectious and are being treated with first-line agents. Conversely, drugs in breast milk should not be considered an effective treatment for TB in a nursing infant.[52]

Pyridoxine supplementation (25–50 mg/day) is recommended for all women taking INH who are either pregnant or breastfeeding.[53] According to the AAP, supplementary pyridoxine (1–2 mg/kg/day) is also prescribed to exclusively breastfed infants, even those not receiving INH.

## Tuberculosis in children

A pediatric patient is a person under the age of 12.

Because of the high risk of disseminated TB in infants and children younger than 5 years of age, treatment should be started as soon as the diagnosis of TB is suspected.[54]

The following recommendations have been developed for children:

- Regimens recommended for infants, children, and adolescents with TB are generally the same as those for adults.
- Duration of treatment in children is at minimum six months (26 weeks).

  **Exception:** For disseminated disease, or TB meningitis, treatment may be extended nine- to 12 - months.[55] For other exceptions, refer to “Duration of Treatment” in the “Treatment Regimens and Dosages” topic in this section.
- Directly observed therapy (DOT) always should be used in treating children regardless of site of disease.[56]

Due to the difficulty of isolating *M. tuberculosis* in a child with pulmonary TB, the choice of drugs for the child is frequently guided by the drug susceptibility test results of the presumed source case. If drug-resistant TB is suspected or the source case isolate is not available, specimens for

microbiological evaluation should be obtained via early morning gastric aspiration, bronchoalveolar lavage, or biopsy.[57]

### Resources

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- American Academy of Pediatrics. In: Pickering LK, Baker CJ, Long SS, McMillan JA, eds. Red Book: 2006 Report of the Committee on Infectious Diseases. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006 (Red Book® Online Web site).

# Resources and References

## Resources

- ATS, CDC, IDSA. Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clinical Infectious Diseases, Volume 63, Issue 7, 1 October 2016, Pages 853–867,
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