



Treatment of Tuberculosis Disease

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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. One of the recommended strategies to reduce 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 the community in which the patient resides.

Use this chapter to understand and follow national and Idaho guidelines to:

- 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) co-infection; and
- Hospitalize and coordinate hospital discharges of patients with infectious TB.

Guidance

Patients diagnosed with TB disease should receive and complete treatment in accordance with the national treatment guidelines set forth by the American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC), and Infectious Diseases Society of America (IDSA). The information contained in this chapter reflects guidance published in the 2016 *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis* found here: <https://academic.oup.com/cid/article/63/7/e147/2196792>.



For consultation regarding the treatment of TB, readers should always feel free to contact the Idaho Division of Public Health TB Program by phone [(208) 334-5939], email, or other secure messaging.

Basic Treatment Principles

Follow the basic treatment principles for tuberculosis (TB) disease as outlined below in Table 1.

TABLE 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 his or her clinical and social circumstances (patient-centered care). The plan should include DOT where feasible, especially for infectious patients.
	Cultural sensitivity. It is imperative to become culturally competent and guide other healthcare providers toward culturally competent health care. A culturally competent system acknowledges cultural differences regarding healthcare and incorporates them into all levels of the healthcare delivery system, from policy to provider to patient.
	Human immunodeficiency virus (HIV) testing. All patients with TB disease should be offered testing for HIV. Explain this test is part of routine evaluation and treatment for tuberculosis. Document if patient declines to be tested for HIV.
Regimen During Treatment	Medical supervision. Patients with confirmed or suspected tuberculosis (TB) disease must be under the medical supervision of a provider, ideally one who is a licensed physician.
	Prompt start. Start patients with confirmed or suspected TB disease promptly on appropriate treatment. It is not necessary to wait for laboratory confirmation.
	Multiple drugs. Treatment regimens must contain 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 may delay or moderately decrease the absorption of the medications, the effects are usually of little clinical significance.



Phase	Principles
	<p>Pyridoxine to prevent neuropathy. Pyridoxine (Vitamin B-6) is recommended for some individuals receiving isoniazid (INH) as part of their treatment regimen to prevent peripheral neuropathy. It should be used in persons at risk for neuropathy (women who are pregnant or breastfeeding, and for persons with nutritional deficiency, diabetes, HIV infection, renal failure, or alcoholism). If isoniazid-related neuropathy is suspected in a patient already taking pyridoxine, symptoms may be reduced or resolved with increased doses of pyridoxine (e.g. increase dose by 25 mg up to a max dose of 100-150 mg, as indicated).</p> <p><u>Remember that pyridoxine can cause gastrointestinal irritation and routine co-administration with isoniazid is not necessary for all patients.</u></p>
Persistent Positive Cultures	<p>Evaluation when positive cultures persist. Monitor for culture conversion and promptly evaluate patients with persistently positive cultures after 3 months of therapy to identify the cause. Treatment failure is defined as continued or recurrent positive cultures after 4 months of treatment in a patient receiving appropriate chemotherapy.</p>
At Completion of Treatment	<p>Completion in terms of the number of doses. The criteria for treatment completion are based upon the total number of doses taken and not solely on the duration of therapy.</p>

Treatment Regimens and Dosages

Use this information to:

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

The information presented here is based on the 2016 guidelines for treatment of drug-susceptible tuberculosis (TB), *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis* that can be found here: <https://academic.oup.com/cid/article/63/7/e147/2196792>.



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

As you use this section, remember the abbreviations for first-line drugs that are listed below.

TABLE 2: ABBREVIATIONS FOR FIRST-LINE DRUGS

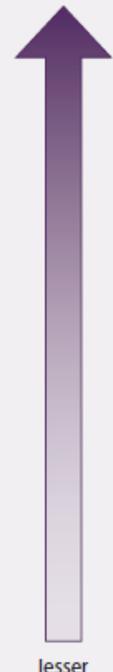
<ul style="list-style-type: none"> ▪ Ethambutol: EMB ▪ Isoniazid: INH ▪ Pyrazinamide: PZA 	<ul style="list-style-type: none"> ▪ Rifabutin: RFB ▪ Rifampin: RIF ▪ Rifapentine: RPT
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Regimens

Identify the appropriate regimen for the patient. There are four basic regimens recommended for treating adults with pulmonary 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 consists of an initial two-month intensive phase of four drugs: INH, RIF, PZA, and EMB followed by a four-month continuation phase of INH and RIF.²

Directly observed therapy (DOT) is the preferred initial management strategy for all regimens, especially for potentially infectious cases, and should be used whenever feasible.

TABLE 3: DRUG REGIMENS FOR MICROBIOLOGICALLY CONFIRMED PULMONARY TUBERCULOSIS CAUSED BY DRUG-SUSCEPTIBLE ORGANISMS³

Intensive Phase			Continuation Phase				Regimen effectiveness
Regimen	Drugs ¹	Interval and Doses ² (minimum duration)	Drugs	Interval and Doses ^{2,3} (minimum duration)	Range of Total Doses	Comments ^{3,4}	
1	INH RIF PZA EMB	7 days/week for 56 doses (8 weeks) or 5 days/week for 40 doses (8 weeks)	INH RIF	7 days/week for 126 doses (18 weeks) or 5 days/week for 90 doses (18 weeks)	182 to 130	This is the preferred regimen for patients with newly diagnosed pulmonary TB.	 <p>greater</p> <p>lesser</p>
2	INH RIF PZA EMB	7 days/week for 56 doses (8 weeks) or 5 days/week for 40 doses (8 weeks)	INH RIF	3 times weekly for 54 doses (18 weeks)	110 to 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 weeks)	INH 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 RIF PZA EMB	7 days/week for 14 doses then twice weekly for 12 doses ⁵	INH RIF	Twice weekly for 36 doses (18 weeks)	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.	

INH = isoniazid RIF = rifampin PZA = pyrazinamide EMB = ethambutol

* For dosing information, refer to the *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis*.

¹ Other combinations may be appropriate in certain circumstances; additional details are provided in the *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis*.

² 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 less than 7 days per week.

³ 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.

⁴ Pyridoxine (vitamin B6), 25–50 mg/day, is given with INH to all persons at risk of neuropathy (e.g., 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.

⁵ Alternatively, some U.S. TB control programs have administered intensive-phase regimens 5 days per week for 15 doses (3 weeks), then twice weekly for 12 doses.

Dosages

TABLE 4: DOSES*OF FIRST-LINE ANTITUBERCULOSIS DRUGS FOR ADULTS AND CHILDREN^{†4}

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 (max.)	5 mg/kg (300 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)
		Children (max.)	10–15 mg/kg (300 mg)	—	20–30 mg/kg (900 mg)	—
RIF	Capsule (150 mg, 300 mg); powder may be suspended for oral administration; aqueous solution for intravenous injection	Adults [†] (max.)	10 mg/kg (600 mg)	—	10 mg/kg (600 mg)	10 mg/kg (600 mg)
		Children (max.)	10–20 mg/kg (600 mg)	—	10–20 mg/kg (600 mg)	—
RFB	Capsule (150 mg)	Adults [†] (max.)	5 mg/kg (300 mg)	—	5 mg/kg (300 mg)	5 mg/kg (300 mg)
		Children	Appropriate dosing for children is unknown			
RPT RPT	Tablet (150 mg, film coated) Tablet (150 mg, film coated)	Adults [†]	—	10 mg/kg (continuation phase) (600 mg)	—	—
		Children	This drug is not approved for treatment of active TB in children < 12 y of age	This drug is not approved for treatment of active TB in children < 12 y of age	This drug is not approved for treatment of active TB in children < 12 y of age	This drug is not approved for treatment of active TB in children < 12 y of age
PZA	Tablet (500 mg, scored)	Adults	See Table 5	—	See Table 5	See Table 5
		Children	30-40 mg/kg	—	50 mg/kg	—

TABLE 4: DOSES*OF FIRST-LINE ANTITUBERCULOSIS DRUGS FOR ADULTS AND CHILDREN†4

Drug	Preparation	Adults/children	Doses			
			Daily	1x/wk	2x/wk	3x/wk
EMB	Tablet (100 mg, 400 mg)	Adults	See Table 6	—	See Table 6	See Table 6
		Children§	15–25 mg/kg daily	—	50 mg/kg	—

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

* Dose per weight is based on ideal body weight. Children weighing more than 40 kg should be dosed as adults.

† For the purposes of this document, adult dosing begins at the age of 15 years.

¶ INH is used, but not FDA-approved, for intravenous administration. For intravenous use of INH, please consult with the Idaho Division of Public Health TB Program at 208-334-5939.

‡ All rifamycins (RIF, RPT, RFB) can interact with antiretrovirals. RIF and RPT will decrease therapeutic levels of PIs and NNRTIs commonly used to treat HIV infection. Dose modifications may be needed. Consult HIV specialist prior to initiating TB treatment.

§ Children receiving EMB should be monitored for visual changes. In order to avoid 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 to drug-resistant tuberculosis.

TABLE 5: SUGGESTED PYRAZINAMIDE DOSES, USING WHOLE TABLETS, FOR ADULTS WEIGHING 40 TO 90 KILOGRAMS⁵

Interval	Weight (kg) [*]		
	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)
<p>* Based on estimated lean body weight. † Maximum dose regardless of weight.</p>			

TABLE 6: SUGGESTED ETHAMBUTOL DOSES, USING WHOLE TABLETS, FOR ADULTS WEIGHING 40 TO 90 KILOGRAMS⁶

Interval	Weight (kg) [*]		
	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)
<p>* Based on estimated lean body weight. † Maximum dose regardless of weight.</p>			

Duration of Treatment

The standard duration of treatment for drug-susceptible pulmonary TB is six months (2 months of intensive phase followed by 4 months of continuation phase) unless **both** cavitory disease is present **and** the patient is still culture positive after two months, in which case extension of the continuation phase for an additional 3 months (ie, continuation phase of 7 months) is recommended. Prolonging the continuation phase may also be considered in patients with **either** cavitation **or** a positive culture at 2 months **and** any of the following additional risk factors: weight > 10% below ideal body weight; active smoker; presence of diabetes, HIV infection, or other immunosuppressing condition; and extensive disease on chest xray.⁷

Detailed recommendations about treatment in special situations (HIV infection, extrapulmonary tuberculosis, children, and others) are outlined in the *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinic Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis* found here: https://www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf. The guideline should be consulted when treating patients in these circumstances. A few highlights regarding duration of treatment in special situations include:

- 1) When an HIV-infected patient does not receive antiretroviral therapy (ART) during tuberculosis treatment, the continuation phase with INH and RIF should be extended for an additional 3 months (ie, a continuation phase of 7 months and total treatment duration of 9 months).
- 2) For bone, joint, and spinal tuberculosis (without meningitis), some experts favor a 9-month duration of rifampin-containing regimens. Spinal tuberculosis with meningitis is managed as tuberculous meningitis.
- 3) Tuberculosis meningitis is generally treated for 9-12 months, although optimal duration of treatment is not defined. Adjuvant corticosteroids confer a mortality benefit, and adjunctive dexamethasone or prednisolone tapered over 6-8 weeks is recommended for patients with tuberculosis meningitis.
- 4) A 4-month treatment regimen may be adequate for HIV-uninfected adults with culture-negative pulmonary tuberculosis.

Monitoring, Side Effects and Adverse Reactions

Basic Monitoring Steps

1. All healthcare workers providing treatment for TB disease should be familiar with national treatment guidelines.
 - a) All jurisdictions should follow the national monitoring guidelines identified in the current guidelines for treatment of drug-susceptible TB, *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis* at <https://academic.oup.com/cid/article/63/7/e147/2196792>. Recommended baseline and follow-up evaluations for patients treated with first-line medications are summarized in Table 7, below.
 - b) It is also important to check for guideline updates posted on the CDC's Division of Tuberculosis Elimination home page at this hyperlink: <http://www.cdc.gov/TB/> and the list of guidelines by date at this hyperlink: <http://www.cdc.gov/tb/publications/guidelines/default.htm>.
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. Some common side effects of and adverse reactions to drugs used to treat TB disease are listed below in Table 8: **Some Reactions to Antituberculosis Medications**. Educate patients to promptly report any of the symptoms or signs listed in Table 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 Idaho Division of Public Health TB Program.
 - b) If a patient reports a potentially less severe side effect, call the patient's provider immediately for instructions.
4. If you suspect that an antituberculosis drug may be interacting with other medications that the patient is taking, consult with the patient's provider. Some drug-drug interactions are discussed in the current guidelines for treatment of drug-susceptible TB, *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinic Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis* at <https://academic.oup.com/cid/article/63/7/e147/2196792>.
5. The following information should be documented at each follow-up visit:
 - a. Review of symptoms, side effects, and adverse reactions (and any labs that were drawn)
 - b. Education given



- c. Refill provided
- d. Description of any problems encountered and action taken for that visit
- e. Next appointment

Basic Monitoring

TABLE 7: BASELINE AND FOLLOW-UP EVALUATIONS FOR PATIENTS TREATED WITH FIRST-LINE TUBERCULOSIS MEDICATIONS⁸

Activity	Month of Treatment Completed								End of Treatment Visit	
	Baseline	1	2	3	4	5	6	7		8
MICROBIOLOGY										
Sputum smears and culture ¹	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>					<input type="checkbox"/>
Drug susceptibility testing ²	<input type="checkbox"/>			<input type="checkbox"/>						
IMAGING										
Chest radiograph or other imaging ³	<input type="checkbox"/>		<input type="checkbox"/>							<input type="checkbox"/>
CLINICAL ASSESSMENT										
Weight ⁴	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Symptom and adherence review ⁵	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Vision assessment ⁶	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
LABORATORY TESTING										
AST, ALT, bilirubin, alkaline phosphatase ⁷	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Platelet count ⁸	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Creatinine ⁸	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
HIV ⁹	<input type="checkbox"/>									
Hepatitis B and C screen ¹⁰	<input type="checkbox"/>									
Diabetes Screen ¹¹	<input type="checkbox"/>									

Shading around boxes indicates activities that are optional or contingent on other information. ¹Obtain 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. ²Drug 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. ³Obtain 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. ⁴Monitor weight monthly to assess response to treatment; adjust medication dose if needed. ⁵Assess 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). ⁶Patients on EMB: baseline visual acuity (Snellen test) and color discrimination tests, followed by monthly inquiry about visual disturbance and monthly color discrimination tests. ⁷Liver 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. ⁸Baseline for all patients. Further monitoring if there are baseline abnormalities or as clinically indicated. ⁹HIV testing in all patients. CD4 lymphocyte count and HIV RNA load if positive. ¹⁰Patients 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. ¹¹Fasting 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/m², first-degree relative with diabetes, and race/ethnicity of African American, Asia, Hispanic, American Indian/Alaska Native, or Hawaiian Native/Pacific Islander. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Side Effects and Reporting Adverse Reactions

The table below is intended for use by a case manager. The case manager should instruct the patient to report to the provider the side effects and adverse reactions listed in Table 8.

If a patient reports to the case manager a potentially serious adverse reaction, the case manager should call the patient’s provider immediately and alert the Idaho Division of Public Health TB Program.

If a patient reports to a case manager a potentially less severe side effect, the healthcare worker should call the patient’s provider immediately for instructions.

TABLE 8: SOME REACTIONS TO ANTITUBERCULOSIS MEDICATIONS⁹

Potentially Serious Adverse Reactions*	Less Severe Signs and Symptoms*
<p>Immediately report the following signs and symptoms or other abnormalities or unexpected events to the patient’s provider. These signs and symptoms suggest severe side effects, including possible hepatotoxicity:</p> <ul style="list-style-type: none"> ▪ Jaundice ▪ Dark urine ▪ Vomiting ▪ Abdominal pain ▪ Fever ▪ Visual changes (including changes in color perception) ▪ Rash <p>In consultation with the provider, instruct the patient to stop TB medications until evaluated by the provider.</p>	<p>Report the following signs and symptoms to the patient’s provider within 24 hours:</p> <ul style="list-style-type: none"> ▪ Anorexia ▪ Nausea ▪ Malaise ▪ Peripheral neuropathy: tingling or burning sensation in hands or feet
<p>* These lists are not all-inclusive. Second-line drugs are not included. For a more complete discussion of common adverse effects, refer to the current guidelines for treatment of drug-susceptible TB at https://academic.oup.com/cid/article/63/7/e147/2196792.</p>	

Source: Adapted from California Department of Public Health (CDPH)/California Tuberculosis Controllers Association (CTCA). TB Case Management – Core Components. CDPH/CTCA Joint Guidelines. Revised November 2011. Available at this hyperlink: https://www.ctca.org/filelibrary/file_238.pdf. Accessed July 30, 2018.

Checking for Side Effects or Adverse Reactions to Antituberculosis Drug

Refer to Table 9: **Monitoring and Interventions for Side Effects and Adverse Reactions** to:

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

TABLE 9: MONITORING AND INTERVENTIONS FOR SIDE EFFECTS AND ADVERSE REACTIONS^{10,11,12}

Anti-tuberculosis Drug	Side Effects/ Adverse Reactions	Monitoring	Comments
Isoniazid (INH)	<ul style="list-style-type: none"> ▪ Rash ▪ Hepatic enzyme elevation ▪ Hepatitis ▪ Peripheral neuropathy ▪ Mild central nervous system effects 	<p>Clinical monitoring monthly.</p> <p>See Table 7 for laboratory testing recommendations. In general, liver function tests are checked only at baseline unless symptoms consistent with hepatotoxicity develop or other conditions are present (e.g., abnormal liver function tests at baseline, patient chronically consumes alcohol, history of liver disease, HIV infection, advanced age, etc).</p>	<p>Hepatitis risk increases with age and alcohol consumption.</p> <p>Pyridoxine (vitamin B6, 25–50 mg/d) might prevent peripheral neuropathy and central nervous system effects. The dose of B6 may be titrated to a max dose of 100-150 mg, with expert consultation. Keep in mind that higher doses of pyridoxine may cause gastrointestinal symptoms (e.g. abdominal pain, nausea, vomiting).</p> <p>INH inhibits several CYP isoenzymes and can therefore increase the concentrations of some medications including phenytoin, carbamazepine, certain benzodiazepines (e.g., diazepam, triazolam), warfarin, and others. The treating provider may want to consider consultation with a clinical pharmacist or use of a web-based drug interaction program to determine whether specific drug-drug interactions exist and if medication dosages need to be adjusted.</p>



Anti-tuberculosis Drug	Side Effects/ Adverse Reactions	Monitoring	Comments
<p>Rifampin (RIF)</p>	<ul style="list-style-type: none"> ▪ Rash ▪ Gastrointestinal upset ▪ Hepatitis ▪ Fever ▪ Bleeding problems ▪ Thrombocytopenia ▪ Renal failure ▪ Flu-like symptoms ▪ Orange-colored body fluids (secretions, urine, tears) 	<p>Clinical monitoring monthly.</p> <p>See Table 7 for laboratory testing recommendations. In general, liver function tests are checked only at baseline unless symptoms consistent with hepatotoxicity develop or other conditions are present (e.g., abnormal liver function tests at baseline, patient chronically consumes alcohol, history of liver disease, HIV infection, advanced age, etc).</p>	<p>There are a number of drug interactions with potentially serious consequences. Significant interactions exist with methadone, hormonal contraceptives, antiretroviral agents, and many other drugs.</p> <p>Drug-drug interactions with RIF are extensive; consult with a tuberculosis expert and/or pharmacist first.</p> <p>For more information, refer to "Table 8. Clinically Significant Drug-Drug Interactions Involving the Rifamycins" in <i>Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis</i> at https://academic.oup.com/cid/article/63/7/e147/2196792</p> <p>Because information regarding rifamycin drug interactions is evolving rapidly, consult the CDC's Division of Tuberculosis "News and Updates" Web page at this hyperlink: http://www.cdc.gov/tb/default.htm to obtain the most up-to-date information.</p> <p>Colors body fluids orange.</p> <p>May permanently discolor soft contact lenses.</p>



Anti-tuberculosis Drug	Side Effects/ Adverse Reactions	Monitoring	Comments
<p>Rifabutin (RFB)</p>	<ul style="list-style-type: none"> ▪ Rash ▪ Hepatitis ▪ Fever ▪ Thrombocytopenia ▪ Orange-colored body fluids (secretions, urine, tears) <p>With increased levels of RFB:</p> <ul style="list-style-type: none"> ▪ Severe arthralgias ▪ Uveitis ▪ Leukopenia 	<p>Clinical monitoring monthly.</p> <p>See Table 7 for laboratory testing recommendations. In general, liver function tests are checked only at baseline unless symptoms consistent with hepatotoxicity develop or other conditions are present (e.g., abnormal liver function tests at baseline, patient chronically consumes alcohol, history of liver disease, HIV infection, etc).</p> <p>Consult with an expert for patients who are also on antiretroviral therapy for HIV infection.</p>	<p>Although drug interactions are less problematic with RFB, they still occur and close monitoring is required.</p> <p>Similar to rifampin but less potent of an inducer, rifabutin reduces levels of many drugs (e.g., PIs, NNRTIs, methadone, dapsone, ketoconazole, coumadin derivatives, hormonal contraceptive, many corticosteroids, digitalis, sulfonylureas, diazepam, β-blockers, anticonvulsants, and theophylline). Drug-drug interactions with RFB are extensive, consult with a tuberculosis expert and/or pharmacist first.</p> <p>For more information, refer to "Table 8. Clinically Significant Drug-Drug Interactions Involving the Rifamycins" in <i>Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis</i> at https://academic.oup.com/cid/article/63/7/e147/2196792</p> <p>Because information regarding rifamycin drug interactions is evolving rapidly, consult the CDC's Division of Tuberculosis "News and Updates" Web page at this hyperlink: http://www.cdc.gov/tb/default.htm to obtain the most up-to-date information.</p> <p>May permanently discolor soft contact lenses.</p>



Anti-tuberculosis Drug	Side Effects/ Adverse Reactions	Monitoring	Comments
Rifapentine (RPT)	Similar to those associated with rifampin	Similar to rifampin	<p>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.</p> <p>Rifapentine decreases levels of beta blockers, estrogen containing oral contraceptives, calcium channel blockers, hydrocodone and methadone (potentially causing opioid withdrawal symptoms), some corticosteroids, all statins but less so with pravastatin, medications used for treatment of HCV infection, etc. Drug-drug interactions with RPT are extensive, consult with a tuberculosis expert and/or pharmacist first.</p> <p>For more information, refer to "Table 8. Clinically Significant Drug-Drug Interactions Involving the Rifamycins" in <i>Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis</i> at https://academic.oup.com/cid/article/63/7/e147/2196792</p> <p>Because information regarding rifamycin drug interactions is evolving rapidly, consult the CDC's Division of Tuberculosis "News and Updates" Web page at this hyperlink: http://www.cdc.gov/tb/default.htm to obtain the most up-to-date information.</p>



Anti-tuberculosis Drug	Side Effects/ Adverse Reactions	Monitoring	Comments
Pyrazinamide (PZA)	<ul style="list-style-type: none"> ▪ Gastrointestinal upset ▪ Hepatotoxicity and hepatitis ▪ Rash ▪ Photosensitive dermatitis ▪ Hyperuricemia ▪ Joint aches ▪ Gout (rare) 	<p>Clinical monitoring monthly.</p> <p>See Table 7 for laboratory testing recommendations. In general, liver function tests are checked only at baseline unless symptoms consistent with hepatotoxicity develop or other conditions are present (e.g., abnormal liver function tests at baseline, patient chronically consumes alcohol, history of liver disease, HIV infection, advanced age, etc).</p> <p>Consider baseline measurements of uric acid.</p>	<p>Treat hyperuricemia only if patient has symptoms.</p> <p>Might make glucose control more difficult in persons with diabetes.</p> <p>Serum uric acid measurements are not recommended as a routine, but may serve as a surrogate marker for compliance.</p>
Ethambutol (EMB)	<ul style="list-style-type: none"> ▪ Optic neuritis with changes in color perception and/or visual acuity ▪ Rash 	<p>Baseline tests of visual acuity (Snellen chart) and color discrimination (Ishihara tests)</p> <p>At each monthly visit, patients should be questioned regarding possible visual disturbances, including blurred vision or scotomata</p> <p>Monthly inquiry about visual disturbances and monthly color discrimination tests (e.g., Ishihara test).</p>	<p>Optic neuritis may be unilateral; check each eye separately.</p> <p>Patients should be instructed to contact their physician or public health clinic immediately if they experience a change in color vision and/or visual acuity.</p> <p>EMB should be discontinued immediately and permanently if there are any signs of visual toxicity.</p>
Rifamate® (INH and RIF) Rifater® (INH, RIF, PZA)	<p>See comments under individual drugs above</p>		



Anti-tuberculosis Drug	Side Effects/ Adverse Reactions	Monitoring	Comments
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) [DTBE Web site]. November 2001. Available at this hyperlink: <http://www.cdc.gov/tb/education/corecurr/index.htm>. Accessed March 3, 2010.

Response to Treatment

Monitoring Sputum

There are two main reasons for sputum collections after a patient with proven culture positive pulmonary TB has started treatment:

1. Documenting conversion to AFB-smear negative, in those patients with initially smear-positive disease. This is critical in determining when to allow someone to return to work, school, etc.
2. Documenting response to treatment. Conversion to culture-negative is a key indicator of treatment success, and is considered more critical than smear conversion to demonstrate effectiveness, as smear positivity may linger (see notes below about lingering smear-positivity). Failure to quickly convert to culture-negative should prompt an evaluation of the effectiveness of therapy, and a persistently positive culture after the completion of 2 months of therapy may need extension of the continuation phase of treatment.¹³

During treatment of patients with pulmonary tuberculosis, at a minimum, 3 sputa samples for AFB smear and culture should be collected at monthly intervals after initiation of treatment until 2 consecutive specimens are negative on culture.¹⁴

For patients who had positive AFB smears at the time of diagnosis, follow-up smears may be obtained at more frequent intervals (e.g., every 2 weeks) to provide an early assessment of the response to treatment, or make decisions on returning to school or work, especially for patients in situations in which the risk of transmission is high.

Occasionally, AFB-positive sputa are culture negative. This occurs most frequently among patients with advanced cavitory tuberculosis during the first months of treatment. It is assumed the MTB organisms are dead and that their presence is not a sign of treatment failure or poor adherence, even if treatment failure is noted later in the course of therapy. However, repeat cultures always should be obtained to confirm that the earlier culture result was correct (no growth) and not a false negative.

In some cases, a patient may not be able to produce a sputum specimen after completing the initial 1-2 months of treatment. If the patient has improved clinically and demonstrates chest radiograph improvement, treatment may be continued as if the patient had had a negative sputum specimen at two months.

Other Monitoring Considerations

In addition to sputa evaluations, it is essential that patients have clinical evaluations at least monthly while on treatment to identify possible adverse effects of the antituberculosis medications, document clinical improvement, and assess adherence. Depending on the age of the patient, and other risk factors, laboratory monitoring may

also be indicated. For detail, see the 2016 guidelines for treatment of drug-susceptible tuberculosis (TB), *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis* that can be found here: <https://academic.oup.com/cid/article/63/7/e147/2196792>.

Radiographic evaluations during treatment are of less importance than sputum evaluation, and often no further radiographs are taken after diagnosis. A chest radiograph at completion of treatment is not required but can provide a baseline for comparison with future films, and should be considered, especially when the initial radiograph is highly abnormal.

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 should include monthly clinical evaluation, and may include radiographic, ultrasound, or laboratory monitoring, depending on the site of disease.

Patients whose cultures have not become negative or whose symptoms do not resolve despite three months of therapy should be reevaluated for potential drug-resistant disease, as well as for other possible causes of poor treatment response, and prolongation of the continuation phase should be considered.

Evaluation for drug resistance at baseline is a routine component of overall TB disease treatment in Idaho (performed on the first sputa samples that demonstrate positive growth on AFB culture), but persistent positive growth on monthly sputa cultures should always raise the question that the case may involve drug resistance. When in doubt, discuss the case with the managing physician and the Idaho Division of Public Health TB Program. If for any reason a patient in this scenario is receiving self-administered therapy, the remainder of treatment should be directly observed if at all possible. Other possible causes of poor treatment response may include malabsorption or diabetes. Lab error is a possible cause of a positive culture in a person who is otherwise doing well clinically.¹⁵



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 two months, contact the Idaho Division of Public Health TB Program at (208) 334-5939 to discuss next steps.

In patients being treated for culture-negative pulmonary TB (*i.e.*, patients with clinical and/or radiologic findings suggestive of pulmonary TB but with negative baseline sputum cultures despite thorough evaluation), the major indicators of response to therapy are the chest radiograph and clinical evaluation. At a minimum, a thorough clinical and radiographic follow-up should be undertaken after 2 months of therapy. If there is clinical or radiographic improvement and no other etiology has been identified, treatment is usually continued.¹⁶ If neither the clinical evaluation nor the radiograph improve after the patient has received 2 months of treatment, the diagnosis of active TB should be

reconsidered; the abnormality may be the result of either previous (not current) TB or another disease process.¹⁷

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 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 may be adequate if there is clinical or radiographic improvement and no other etiology identified.¹⁸

In some cases, either because of drug toxicity or nonadherence to the treatment regimen, the specified number of doses cannot be administered within a targeted period, in which case the patient can still be deemed to have successfully completed therapy. In such cases, the goal is to deliver the specified number of doses within a recommended maximum time. For example, for a six-month daily regimen, if the total doses are completed within nine months of beginning treatment, the patient can still be considered to have completed therapy. 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.

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 (e.g., cavitory versus noncavitory 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.¹⁹



For consultation regarding completion of therapy or considerations for retreatment, contact the Idaho Division of Public Health TB Program. For details on the management of treatment interruptions, see Table 6 in the *ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis* at

<https://academic.oup.com/cid/article/63/7/e147/2196792>.



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. In some cases, where treatment was difficult or prolonged, or drug resistance was documented, follow-up may be needed and will be individualized.



For consultation regarding post-treatment evaluation, contact the Idaho Division of Public Health TB Program at (208) 334-5939.

Treatment in Special Situations

Treatment of tuberculosis (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
- Liver disease (hepatitis B or C, hemochromatosis, autoimmune liver disease, steatohepatitis, etc.)
- Renal insufficiency and end-stage renal disease (ESRD)
- TB associated with tumor necrosis factor-alpha (TNF- α) antagonists
- Culture-negative pulmonary TB
- Extrapulmonary TB
- Pregnancy and breastfeeding
- TB in children

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.

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).

Ensure that patients with any resistance to first-line therapy (rifampin, isoniazid, ethambutol, and pyrazinamide) are managed with assistance from a TB specialist (e.g., an infectious disease physician or pulmonologist familiar with drug-resistant TB) or with consultation by a specialist at a specialized TB treatment center.

Acquired drug resistance usually develops when an inadequate drug regimen is prescribed (e.g., 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.²⁰

Human Immunodeficiency Virus Infection

Routine HIV testing is recommended for all patients with presumptive or diagnosed active tuberculosis. Management of 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 which have the potential to interact significantly 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.



It is recommended that treatment of HIV-related tuberculosis be given daily in the intensive and continuation phases to avoid recurrent disease and the emergence of rifamycin resistance. Generally, a standard 6-month daily regimen is adequate for HIV-infected patients receiving ART.²¹



Patients with HIV-related TB may experience a temporary exacerbation of symptoms, signs, or radiographic manifestations (a paradoxical reaction known as immune reconstitution inflammatory syndrome or "IRIS") of TB while receiving antituberculosis and/or antiretroviral treatment.²² This reaction can be very serious, and potentially life-threatening, and an expert should be consulted to help prevent, and manage, IRIS.



Treatment of HIV is usually initiated after TB treatment is started. Please contact the Idaho Division of Public Health TB Program and your local HIV specialist if a TB patient is also newly diagnosed with HIV or has known untreated HIV.

Resources

- *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis* available at: <https://academic.oup.com/cid/article/63/7/e147/2196792>.
- CDC. *Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis* [online]. 2013. Available from URL: https://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/default.htm
- CDC. *Self-Study Modules on Tuberculosis* (Division of Tuberculosis Elimination Web site; 2016). Available at: <http://www.cdc.gov/tb/education/ssmodules/default.htm>
- CDC. "Special Considerations for Treatment of TB Disease in Persons Infected with HIV" (*TB Elimination Fact Sheet*, August 2016). Available at: <http://www.cdc.gov/tb/publications/factsheets/treatment/treatmentHIVpositive.htm>

- [AIDSinfo](https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/325/tb). “Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents.” Available at: <https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/325/tb>

Chronic Alcohol Use

Because of the effectiveness of isoniazid (INH), rifampin (RIF), and pyrazinamide (PZA), they should be used if at all possible, even in the presence of preexisting liver disease. Once treatment has started, drug-induced hepatitis is suspected when the serum alanine aminotransferase (ALT) level is more than three times the upper limit of normal in the presence of symptoms, or more than five times the upper limit of normal in absence of symptoms, or in persons with abnormal baseline values, any increase in those values.

It should be noted that TB itself may involve the liver, causing abnormal liver function. Hepatic abnormalities caused by TB will improve with effective treatment.²³

Prior to treatment, patients should be asked about alcohol use, and baseline liver function tests should be checked. Further testing, e.g., viral hepatitis testing, may be indicated if liver function tests are abnormal. Patients should be counseled that chronic alcohol use in the setting of TB treatment increases their risk for drug-induced hepatitis and peripheral neuropathy; in general, avoidance of alcohol altogether during TB treatment is recommended. Pyridoxine (vitamin B6) 25-50 mg/day should be given with INH to persons who regularly consume alcohol to reduce the risk of peripheral neuropathy. Close monitoring with repeat (typically monthly) measurements of liver transaminases and symptom review is essential in managing a patient with chronic alcohol use.²⁴

To monitor for adverse reactions:

- Conduct clinical monitoring on the first visit and repeat at least monthly to check for signs and symptoms of hepatitis.
- Educate patients about symptoms and signs of adverse reactions, and instruct patients to stop treatment and notify either their medical provider or public health contact as soon as possible should symptoms occur. Symptoms of adverse drug reactions include anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesias of hands and/or feet, persistent fatigue, weakness or fever lasting three or more days, abdominal tenderness (right upper quadrant), easy bruising or bleeding, and arthralgia.²⁵
- If the patient is on directly observed therapy, perform a symptom review at each directly observed therapy visit to assess if there are any side effects or adverse reactions.

Liver Disease

Management of TB in patients with unstable or advanced liver disease is difficult. The risk of drug-induced hepatitis is greater in these patients, and expert consultation is advised.



For all patients with preexisting liver disease, frequent clinical and laboratory monitoring (every 1-4 weeks for at least the first 2-3 months of treatment) should be performed to detect drug-induced hepatic injury.²⁶

Resources

- *ATS/CDC/IDSA. Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis* found here: <https://academic.oup.com/cid/article/63/7/e147/2196792>

Renal Insufficiency and End-Stage Renal Disease

Renal insufficiency complicates the management of TB because some antituberculosis medications are cleared by the kidneys. Dose adjustment of some medications may be required. Management may be further complicated by the removal of some antituberculosis agents via hemodialysis. Postdialysis administration of all antituberculosis medications is preferred.²⁷ In many cases, dialysis centers will work with public health to facilitate DOT (three times per week), even for extrapulmonary cases, and avoid premature removal of the drugs, by administering antituberculosis drugs to the patient immediately after hemodialysis. The Idaho Division of Public Health TB program can help arrange this if needed.

Resources

- *ATS/CDC/IDSA. Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis* found here: <https://academic.oup.com/cid/article/63/7/e147/2196792>

Tuberculosis Associated with Tumor Necrosis Factor-Alpha Antagonists

Activation of latent 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. Patients should

be screened for risk factors for *Mycobacterium tuberculosis* infection and tested for infection before initiating immunosuppressive therapies, including TNF- α antagonists. If testing suggests latent TB infection, active TB should be ruled out clinically, and treatment for latent disease should be initiated. While there is no clear guidance, most providers prefer the patient to have at least 1 month of latent TB treatment before initiating any form of immunosuppressive agent. The treatment for latent TB can then be completed while the patient initiates their immunosuppressive therapy.

Even if the patient completes treatment for latent TB, healthcare providers should take steps to prevent TB in immunocompromised patients and remain vigilant for TB as a cause of unexplained febrile illness.²⁸ TNF- α antagonists should be held in a patient with suspected or confirmed active TB, if clinically feasible.²⁹

Resources

- CDC. “Tuberculosis Associated with Blocking Agents against Tumor Necrosis Factor - Alpha - California, 2002–2003” (MMWR 2004;53[No. 30]: 83–686) at <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5330a4.htm>

Culture-Negative Pulmonary Tuberculosis

A diagnosis of TB is not ruled out if *M. tuberculosis* cannot be isolated from persons 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 persons with apparent culture-negative TB.³⁰

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. (Note: In pulmonary TB, this requires three sputum specimens, but one specimen may be all that is done for extrapulmonary sites.)
- Signs and symptoms are highly suspect of MTB infection and no other diagnosis has been established.
- Clinical or radiographic improvement occurs within two months of initiation of TB therapy.

After the initial phase (first two months), treatment with an additional two months of isoniazid and rifampin during the continuation phase can be considered to complete a total of four months of treatment.³¹ However, HIV-infected patients with culture-negative pulmonary TB should be treated for a minimum of six months.³²

Resources

- *ATS/CDC/IDSA. Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis* found here: <https://academic.oup.com/cid/article/63/7/e147/2196792>

Extrapulmonary Tuberculosis

Tuberculosis can involve any organ or tissue in the body, and the basic principles for treating pulmonary TB also apply to extrapulmonary forms of the disease. However, there are some important exceptions such as:

- Tuberculosis meningitis should be treated with a 9- to 12-month regimen, and adjunctive corticosteroids should be prescribed.³³
- Bone, joint, and spinal tuberculosis may require a 9-month regimen.³⁴
- Disseminated TB usually requires a 9-12 month regimen.
- The preferred frequency of dosing for extrapulmonary tuberculosis is once daily for both the intensive and continuation phases.³⁵

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 include isoniazid (INH), rifampin (RIF), and ethambutol (EMB). Use of pyrazinamide (PZA) in the treatment regimen for pregnant women is controversial in the United States; consultation with an expert in TB is recommended. If PZA is not used then the minimum duration of therapy is nine months. There is little information about the safety of PZA in pregnancy. However, when there are sound reasons to utilize a 6-month course of treatment, or when the pregnant woman with tuberculosis also has HIV, extrapulmonary, or severe TB, the benefits of PZA may outweigh the possible (but unquantified) risk.³⁶ The WHO and the IUATLD recommend this drug for use in pregnant women with tuberculosis. All TB drugs cross the placenta, and they do not appear to have teratogenic effects.

Breastfeeding should not be discouraged in women being treated with first-line antituberculosis agents because the small concentrations of drugs in breast milk do not produce toxicity in the nursing newborn. Conversely, drugs in breast milk should not be considered an effective treatment for TB in a nursing infant.³⁷

Pyridoxine supplementation (25-50 mg/day) is recommended for all women taking INH who are either pregnant or breastfeeding.³⁸ Guidelines differ regarding the need for pyridoxine supplementation in the breastfed infants of women taking INH.^{39,40} Consult with the infant's pediatrician to determine if pyridoxine supplementation is needed.

Resources

- *ATS/CDC/IDSA. Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis* found here: <https://academic.oup.com/cid/article/63/7/e147/2196792>

- CDC. Self-Study Modules on Tuberculosis (2016) at <http://www.cdc.gov/tb/education/ssmodules/default.htm>
- American Academy of Pediatrics. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. American Academy of Pediatrics; 2018; (Red Book® Online Web site). Available at: <http://www.aapredbook.org>

Tuberculosis in Children

A pediatric patient is a person below the age of 18 years.



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.⁴¹

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. However, the use of ethambutol (EMB) can be controversial because of the risk of ocular toxicity. Expert consultation is recommended.⁴²
- Duration of treatment for drug-susceptible pulmonary tuberculosis in children is six months.⁴³
- Directly observed therapy (DOT) should always be used in treating children.⁴⁴

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.⁴⁵

Resources

- *ATS/CDC/IDSA. Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis* found here: <https://academic.oup.com/cid/article/63/7/e147/2196792>
- CDC. Self-Study Modules on Tuberculosis (2016) at <http://www.cdc.gov/tb/education/ssmodules/default.htm>
- Francis J. Curry National Tuberculosis Center. Pediatric Tuberculosis: An Online Presentation (2018) at: http://www.nationaltbcenter.ucsf.edu/products/product_details.cfm?productID=ONL-10
- American Academy of Pediatrics. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. American



Academy of Pediatrics; 2018; (Red Book® Online Web site). Available at:
<http://www.aapredbook.org>

Hospitalization

A medically stable patient with infectious TB can be treated entirely in the outpatient setting. It is not necessary to hospitalize a patient to initiate treatment of TB unless extenuating circumstances exist. In addition, it is not necessary that an individual be noninfectious prior to discharge from the hospital if specific parameters have been met to ensure appropriate treatment and follow up and to minimize risk of transmission to others.⁴⁶



For the criteria for noninfectiousness and for quarantine procedures, see the “Isolation” section of Chapter 16, “Infection Control.”

If the patient is hospitalized at the initiation of treatment, the decision to discharge the patient should be made by the patient’s medical providers.⁴⁷ However, discharge from a hospital should be coordinated with the public health agency to facilitate continuity of treatment and directly observed therapy.⁴⁸



For consultation regarding hospitalization and discharge procedures, contact the Idaho Division of Public Health TB Program at 208-334-6961.

Electronic Directly Observed Therapy (eDOT)

eDOT is the use of electronic technologies to remotely observe an individual taking her/his tuberculosis medications. Programs interested in developing and implementing eDOT can consult the toolkit developed by the CDC for this type of program at <https://www.cdc.gov/tb/publications/pdf/TBeDOTToolkit.pdf>. Also, please contact the Idaho Division of Public Health TB Program for assistance if needed.

Resources and References

Resources

- ATS/CDC/IDSA. *Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis* found here: <https://academic.oup.com/cid/article/63/7/e147/2196792>
- CDC. Self-Study Modules on Tuberculosis (2016) at <http://www.cdc.gov/tb/education/ssmodules/default.htm>
- CDC. *Core Curriculum on Tuberculosis (2013)* [Division of Tuberculosis Elimination Web site]. Available at <http://www.cdc.gov/tb/education/corecurr/index.htm>

References

- ¹ ATS, CDC, IDSA. Controlling tuberculosis in the United States: Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America, *MMWR* 2005;54(No. RR-12):15.
- ² ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. *Clin Infect Dis*. 2016 Oct 1;63(7):e150
- ³ CDC Division of Tuberculosis Elimination, *Self-Study Modules on Tuberculosis*. Module 4: Treatment of Latent Tuberculosis Infection and Tuberculosis Disease, 2016. Available at: https://www.cdc.gov/tb/education/ssmodules/pdfs/2017SelfStudy_Module4.pdf . Accessed September 19, 2018.
- ⁴ ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. *Clin Infect Dis*. 2016 Oct 1;63(7):e151-152
- ⁵ ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. *Clin Infect Dis*. 2016 Oct 1;63(7):e172.
- ⁶ ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. *Clin Infect Dis*. 2016 Oct 1;63(7):e172.
- ⁷ ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. *Clin Infect Dis*. 2016 Oct 1;63(7):e153
- ⁸ ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. *Clin Infect Dis*. 2016 Oct 1;63(7):e153
- ⁹ California Department of Health Services(CDHS)/California Tuberculosis Controllers Association(CTCA). TB case management – core components. *CDHS/CTCA Joint Guidelines* 1998:9. Available at http://www.ctca.org/index.cfm?fuseaction=page&page_id=5074 . Accessed March 4, 2010.
- ¹⁰ CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):26–29, 38–39.
- ¹¹ CDC Division of Tuberculosis Elimination, *Self-Study Modules on Tuberculosis*. Module 4: Treatment of Latent Tuberculosis Infection and Tuberculosis Disease, 2016. Available at: https://www.cdc.gov/tb/education/ssmodules/pdfs/2017SelfStudy_Module4.pdf . Accessed September 19, 2018.
- ¹² 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.



- 13 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e153
- 14 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e153
- 15 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e183
- 16 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e179
- 17 CDC. In: Chapter 6: Treatment of Tuberculosis Disease. *Core Curriculum on Tuberculosis (2013)* [Division of Tuberculosis Elimination Web site]. Available at <http://www.cdc.gov/tb/education/corecurr/index.htm> Accessed October 2, 2018.
- 18 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e159
- 19 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e153
- 20 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e184
- 21 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e172
- 22 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e175
- 23 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e181
- 24 ATS, CDC, IDSA. Treatment of tuberculosis. American Thoracic Society, CDC, and Infectious Diseases Society of America. *MMWR* 2003;52(No. RR-11):8.
- 25 CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):39.
- 26 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e182.
- 27 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e180.
- 28 CDC. Tuberculosis associated with blocking agents against tumor necrosis factor-alpha — California, 2002–2003. *MMWR* 2004;53(No. 30):683.
- 29 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e182.
- 30 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e179.
- 31 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e179.
- 32 ATS, CDC, IDSA. Treatment of tuberculosis. American Thoracic Society, CDC, and Infectious Diseases Society of America. *MMWR* 2003;52(No. RR-11):52.
- 33 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e178
- 34 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e177
- 35 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e177
- 36 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e180
- 37 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e180
- 38 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e180
- 39 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis.](#) 2016 Oct 1;63(7):e180



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- ⁴⁰ American Academy of Pediatrics. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. American Academy of Pediatrics; 2018;
- ⁴¹ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis](#). 2016 Oct 1;63(7):e176.
- ⁴²ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis](#). 2016 Oct 1;63(7):e176
- ⁴³ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis](#). 2016 Oct 1;63(7):e176
- ⁴⁴ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis](#). 2016 Oct 1;63(7):e176
- ⁴⁵ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. [Clin Infect Dis](#). 2016 Oct 1;63(7):e176
- ⁴⁶ CDC. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *MMWR* 2005;54(No. RR-17):43-44.
- ⁴⁷ CDC. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *MMWR* 2005;54(No. RR-17):43.
- ⁴⁸ CDC. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *MMWR* 2005;54(No. RR-17):43.