

Treatment of Tuberculosis Disease

CONTENTS

Introduction.....	6.2	Tuberculosis associated with tumor necrosis factor-alpha antagonists	6.35
Purpose.....	6.2	Culture-negative pulmonary tuberculosis	6.35
Policy	6.2	Extrapulmonary tuberculosis	6.36
Forms.....	6.3	Pregnancy and breastfeeding	6.37
Basic Treatment Principles	6.4	Resources and References.....	6.38
Treatment Regimens and Dosages.....	6.6		
Regimens.....	6.6		
Table 3: Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms.....	6.8		
Dosages.....	6.9		
Table 4: Doses of First-Line Antituberculosis Drugs For Adults And Children	6.10		
Duration of treatment	6.12		
Side Effects and Adverse Reactions	6.13		
Basic monitoring steps.....	6.13		
Reporting reactions.....	6.20		
Monitoring for side effects and adverse reactions by antituberculosis drug	6.20		
Response to Treatment.....	6.21		
Completion of Therapy	6.22		
Figure 1: Management of Treatment			
Interruptions	6.23		
Case Closing and End-of-Treatment Evaluation.....	6.24		
Post-Treatment Evaluation	6.25		
Treatment in Special Situations	6.27		
Drug-resistant tuberculosis	6.27		
Human immunodeficiency virus infection.....	6.28		
Alcohol Use Disorder	6.30		
Restarting Anti-TB Medications in Patients with Drug-induced Hepatitis	6.31		
Figure 3: Restarting Anti-TB Medications in Patients with Drug-induced Hepatitis	6.33		
Liver disease.....	6.34		
Renal insufficiency and end-stage renal disease.....	6.34		
		Quick Guide to Important Tuberculosis Treatment Resources	
		Table 3: Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms	6.8
		Table 4: Doses of First-line Antituberculosis Drugs for Adults and Children	6.10
		Figure 1: Management of Treatment	
		Interruptions	6.23
		Figure 3: Restarting Anti-TB Medications in Patients with Drug-induced Hepatitis.....	6.33

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. Successful treatment of TB has benefits both for the individual patient and the community in which the patient resides.

Use this section to understand and follow national and Alaska 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) coinfection
- hospitalize and coordinate hospital discharges of patients with infectious TB.

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

Policy

Patients with TB disease in Alaska or who move to Alaska with reported TB disease should receive and complete treatment in accordance with the national guidelines set forth in this manual and in accordance with Alaska laws and regulations.

State Laws and Regulations

AS 18.15.380. Medical treatment

A health care practitioner or public health agent who examines or treats an individual who has or may have been exposed to a contagious disease shall instruct the individual about the measures for preventing transmission of the disease and the need for treatment. The Alaska Department of Health and Social Services may administer treatment, including the use of directly observed therapy where appropriate, to a consenting individual who has or may have been exposed to a contagious disease. An individual has the right to refuse treatment if they are willing to take steps outlined by the state medical officer to prevent the spread of communicable disease to others.



See the Statutes and Regulations section of this manual (**19.1**) or *Conditions Reportable to Public Health*, pages 19-40, available at:

<http://dhss.alaska.gov/dph/Epi/Documents/pubs/conditions/ConditionsReportable.pdf>

Program Standards

- Persons with newly diagnosed TB, for whom therapy for ≤ 1 year is indicated, will complete therapy within 12 months.
- Persons with newly diagnosed pulmonary TB will receive an ATS/IDSA/CDC recommended treatment regimen.²
- All persons with pulmonary tuberculosis will receive treatment using directly observed therapy (DOT).

*ATS – American Thoracic Society; IDSA – Infectious Disease Society of America; CDC – Centers for Disease Control and Prevention

Forms

See *Conditions Reportable to Public Health* for forms and instructions on how to report suspected or confirmed cases of tuberculosis in Alaska. It is available at:



<http://dhss.alaska.gov/dph/Epi/Documents/pubs/conditions/ConditionsReportable.pdf>



For roles and responsibilities, refer to the “Roles, Responsibilities, and Contact Information” topic in the Introduction **1.11**.

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), as well as emphasizing DOT.
	Cultural competence. It is imperative to become culturally competent and guide other healthcare providers toward culturally competent healthcare. 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. HIV testing should be offered to all patients with TB disease, regardless of age.
	Medical supervision. Patients with confirmed or suspected tuberculosis (TB) disease must be under the medical supervision of a health care provider who is licensed in the State of Alaska.
	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 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 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 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 or persons with nutritional deficiency, diabetes, HIV infection, renal failure, or alcohol use disorder).

Phase	Principles
<p>Persistent Positive Cultures</p>	<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.</p>
<p>At Completion of Treatment</p>	<p>Completion in terms of the number of doses. The criteria for treatment completion are based upon the total number of doses taken and the number of full weeks of treatment, 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 in this topic was provided using guidelines for treating tuberculosis (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; or when the patient is pregnant or breastfeeding.



For detailed information on the treatment of tuberculosis in children, refer to the Diagnosis and Treatment of Latent Tuberculosis Infection (LTBI) and Tuberculosis Disease in Children (under 15 years of age) section **9.1**.

As you use this section, remember the abbreviations for first-line drugs, which 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 TB caused by organisms that are known or presumed to be susceptible to isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB).

Each regimen has an initial phase of two months, followed by a choice of several options for a continuation phase of either four or seven months. In Table 3: **Four Treatment Regimens for Drug-Susceptible Tuberculosis**, the initial phase is denoted by a

number (1, 2, 3, or 4) according to effectiveness of the regimen with regimen 1 having the greatest effectiveness.

Ethambutol helps to prevent rifampin resistance when primary isoniazid resistance is present. Ethambutol can be discontinued as soon as once drug susceptibility results are known and the organisms are fully susceptible.³ Pyrazinamide has potent sterilizing ability which allows shortening the regimen from 9 months to 6 months when two (2) months of PZA are included in the 2-month initial phase of treatment. See Table 3: **Four Treatment Regimens for Drug-Susceptible Tuberculosis** for additional information.

Directly observed therapy (DOT) is the standard of care for all persons with tuberculosis. It is required for all persons being treated for pulmonary tuberculosis.

The recommended regimens, and the number of doses specified by each regimen, are described in Table 3. Providers writing prescriptions for anti-TB medications and PHNs ordering these medications should use this reference to determine how many doses of each drug should be ordered from the SOE Drug Room.



For detailed information on the treatment of tuberculosis in children, refer to the Diagnosis and Treatment of Latent Tuberculosis Infection (LTBI) and Tuberculosis Disease in Children (under 15 years of age) section 9.1.

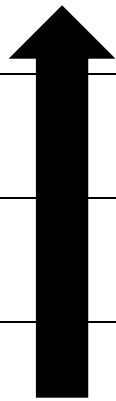


For consultation regarding the treatment of TB, contact the Alaska TB Program at 907-269-8000.



When using three times weekly doses of TB medications, doses should be scheduled on Monday, Wednesday, and Friday to avoid long intervals between doses.

Table 3: DRUG REGIMENS FOR MICROBIOLOGICALLY CONFIRMED PULMONARY TUBERCULOSIS CAUSED BY DRUG-SUSCEPTIBLE ORGANISMS

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

Source: ATS, CDC, IDSA. Treatment of Drug-Susceptible Tuberculosis. *Clinical Infectious Diseases* 2016; 63(7):147-95.

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

^a Other combinations may be appropriate in certain circumstance; additional details are provided in the section “recommended Treatment Regimens.”

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

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

^d Pyridoxine (vitamin B6), 25-50 mg/day, is given with INH to all persons at risk of neuropathy (e.g., pregnant women; breastfeeding infants; persons with HIV; patients with diabetes, alcohol use disorder, 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 US tuberculosis control programs have administered intensive-phase regimens 5 days per week for 15 doses (3 weeks), then twice weekly for 12 doses.

Dosages

Once the appropriate regimen has been identified, refer to Table 4: **Doses of First-line Antituberculosis Drugs for Adults and Children** for instructions on dosages for each drug. First-line antituberculosis medications should be administered together; split dosing should not be used

The following drugs are available in the state of Alaska for treating TB disease. These drugs are provided free of charge upon approval of the TB Program.

- Isoniazid (INH)
- Rifampin (RIF)
- Rifabutin (RFB)
- Rifapentine (RPT)
- Ethambutol (EMB)
- Pyrazinamide (PZA)
- Aminoglycoside (amikacin, streptomycin)
- Moxifloxacin



For information regarding second-line drugs, contact the Alaska TB Control Officer at 907-269-8000.



Daily dosing (5 days/week) is preferred during the initiation phase of treatment and should be used during the continuation phase whenever possible. If daily dosing is not an option, three (3) times weekly dosing should be used. Twice-weekly dosing is the least effective of the approved treatment regimens.

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

Drug	Preparation	Adult/Child	Daily	Once-weekly (1x/week)	Twice-weekly (2x/week)	Thrice-weekly (3x/week)
Isoniazid	Tablets (50, 100, 300 mg); Elixir (50 mg/5 ml); Aqueous IV/IM solution (100 mg/ml) [‡]	Adults	5 mg/kg (Typically 300 mg)	15 mg/kg (typically 900 mg)	15 mg/kg (900 mg)	15 mg/kg (typically 900 mg)
		Children	10-15 mg/kg	----	20-30 mg/kg	----†
Rifampin	Capsule (150, 300 mg); suspend powder for PO; Aqueous IV solution	Adults**	10 mg/kg (typically 600 mg)	----	10 mg/kg (typically 600 mg)	10 mg/kg (600 mg)
		Children	10-20 mg/kg	----	10-20 mg/kg	----†
Rifabutin††	Capsule (150 mg)	Adults**	5 mg/kg (typically 300 mg)	----	Not recommended	Not recommended
		Children	Appropriate dosing for children is unknown. Estimated at 5mg/kg.			
Pyrazinamide	Tablet (500 mg)	Adults	40-55 kg → 1,000 mg 56-75 kg → 1,500 mg 76-90 kg → 2,000 mg	----	40-55 kg → 2,000 mg 56-75 kg → 3,000 mg 76-90 kg → 4,000 mg	40-55 kg → 1,500 mg 56-75 kg → 2,500 mg 76-90 kg → 3,000 mg
		Children	35 (30-40) mg/kg	----	50 mg/kg	----†
Ethambutol	Tablet (100 and 400 mg)	Adults	40-55 kg → 800 mg 56-75 kg → 1,200 mg 76-90 kg → 1,600 mg	----	40-55 kg → 2,000 mg 56-75 kg → 2,800 mg 76-90 kg → 4,000 mg	40-55 kg → 1,200 mg 56-75 kg → 2,000 mg 76-90 kg → 2,400 mg
		Children	20 (15-25) mg/kg	----	50 mg/kg	----†

Daily and thrice-weekly dosing is preferred. See Table 3.

Abbreviation: FDA: US Food and Drug Administration; IM: intramuscular; IV: intravenous; PO:

*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 x (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.

† For purpose 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.

±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, alcohol use disorder, malnutrition, or chronic renal failure; patients with advanced age). For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/d.

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

†† Rifabutin dose may need to be adjusted when used with protease inhibitors or nonnucleoside reverse transcriptase inhibitors.

Duration of Treatment

The four recommended regimens for treating patients with TB caused by drug-susceptible organisms have a duration of six to nine months. Each regimen has an initial phase of two months, followed by a continuation phase of either four or seven months.

The standard duration of treatment for pulmonary TB should be six months unless cavitation is present **and** the patient is still culture positive after two months, in which case nine months is recommended. Note that there are three exceptions to the standard six-month duration of treatment:

1. For tuberculous meningitis, the optimal length of therapy has not been established, although some experts recommend 9 to 12 months.⁴
2. Treatment for bone or joint TB may need to extend to nine months.⁵
3. In HIV-negative, culture-negative patients, treatment for four months may be adequate if there is clinical or radiographic improvement and no other etiology identified.⁶ However, HIV-infected patients with culture-negative pulmonary TB should be treated for a minimum of six months.⁷

In addition to patients who have cavitation on initial chest radiograph and who have positive cultures at the completion of two (2) months of treatment, an extended continuation phase of 7 months should be considered in the following situations:

- Cavitation or positive cultures at 2 months of treatment by DOT
- Body weight > 10% below ideal body weight
- Active cigarette smoking
- Diabetes
- HIV infection
- Other immunosuppressing conditions
- Extensive disease on chest radiograph⁸

Side Effects and Adverse Reactions

The patient should be monitored by a registered nurse and/or 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 at initiation of tuberculosis treatment and repeated as indicated by clinical signs and symptoms. See Table 5: **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.⁹

Adverse effects are fairly 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.¹⁰ 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.¹¹ In addition, proper management of more serious adverse reactions often requires expert consultation.¹²

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

Basic Monitoring Steps

1. Healthcare workers providing treatment for TB disease should be familiar with the American Thoracic Society (ATS)/Centers for Disease Control and Prevention (CDC) guidelines.
 - a. Follow the national monitoring guidelines identified in the current guidelines for treatment of TB, “Treatment of Drug-Susceptible Tuberculosis” (ATS, CDC, IDSA.. *Clinical Infectious Diseases* 2016; 63(7):147-95.) at https://www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf .
 - b. Check for guideline updates posted on the CDC’s Division of Tuberculosis Elimination home page at <http://www.cdc.gov/tb/publications/guidelines/default.htm>
2. While on treatment, all patients should be evaluated in person whenever possible, at baseline (before starting treatment) and then at least monthly for side effects and adverse reactions.

- a. In remote locations in Alaska, monitoring may be done by telephone, however all patients should be evaluated in person at least once during their treatment regimen.
 - b. Patients who are potentially infectious and must fly by a commercial conveyance into regional health care hubs for evaluation and/or chest x-ray should receive at least 2 weeks of treatment prior to traveling. Patients are considered to be non-infectious and safe to travel when they have had three (3) consecutive negative AFM sputum smears and clinical improvement in addition to 2 weeks of antituberculosis treatment.
3. The common side effects of, and adverse reactions to, drugs used to treat TB disease are listed in Table 6: **Reporting Reactions to Antituberculosis Medications**. Educate patients to first stop the medicine and then promptly report any of the symptoms or signs listed in Table 6 or any unexplained illness to the prescribing provider immediately.
 - a. If a patient reports a potentially serious adverse reaction, call the patient's provider immediately and alert the Alaska TB program by calling 907-269-8000.
 - 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 5: **Monitoring and Interventions for Side Effects and Adverse Reactions**.
 - b. Consult with the Alaska TB Program by calling 907-269-8000.

If you suspect that an antituberculosis drug may be interacting with other medications that the patient is taking, refer to pages 168–70 in the “Treatment of Drug-Susceptible Tuberculosis” (ATS, CDC, IDSA. *Clinical Infectious Diseases* 2016; 63(7):147-95.) at https://www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf .

5. Document the following patient information:
 - 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 actions taken for that visit
 - e. Next appointment

Table 5: **MONITORING AND INTERVENTIONS FOR SIDE EFFECTS AND ADVERSE REACTIONS**^{13, 14, 15}

Anti-tuberculosis Drug	Side Effects/ Adverse Reactions	Monitoring	Comments
<p>Isoniazid (INH)</p>	<ul style="list-style-type: none"> ▪ Rash ▪ Hepatic enzyme elevation ▪ Hepatitis ▪ Peripheral neuropathy ▪ Mild central nervous system effects 	<p>Clinical monitoring monthly</p> <p>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, alcohol use disorder, and pregnancy)</p> <p>Repeat measurements if</p> <ul style="list-style-type: none"> ▪ Baseline results are abnormal ▪ Patient is pregnant, in the immediate postpartum period, or at high risk for adverse reactions ▪ Patient has symptoms of adverse reactions 	<p>Hepatitis risk increases with age and alcohol consumption.</p> <p>Pyridoxine (vitamin B6), 25-50 mg/day, is given with INH to persons at risk of neuropathy (e.g., pregnant women; breastfeeding infants; persons with HIV; patients with diabetes, alcohol use disorder, malnutrition, or chronic renal failure; or patients with advance age). For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/day.¹⁶</p> <p>Serum concentrations of phenytoin, disulfiram (Antabuse), and carbamazepine may be increased in persons taking INH. Measure serum concentrations of phenytoin and carbamazepine in patients receiving INH (with or without rifampin) and adjust the dose if necessary.</p>

Anti-tuberculosis Drug	Side Effects/ Adverse Reactions	Monitoring	Comments
Rifampin (RIF)	<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>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, alcohol use disorder, and pregnancy)</p> <p>Repeat measurements if</p> <ul style="list-style-type: none"> ▪ Baseline results are abnormal ▪ Patient has symptoms of adverse reactions 	<p>There are a number of drug interactions with potentially serious consequences. Significant interactions with methadone, birth control hormones, and many other drugs.</p> <p>Contraindicated or should be used with caution when administered with protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs). Reduces levels of many drugs (e.g., PIs, NNRTIs, methadone, dapson, ketoconazole, coumadin derivatives, hormonal contraceptives, digitalis, sulfonyleureas, diazepam, β-blockers, anticonvulsants, and theophylline).</p> <p>For more information, refer to "Table 8: Clinically Significant Drug-Drug Interactions Involving the Rifamycins" page 10 in "Treatment of Tuberculosis" at https://www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf.¹⁷</p> <p>Because information regarding rifamycin drug interactions is evolving rapidly, consult the CDC's Division of Tuberculosis "News and Updates" Web page at 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
Rifabutin (RFB)	<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>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, alcohol use disorder, and pregnancy)</p> <p>Repeat measurements if</p> <ul style="list-style-type: none"> ▪ Baseline results are abnormal ▪ Patient has symptoms of adverse reactions <p>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)</p>	<p>Although drug interactions are less problematic with RFB, they still occur, and close monitoring is required.</p> <p>For detailed information on the use of Rifabutin for HIV-infected patients refer to “Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents” https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/mycobacterium-tuberculosis-infection-and?view=full</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 contraceptives, digitalis, sulfonyleureas, diazepam, β-blockers, anticonvulsants, and theophylline).</p> <p>May permanently discolor soft contact lenses.</p>
Rifapentine (RPT)	<p>Similar to those associated with rifampin</p>	<p>Similar to that for rifampin</p>	<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. For more information, refer to “Table 8: Clinically Significant Drug-Drug Interactions Involving the Rifamycins” page 10 in “Treatment of Tuberculosis” at https://www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis-2016-nahid-cid_ciw376.pdf.¹⁸</p>

Anti-tuberculosis Drug	Side Effects/ Adverse Reactions	Monitoring	Comments
Pyrazinamide (PZA)	<ul style="list-style-type: none"> ▪ Gastrointestinal upset ▪ Hepatitis ▪ Rash ▪ Photosensitive dermatitis ▪ Hyperuricemia ▪ Joint aches ▪ Gout (rare) 	<p>Clinical monitoring at weeks 2, 4, and 8</p> <p>If the drug is used in patients with underlying liver disease, laboratory and clinical monitoring should be increased</p> <p>Baseline measurements of uric acid</p> <p>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, alcohol use disorder, or pregnancy)</p> <p>Repeat measurements if</p> <ul style="list-style-type: none"> ▪ Baseline results are abnormal ▪ Patient has symptoms of adverse reactions 	<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>

Anti-tuberculosis Drug	Side Effects/ Adverse Reactions	Monitoring	Comments
Ethambutol (EMB)	<ul style="list-style-type: none"> ▪ Optic neuritis ▪ 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 testing of visual acuity and color discrimination is recommended for</p> <ul style="list-style-type: none"> ▪ Patients taking doses >15–25 mg/kg ▪ Patients receiving EMB for >2 months ▪ Patients with renal insufficiency 	<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 vision.</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)	See comments under individual drugs above		
<p>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.</p>			

Sources: CDC. Treatment of Drug-Susceptible Tuberculosis. *Clinical Infectious Diseases* 2016; 63(7):147-95.; 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. Chapter 6: Treatment of Tuberculosis Disease. *Core Curriculum on Tuberculosis (2013)* [Division of Tuberculosis Elimination Web site]. Updated 2013. Available at: <https://www.cdc.gov/tb/education/corecurr/pdf/chapter6.pdf> . Accessed January 8, 2021.

Reporting Reactions

The table below is intended for use by providers and public health nurses who perform case management services. Instruct the patient to report any side effects and adverse reactions listed in Table 6.

If a patient reports an adverse reaction, the provider or PHN case manager should alert the Alaska TB program by calling 907-269-8000.

Table 6: **REPORTING REACTIONS TO ANTITUBERCULOSIS MEDICATIONS**¹⁹

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 side effects, including hepatotoxicity:</p> <ul style="list-style-type: none"> ▪ Jaundice ▪ Dark urine ▪ Vomiting ▪ Abdominal pain ▪ Fever ▪ Visual changes ▪ Marked clinical 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 ▪ Rashes
<p>*These lists are not all-inclusive. Second-line drugs are not included. For a complete list, refer to the current guidelines for treatment of TB, "Treatment of Drug-Susceptible Tuberculosis" (ATS, CDC, IDSA. <i>Clinical Infectious Diseases</i> 2016; 63(7):147-95.), at https://www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf.</p>	

Source: California Department of Health Services (CDHS)/California Tuberculosis Controllers Association (CTCA). TB Case Management Core Components. CDHS/CTCA Joint Guidelines [CTCA Web site]. November 2011. Available at: https://ctca.org/wp-content/uploads/2018/11/ctca_case_management_5_.pdf. Accessed January 8, 2021.

Monitoring for Side Effects and Adverse Reactions by Antituberculosis Drug

Refer to Table 5: **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

Response to Treatment



For consultation regarding a patient's response to treatment, contact Alaska Tuberculosis Program at 907-269-8000.

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 the cultures convert to negative. 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 than sputum evaluation. However, a chest radiograph may be obtained at completion of treatment to provide a baseline for comparison with future films.

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 potential failure to adhere to the regimen.



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 tuberculosis (TB) medical expert should be consulted. Contact the Alaska Tuberculosis Control Officer at the Alaska TB Program at 907-269-8000 immediately.

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.²⁰

Completion of Therapy

A full course of therapy (completion of treatment) is determined more accurately if the total number of doses ingested and full weeks of treatment are 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.²¹



For consultation regarding the treatment of tuberculosis (TB) in a patient with negative cultures, contact the Alaska Tuberculosis Control Officer at 907-269-8000.

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 time. 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.

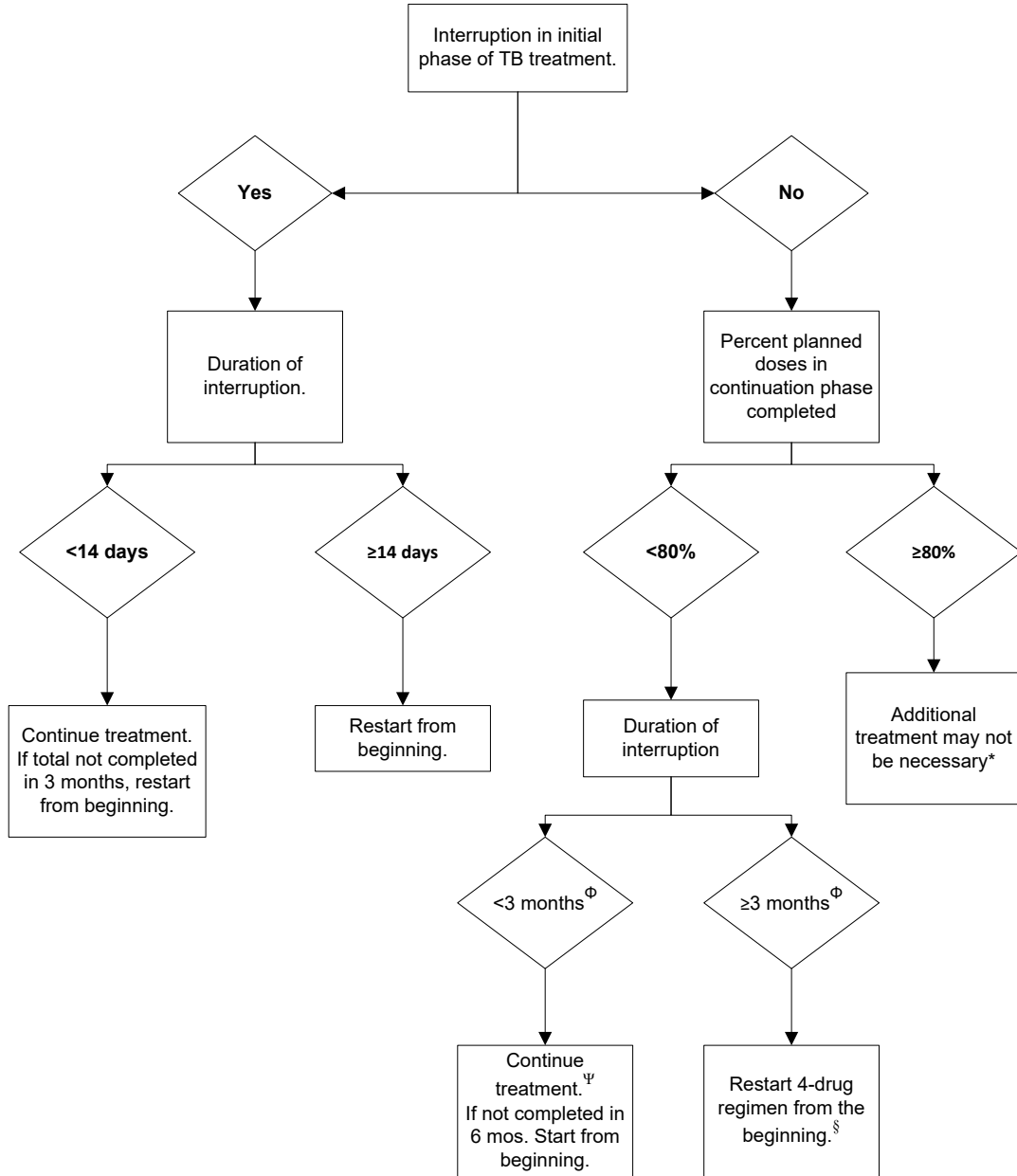


Treating a patient for a defined duration, without accounting for the number of doses taken, can result in under treatment and increased risk for relapse.

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.

See Figure 1: **Management of Treatment Interruptions**²² for additional information.

Figure 1: **MANAGEMENT OF TREATMENT INTERRUPTIONS**²³



* Patients who were initially AFB smear-positive should receive additional therapy.

Φ Recheck smears and cultures and if positive, check drug susceptibility results. Start DOT if not already being used.

Ψ If repeat culture is positive, restart four-drug regimen while waiting for drug susceptibility results. If repeat culture is negative, continue therapy to complete regimen within 9 months of original start date.

§ If repeat culture is positive, continue four-drug regimen while waiting for drug susceptibility results. If repeat culture is negative, consider stopping therapy if patient has received a total of 9 months of therapy.

Case Closing and End-of-Treatment Evaluation

When patients complete treatment for pulmonary TB, three sputum specimens for AFB and culture and a chest radiograph should be considered, especially for those diagnosed initially with advanced tuberculosis disease. Although a chest radiograph may be difficult and costly for patients living in remote locations, sputa can be collected and mailed to the ASPHL. PHN case managers should also provide their patients with an *End of Treatment Letter* and *Summary (18.1)* documenting treatment.



For consultation regarding completion of therapy, end-of-treatment evaluation, or considerations for retreatment, contact the Alaska Tuberculosis Program at 907-269-8000.

Post-Treatment Evaluation

Routine follow-up after completion of therapy is not necessary for patients with *M. tuberculosis* isolates that are susceptible to all first-line anti-tuberculosis drugs and who received a satisfactory and prompt bacteriologic response to a six- or nine-month treatment regimen that included both isoniazid and rifampin. Post-treatment evaluation is also not required for most patients who have *M. tuberculosis* isolates resistant to isoniazid only but susceptible to rifampin, pyrazinamide, and ethambutol and have completed 9 months of treatment with all three of these medications.

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 7: **GUIDELINES FOR POST-TREATMENT EVALUATION** **

Category of Patient	Frequency of Post-Treatment Evaluation
Drug-susceptible organisms	No reevaluation necessary. Instruct the patient to promptly report the development of any symptoms, particularly prolonged cough, fever, or weight loss. Consider end of treatment evaluation if advanced disease at diagnosis (e.g. 4+ AFB smears and cavitation)
Monoresistance to INH with 6-9 mo. treatment with RIF, PZA, and EMB	No reevaluation necessary. Instruct the patient to promptly report the development of any symptoms, particularly prolonged cough, fever, or weight loss.
INH and RIF resistance	4,8,12,18, and 24 months*
RIF or Rifabutin not used in regimen	4,8,12,18, and 24 months*
Self-administered treatment regimen	4,8, and 12 months*
History of previous treatment, but who have (1) no details available about the treatment, (2) negative sputum cultures, (3) significant changes on CXR, and (4) refuse retreatment	4,8, and 12 months*
No history of previous treatment and who have (1) negative sputum cultures, (2) significant changes on the CXR, and (3) refuse retreatment	4,8, and 12 months*
TB-skin-test-positive and culture-negative who are treated empirically because CXR findings are consistent with TB, but who also have other non-TB pulmonary disease.	Refer for further pulmonary evaluation if no response to anti-TB treatment and/or re-evaluate with a CXR every 3-4 months for 1 year.

*Evaluation should include a chest x-ray and the collection of a sputum specimen for smear and culture.

**Adapted from *Clinical Policies and Protocols. Bureau of Tuberculosis Control, New York City Department of Health, 4th Edition, March 2008, page p. 116*



For consultation regarding post-treatment evaluation, contact the Alaska Tuberculosis Control Officer at 907-269-8000.

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
- 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
- Advanced age²⁴



For consultation regarding treatment in the following situations, contact the Alaska Tuberculosis Control Officer at 907-269-8000.



For detailed information on the treatment of tuberculosis in children, refer to the Diagnosis and Treatment of Latent Tuberculosis Infection (LTBI) and Tuberculosis Disease in Children (under 15 years of age) section **9.1**.



For detailed information on the treatment of tuberculosis in special situations, refer to ATS, CDC, IDSA Treatment of Drug-Susceptible Tuberculosis. Available at:

https://www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf .

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.²⁵

Drug resistance is proven only by drug-susceptibility testing performed in a competent laboratory. Resistance to rifampin (RIF) can be a marker for multi-drug resistance. Molecular testing to quickly identify potential resistance to RIF is available through the Alaska State Public Health 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.²⁶



Whenever drug resistance is suspected, please contact the Alaska TB Program at 907-269-8000 to request GeneXpert molecular testing to quickly identify potential RIF resistance.

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.²⁷

For consultation regarding the management and treatment of drug-resistant TB, contact the Alaska Tuberculosis Control Officer at 907-269-8000.



Clinical consultation is also available from the Curry International Tuberculosis Center's Warm Line at 877-390-6682.

<http://www.currytbcenter.ucsf.edu/consultation>

Resources

- ATS, CDC, IDSA. Treatment of Drug-Susceptible Tuberculosis. *Clinical Infectious Diseases* 2016; 63(7):147-95. Available at: https://www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf .
- CDC. "Multidrug-Resistant Tuberculosis" (*TB Elimination Fact Sheet*; accessed January 16, 2021). May 2012. Available at: <http://www.cdc.gov/tb/publications/factsheets/drtb/MDRTB.pdf> .

Human Immunodeficiency Virus Infection

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 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:

- Isoniazid-rifapentine (INH-RPT) once weekly
- Twice-weekly rifampin (RIF)- or rifabutin (RFB)-based regimens in patients with CD4+ cell counts of less than 100 per microliter ²⁸



Patients with HIV-related TB may experience a temporary exacerbation of symptoms, signs, or radiographic manifestations (paradoxical reactions) of TB while receiving antituberculosis treatment.²⁹



For consultation regarding the treatment of tuberculosis in HIV-infected patients, contact the Alaska Tuberculosis Control Officer at 907-269-8000.

Clinical consultation is also available from the Curry International Tuberculosis Center's Warm Line at 877-390-6682.

<http://www.currytbcenter.ucsf.edu/consultation>

Resources

- ATS, CDC, IDSA. Treatment of Drug-Susceptible Tuberculosis. *Clinical Infectious Diseases* 2016; 63(7):147-95. Available at: https://www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf .
- CDC. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis [online]. 2013. Available at: http://www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/PDF/tbhiv.pdf
- CDC. *Self-Study Modules on Tuberculosis* (Division of Tuberculosis Elimination Web site; 1-5, 2019; 6-9 2014). Available at: <http://www.cdc.gov/tb/education/ssmodules/default.htm>
- CDC. Treatment of Drug-Susceptible TB in HIV-Infected Persons” (*TB Elimination Fact Sheet*; August 2013). Available at: <http://www.cdc.gov/tb/publications/factsheets/treatment/treatmentHIVpositive.pdf>
- CDC. “Treating Opportunistic Infections Among HIV-exposed and Infected Children” (*MMWR* 2004;53[No. RR-14]). Available at: <http://www.cdc.gov/mmwr/PDF/rr/rr5314.pdf> .

Alcohol Use Disorder

Alcohol-Related Treatment Complications

Persons with TB disease or latent tuberculosis infection (LTBI) who are known or suspected to have an alcohol use disorder or who regularly consume alcohol are at risk for drug-induced liver injury and nonadherence during the course of treatment.

Alcohol consumption increases health risks and can complicate the treatment of tuberculosis and LTBI. Several examples are listed below:

- **Immunosuppression:** Persons 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 persons, alcohol use has been difficult to identify as a separate risk factor for TB.³⁰ However, studies have shown that “alcohol consumption is a major risk factor for infection with opportunistic bacterial, viral, fungal, and parasitic pathogens.”³¹
- **Liver injury and death:** Drug-induced liver injury “may occur with all currently recommended regimens for the treatment of ...LTBI”.³² 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.”³³ However, it is not fully understood yet how antituberculosis medications cause drug-induced liver injury.³⁴

Persons taking **isoniazid** may have a fourfold greater risk of hepatitis if alcohol is consumed on a daily basis when compared to those who do not drink alcohol.³⁵ 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.^{36,37}

Pyrazinamide has slightly lower rates of hepatotoxicity than isoniazid or rifampin, but pyrazinamide can cause liver injury that is severe and prolonged.³⁸

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.³⁹

- **Non-adherence 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, or lack of interpreters.⁴⁰

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.”⁴¹ In a study of 237 patients in the Russian Federation undergoing DOTS (Directly Observed Treatment, Short-course) 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.”⁴² DOTS programs that have explicitly offered substance abuse treatment have reported better outcomes than those that have not.⁴³

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 and 1991.⁴⁴

Safe Treatment Guidelines

In 2006, the American Thoracic Society (ATS) issued “An Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy.”⁴⁵ Consult these recommendations at <http://www.atsjournals.org/doi/abs/10.1164/rccm.200510-1666ST#readcube-epdf> on pages 943-947 for guidance in the following areas for the safe treatment of LTBI and TB Disease:

- Program Infrastructure
- Provider Education and Resources
- Pretreatment Clinical Evaluation
- Patient Education
- Medication Administration and Pharmacy
- Treatment of LTBI and Treatment of TB Disease

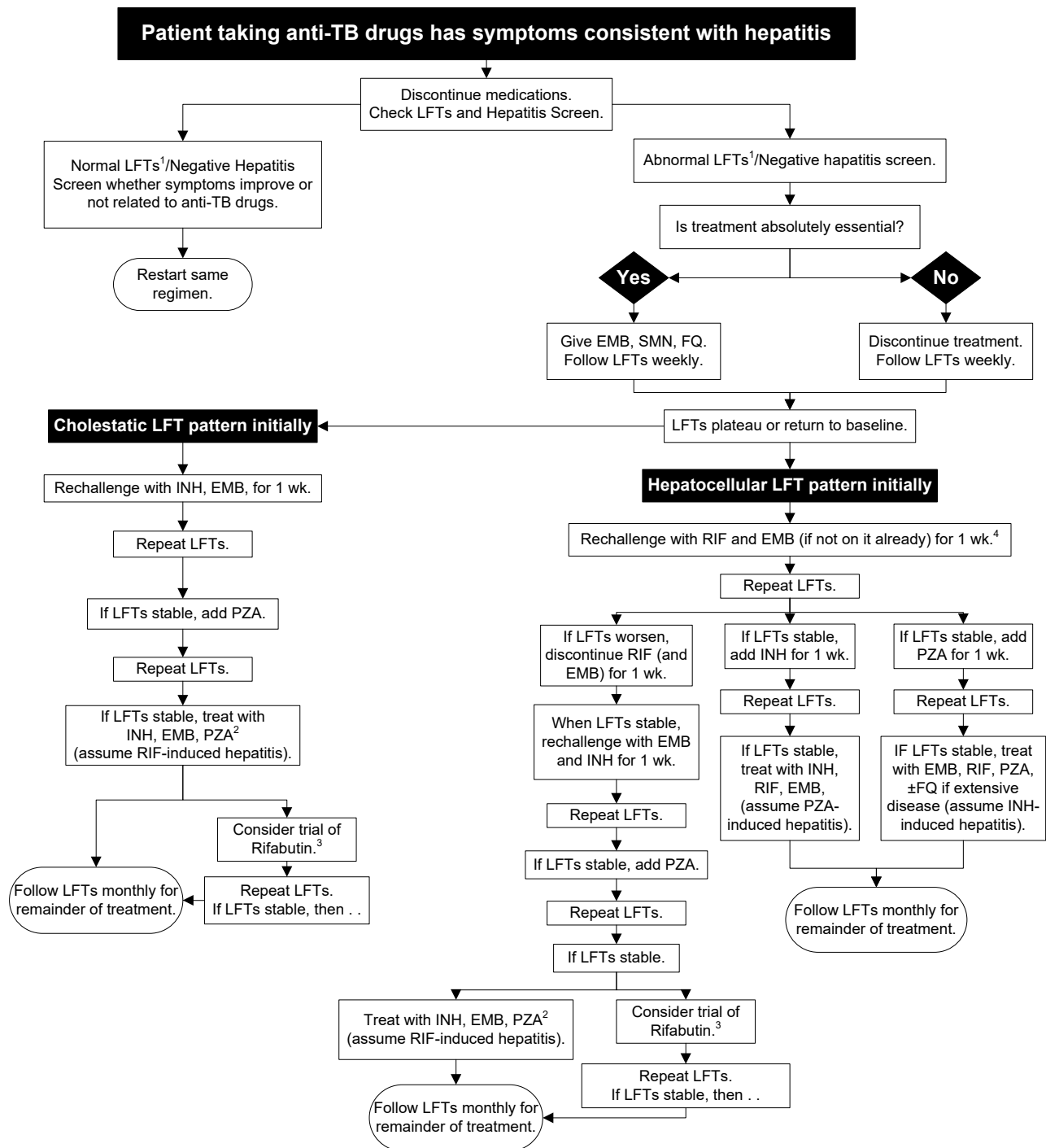
Restarting Anti-TB Medications in Patients with Drug-induced Hepatitis

For additional information about anti-TB medication reintroduction and monitoring see Figure 3: **Restarting Anti-TB Medications in Patients with Drug-Induced Hepatitis.**



When treating patients with drug-induced hepatitis, consultation is available from the Alaska TB Program at 907-269-8000.

Figure 3: **RESTARTING ANTI-TB MEDICATIONS IN PATIENTS WITH DRUG-INDUCED HEPATITIS**



Abbreviations: EMB-ethambutol; FQ-fluoroquinolone; INH-isoniazid; LFTs-liver function tests; PZA-pyrazinamide; RIF-rifampin; RBT-rifabutin; SMN-streptomycin

1. Abnormal LFTs are ≥ 3 times the upper limit of normal with symptoms or ≥ 5 times the upper limit of normal without symptoms.
2. Capreomycin or an appropriate aminoglycoside, and in selected cases a fluoroquinolone, should be considered for the regimen. Treatment needs to last for 18 months unless rifabutin is added successfully. An alternate shorter regimen is isoniazid, streptomycin and pyrazinamide, all given for 9 months.
3. There may be times when rifabutin may be tried in an attempt to decrease duration of treatment from 18 months to 6-9 months.
4. Some clinicians may prefer to challenge with ethambutol and rifampin sequentially rather than simultaneously.

*From *Clinical Policies and Protocols. Bureau of Tuberculosis Control, New York City Department of Health and Mental Hygiene, 4th Edition, March 2008, page p. 109. Found at <http://www.nyc.gov/health/tb>.*

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. Some patients with underlying liver disease may require treatment with regimens unlikely to cause additional liver injury. Also, fluctuations in the biochemical indicators of liver function (with or without symptoms) related to the preexisting liver disease confound monitoring for drug-induced hepatitis.⁴⁶



For all patients with preexisting liver disease, frequent clinical and laboratory monitoring should be performed to detect drug-induced hepatic injury.⁴⁷

Resources

- ATS, CDC, IDSA. Treatment of Drug-Susceptible Tuberculosis. *Clinical Infectious Diseases* 2016; 63(7):147-95. Available at: https://www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf .



For consultation regarding the treatment of tuberculosis in patients with liver disease, contact the Alaska Tuberculosis Control Officer at 907-269-8000.

Clinical consultation is also available from the Francis J. Curry International Tuberculosis Center's Warm Line at 877-390-6682.

<http://www.currytbcenter.ucsf.edu/consultation>

Renal Insufficiency and End-Stage Renal Disease

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. To facilitate DOT (three times per week) and avoid premature removal of the drugs, administer all antituberculosis drugs immediately after hemodialysis.⁴⁸

Resources

- ATS, CDC, IDSA. Treatment of Drug-Susceptible Tuberculosis. *Clinical Infectious Diseases* 2016; 63(7):147-95. Available at: https://www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf .

Tuberculosis Associated with Tumor Necrosis Factor-Alpha Antagonists

Activation of latent TB infection 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 latent TB infection (LTBI). Healthcare providers should take steps to prevent TB in immunocompromised patients and remain vigilant for TB as a cause of unexplained febrile illness.⁴⁹



Patients should be screened for risk factors for *M. tuberculosis* infection and tested for infection before initiating immunosuppressive therapies, including TNF- α antagonists. Diagnosis and treatment of LTBI and TB disease should be in accordance with published guidelines.⁵⁰

Resources

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

Culture-Negative Pulmonary Tuberculosis

A diagnosis of TB should not be 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.⁵¹

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

- Initial acid-fast bacilli (AFB) smears, NAA and cultures are negative.
- Clinical or radiographic response occurs within two months of initiation of therapy.
- No other diagnosis has been established.⁵²

After the initial phase (first two months), continue treatment with an additional two months of isoniazid and rifampin during the continuation phase to complete a total of four months of treatment.⁵³ However, HIV-infected patients with culture-negative pulmonary TB should be treated for a minimum of six months.⁵⁴



For consultation regarding the treatment of TB in a patient with negative cultures, contact the Alaska Tuberculosis Control Officer at 907-269-8000.

Resources

- ATS, CDC, IDSA. Treatment of Drug-Susceptible Tuberculosis. *Clinical Infectious Diseases* 2016; 63(7):147-95. Available at: https://www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf .

Extrapulmonary Tuberculosis

The basic principles for treating pulmonary TB also apply to extrapulmonary forms of the disease. The addition of corticosteroids is recommended for patients with TB pericarditis and TB meningitis. Recommendations concerning duration of therapy are as follows:

- Use a six-month course of therapy for TB involving any site.⁵⁵ **Exceptions:** For bone or joint TB, use a six- to nine-month regimen.⁵⁶ For the meninges, use a 9- to 12-month regimen.⁵⁷
- Consider prolonging therapy for patients with TB in any site that is slow to respond.⁵⁸

Note: Affected lymph nodes may enlarge while patients are receiving appropriate therapy or after treatment has ended without any evidence of bacteriological relapse. On occasion, new nodes can appear during or after treatment as well.⁵⁹



For consultation regarding the treatment of extrapulmonary tuberculosis, contact the Alaska Tuberculosis Control Officer at 907-269-8000.

Clinical consultation is also available from the Francis J. Curry International Tuberculosis Center's Warm Line at 877-390-6682.

<http://www.currytbcenter.ucsf.edu/consultation>

Resources

- ATS, CDC, IDSA. Treatment of Drug-Susceptible Tuberculosis. *Clinical Infectious Diseases* 2016; 63(7):147-95. Available at:

https://www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf .

- Division of Tuberculosis Elimination. *Fact Sheets* (Division of Tuberculosis Elimination Web site; accessed January 2021). Available at: <http://www.cdc.gov/tb/publications/factsheets/default.htm>
- CDC. *Self-Study Modules on Tuberculosis* (Division of Tuberculosis Elimination Web site; Modules 1-5, 2019; Modules 6-9, 2014). Available at: <http://www.cdc.gov/tb/education/ssmodules/default.htm>

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). Although these drugs cross the placenta, they do not appear to have teratogenic effects. As pyrazinamide (PZA) generally is not included in the initial treatment regimen, the minimum duration of therapy is nine months.

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.⁶⁰

Pyridoxine supplementation (25 mg/day) is recommended for all women taking INH who are either pregnant or breastfeeding.⁶¹

Resources

- ATS, CDC, IDSA. Treatment of Drug-Susceptible Tuberculosis. *Clinical Infectious Diseases* 2016; 63(7):147-95. Available at: https://www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf .
- CDC. *Self-Study Modules on Tuberculosis* (Division of Tuberculosis Elimination Web site; Modules 1-5, 2019; Modules 6-9, 2014). Available at: <http://www.cdc.gov/tb/education/ssmodules/default.htm>

Resources and References

Resources

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