# Treatment of Latent Tuberculosis Infection

## CONTENTS

# Introduction

## Purpose

Use this section to understand and follow national and Alaska TB Program guidelines to

- determine whom to treat for latent tuberculosis infection (LTBI)
- select appropriate treatment regimens and dosages
- monitor patients for adverse reactions
- monitor patients' adherence to treatment
- determine whether and when therapy is completed
- provide treatment in special situations, such as when a patient is pregnant or is co-infected with both tuberculosis (TB) and human immunodeficiency virus (HIV).

Prevention of TB has major public health implications, so it is essential to identify and treat all those with risk factors for TB disease.[1] LTBI is infection with *Mycobacterium tuberculosis* organisms (tubercle bacilli), with no symptoms and no radiographic or bacteriologic evidence of TB disease.[2] A person with LTBI is not infectious but can go on to develop active TB disease. **Persons with increased risk for developing TB disease include those who have recently been infected with *M. tuberculosis* and those who have clinical conditions associated with an increased risk for the progression of LTBI to TB disease (e.g., diabetes, HIV, immunocompromise).**

To control and prevent TB, our healthcare resources and efforts should be directed to meet the priorities outlined 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 identification and treatment of persons with LTBI at risk for progression to TB.[3]

Healthcare providers must communicate the risks and benefits of treatment to their patients and encourage adherence and treatment completion. Treatment of LTBI is essential to controlling and eliminating TB in the United States. LTBI treatment substantially reduces the risk that TB infection will progress to disease.[4] Depending upon adherence and length of treatment, completing treatment for LTBI can reduce the risk of TB disease by 65–90%.[5]

Detailed information on the diagnosis and treatment of LTBI in children can be found in the Diagnosis and Treatment of Latent Tuberculosis Infection (LTBI) and Tuberculosis Disease in Children section **9.1**.

## Policy

Treatment should be encouraged for all persons with tuberculosis infection who are determined to be candidates for treatment of LTBI.

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

PHNs should provide oversight for all persons taking anti-tuberculosis medications for the treatment of LTBI. This may include health education; assessing adherence with the prescribed regimen; ordering medications; arranging and monitoring DOT for high-risk individuals; assessing for adverse reactions; facilitating evaluation or diagnostic testing; and reporting status and completion of treatment, as needed, to the Alaska TB Program.

For more information on PHN case management, please refer to "Latent Tuberculosis Infection: A Quick Guide to Case Management for Public Health Nurses" in **Appendix to Chapter 10**.

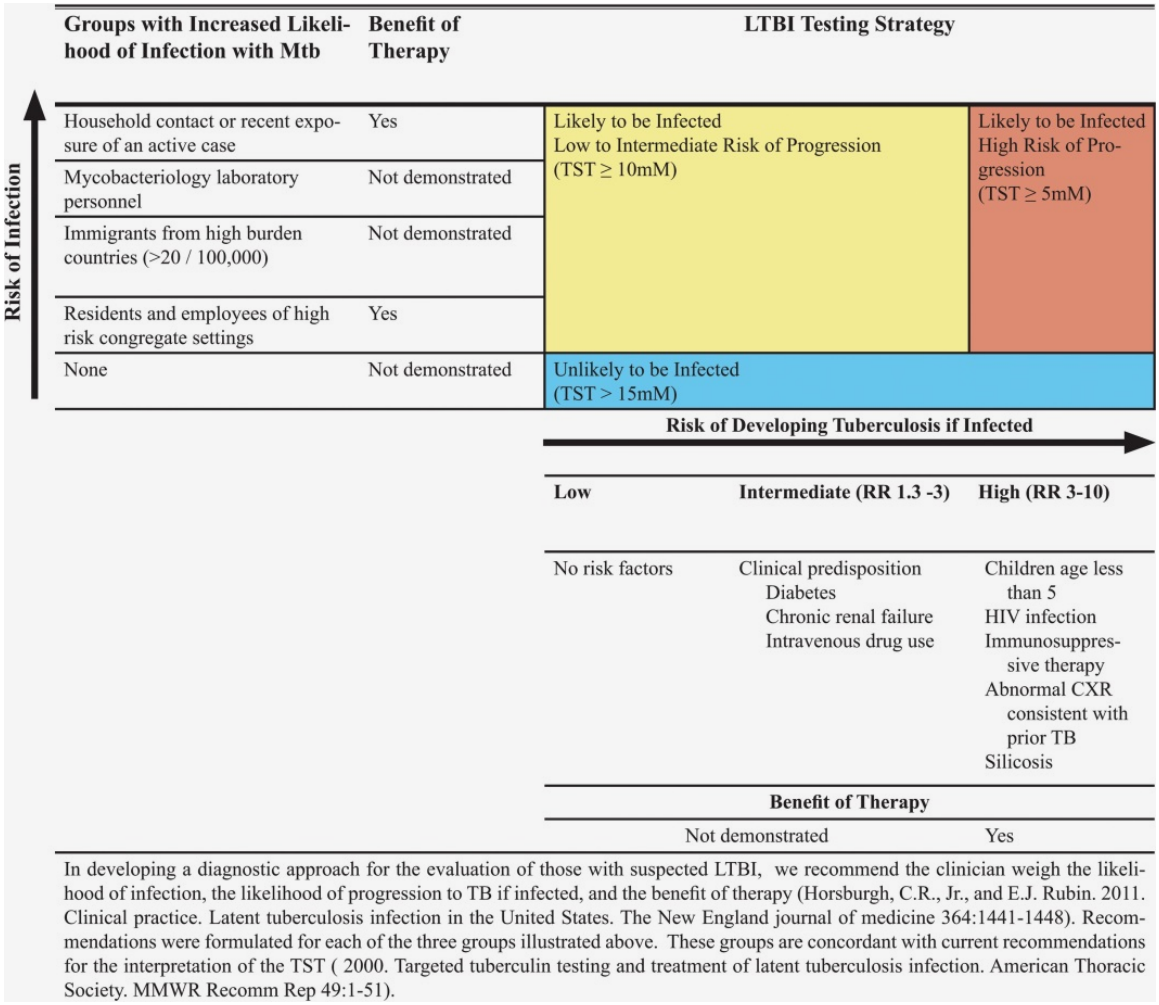
## Forms

The *Latent Tuberculosis Infection (LTBI) Treatment Report*, which is used to report LTBI treatment start and completion, is available in the Forms section **18.1**.

# Whom to Treat

Certain groups are at higher risk to develop active tuberculosis (TB) disease once infected, so make every effort to begin appropriate treatment and to ensure those persons complete the entire course of treatment for LTBI.[6]

Figure 1. **PARADIGM FOR EVALUATION OF THOSE WITH LATENT TUBERCULOSIS INFECTION (LTBI) BASED ON RISK OF INFECTION, RISK OF PROGRESSION TO TUBERCULOSIS, AND BENEFIT OF THERAPY**[7]




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

High-risk contacts (under 5 years of age or immunocompromised) should be started promptly on treatment for LTBI regardless of TB test (TST, IGRA) results. For more information on time frames, see the “Time Frames for Contact Investigation” topic in the Contact Investigation section **11.12**.

Detailed information on the diagnosis and treatment of LTBI in children can be found in the Diagnosis and Treatment of Latent Tuberculosis Infection (LTBI) and Tuberculosis Disease in Children section **9.1**.

Several treatment regimens are available for the treatment of LTBI, and providers should discuss treatment options with their patients.[8,9]

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

## Window Period Prophylaxis for Susceptible and Vulnerable Contacts

A contact is someone who has been exposed to *M. tuberculosis* infection by sharing air space with a person with infectious TB.[10] Susceptible contacts are those who are more likely to become ill with TB disease if they are infected, and vulnerable contacts are those who could suffer severe morbidity if they had TB disease.[11] Persons who are susceptible and/or vulnerable to TB disease are candidates for **window period prophylaxis.**

**Window period prophylaxis** is treatment for presumptive TB infection during the interval between infection and detectable skin test or IGRA test reactivity. The National Tuberculosis Controllers Association (NTCA) and the CDC recommend that the window period be estimated at 8 to 10 weeks.[12]

The following contacts with initially negative TST or IGRA results should begin presumptive treatment for LTBI immediately after TB disease has been ruled out by clinical examination and chest radiograph:

1. contacts younger than 5 years of age (with highest priority given to those under 3 years of age)
2. contacts who have human immunodeficiency virus (HIV) infection or who are otherwise immunocompromised

If the second skin test or IGRA result is negative at 8 – 10 weeks post exposure and the contact is immunocompetent (including immunocompetent young children) and no longer exposed to infectious TB, treatment for LTBI may be discontinued, and further follow-up is unnecessary. If the contact is HIV-infected or otherwise immunocompromised, consideration may be given to advising completion of LTBI treatment even in light of a second negative TB test.

Persons known to be, or suspected of being, immunocompromised, such as HIV-infected persons, should be given treatment for LTBI regardless of the TST or IGRA reaction.[13]

## IGRA Test Results

Persons with a positive IGRA test are generally determined to have TB infection and should be considered for treatment of LTBI.

## Tuberculin Skin Test Results of 5 mm or More

Persons in the following high-risk groups are candidates for treatment of LTBI if their skin test result is 5 mm or more:

- Persons with HIV infection
- Recent contacts of persons with newly diagnosed infectious TB
- Persons with fibrotic changes consistent with old TB on their chest radiograph
- Persons with organ transplants and other immunosuppressed patients (e.g., receiving the equivalent of 15 mg or more/day of prednisone for at least one month)[14]

## Tuberculin Skin Test Results of 10 mm or More

In Alaska, all persons with skin test results of 10 mm or more are considered to be positive and should be considered for treatment of LTBI.

# Treatment Regimens and Dosages

Select appropriate treatment durations, regimens, and dosages. Treatment of latent tuberculosis infection (LTBI) is an essential part of the strategy to eliminate tuberculosis (TB) in the United States. Persons with LTBI, especially those who are at increased risk

for TB disease, should be strongly encouraged to start treatment for their tuberculosis infection.[15]

For a list of high-risk groups, see the “Whom to Treat” topic in this section.

High-risk contacts (under 5 years of age or immunocompromised) should be started promptly on treatment for LTBI. For information on time frames, see the “Time Frames for Contact Investigation” topic in the Contact Investigation section. For more information on treatment of LTBI in children, see the Diagnosis and Treatment of Latent Tuberculosis Infection (LTBI) and Tuberculosis Disease in Children section **9.1**.

For more information on treatment of LTBI, see the “Treatment Regimens and Dosages” topic in this section and the Centers for Disease Control and Prevention (CDC) webpage, “Treatment Regimens for Latent TB Infection (LTBI)” https://www.cdc.gov/tb/topic/treatment/ltbi.htm

**Persons who are at especially high risk for TB or at high risk for nonadherence should be treated using directly observed therapy (DOT)**. This method of treatment is especially appropriate when a household member is on DOT for TB disease, or in institutions and facilities where a staff member can observe treatment.

# Regimens

Identify an appropriate regimen for the patient using the national guidelines provided in Table 1 below.

**Table 1: LTBI TREATMENT OPTIONS**

| Drug(s) | Duration | Dose | Frequency | Total Doses |
|---|---|---|---|---|
| Isoniazid (INH)* and Rifapentine (RPT)† | 3 months | Adults and Children 12 years of age and over:<br>INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum<br>RPT:<br>10.0-14.0 kg 300 mg<br>14.1-25.0 kg 450 mg<br>25.1-32.0 kg 600 mg<br>32.1-49.9 kg 750 mg<br>≥50.0 kg 900 mg max<br>Children 2-11 years of age:<br>INH*: 25 mg/kg, rounded to the nearest 50 or 100 mg, 900 mg maximum<br>RPT†: as above | Once weekly | 12 |
| Rifampin (RIF)§ | 4 months | Adults: 10 mg/kg<br>Children: 15-20 mg/kg‖<br>Maximum dose: 600 mg | Daily | 120 |
| Isoniazid (INH)* and Rifampin (RIF)§ | 3 months | Adults:<br>INH*: 5 mg/kg; 300 mg maximum<br>RIF§: 10 mg/kg**; 600 mg maximum<br>Children:<br>INH*: 10-20 mg/kg; 300 mg maximum<br>RIF§: 15-20 mg/kg; 600 mg maximum | Daily | 90 |
| Isoniazid (INH) | 9 Months | Adults: 5 mg/kg<br>Children: 10-20 mg/kg¶<br>Maximum dose: 300 mg | Daily | 270 |
| | | Adults: 15 mg/kg<br>Children: 20-40 mg/kg¶<br>Maximum dose: 900 mg | Twice weekly‡ | 76 |
| | 6 months | Adults: 5 mg/kg<br>Children: 10-20 mg/kg¶<br>Maximum Dose: 300 mg | Daily | 180 |
| | | Adults: 15 mg/kg<br>Children: 20-40 mg/kg¶<br>Maximum dose: 900 mg | Twice weekly‡ | 52 |

Source: CDC. *Treatment Regimens for Latent TB Infection (LTBI). Available at:* https://www.cdc.gov/tb/topic/treatment/ltbi.htm

*Isoniazid (INH) is formulated as 100 mg and 300 mg tablets.
†Rifapentine (RPT) is formulated as 150 mg tablets in blister packs that should be kept sealed until use.
‡Intermittent regimens must be provided via directly observed therapy (DOT), that is, a health care worker observes the ingestion of medication.
§Rifampin (rifampicin; RIF) is formulated as 150 mg and 300 mg capsules.
‖The American Academy of Pediatrics acknowledges that some experts use RIF at 20–30 mg/kg for the daily regimen when prescribing for infants and toddlers (American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:829–853).
¶The American Academy of Pediatrics recommends an INH dosage of 10–15 mg/kg for the daily regimen and 20–30 mg/kg for the twice weekly regimen.

## The 12-week Isoniazid-Rifapentine regimen

In 2011 the CDC added a new treatment option for LTBI referred to as the 12-week or 3HP regimen, a combination of isoniazid (INH) and rifapentine (RPT) given in 12 once-weekly doses.[16] Recommendations for use of this regimen were updated in 2018.[17]

The choice to use INH/RPT depends on eligibility criteria of patients, medical and social circumstances, ability to monitor the patient, and commitment to complete treatment without missing doses.

Table 2: **RECOMMENDATIONS AND CONSIDERATIONS FOR USING THE 12-WEEK ISONIAZID-RIFAPENTINE REGIMEN**[18,19]

| Consider the regimen for: | Regimen is NOT recommended for: |
|---|---|
| Healthy persons aged 2 years or older | Children younger than 2 years of age |
| Recently exposed contacts of infectious TB and new TB converters | People presumed to be infected with INH or RIF-resistant *M. tuberculosis* |
| Persons with radiographic findings of healed pulmonary TB | Pregnant women or women expecting to become pregnant within the 12–week treatment |
| HIV-infected persons who are taking antiretroviral medications with acceptable drug-drug interactions with rifapentine | Individuals who had prior adverse events or hypersensitivity to rifampin |

Source: CDC. Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection. MMWR 2011; 60(48); 1650-1653.

The regimen of rifampin (RIF) and pyrazinamide (PZA) for two months is no longer recommended for treatment of LTBI because of its association with severe liver injury. For more information, see the CDC's "Update: Adverse Event Data and Revised American Thoracic Society (ATS)/Centers for Disease Control and Prevention (CDC) Recommendations Against the Use of Rifampin and Pyrazinamide for Treatment of Latent Tuberculosis Infection" (*MMWR* 2003;52[No. 31]:735) at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5231a4.htm

## Obtaining/Administering Meds

The following medications are available from the Alaska TB Program for treating LTBI. These medications are provided free of charge upon approval of the TB Program.

- Isoniazid (INH)
- Rifampin (RIF)
- Rifapentine (RPT)

If children have difficulty taking medications, capsules may be opened and contents sprinkled, or tablets crushed, and then hidden in soft foods or liquids. Possible foods include maple syrup, Nutella, spinach baby food, and chocolate whipped cream. Layer the food and drug on a spoon and teach the child to take the contents of the spoon without chewing.[20] To avoid medication decay, administer as soon as possible after mixing with the food. The use of INH elixir is discouraged, as it commonly causes diarrhea and cramping in children.

For information on ordering medications, see the Supplies, Materials, and Services section **(16.1).** Additional information can be found in the Case Management section of this manual **10.17.**

For consultation regarding the treatment of LTBI in persons who have been in contact with a case who is resistant to isoniazid and/or rifampin, contact the Alaska TB Program at 907-269-8000.

## Pyridoxine (Vitamin B6)

Pyridoxine (Vitamin B6) is recommended for some clients taking INH to help prevent peripheral neuropathy. Pyridoxine (vitamin B6) 25-50mg/day or 50 mg weekly is given with INH to all persons at risk of neuropathy, including pregnant women; breastfeeding infants; and persons with HIV, diabetes, alcohol use disorder, malnutrition, advanced age, and or chronic renal failure.[21] For patients with peripheral neuropathy, experts recommend increasing the pyridoxine dose to 100mg/d.[22]

# Adverse Effects of Drugs Used to Treat LTBI

The patient should be monitored by a public health 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

Some health care providers have concerns about treating patients for LTBI. These concerns are generally related to the length of treatment and the potential side effects of medications. As with any treatment, the health care provider must weigh the risks and benefits for each individual. Obtaining a detailed and accurate medical history, and updating information at frequent intervals, will identify persons who require close monitoring; this will aid the health care provider in determining the most appropriate course of action. In addition, CDC guidelines, drug package inserts, and other authoritative medical sources should be consulted whenever there is a question about side effects or drug-drug interactions.

The sections that follow discuss some of the adverse effects of INH and rifamycins, as well as recommendations for monitoring during treatment and for assessing and ensuring adherence.

**Possible adverse effects of INH**[23]

- Asymptomatic elevation of serum liver enzyme concentrations occurs in 10%–20% of people taking INH; liver enzyme concentrations usually return to normal even when treatment is continued. It is generally recommended that INH be withheld if a patient's transaminase level exceeds 3 times the upper limit of normal if associated with symptoms or 5 times the upper limit of normal if the patient is asymptomatic.
- Clinical hepatitis occurs in about 0.1% of people taking INH and is more common when INH is combined with other hepatotoxic agents. Factors that may increase the rates or severity of hepatitis include daily alcohol consumption, underlying liver disease or risks for liver disease, and the concurrent use of other medications which are metabolized in the liver. Symptomatic hepatitis is rare in patients younger than 20 years of age, but severe and fatal cases have been reported. Younger patients with underlying risk factors for liver disease should be monitored clinically with the same precautions as older patients.
- Peripheral neuropathy occurs in less than 0.2% of people taking INH at conventional doses. It is more likely in the presence of other conditions associated with neuropathy such as diabetes, HIV, renal failure, and alcoholism. Pyridoxine (vitamin B6) supplementation is recommended in patients with such conditions as well as in pregnant or breastfeeding women.

**Possible adverse effects of Rifampin (RIF) and Rifapentine (RPT)[24]**

- Hepatotoxicity, evidenced by transient asymptomatic hyperbilirubinemia, may occur in 0.6% of persons taking RIF. Hepatitis is more likely when RIF is combined with INH.
- Cutaneous reactions, such as pruritis (with or without a rash), may occur in 6% of persons taking RIF. They are generally self-limited and may not be a true hypersensitivity; continued treatment may be possible.
- Rarely, rifamycins can be associated with hypersensitivity reactions, including hypotension, nephritis, or thrombocytopenia, and manifested by symptoms such as fever, headache, dizziness/lightheadedness, musculoskeletal pain, petechiae, and pruritis.
- Gastrointestinal symptoms such as nausea, anorexia, and abdominal pain are rarely severe enough to discontinue treatment.
- Orange discoloration of body fluids is expected and harmless, but patients should be advised beforehand. Soft contact lenses and dentures may be permanently stained.
- RIF and RPT interact with a number of other medications. They are known to reduce concentrations of methadone, warfarin, hormonal contraceptives, and phenytoin. Women using hormonal contraceptives should be advised to consider an alternative method of contraception (e.g., a barrier method).
  RIF and RPT may be contraindicated, or should be used with caution, in HIV-infected individuals being treated with certain antiretroviral medications. Substitution of rifabutin for RIF in the 4-month regimen many be considered for such patients as it tends to have a lower risk of drug-drug interaction.

**Patient Monitoring and Education During Treatment[25]**

To ensure safe and efficacious treatment for LTBI, the health care provider should periodically assess the patient's progress. This evaluation involves clinical monitoring and may include laboratory testing, as well as patient education.

**Clinical Monitoring[26]**

- Patients should visit the health care provider who is managing their treatment on a monthly basis to be assessed for the following:
  - Signs of hepatitis
  - Adherence to medication regimen
  - Symptoms of possible adverse drug reactions or interactions
  - Symptoms of active TB disease
- Patients being treated for LTBI who experience possible adverse reactions should be advised to stop medication and consult their health care provider immediately.

**Patient Education**[27]

- Explain the disease process and rationale for medication in the absence of symptoms or radiographic abnormalities.
- Review the importance of completing treatment for LTBI.
- Discuss possible side effects of LTBI medications that may include:
    - Fever
    - Unexplained anorexia
    - Dark urine (color of coffee or cola)
    - Icterus
    - Rash
    - Persistent paresthesia of hands and feet
    - Persistent fatigue or weakness lasting 3 or more days
    - Abdominal tenderness, especially in right upper quadrant
    - Easy bruising or bleeding
    - Arthralgia
    - Nausea
    - Vomiting
- Discuss management of common side effects and the need to report them to health care provider.

**Laboratory Testing**[28]

- Baseline laboratory testing (measurements of serum AST, ALT, and bilirubin) is not necessary for most patients.
- Laboratory testing at the start of LTBI therapy is recommended for patients with any of the following:
    - Liver disorders
    - History of liver disease (e.g., hepatitis B or C, alcoholic hepatitis, or cirrhosis)
    - Regular use of alcohol
    - Risks for chronic liver disease
    - HIV infection
    - Pregnancy or the immediate postpartum period (i.e., within 3 months of delivery)
- Baseline testing can be considered on an individual basis, especially for patients taking other medications for chronic medical conditions.
- After baseline testing, routine periodic retesting is recommended for persons who had abnormal initial results and other persons at risk for hepatic disease.
- At any time during treatment, whether or not baseline tests were done, laboratory testing is recommended for patients who develop symptoms suggestive of hepatitis (e.g., fatigue, weakness, malaise, anorexia, nausea, vomiting, abdominal pain, pale stools, dark urine, chills) or who have jaundice. Patients should be instructed, at the start of treatment and at each monthly visit, to stop taking medications and to seek medical attention immediately if symptoms of

hepatitis develop. They should not wait until the next clinic visit to stop treatment.

- It is generally recommended that medication be withheld if a patient's transaminase levels exceed 3 times the upper limits of normal if associated with symptoms or 5 times the upper limits of normal if the patient is asymptomatic.

## Reporting Reactions

The table below is intended for use by the healthcare worker who performs case management services, such as a public health nurse or a community health aide. The healthcare worker should instruct the patient to report to the provider the side effects and adverse reactions listed in Table 3.

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

If a patient reports a potentially serious adverse reaction to a healthcare worker, the healthcare provider should call the patient's provider immediately and alert the Alaska TB Program by calling 1-907-269-8000.

Table 5: **REPORTING REACTIONS TO ANTITUBERCULOSIS MEDICATIONS**[29]

| Potentially Serious Adverse Reactions* | Less Severe Signs and Symptoms* |
|---|---|
| Immediately report the following signs and symptoms or other abnormalities or unexpected events to the patient's provider. These signs and symptoms suggest side effects, including hepatotoxicity:<br>▪ Jaundice<br>▪ Dark urine<br>▪ Vomiting<br>▪ Abdominal pain<br>▪ Fever<br>▪ Visual changes<br>▪ Marked clinical rash<br>In consultation with the provider, instruct the patient to stop TB medications until evaluated by the provider. | Report the following signs and symptoms to the patient's provider within 24 hours:<br>▪ Anorexia<br>▪ Nausea<br>▪ Malaise<br>▪ Peripheral neuropathy: tingling or burning sensation in hands or feet<br>▪ Rashes |
| *These lists are not all-inclusive. For a complete list, refer to the current guidelines for treatment of TB, "Treatment of Drug-Susceptible Tuberculosis" (*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 | |

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 February 5, 2021.

Report all severe adverse events (e.g., liver injury, pancreatitis, metabolic acidosis, anaphylaxis, seizure, severe dermatitis) leading to hospitalization or death of a person receiving treatment for LTBI to the Alaska TB Program by calling 907-269-8000.

## Monitoring for Side Effects and Adverse Reactions by Antituberculosis Drug

Refer to Table 6**: Monitoring and Interventions for Side Effects and Adverse Reactions** to

- identify the side effects and adverse reactions associated with antituberculosis drugs
- determine how to monitor for side effects and adverse reactions

Table 6: **MONITORING AND INTERVENTIONS FOR SIDE EFFECTS AND ADVERSE REACTIONS**[30,31,32]

| Antituberculosis Drug | Side Effects/ Adverse Reactions | Monitoring | Comments |
|---|---|---|---|
| **Isoniazid (INH)** | ▪ Rash<br>▪ Hepatic enzyme elevation<br>▪ Hepatitis<br>▪ Peripheral neuropathy<br>▪ Mild central nervous system effects | Clinical monitoring monthly<br><br>In selected cases (human immunodeficiency virus [HIV] infection, history of liver disease, alcoholism, and pregnancy), liver function tests at baseline<br>▪ aspartate aminotransferase [AST]<br>▪ alanine aminotransferase [ALT]<br>▪ serum bilirubin)<br><br>Repeat measurements if<br>▪ Baseline results are abnormal<br>▪ Patient is pregnant, in the immediate postpartum period, or at high risk for adverse reactions<br>▪ Patient has symptoms of adverse reactions | Hepatitis risk increases with age and alcohol consumption.<br><br>Pyridoxine (vitamin B6) 25-50mg/day is given with INH to all persons at risk of neuropathy. It should be considered for clients who are: pregnant women, breastfeeding infants, persons with HIV, patients with diabetes, alcoholism, malnutrition, or chronic renal failure, or patients with advanced age.[33] For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100mg/d.[34]<br><br>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. |

| Antituberculosis Drug | Side Effects/ Adverse Reactions | Monitoring | Comments |
|---|---|---|---|
| **Rifampin (RIF)**<br><br>Rifapentine (RPT) is a rifamycin derivative with a longer half-life. Side-effects and adverse reactions are similar to Rifampin. | ▪ Rash<br>▪ Gastrointestinal upset<br>▪ Hepatitis<br>▪ Fever<br>▪ Bleeding problems<br>▪ Thrombocytopenia<br>▪ Renal failure<br>▪ Flu-like symptoms<br>▪ Orange-colored body fluids (secretions, urine, tears) | In selected cases (human immunodeficiency virus [HIV] infection, history of liver disease, alcoholism, and pregnancy), complete blood count, platelets and liver function tests at baseline<br>▪ aspartate aminotransferase [AST]<br>▪ alanine aminotransferase [ALT]<br>▪ serum bilirubin<br><br>Repeat measurements if<br>▪ Baseline results are abnormal<br>▪ Patient has symptoms of adverse reactions | There are a number of drug interactions with potentially serious consequences. Significant interactions with methadone, birth control hormones, and many other drugs.<br><br>Contraindicated or should be used with caution when administered with protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs). Reduces levels of many drugs (e.g., PIs, NNRTIs, methadone, dapsone, ketoconazole, coumadin derivatives, hormonal contraceptive, digitalis, sulfonylureas, diazepam, ß-blockers, anticonvulsants, and theophylline).<br><br>For more information, refer to “Section 7: Drug Interactions” on page 45 in “Treatment of Tuberculosis” at http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf .<br><br>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.<br><br>Colors body fluids orange.<br><br>May permanently discolor soft contact lenses. |

# Adherence

Monitor patients for adherence to self-administered latent tuberculosis infection (LTBI) treatment regimens at least every month throughout treatment.[35] It is difficult to identify who will and who will not be adherent.[36] If the patient does not take medicine as directed, the effectiveness of the regimen decreases, and the patient will be at greater risk of progressing to active disease and infecting others in the future.

## Monthly Assessment of Adherence

At each visit, the clinician should assess adherence by doing the following:

1. Ask patients how many doses they have missed since their last refill. If patients are asked, “Did you take all your pills last month?” the natural inclination is to agree and say “yes,” even if they did not.
2. Have patients bring their bottle of medicine to the refill appointment and count how many pills are left.
3. If adherence problems are identified, include patients in the problem-solving process.
   a. Ask patients why they think that doses are missed and what could be done better: change the time of day, the location where they keep or take their pills, etc.
   b. Find out if there are barriers to obtaining refills in a timely manner that could be corrected.
   c. Review with patients what they believe is their risk of developing tuberculosis (TB) if medicine is not taken. Provide more education as needed.
   d. Mutually agree on a plan to improve adherence.
   e. Praise patients for cooperation.
4. If adherence seems to be good, praise patients.

For information on what to include in a patient education session, see the Patient Education section **13.1**.

## Directly Observed Therapy

Patients in the following high-risk groups are strongly recommended for directly observed therapy (DOT).

- DOT is mandatory for the twice-weekly INH regimens.
- DOT is no longer mandatory but may be considered for the 3HP (INH/RPT) 12-week regimen.

- DOT is strongly encouraged for those with the greatest risk for progressing to tuberculosis (TB) disease:
  - Young children who are recent contacts to infectious cases.
  - Human immunodeficiency virus (HIV)-infected persons.

For more information, see the “Directly Observed Therapy” topic in the Case Management section **10.37**.

For more information on adherence strategies for different developmental stages, see Appendix B in the Rutgers Global Tuberculosis Institute’s *Management of Latent Tuberculosis Infection in Children and Adolescents: A Guide for the Primary Care Provider* (Rutgers Global Tuberculosis Institute Web site; 2019) at

http://globaltb.njms.rutgers.edu/educationalmaterials/Products/2020%20Peds%20LTBI%20Guide/Pediatric%20LTBI%20Handbook%202020.pdf

# Completion of Therapy

Completion of therapy is determined by the total number of doses administered, not the duration of therapy. When patients have had lapses in therapy but will still be able to complete the recommended number of doses in the allotted time period, encourage them to complete therapy.

Assess patients who will not complete appropriate therapy within the time frame specified to determine whether or not to restart treatment. If the decision is made to retreat the patient, then restart the entire regimen and follow the recommended treatment plan of therapy. Specific factors to consider when determining whether to restart treatment include the following:

- Individual's risk for developing tuberculosis (TB) disease
- Total number of doses of latent tuberculosis infection (LTBI) treatment administered
- Time elapsed since the last dose of treatment for LTBI
- Patient adherence issues (previous attempts at completion, willingness to continue, etc.)

Give nonadherent patients at very high risk of developing TB disease every opportunity to complete treatment for LTBI. Consider these patients for intermittent therapy with directly observed therapy (DOT) and evaluate for the use of incentives and enablers.[37]

Treatment of LTBI in contacts is considered a priority in TB control activities. Make every effort to assure that contacts complete treatment.

All contacts who are being treated for infection should be seen face-to-face by a healthcare provider at least every month or more often. When available, incentives and enablers are recommended as aids to adherence, and the healthcare provider should educate the patient about TB, its treatment, and the signs of adverse drug effects at each patient encounter.[38]

Table 7 describes the duration of therapy and the number of doses that patients are required to take to complete therapy and the time frame within which the total number of doses must be administered for completion of therapy. Please report completion of treatment to the Alaska TB Program.

Table 7: **RECOMMENDED REGIMENS FOR COMPLETION OF THERAPY**[39]

| Regimen | Age | Duration of Therapy | Number of Doses | Must be Administered Within |
|---|---|---|---|---|
| **RIF daily** | Adult and child | 4 months | 120 | 6 months |
| **INH/RPT once weekly** | ≥ 2 years of age | 12 weeks | 12 | 16 weeks |
| **INH/RIF daily** | Adult and child | 3 months | 90 | 4 months |
| **INH daily** | Adult and child | 9 months | 270 | 12 months |
| **INH daily** | Adult | 6 months | 180 | 9 months |
| Definitions of abbreviations: INH = isoniazid; RIF = rifampin, RPT= Rifapentine. | | | | |

Sources: CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 2000;49(No. RR-6):26–27; CDC. Regimens. In: Chapter 5: Treatment for Latent Tuberculosis Infection. *Core Curriculum on Tuberculosis: What the Clinician Should Know (2016)* [Division of Tuberculosis Elimination Web site]. Updated May 2016. Available at: https://www.cdc.gov/tb/education/corecurr/pdf/chapter5.pdf . and New England Journal of Medicine. "Three Months of Rifapentine and Isoniazid for Latent TB Infection". 12/8/2011; (vol365)23. p 2155-2165.

Make every effort to encourage patients to adhere to the LTBI treatment regimen. However, if a patient has failed three attempts to complete treatment, no further effort may be merited. The healthcare provider should contact patients who interrupt therapy and are at high risk of developing TB disease (for example, contacts of patients with infectious TB, young children, or persons with human immunodeficiency virus (HIV) for reevaluation.[40]

For consultation regarding completion of therapy and considerations to examine when restarting treatment in noncompliant patients, contact the Alaska TB Control Program at 907-269-8000.

Use the *Latent Tuberculosis Infection* (*LTBI) Treatment Form* to report LTBI treatment Completion. It is available in the Forms section **18.1**.

# Treatment in Special Situations

## Human Immunodeficiency Virus and Latent Tuberculosis Infection

Treatment of latent tuberculosis infection (LTBI) in a person with human immunodeficiency virus (HIV) infection can be extremely complicated. Rifampin and rifapentine can adversely interact with many of the antiretroviral HIV medications. Before treatment is initiated, contact the Alaska TB Program at 269-8000 for consultation.

HIV infection is the strongest known risk factor for the progression of LTBI to tuberculosis (TB) disease. HIV-infected persons with LTBI are 100 times more likely to progress to TB disease than are those patients without HIV infection. Coinfected HIV and LTBI patients have a 7 to 10 percent yearly risk of developing TB disease, as compared with a 10 percent lifetime risk of developing TB disease for HIV-negative LTBI patients.

High-risk contacts (less than 5 years of age or immunocompromised) should be started promptly on treatment for LTBI. For more information on time frames, see the “Time Frames for Contact Investigation” topic in the Contact Investigation section **11.12**.

### Resources

- CDC. “TB Guidelines: HIV/AIDS” (DTBE Web site; accessed February 2021). Available at: http://www.cdc.gov/tb/publications/guidelines/HIV_AIDS.htm
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- CDC. “Updated Guidelines for the Use of Rifabutin or Rifampin for the Treatment and Prevention of Tuberculosis among HIV-infected Patients Taking Protease Inhibitors or Nonnucleoside Reverse Transcriptase Inhibitors” (*MMWR* 2000;49[No. 9]:185). Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm4909a4.htm

# Alcohol Use Disorder

## Alcohol-Related Treatment Complications

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

Alcohol consumption increases health risks and can complicate the treatment of patients with TB.

**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.[41] However, studies have shown that "alcohol consumption is a major risk factor for infection with opportunistic bacterial, viral, fungal, and parasitic pathogens."[42]

**Liver injury and death**: Drug-induced liver injury "may occur with all currently recommended regimens for the treatment of …LTBI".[43] In the treatment of TB disease, "the crucial efficacy of isoniazid, and particularly, rifampin, warrants their use and retention, (RIF), and pyrazinamide (PZA), they should be used if at all possible, even in the face of preexisting liver disease."[44] However, it is not fully understood yet how antituberculosis medications cause drug-induced liver injury.[45]

For persons taking isoniazid, an association between alcohol consumption and hepatitis has been found, with rates being fourfold higher among persons consuming alcohol daily than among those who did not drink alcohol.[46] 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 still 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.[47,48]

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.[49]

**Nonadherence to treatment:** Patients who do not complete LTBI treatment risk progression to TB disease, and those who do not complete treatment for TB disease

risk relapse, development of drug-resistant TB, serious illness, and possible death.

Barriers to adherence may be patient-related, such as conflicting health beliefs, alcohol or drug dependence, or mental illness, or they may be system-related, such as lack of transportation, inconvenient clinic hours, or lack of interpreters.[50]

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."[51] In a study of 237 patients in the Russian Federation undergoing Directly Observed Therapy Short-Course (DOTS) treatment for TB disease, "substance abuse was identified as the only factor that was strongly associated with non-adherence…These results suggest that DOTS programmes [sic] might be more likely to achieve TB control targets if they include interventions aimed at improving adherence by diagnosing and treating substance abuse concurrently with standard TB therapy."[52]

DOTS programs that have explicitly offered substance abuse treatment have reported better outcomes that those that have not.[53] In South Carolina, joint treatment programs to treat patients with TB who have alcohol and substance abuse problems were used in conjunction with incentives, enablers, and a process of increasing restrictions (health department warnings, then court-ordered directly observed therapy, then involuntary confinement) as needed to address noncompliance. This combination of strategies was associated with an increase in overall completion of antituberculosis therapy and a decrease in new cases between 1986-1991.[54]

## Safe Treatment Guidelines

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

- **Program Infrastructure**

  Adopt these standardized approaches to develop safe treatment of LTBI and TB disease.

- **Provider Education and Resources**

  Develop these written resources, educational programs, and referral mechanisms to assure that healthcare providers have the skills, knowledge, and resources to safely diagnose and treat patients with TB disease and LTBI.

- **Pretreatment Clinical Evaluation**

  Refer here for a list of what to include in the pretreatment clinical evaluation and the initial physical examination and when to screen for viral hepatitis.

- **Patient Education**

  Follow these suggestions to improve patients' awareness of and communication about their symptoms of liver disorders. Communicate with patients in their preferred language[55] and carefully confirm that they understand the educational points being made.

- **Medication Administration and Pharmacy**

  Use these tips to distribute antituberculosis medications in ways that encourage and reinforce prompt reporting by patients of adverse effects.

- **Treatment of LTBI and Treatment of TB Disease**

  Use these recommendations to guide treatment decisions and monitoring activities. Numbered lists of recommendations provide detailed information. Three flowcharts show key data and decisions in the following areas: LTBI pretreatment clinical evaluation and counseling, monitoring for hepatotoxicity during LTBI treatment, and monitoring for hepatotoxicity during treatment of TB disease.[56]

## Pregnancy and Breastfeeding

Pregnancy has minimal influence on the pathogenesis of TB or the likelihood of LTBI progressing to disease. Pregnant women should be targeted for testing only if they have a specific risk factor for LTBI or for progression of LTBI to disease. For most pregnant women, treatment for LTBI can be delayed until 2-3 months postpartum. For women who are at high risk for progression from LTBI to TB disease, especially those who are a recent contact of someone with infectious TB disease, treatment for LTBI should not be delayed on the basis of pregnancy alone, even during the first trimester.

Extensive use of INH during pregnancy has shown that although it readily crosses the placental barrier, the drug is not teratogenic, even when given during the first four months of gestation. Pregnant women taking INH should receive pyridoxine supplementation.

Women who are pregnant or planning to become pregnant during treatment should not receive the INH/RPT regimen. Safety in pregnancy is unknown. All of the other approved regimens are appropriate for use in pregnancy.

Breastfeeding is not contraindicated when the mother is being treated for LTBI. However, exclusively breastfed infants whose mothers are taking INH should receive supplemental pyridoxine. There is currently insufficient data to indicate whether the 3HP regimen is safe during breastfeeding. It should also be noted that the concentrations of TB drugs in breast milk are inadequate to provide treatment of the infant.[57]

# Resources and References

## Resources

### Whom to Treat

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- CDC. Core Curriculum on Tuberculosis (2016) [Division of Tuberculosis Elimination Web site]. Updated May 2016. Available at: http://www.cdc.gov/tb/education/ce/interactive-corecurr.htm

### Treatment Regimens and Dosages

- CDC. "Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection" (*MMWR* 2000;49[No. RR-6]). Available at: http://www.cdc.gov/mmwr/PDF/rr/rr4906.pdf
- CDC. "Update: Adverse Event Data and Revised American Thoracic Society (ATS)/Centers for Disease Control and Prevention (CDC) Recommendations Against the Use of Rifampin and Pyrazinamide for Treatment of Latent Tuberculosis Infection" (*MMWR* 2003;52[No. 31]). Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5231a4.htm
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- CDC. "Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection. MMWR 2011; 60(48); 1650-1653. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w
- CDC. Errata: Vol. 60, No. 48. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6104a7.htm?s_cid=mm6104a7_w
- CDC. "The 12 Dose Regimen for Latent TB Infection". Patient Brochure. Available at: http://www.cdc.gov/tb/publications/pamphlets/12DoseLTBITreatmentbrochure8.5x11.pdf

### Side Effects and Adverse Reactions

- CDC. "Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection" (*MMWR* 2000;49[No. RR-6]:26–29, 38–39). Available at: http://www.cdc.gov/mmwr/PDF/rr/rr4906.pdf .

- National Tuberculosis Controllers Association–National Tuberculosis Nurse Consultant Coalition. *Tuberculosis Nursing: A Comprehensive Guide to Patient Care* (Atlanta, GA;1997:47–51, 63–64).
- CDC. Module 4: "Treatment of Tuberculosis and Tuberculosis Infection" (*Self-Study Modules on Tuberculosis* [Division of Tuberculosis Elimination Web Site]; 2016). Available at: http://www.cdc.gov/tb/education/ssmodules/default.htm
- Saukkonen, J. Et al. An Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy. Am J Respir Crit Care Med. 2006:174, 935-952. Available at http://www.thoracic.org/statements/resources/mtpi/hepatotoxicity-of-antituberculosis-therapy.pdf

## Adherence

- CDC. Module 6: "Managing Tuberculosis Patients and Improving Adherence" (S*elf-Study Modules on Tuberculosis.* Division of Tuberculosis Elimination Web Site; 2016). Available at: https://www.cdc.gov/tb/education/ssmodules/
- Module is entirely devoted to assessing and promoting adherence. It covers the many areas that need to be addressed, such as:
  - Case management: assigning responsibility to the healthcare worker
  - Communication and problem-solving skills
  - Education of the patient
  - Using interpreters when needed
  - Using incentives (rewards) and enablers (things that remove barriers for patients)
  - Using directly observed therapy (DOT)
- CDC. *Improving Patient Adherence to Tuberculosis Treatment.* (1994)
- National Tuberculosis Controllers Association–National Tuberculosis Nurse Consultant Coalition. *Tuberculosis Nursing: A Comprehensive Guide to Patient Care* (Atlanta, GA; 1997:69–84).

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