Chapter 8: Treatment of Latent Tuberculosis Infection

Contents

Introduction

Purpose

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

- 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 has tuberculosis (TB)-human immunodeficiency virus (HIV) coinfection

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 the presence of *Mycobacterium tuberculosis* organisms (tubercle bacilli), with no symptoms and no radiographic or bacteriologic evidence of TB disease.[2] **A person with LTBI is noninfectious** but can develop active TB disease. People with increased risk for developing TB include those who have had recent infection with *M. tuberculosis* and those who have clinical conditions associated with an increased risk for the progression of LTBI to TB disease.

Treatment of LTBI is essential to controlling and eliminating TB in the United States. To control and prevent TB, our health care 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 the identification and treatment of people with LTBI at risk for progression to TB.[3]

Health care providers must communicate the risks and benefits of treatment to their patients and encourage adherence and treatment completion. LTBI treatment substantially reduces the risk that TB infection will progress to disease: depending upon adherence and length of treatment, completing treatment for LTBI can reduce the risk of TB disease by 65–90%.[4,5]

Policy

Treatment should be considered for all people who are determined to be candidates for the treatment of LTBI.

Forms

Required and recommended forms are available on the Wisconsin Tuberculosis Program's webpage.

Reporting requirements

Latent Tuberculosis Infection (LTBI) is a Category II reportable condition in Wisconsin

What condition	Who reports	When to report	How to report
Confirmed or suspected cases of latent LTBI	• Physicians • Other health care providers • Hospitals • Other similar private or public institutions • Anyone providing treatment for LTBI **Note:** The attending physician or other health care provider must report even if the laboratory is also reporting the test results.	**Report within 72 Hours**	Category II diseases **should be reported by fax, mail, or electronic reporting to the patient's local health officer or to the local health officer's designee** on an Acute and Communicable Disease Case Report or by other means or by entering the data into the Wisconsin Electronic Disease Surveillance System **within 72 hours of the identification of a case or suspected case**

Whom to treat

Determine whom to treat for LTBI. Treatment of LTBI is an essential part of the strategy to eliminate TB in the United States. People with LTBI who are considered at increased risk for TB should be offered treatment.[6] Certain groups are at high risk of developing TB disease once infected, so make every effort to begin appropriate treatment and to ensure those people complete the entire course of treatment for LTBI.[7]

For a list of high-risk groups by tuberculin skin test (TST) results, see the Tuberculin Skin Test Results listings below. For more information on targeted testing, see the Targeted Testing for Latent Tuberculosis Infection section.

High-risk contacts (under 5 years of age or immunocompromised) should be started promptly on treatment for LTBI. Contacts of children under 5 years of age who are diagnosed with LTBI should be evaluated for active disease (a “source case” investigation). For more information on time frames, see the “Time Frames for Contact Investigation” topic in the Contact Investigation section.

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

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) Treatment Regimens for Latent TB Infection webpage.

For consultation regarding the treatment of LTBI, call the Wisconsin Tuberculosis Program at 608-261-6319.

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.[9] 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 progress to TB disease.[10] People who are susceptible or vulnerable to TB disease are candidates for window period or prophylaxis treatment, which is administering treatment for presumptive TB infection during the interval between infection and detectable skin test reactivity or positive blood testing (interferon gamma release assay [IGRA] such as the QuantiFERON®-TB Gold test). The National Tuberculosis Controllers Association (NTCA) and the CDC recommend that the window period be estimated at eight to ten weeks.[11] The following contacts with initially negative TST or IGRA results should receive treatment for LTBI after TB disease has been ruled out by clinical examination and chest radiograph:

- Contacts younger than 5 years of age (with highest priority given to those under 3 years)
- Contacts with HIV infection or who are otherwise immunocompromised.

If the second skin test or IGRA result is negative, 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 second test is negative, but the contact is immunocompromised (for example, with human HIV infection), a course of therapy for LTBI should be completed.

If the second test result is negative, but the person remains in close contact with an infectious patient or the person is less than 6 months of age, treatment for LTBI should be continued for contacts in the following age ranges or with the following medical conditions:

- Contacts younger than five years old
- Contacts aged five to fifteen years, at the clinician’s discretion.

- Contacts who are HIV-seropositive or otherwise immunocompromised[12]

People known to be (or suspected of being) immunocompromised, such as people living with HIV, should be given treatment for LTBI regardless of the TST or IGRA reaction.[13]

Tuberculin skin test results of 5 mm or more

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

- People living with HIV
- Recent contacts of people with infectious TB
- People with fibrotic changes on their chest radiographs suggestive of previous TB
- People with organ transplants and other immunosuppressed patients (receiving the equivalent of 15 mg or more per day of prednisone for at least one month, or those taking TNF-alpha antagonists)[14]

Tuberculin skin test results of 10 mm or more

People in the following high-risk groups are candidates for treatment of LTBI if their skin test result is greater than or equal to 10 mm:

- People born in countries where TB disease is common, including Mexico, the Philippines, Vietnam, India, China, Haiti, and Guatemala, or other countries with high rates of TB.
- People with substance use disorders or excessive substance use (including alcohol or IV drugs).
- People who live or work in high-risk, congregate settings (for example, correctional institutions; long-term residential care facilities, such as nursing homes, mental health facilities, homeless shelters; and refugee camps) Mycobacteriology laboratory personnel.
- People with medical conditions or undergoing treatments that increase the risk of TB disease (diabetes mellitus, silicosis, recent infection with *M. tuberculosis* within the past two years, bone marrow and organ transplant recipients, prolonged high-dose corticosteroid therapy and other immunosuppressive therapy, chronic renal failure, hemodialysis, some hematological disorders [for example, leukemias and Hodgkin's disease], other specific malignancies [For example, carcinoma of the head, neck, or lung], chronic malabsorption syndromes, weight of 10% or more below ideal body weight, and intestinal bypass or gastrectomy).
- Children less than 5 years of age.
- Infants, children, and adolescents exposed to adults in high-risk categories.

Tuberculin skin tests results of 15 mm or more

People in the following groups may be considered for treatment of LTBI if their skin test result is greater than or equal to 15 mm. These groups should be given a lower priority for prevention efforts than the groups already listed above:

- People with no known risk factors for TB disease.
- Health care workers* who are otherwise at low risk for TB disease and who received baseline testing at the beginning of employment as part of a TB screening program.[15]
- For health care workers (HCWs) who are otherwise at low risk for LTBI and progression to TB disease if infected and who received baseline testing at the beginning of employment as part of a TB infection-control screening program, a TST result of 15 mm or more (instead of 10 mm or more) is considered to be positive. Although a result of 10 mm or more on baseline or follow-up testing is considered a positive result for HCWs for the purposes of referral for medical and diagnostic evaluation, if the TST result is 10–14 mm on baseline or follow-up testing, the referring clinician might not recommend treatment of LTBI.[16]

Treatment regimens and dosages

Select appropriate treatment durations, regimens, and dosages. There are several treatment regimens available for the treatment of LTBI, and providers should discuss options with patients. People who are at especially high risk for TB, have barriers to adherence, or are on an intermittent dosing regimen, 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.

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 window prophylaxis or treatment for LTBI. For more information on time frames, see the “Time frames for contact investigation” topic in the Contact Investigation section.

Regimens

Identify an appropriate regimen for the patient using the national guidelines provided in table 8.1 below:

Table 8.1: Approved treatment regimens for patients with drug-susceptible LTBI

Priority rank*	Regimen	Recommendation	Evidence (high, moderate, low, or very low)
Preferred	3 months isoniazid plus rifapentine given once weekly	Strong	Moderate
Preferred	4 months rifampin given daily	Strong	Moderate
Alternative	3 months isoniazid plus rifampin given daily	Conditional	Low (HIV positive) Very low (HIV negative)
Alternative	6 months isoniazid given daily	Strong	Moderate (HIV negative)
Alternative	6 months isoniazid given daily	Conditional	Moderate
Alternative	9 months isoniazid given daily	Conditional	Moderate

Abbreviation: HIV = human immunodeficiency virus.
* *Preferred:* excellent tolerability and efficacy, shorter treatment duration, higher completion rates than longer regimens and therefore higher effectiveness; *alternative:* excellent efficacy but concerns regarding longer treatment duration, lower completion rates, and therefore lower effectiveness.
† In HIV-positive people, providers should be aware of possible drug-drug interactions between rifamycins and antivirals and take appropriate monitoring precautions.
§ Strong recommendation for those people unable to take a preferred regimen (due to drug intolerability or drug-drug interactions).

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).

Dosages

Once the appropriate regimen has been identified, refer to Table 8.2 for instructions on dosages for each drug. The information in Table 2 is taken from ATS, CDC, and Infectious Diseases Society of America (IDSA) guidelines.

The following drugs for treating LTBI are provided free of charge by the Wisconsin TB Dispensary upon approval by the TB Program:

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

Table 8.2. Dosages for recommended latent tuberculosis infection treatment regimens

Drug	Duration	Dose and age group	Frequency	Total doses
Isoniazid* and rifapentine †	3 months	Adults and children aged 12 years and older: Isoniazid: 15mg/ kg rounded up to the nearest 50 or 100mg; 900mg maximum Rifapentine: 10-14 kg: 300mg 14.1-25kg: 450mg 25.1-32kg: 600mg 32.1- 49.9kg: 750mg ≥ 50kg, 900mg max Children aged 2-11 years: Isoniazid: 25mg/kg, 900mg max Rifapentine †: see above.	Once weekly	12
Rifampin §	4 months	Adults: 10mg/kg Children: 15-20mg/kg ‖ Maximum dose: 600mg	Daily	120
Isoniazid and rifampin	3 months	Adults: Isoniazid: 5mg/kg, 300mg maximum Rifampin: 10mg/kg: 600mg maximum Children: Isoniazid: 10-20mg/kg: 300mg maximum Rifampin: 15-20mg/kg: 600mg maximum	Daily	90
Isoniazid	6 months	Adults: 5mg/kg	Daily	180

		Children: 10-20mg/kg Maximum dose: 300mg		
Isoniazid	6 months	Adults: 15mg/kg Children: 20-40mg/kg Maximum dose: 900mg	Twice weekly ‡	52
Isoniazid	9 months	Adults: 5mg/kg Children: 10-20mg/kg Maximum dose: 300mg	Daily	270
Isoniazid	9 months	Adults: 15mg/kg Children: 20-40mg/kg Maximum dose: 900mg	Twice weekly ‡	76

* Isoniazid is formulated as 100-mg and 300-mg tablets.
† Rifapentine 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 (i.e., a health care worker observes the ingestion of medication). § Rifampin (rifampicin) is formulated as 150-mg and 300-mg capsules.
‖ The American Academy of Pediatrics acknowledges that some experts use rifampin at 20–30 mg/kg for the daily regimen when prescribing for infants and toddlers (**Source:** 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; 2018:829–53).
¶ The American Academy of Pediatrics recommends an isoniazid dosage of 10–15 mg/kg for the daily regimen and 20–30 mg/kg for the twice-weekly regimen.

The use of the commercially prepared INH elixir is discouraged, as it contains sorbitol that commonly causes diarrhea and cramping in children. If children have difficulty taking medications, open capsules and crush tablets, and then mix in soft foods or liquids. Examples (but not limited to) of foods include yogurt, thick soups or grain porridges, apple sauce, maple syrup, hot fudge or chocolate sauce, nut or seed butters, jams and jellies, pureed vegetables or fruits. Layer the food and drug on a spoon with a small amount of food only, so all the medication can be finished promptly and teach the child to take the contents of the spoon without chewing.[17]

For information on ordering drugs, see the Supplies, Materials, and Services section.

For consultation regarding the treatment of LTBI in people who have been in contact with a case who is resistant to drugs in the recommended regimens, contact the Wisconsin Tuberculosis Program at 608-261-6319.

Side effects and adverse reactions

The patient should be monitored by a registered nurse 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 periodically. See Table 8.4**: Monitoring and Interventions for Side Effects and Adverse Reactions** in this section.

As is true with all medications, combination chemotherapy for TB is associated with a predictable incidence of adverse effects, some mild, some serious.[18]

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 the drugs with the highest evidence rating not be stopped without adequate justification.[19] 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.[20] In addition, proper management of more serious adverse reactions often requires expert consultation.[21]

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

Basic monitoring steps

1. All health care workers providing treatment for LTBI should be familiar with the American Thoracic Society (ATS) and Centers for Disease Control and Prevention (CDC) guidelines.
    a. All jurisdictions should follow the national monitoring guidelines identified in the current treatment guidelines for treatment of LTBI, Treatment Regimens for Latent TB Infection and "Guidelines for the treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020."
2. While on treatment, all patients should be evaluated in person, at baseline (before starting treatment), and then at least every month for side effects and adverse reactions.
3. The common side effects of and adverse reactions to drugs used to treat for LTBI are listed in Table 8.3: **Reporting Reactions to Antituberculosis Medications**. Educate patients to stop the medicine and promptly report any of the symptoms or signs listed in Table 3 or any unexplained illness to the prescribing clinic immediately.
    a. If a patient reports a potentially serious adverse reaction, based on severity call 911 or direct them to the ED or call the patient's provider immediately. After the patient is

safe, alert the state TB program by calling the Wisconsin Tuberculosis Program at 608-261-6319.

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

4. If you suspect that an antituberculosis drug may be causing a particular side effect or adverse reaction:
   a. Refer to Table 8.4: **Monitoring and Interventions for Side Effects and Adverse Reactions** below.
   b. Consult with the patient's medical provider and contact the Wisconsin Tuberculosis Program at 608-261-6319.
5. If you suspect that an antituberculosis drug may be interacting with other medications that the patient is taking, refer to NTCA guidelines on LTBI.
6. Document the following patient information:
   a. Review of symptoms, test results, side effects, and adverse reactions
   b. Education given
   c. Refill provided
   d. Description of any problems encountered, and action taken for that visit
   e. Next appointment

Reporting reactions

The table below is intended for use by a health care worker who performs case management services. The health care worker should instruct the patient to report to the provider the side effects and adverse reactions listed in Table 8.3.

If a patient reports to a health care worker a potentially serious adverse reaction, the health care worker should, depending on severity of the reaction, call 911 or direct the patient to the ED, call the patient's provider immediately, and once patient is safe, alert the Wisconsin Tuberculosis Program at 608-261-6319.

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

Table 8.3: Reporting reactions to antituberculosis medications[22]

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	Report the following signs and symptoms to the patient's provider within 24 hours: • Anorexia

symptoms suggest side effects, including hepatotoxicity: • Jaundice • Dark urine • Vomiting • Abdominal pain • Fever • Ototoxicity • Visual changes • Vestibular changes • Marked clinical rash In consultation with the provider, instruct the patient to stop TB medications until evaluated by the provider.	• Nausea • Malaise • Peripheral neuropathy: tingling or burning sensation in hands or feet • Rashes
* These lists are not all-inclusive. For a complete list, refer to the current guidelines for treatment of TB and LTBI: Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020 Testing and Treatment of Latent Tuberculosis Infection in the United States: A Clinical Guide for Health Care Providers and Public Health Programs	

Source: California Department of Health Services (CDHS)/California Tuberculosis Controllers Association (CTCA). TB case management—core components. *CDHS/CTCA Joint Guidelines* [CTCA Web site]. 2011 Available at: CDPH-CTCA Joint Guidelines - CTCAMonitoring for Side Effects and Adverse Reactions by Antituberculosis Drug

Refer to **Table 8.4**: **Monitoring and Interventions for Side Effects and Adverse Reactions** to do the following:

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

Table 8.4: Monitoring and interventions for side effects and adverse reactions[23,24,25]

Antituberculosis drug	Side effects/ adverse reactions	Monitoring	Comments
Isoniazid (INH)	• Rash • Hepatic enzyme elevation • Hepatitis • Peripheral neuropathy • Mild central nervous system	Clinical monitoring monthly Liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and serum bilirubin) at baseline in selected	Hepatitis risk increases with age and alcohol consumption. Pyridoxine (vitamin B6, 10–25 mg/d) might prevent peripheral neuropathy and central nervous system

Antituberculosis drug	Side effects/ adverse reactions	Monitoring	Comments
	effects	cases HIV infection, history of liver disease, alcoholism, and pregnancy) Repeat measurements if Baseline results are abnormal If the patient is pregnant, in the immediate postpartum period, or at high risk for adverse reactions, monitor more frequently. If patient has symptoms of adverse reactions, monitor more frequently.	effects. Serum concentrations of phenytoin, disulfiram (Antabuse), and carbamazepine may be increased in people taking INH. Measure serum concentrations of phenytoin and carbamazepine in patients receiving INH (with or without rifampin) and adjust the dose if necessary.
3HP (Isoniazid/ Rifapentine)	• Rash • Fever • Pruritus • Hypersensitivity • Hypotension • Dizziness or nausea/vomiting • Syncope/ fainting • Flu-like syndrome • Thrombocytopenia • Shortness of Breath • Wheezing • Acute bronchospasm • Urticaria • Petechiae • Purpura • Conjunctivitis • Angioedema • Shock • Life-threatening events	Evaluate the patient at a monthly visit to identify adverse events and to assess treatment adherence. Some experts recommend baseline complete blood count (CBC) due to a possible adverse reaction decreasing the white blood cell count and platelet counts and comprehensive metabolic panel (CMP). Hepatitis panel may also be obtained. Baseline hepatic chemistry is recommended for patients with these specific conditions: • People with HIV • Liver disorders • In the postpartum period (3 or less months after delivery) • Regular alcohol or injection drug use In addition, consider baseline	For mild to moderate adverse events such as rash, fever, and pruritis, continue to monitor the patient closely with a low threshold for discontinuing treatment. For the remaining adverse reactions listed, treatment should be discontinued and prompt clinical assessment with appropriate lab monitoring should occur.

Antituberculosis drug	Side effects/ adverse reactions	Monitoring	Comments
		hepatic chemistry for older people and for people taking medications for chronic medical conditions. If baseline hepatic chemistry testing is abnormal, determine the risk vs. benefit of treatment. If a decision is made to treat, continue with subsequent hepatic chemistry testing until the patient is determined to be stable. If baseline hepatic chemistry is within normal limits and the treatment is self-administered, some experts recommend additional laboratory monitoring monthly to ensure that the patient does not develop hepatotoxicity. When or after the final dose is taken, conduct a final visit with the patient to monitor for any adverse events.	

Antituberculosis drug	Side effects/ adverse reactions	Monitoring	Comments
Rifampin (RIF)	• Rash • Gastrointestinal upset • Hepatitis • Fever • Bleeding problems • Thrombocytopenia • Renal failure • Flu-like symptoms • Orange-colored body fluids (secretions, urine, tears)	Complete blood count, platelets, and liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and serum bilirubin) at baseline in selected cases (HIV infection, history of liver disease, alcoholism, and pregnancy) Repeat measurements if Baseline results are abnormal 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. Contraindicated or should be used with caution when administered with protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs). Reduces levels of many drugs (for example., PIs, NNRTIs, methadone, dapsone, ketoconazole, coumadin derivatives, hormonal contraceptive, digitalis, sulfonylureas, diazepam, ß-blockers, anticonvulsants, and theophylline). For more information, refer to Testing and Treatment of Latent Tuberculosis Infection in the United States: A Clinical Guide for Health Care Providers and Public Health Programs Because information regarding rifamycin drug interactions is evolving rapidly, consult the CDC's Division of Tuberculosis "News and Updates" Web page for the most up-to-date information. Colors body fluids orange. May permanently discolor soft contact lenses.

Adherence

Monitor patients for adherence to self-administered LTBI treatment regimens at least every month throughout treatment.[26] It is difficult to identify who will and who will not be able to adhere to the prescribed regimen for a variety of reasons[27] If patients do not take medicine as directed, the effectiveness of the regimen decreases, and the patient will be at greater risk of progressing to disease in the future and of infecting others. For this reason, the state TB program requires DOT for all patients on intermittent regimens such as 3HP, if supplied via the dispensary pharmacy.

Monthly assessment of adherence

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

- 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.
- Have patients bring their bottle of medicine to the refill appointment and count how many pills are left.
- If adherence barriers are identified, include patients in the problem-solving process.
    - Ask patients why they think that doses are missed and what could be done better: change the time of day or the location where they keep or take their pills.
    - Address any side effects with the patient’s provider and consult the state TB program on nursing interventions that might assist in alleviating some common side effects.
    - Review with patients what they believe is their risk of developing TB if medicine is not taken. Provide education again, as needed.
    - Mutually agree upon a plan to improve adherence.
    - Utilize incentives and enablers via the TB program Treatment Assistance Program (TAP).

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

Directly observed therapy

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

DOT is mandatory for any intermittent regimen (for example, twice weekly INH, 3HP) obtained through the Wisconsin TB Dispensary Program.

DOT is strongly encouraged for those with the greatest risk for progression to TB disease:

- Young children who are recent contacts to infectious cases
- People living with HIV

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

For more information on adherence strategies for different developmental stages, see the Rutgers Global Tuberculosis Institute’s Management of Latent Tuberculosis Infection in Children and Adolescents: A Guide for the Primary Care Provider.

Completion of therapy

Determine whether and when therapy is completed based upon the total number of doses administered, not on the duration of therapy. When patients have had lapses in therapy but are still 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:

- Individual’s risk for developing TB disease.
- Total number of doses of LTBI treatment administered.
- Time elapsed since the last dose of treatment for LTBI.
- Patient adherence issues (previous attempts at completion, willingness to continue, appropriateness of regimen type and duration).

Give patients with adherence barriers, who are 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) with a shorter regimen such as 3HP and evaluate the use of incentives and enablers.[28]

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

All contacts who are being treated for infection should be seen by a health care provider at least every month or more often. Incentives and enablers are recommended as aids to adherence,

and the health care provider should educate the patient about TB, its treatment, and the signs of adverse drug effects at each patient encounter.[29] Table 8.5 describes the duration of therapy and the number of doses that patients are required to take to complete therapy as well as the time frame within which the total number of doses must be administered for completion of therapy.

Table 8.5: Recommended regimens for completion of therapy[30]

Regimen	Age	Duration of therapy	Number of doses	Must be administered within
INH and RPT once weekly	Adult and children over 2 years old	3 months	12	16 weeks
INH daily	Adult and child	9 months	270	12 months
INH daily	Adult	6 months	180	9 months
INH twice weekly	Adult and child	9 months	76	12 months
INH twice weekly	Adult	6 months	52	9 months
RIF daily	Adult Child	4 months 6 months	120 180	6 months 9 months
Definitions of abbreviations: INH = isoniazid; RIF = rifampin.				

Sources: CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2021;49(No. RR-6):26–27; CDC. Regimens. In: Chapter 4: treatment of LTBI. *Core Curriculum on Tuberculosis (2021)* [Division of Tuberculosis Elimination Web site]. Updated 2021. Available at: *https://www.cdc.gov/tb/hcp/education/core-curriculum-on-tuberculosis.html*

Make every effort to encourage patients to adhere to the LTBI treatment regimen. The health care provider should contact patients who interrupt therapy and are at high risk of developing TB disease (for example, contacts of patients with infectious TB, patients with HIV, or patients with other risk for progression to TB disease) for reevaluation.[31]

For consultation regarding completion of therapy and factors to consider when restarting treatment, contact the Wisconsin Tuberculosis Program at 608-261-6319.

Treatment in special situations

Treatment of LTBI in the following situations requires special consideration:

- HIV infection

- Alcohol use disorder or excessive alcohol consumption
- Pregnancy and breastfeeding

Human immunodeficiency virus and latent tuberculosis infection

Treatment of LTBI in a person with HIV infection can be extremely complicated. Before treatment is initiated, contact the Wisconsin Tuberculosis Program at 608-261-6319 for consultation.

HIV infection is the strongest known risk factor for the progression of LTBI to TB disease. People who are co-infected with HIV and 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% yearly risk of developing TB disease. Patients with only LTBI have a 10% lifetime risk of developing TB disease.

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.

Resources

CDC. "TB Guidelines: TB & HIV", Available here: https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/whats-new

CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2021;49(No. RR-6):26–27; CDC. *Core Curriculum on Tuberculosis: What the Clinician Should Know*

Centers for Disease Control and Prevention. Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. *MMWR Morb Mortal Wkly Rep*. 2004;53(2):37.

Alcohol use disorder and excessive alcohol consumption

For information on treating patients for LTBI who also are known or suspected to have an alcohol use disorder, who drink heavily, or who regularly consume alcohol, see the "Alcohol Use Disorder" topic under Special Considerations in the Treatment of Tuberculosis Disease section.

Pregnancy and breastfeeding

Pregnant people should be targeted for testing only if they have a specific risk factor for LTBI or for progression of LTBI to disease. For people 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,

LTBI treatment should not be delayed on the basis of pregnancy alone, even during the first trimester. Pregnant people can take any of the following regimens for the treatment of LTBI:

- 4-month daily regimen of RIF (4R)
- 3-month daily regimen of INH and RIF (3HR)
- 6- or 9-month daily regimen of INH (6H or 9H)

Pregnant people taking INH should receive pyridoxine supplementation. The 3HP regimen is not recommended for pregnant people or people expecting to become pregnant during the treatment period because its safety during pregnancy has not been studied.

Breastfeeding is not contraindicated when the parent is being treated for LTBI. However, infants whose breastfeeding parents are taking INH should receive supplemental pyridoxine. Note that the amount of INH provided by breast milk is inadequate for treatment of the infant.[32]

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Resources and references

Resources

Whom to treat

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Side effects and adverse reactions

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Adherence

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This 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 health care worker
- Communication and problem-solving skills
- Education of the patient
- Using interpreters when needed
- Using incentives and enablers
- Using directly observed therapy (DOT)

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