Chapter 6

Treatment of Latent Tuberculosis Infection

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Introduction

Purpose

Use this section to understand and follow national and Nevada 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. Persons 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 persons diagnosed with LTBI is an essential part of controlling and eliminating TB in the United States. To control and prevent TB, our healthcare resources and efforts in Nevada should be directed to meet the priorities outlined in the most current 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 persons with LTBI at risk for progression to TB.[3]

Screening only those individuals who have an increased risk of having been infected with TB, known as targeted testing for LTBI, is a strategic component of TB control that identifies persons at high risk for developing TB who would benefit by treatment of LTBI, if detected. Persons with increased risk for developing TB include those who have had recent infection with *M. tuberculosis* and those who have clinical conditions that are associated with an increased risk for progress of LTBI to active TB.

Healthcare 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 persons who are determined to be candidates for the treatment of LTBI.

Whom to Treat

Persons at High Risk for TB Infections and Progression to TB Disease

Determine whom to treat for latent tuberculosis infection (LTBI). Certain groups are at high risk of developing tuberculosis (TB) disease once infected (see table 1), so make every effort to begin appropriate treatment and to ensure those persons complete the entire course of treatment for LTBI.[6]

Table 1: PERSONS AT HIGH RISK FOR TUBERCULOSIS INFECTIONS AND PROGRESSION TO TB DISEASE

For Tuberculosis Infection	*For Progression to Tuberculosis Disease*
• **High-priority contacts such as housemates or co-workers or contacts of persons (patients) who have smear-positive pulmonary or laryngeal tuberculosis (TB)** • **Infants, children, and adolescents exposed to adults in high-risk categories** • **Recent immigrants (<5 years) from countries with high incidence of TB. Asian, African, Latin American, and Eastern European countries have TB rates 5–30 times higher than U.S. rates, and an increasing percentage of all TB cases diagnosed in the U.S. is occurring among immigrants from those countries** • **Recent immigrants from Mexico** • **Migrant workers** • **Persons who have recently spent over 3 months in high-incidence countries (such as missionaries)** • **Native Americans** • **Persons with high rates of TB transmission:** - **Injection (IV) drug users** - **Homeless persons** • **Persons with Human Immunodeficiency Virus (HIV) infection** • **Persons living or working in institutions with individuals at risk for TB such as:** - **Hospitals, especially staff in nursing,**	• Persons with HIV infection • Infants and children aged <5 years • Persons infected with *Mycobacterium tuberculosis* within the previous 2 years • Persons with a history of untreated or inadequately treated TB disease • Persons with Chest x-ray findings consistent with previous TB disease • Persons who use alcohol or illegal drugs (such as injection drugs or crack cocaine) • Persons who have one or more of the following clinical or immunocompromising conditions: - Silicosis - Diabetes mellitus - End-Stage Renal Disease (ESRD), chronic renal failure, or patients on hemodialysis - Some hematologic disorders (e.g., leukemias and lymphomas), and other malignancies (e.g., head, neck carcinoma, or lung cancer) - Body weight ≥10% below ideal body weight - Prolonged corticosteroid use, and the use of other immunosuppressive treatments (e.g., prednisone or tumor

emergency departments, and laboratories - **Long-term care facilities** - **Homeless shelters** - **Residences for Acquired Immunodeficiency Syndrome (AIDS) patients** - **Correctional facilities**	necrosis factor-alpha [TNF- α] antagonists) - Organ transplantation - Gastrectomy, chronic malabsorption syndromes, and jejuno-ileal bypass

For more information on targeted testing, see the "Targeted Testing for Latent Tuberculosis Infection" at: http://www.cdc.gov/mmwr/PDF/rr/rr4906.pdf

High-risk contacts (under five years of age or the immunocompromised) should be started promptly on treatment for LTBI (window prophylaxis). For more information on time frames, see the "Time Frames for Contact Investigation" topic in the Contact Investigation section of this manual, or refer to "Guidelines for Investigation of Contacts of Persons with Infectious Tuberculosis" at: http://www.cdc.gov/mmwr/pdf/rr/rr5415.pdf

Several treatment regimens are available for the treatment of LTBI, and providers should discuss treatment options with their patients.[7]

For more information on treatment of LTBI, visit the Centers for Disease Control and Prevention (CDC) webpages, "Latent Tuberculosis Infection: A Guide for Primary Health Care Providers" at: https://www.cdc.gov/tb/publications/ltbi/treatment.htm (page last reviewed March 2019).
Additionally, updated recommended short-course, rifamycin-based LTBI regimens are available from the CDC, "Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020", at: https://www.cdc.gov/mmwr/volumes/69/rr/rr6901a1.htm

For consultation regarding the treatment of LTBI, contact the local or state TB program. Contact information may be found in this TB Manual, *Introduction*, Chapter 1, section "Roles, Responsibilities, and Contact Information," pages 1.14 – 1.20; or, visit DPBH TB Program webpage at: http://dpbh.nv.gov/Programs/TB/Tuberculosis_(TB)_Prevention,_Control_and_Elimination_Program_-Home/

Patients should be provided with a permanent record of their tuberculin skin test, chest x-ray and treatment status. Examples and templates of LTBI cards are available at:
http://globaltb.njms.rutgers.edu/downloads/products/LTBICardProduct.pdf

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.[8] 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[9] (These include children under 5 years of age, and those who are HIV-infected, immunocompromised, or persons having other underlying disease processes). Persons who are susceptible and/or vulnerable to TB disease are candidates for window period treatment, which is administering treatment for presumptive TB infection during the interval between possible infection and detectable skin test reactivity or positive blood testing (interferon gamma release assay [IGRA]). The National Tuberculosis Controllers Association (NTCA) and the CDC recommends that the window period be estimated to be eight to ten weeks from last exposure.[10] The following contacts with initially negative TST or IGRA test results should receive window period treatment for LTBI after TB disease has been ruled out by clinical examination and chest radiograph:

1. Contacts younger than five years of age (with highest priority given to those under three years)
2. 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 (e.g., with HIV infection), a full 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, treatment for LTBI should be continued if the contact is:

1. Less than 5 years old
2. Aged 5-15 years, at the clinician's discretion
3. Those who are HIV-seropositive or otherwise immunocompromised[11]

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.[12]

For information regarding the use of IGRA's, see CDC, NTCA " Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis" at: http://www.cdc.gov/mmwr/pdf/rr/rr5415.pdf and the "Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection --- United States, 2010" at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.htm?s_cid=rr5905a1_w

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 on their chest radiographs that are consistent with old TB
- Persons with organ transplants and other immunosuppressed patients (receiving the equivalent of 15 mg or more/day of prednisone for at least one month)[13]

Tuberculin Skin Test Results of 10 mm or More

Persons 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:

- Foreign-born persons who have recently arrived (within five years) from countries with a high TB incidence or prevalence, or persons who have recently traveled to these countries (most countries in Africa, Asia, Latin America, Eastern Europe, and Russia [formerly the USSR])
- Persons who are alcoholics, who inject drugs, or who use other high-risk substances, such as crack cocaine
- Residents and employees of high-risk congregate settings, such as correctional institutions, homeless shelters, long-term residential care facilities (e.g., nursing homes, mental institutions), hospitals, and other healthcare facilities
- Mycobacteriology laboratory personnel
- Persons 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 [e.g., leukemias and Hodgkin's disease], other specific malignancies [e.g., 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 five years of age
- Infants, children and adolescents exposed to adults at high risk for developing TB disease
- Locally identified groups at high risk[14]

Tuberculin Skin Test Results of 15 mm or More[15]

Persons 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 previously listed.

- Persons with no known risk factors for TB disease
- Healthcare 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[16]

* For healthcare 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 (instead of ≥10 mm) is considered to be positive. Although a result of ≥10 mm 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.[17]

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 who are considered at increased risk for progression to TB disease should be offered treatment.[18]

There are several treatment regimens available for the treatment of LTBI, and providers should discuss options with patients. Persons who are at especially high risk for TB, and either are suspected of nonadherence 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.

High-risk contacts (under 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" section in *Contact Investigation*, Chapter 8 of this manual.

Regimens

Identify an appropriate regimen for the patient using the national guidelines provided in Table 2 below.

The four treatment regimens for latent TB infection (LTBI) use isoniazid (INH), rifapentine (RPT), or rifampin (RIF). Treatment must be modified if the patient is a contact of an individual with drug-resistant TB disease. Consultation with a TB expert is advised if the known source of TB infection has drug-resistant TB.

Table 2: Latent TB Infection Treatment Regimens

Source: CDC. Treatment Regimens for Latent Tuberculosis Infection (LTBI), (Feb. 2020); https://www.cdc.gov/tb/topic/treatment/ltbi.htm

Drug(s)	Duration	Dose	Frequency	Total Doses
Isoniazid (INH)* and Rifapentine (RPT)†	3 months	Adults and Children aged 12 years and older: INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum RPT: 10–14.0 kg 300 mg 14.1–25.0 kg 450 mg 25.1–32.0 kg 600 mg 32.1–49.9 kg 750 mg ≥50.0 kg 900 mg maximum Children aged 2–11 years ***(new):*** INH*: 25 mg/kg; 900 mg maximum RPT†: as above	Once weekly	12

Drug(s)	Duration	Dose	Frequency	Total Doses
Rifampin (RIF)[§]	4 months	Adults: 10 mg/kg Children: 15–20 mg/kg[‖] Maximum dose: 600 mg	Daily	120
Isoniazid (INH)* and Rifampin)[§]	3 months	Adults: INH*: 5 mg/kg; 300 mg maximum RIF[§]: 10 mg/kg; 600 mg maximum Children: INH*: 10-20 mg/kg; 300 mg maximum RIF[§]: 15-20 mg/kg; 600 mg maximum	Daily	90
Isoniazid (INH)	6 months	Adults: 5 mg/kg Children: 10–20 mg/kg[¶] Maximum dose: 300 mg	Daily	180
		Adults:15 mg/kg Children: 20–40 mg/kg[¶] Maximum dose: 900 mg	Twice weekly[‡]	52
	9 months	Adults: 5 mg/kg Children: 10–20 mg/kg[¶] Maximum dose: 300 mg	Daily	270
		Adults: 15 mg/kg Children: 20–40 mg/kg[¶] Maximum dose: 900 mg	Twice weekly[‡]	76

*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.

Note: Due to the reports of severe liver injury and deaths, CDC recommends that the combination of rifampin (RIF) and pyrazinamide (PZA) should generally not be offered for the treatment of latent TB infection.

Dosages

Once the appropriate regimen has been identified, refer to Table 3 for instructions on dosages for each drug. The information in Table 3 is taken from ATS, CDC, and Infectious Diseases Society of America (IDSA) guidelines.

Table 3: RECOMMENDED DOSAGES[19,20]

Drug	Preparation	Adults/ Children	Daily	Twice a Week
INH	Tablets (50 mg, 100 mg, 300 mg); elixir (50 mg/5 ml)	Adults (max.)	5 mg/kg (300 mg)	15 mg/kg (900 mg)
		Children (max.)	10–15 mg/kg (300 mg)	20–30 mg/kg (900 mg)
RIF	Capsule (150 mg, 300 mg); powder may be suspended for oral administration	Adults (max.)	10 mg/kg (600 mg)	10 mg/kg (600 mg)
		Children (max.)	10–20 mg/kg (600 mg)	10–20 mg/kg (600 mg)
Definitions of abbreviations: INH = isoniazid; RIF = rifampin.				

Source: ATS, CDC, IDSA. Treatment of tuberculosis. *MMWR* 2003;52(No. RR-11):4; CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):28–29.

The use of INH elixir is discouraged, as it commonly causes diarrhea and cramping in children. If children have difficulty taking medications, open capsules and crush tablets, and then mix the drugs into soft foods or liquids. Possible foods include yogurt, maple syrup, hot fudge, Nutella, apple sauce, jams and jellies, spinach baby food, and chocolate whipped cream, etc. Layer the food and drug on a spoon, and teach the child to take the contents of the spoon without chewing.[21]

Ann Loeffler, M.D. pediatrician and faculty consultant with the Francis J. Curry National Tuberculosis Center suggests the following for methods to deliver the medications:

"Mix with soft vehicle and deliver in one or two spoonfuls – followed by food without medicine to clear the palate. The best vehicles seem to be strong flavored and darkly colored such as:

- Chocolate sauces, pudding, fudge sauce, ice cream, etc.
- Jelly or marmalade (the texture hides the powder granularity
- Apple sauce or berry-sauce (better to hide the red rifampin color)
- Nutella or peanut butter
- Cream cheese or chili con carne
- Whatever the health provider and family can make work."

For consultation regarding the treatment of LTBI in persons who have been in contact with a case who is resistant to drugs in the recommended regimens, contact the Francis J Curry Warm line at 877-390-6682, or, 415-502-4700.

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. Blood chemistries and a complete blood count (CBC), aspartate aminotransferase (AST)/alanine aminotransferase (ALT), or other tests based on specific drugs should be done periodically. See Table 5**: Monitoring and Interventions for Side Effects and Adverse Reactions** in this chapter, pages 6.14 – 6.15.

As is true with all medications, combination chemotherapy for tuberculosis (TB) is associated with a predictable incidence of adverse effects, some mild, some serious.[22]

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.[23] 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.[24] In addition, proper management of more serious adverse reactions often requires expert consultation.[25]

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

Basic Monitoring Steps

1. All healthcare workers providing treatment for latent tuberculosis infection (LTBI) should be familiar with the American Thoracic Society (ATS)/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, “Targeting Tuberculin Testing and Treatment of Latent Tuberculosis Infection,” pages 26–29 at: http://www.cdc.gov/mmwr/PDF/rr/rr4906.pdf .
    b. It is also important to check for guideline updates posted on the CDC’s Division of Tuberculosis Elimination home page at : http://www.cdc.gov/tb/default.htm and the list of guidelines by date at: http://www.cdc.gov/tb/publications/guidelines/default.htm

2. While on treatment, all patients should be evaluated in person, at baseline (before starting treatment), and then at least monthly thereafter, for side effects and adverse reactions. Providing only a 30-day supply of medications at a time allows healthcare providers to conduct in person evaluations every time a prescription refill is required.
3. The common side effects of and adverse reactions to drugs used to treat for LTBI are listed in Table 4: **Reporting Reactions to Antituberculosis Medications**. Educate patients to stop the medicine and promptly report any of the symptoms or signs listed in Table 4 or any unexplained illness to the prescribing clinic immediately.
    a. If a patient reports a potentially serious adverse reaction, call the patient's provider immediately and/or follow your institutions protocol and act according to the provider's instructions.
    b. If a patient reports a potentially less severe side effect, follow your institution's protocol 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** below.
    b. Consult with the patient's medical provider, Local Health Authority, or the NV State DPBH TB Program.
5. If you suspect that an antituberculosis drug may be interacting with other medications that the patient is taking, refer to pages 45–47 in the "Treatment of Tuberculosis" (*MMWR* 2003;52[No. RR-11]) at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf.
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 healthcare worker who performs case management services. The healthcare worker should instruct the patient to report to the provider the side effects and adverse reactions listed in Table 4.

If a patient reports to a healthcare worker a potentially serious adverse reaction, the healthcare worker should instruct the patient to discontinue the medications and call the patient's provider immediately and take follow-up action according to the provider's instructions.

If a patient reports to a healthcare worker a potentially less severe side effect, the healthcare worker should follow their institutions protocol and/or call the patient's provider immediately and monitor the patient.

Table 4: REPORTING REACTIONS TO ANTITUBERCULOSIS MEDICATIONS[26]

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: ▪ Jaundice ▪ Dark urine ▪ Vomiting ▪ Abdominal pain ▪ Fever ▪ Visual changes ▪ Marked clinical rash 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: ▪ Anorexia ▪ 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, "Treatment of Tuberculosis" (*MMWR* 2003;52[No. RR-11]) at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf and an Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy, available at: http://ajrccm.atsjournals.org/cgi/reprint/174/8/935.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]. 1998:9. Available at: http://www.ctca.org/guidelines/index.html . Accessed July 11, 2006.

The two-month regimen of rifampin and pyrazinamide is no longer recommended due to serious and fatal hepatitis associated with this regimen.[27]

At present, the CDC Division of Tuberculosis Elimination (DTBE) is requesting health departments, hospices, hospitals, jails, prisons, and private medical offices to 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 that occurred after January 1, 2004, to DTBE by calling 404-639-840, or, report via http://www.fda.gov/Safety/MedWatch/HowToReport/ucm085568.htm.

Also, if not done previously, please call DPBH TB Program by calling 775-684-5936 to report severe adverse events

Monitoring for Side Effects and Adverse Reactions by Antituberculosis Drug

Refer to Table 5**: 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 5: MONITORING AND INTERVENTIONS FOR SIDE EFFECTS AND ADVERSE REACTIONS[28,29,30]

Antituberculosis Drug	*Side Effects/ Adverse Reaction*	*Monitoring*	*Comments*
Isoniazid (INH)	▪ Rash ▪ Hepatic enzyme elevation ▪ Hepatitis ▪ Peripheral neuropathy ▪ Mild central nervous system effects	Clinical monitoring monthly Liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and serum bilirubin) at baseline in selected cases ((human immunodeficiency virus [HIV] infection, history of liver disease, alcoholism, and pregnancy) Repeat measurements if ▪ 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	Hepatitis risk increases with age and alcohol consumption. Pyridoxine (vitamin B6, 10–25 mg/d) might prevent peripheral neuropathy and central nervous system effects. 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. More information is available in the Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy, available at: http://ajrccm.atsjournals.org/cgi/reprint/174/8/935.pdf

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 (human immunodeficiency virus [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 (e.g., PIs, NNRTIs, methadone, dapsone, ketoconazole, coumadin derivatives, hormonal contraceptive, digitalis, sulfonylureas, diazepam, ß-blockers, anticonvulsants, and theophylline). Colors body fluids orange. May permanently discolor soft contact lenses. 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 . 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.

Adherence

Monitor patients for adherence to self-administered latent tuberculosis infection (LTBI) treatment regimens at least monthly throughout treatment.[28] It is difficult to identify who will and who will not be adherent.[29] If patients do not take medicine as directed, the effectiveness of the regimen decreases, and the risk of drug resistance increases as well as the risk of future progression to active TB disease and transmission to others.

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. Request patients bring their bottle of medicine or blister pack to the refill appointment, and count how many pills are left.
3. If adherence problems are identified, (doses were missed) 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 TB if medicine is not taken. Provide education again, as needed.
    d. Mutually agree upon a plan to improve adherence.
    e. Praise patients for cooperation.
4. If adherence seems to be good, acknowledge and encourage patients’ success.

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 (once, twice or three times weekly regime).
- DOT is strongly encouraged for those with the greatest risk for progression 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 *Case Management*, Chapter 7, of this manual.

For more information on adherence strategies for different developmental stages, see Appendix C in the New Jersey Medical School National Tuberculosis Center's *Management of Latent Tuberculosis Infection in Children and Adolescents: A Guide for the Primary Care Provider* (New Jersey Medical School Global Tuberculosis Institute Web site; 2004) at: http://globaltb.njms.rutgers.edu/downloads/products/PediatricGuidelines%20(Screen).pdf

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.

Table 6 below 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 6: RECOMMENDED REGIMENS FOR COMPLETION OF THERAPY[30]

Regimen	Age	Duration of Therapy	Number of Doses	Must Be Administered Within
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
INH, Rifapentine once weekly	Adult and child	12 weeks (3 months)	12	Seek expert opinion Curry International TB Center 415-502-4700
Definitions of abbreviations: INH = isoniazid; RIF = rifampin.				

Sources: CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):26–27; CDC. Regimens. In: Chapter 6: treatment of LTBI. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Available at: https://www.cdc.gov/tb/education/corecurr/index.htm . Accessed February 1, 2007.

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 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, etc.)

Give nonadherent patients who are at very high risk of developing TB disease every opportunity to complete treatment for LTBI. Consider these patients for intermittent therapy with DOT and evaluate the use of incentives and enablers.[31]

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 face-to-face by a healthcare provider at least monthly. 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.[32]

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, HIV-infected patients, or TB Class 4 patients) for reevaluation.[33]

Treatment in Special Situations

Treatment of LTBI in the following situations requires special consideration:

- Human immunodeficiency virus (HIV) infection
- Alcoholism
- Pregnancy and breastfeeding

Human Immunodeficiency Virus and Latent Tuberculosis Infection

Treatment of LTBI in a person with HIV infection can be extremely complicated. Consultation with experienced HIV/TB physician or case manager is suggested.

HIV infection is the strongest known risk factor for the progression of LTBI to 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 seven to ten percent yearly risk of developing TB disease. Patients with only LTBI have a ten percent lifetime risk of developing TB disease.

High-risk contacts (less than five 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" section in *Contact Investigation*, Chapter 8 of this manual, or see "Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis" at: http://www.cdc.gov/mmwr/pdf/rr/rr5415.pdf .

Resources

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Alcoholism

Alcohol-Related Treatment Complications

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

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

- **Immunosuppression:** 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.[34] However, studies have shown that “alcohol consumption is a major risk factor for infection with opportunistic bacterial, viral, fungal, and parasitic pathogens.”[35]
- **Liver injury and death**: Drug-induced liver injury “may occur with all currently recommended regimens for the treatment of LTBI.”[36] In the treatment of TB disease, “the crucial efficacy of isoniazid, and particularly (INH), 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.”[37] However, it is not fully understood yet how antituberculosis medications cause drug-induced liver injury.[38] For persons taking isoniazid, an association of hepatitis was found with alcohol consumption, with rates being fourfold higher among persons consuming alcohol daily than among those who did not drink alcohol.[39] 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.[40,41] Pyrazinamide has slightly lower rates of hepatotoxicity than isoniazid or rifampin, but pyrazinamide can cause liver injury that may be severe and prolonged.[42] 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.[43] The most serious common adverse reaction, is defined as a serum aspartate aminotransferase (AST) level more than three times the upper limit of normal in the presence of symptoms or five times the upper limit of normal in the absence of symptoms.

- **Nonadherence to treatment:** Patients who do not complete LTBI treatment risk progression to TB disease, and those who do not complete treatment for TB disease risk relapse, development of drug-resistant TB, serious illness, and possible death. Barriers to adherence may be patient-related, such as conflicting health beliefs, alcohol or drug dependence, or mental illness, or they may be system-related, such as lack of transportation, inconvenient clinic hours, and lack of interpreters.[44] 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."[45] In a study of 237 patients in the Russian Federation undergoing DOT treatment for TB disease, "substance abuse was identified as the only factor that was strongly associated with non-adherence…These results suggest that DOT programs [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."[46] DOTS programs that have explicitly offered substance abuse treatment have reported better outcomes than those that have not.[47] 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.[48]

Liver Disease

Management of LTBI in patients with unstable or advanced liver disease is difficult. The likelihood of drug-induced hepatitis may be greater in these patients. The implications of drug-induced hepatitis for patients with marginal hepatic reserve are potentially serious, even life-threatening. Also, fluctuations in the biochemical indicators of liver function (with/without symptoms) related to the preexisting liver disease confound monitoring for drug-induced hepatitis.[49]

For all patients with preexisting liver disease, frequent clinical and laboratory monitoring should be performed to detect drug-induced hepatic injury.[50]

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 TB disease. Extensive use of isoniazid (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.

Breastfeeding is not contraindicated when the mother is being treated for LTBI. However, infants whose breastfeeding mothers are taking INH should receive supplemental pyridoxine. Note that the amount of INH provided by breast milk is inadequate for treatment of the infant.[51]

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Adherence

- CDC. Module 9: “Patient Adherence to Tuberculosis Treatment” (S*elf-Study Modules on Tuberculosis.* Division of Tuberculosis Elimination Web Site; 1999). Available at: https://www.cdc.gov/tb/education/ssmodules/default.htm

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