Treatment of Latent Tuberculosis Infection

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Quick Start Check List: Treatment of Latent Tuberculosis Infection

This check list is designed to assist public health nurses when treating a patient for latent tuberculosis infection. The tasks below should be performed by licensed nursing, medical, and laboratory staff. This check list requires understanding the instructions in the manual and familiarity with local protocols and standing orders. Required and recommended forms are available on the CDEpi Resource Page for Public Health. For more information on these forms, contact us at 406-444-0273.

Tasks for Diagnosis of Latent Tuberculosis Infection	Instructions and Forms
Diagnose latent tuberculosis infection (LTBI), ruling out tuberculosis (TB) disease	Instructions: Section 7: Diagnosis of Latent Tuberculosis Infection
Tasks for Treatment of Latent Tuberculosis Infection	**Instructions and Forms**
Select an appropriate treatment regimen: ☐ Assure that an appropriate treatment regimen, dosages, and duration are selected ☐ Assure that these special situations are considered: ▪ Human immunodeficiency virus (HIV) infection ▪ Alcoholism ▪ Pregnancy and breastfeeding	Instructions: Section 8: Treatment of Latent Tuberculosis Infection Topics: Treatment Regimens and Dosages (Tables 1 and 2), Treatment in Special Situations Required Forms: ▪ "LTBI Medicine Enrollment Form: State Provided Medicine Application" (required only if requesting medications from the state program) Recommended Forms: ▪ "Biochemistry Data Sheet" ▪ "Treatment of LTBI Education Form" ▪ "Directly Observed Therapy Agreement" (if on directly observed therapy)
Monitor the patient regularly: ☐ Assure that the patient is assessed at least monthly for ▪ Clinical follow-up ▪ Adherence to LTBI treatment ▪ Adverse reactions to LTBI treatment	Instructions: Section 8: Treatment of Latent Tuberculosis Infection Topics: Side Effects and Adverse Reactions (Tables 3 and 4), Adherence Recommended Forms: ▪ "Biochemistry Data Sheet" ▪ "Monthly LTBI Patient Assessment" ▪ "Directly Observed Therapy Form 1 - Treatment Record" (if on directly observed therapy) ▪ "Directly Observed Therapy Form 2 - Side Effects and Adverse Reactions" (if on directly observed therapy)

Tasks for Treatment of Latent Tuberculosis Infection	Instructions and Forms
Confirm the completion of treatment: ☐ Verify completion of treatment 6 to 9 months after treatment was started depending upon ▪ Regimen ▪ Adherence ▪ Number of weeks on treatment and/or ▪ Number of doses taken	Instructions: Section 8: Treatment of Latent Tuberculosis Infection Topic: Completion of Therapy (Table 3) Required Forms: ▪ "LTBI Medicine Enrollment Form: State Provided Medicine Application" (provide completion information on this form and submit it to the Montana TB Program if medications from the state program were used) Recommended Forms: ▪ "Monthly LTBI Patient Assessment" ▪ "Directly Observed Therapy Form 1 - Treatment Record" (if on directly observed therapy)

Introduction

Purpose

Use this section to understand and follow national and Montana 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; and
- 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.

To control and prevent TB, our healthcare resources and efforts in Montana 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 persons with LTBI at risk for progression to TB.[3]

Targeted tuberculin 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. 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]

Forms

Required and recommended forms are available on the CDEpi Resource Page for Public Health. For more information on these forms, contact us at 406-444-0273.

Whom to Treat

Determine whom to treat for latent tuberculosis infection (LTBI). Certain groups are at high risk of developing 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]

For a list of high-risk groups by tuberculin skin test (TST) results, see the Tuberculin Skin Test Results listings, which follow in this topic. 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. 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.[7]

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) publication "Treatment of Latent Tuberculosis Infection (LTBI)" (*TB Elimination Fact Sheet;* April 2006).

For consultation regarding the treatment of LTBI, call the Montana TB Program at 406-444-0273.

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 had TB disease.[9] Persons who are susceptible and/or vulnerable to TB disease are candidates for window period treatment, which is treatment for presumptive TB infection during the interval between infection and detectable skin test reactivity. The National Tuberculosis Controllers Association (NTCA) and the CDC recommend that the window period be estimated at 8 to 10 weeks.[10] The following contacts with initially negative TST results should receive treatment for LTBI after TB disease has been ruled out by clinical examination and chest radiograph:

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

If the second skin test 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 human immunodeficiency virus [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, 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. HIV-seropositive or otherwise immunocompromised.[11]
4. Persons known to be or suspected of being immunocompromised, such as HIV-infected persons, should be given treatment for LTBI regardless of the TST reaction.[12]

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

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 radiograph that is 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)[14]

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)**[the former 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 5 years of age
- Infants, children, and adolescents exposed to adults at high risk for developing TB disease
- Locally identified groups at high risk[15]

Tuberculin Skin Test Results of 15 mm or More[16]

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 already listed above.

- 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[17]

* 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.[18]

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 TB should be offered treatment.[19]

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.

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 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 1 below.

TABLE 1: RECOMMENDED DRUG REGIMENS FOR TREATMENT OF LATENT TUBERCULOSIS INFECTION IN ADULTS[20]

Drug	Interval and Duration	Comments	Rating* (evidence)†	
			HIV–	HIV+
INH	Daily for 9 months‡ §	In HIV-infected patients, INH may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-nucleoside reverse transcriptase inhibitors (NNRTIs).	A (II)	A (II)
	Twice weekly for 9 months‡ §	DOT must be used with twice-weekly dosing.	B (II)	B (II)
INH	Daily for 6 months§	This duration of therapy is not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children.	B (I)	C (I)
	Twice weekly for 6 months§	DOT must be used with twice-weekly dosing.	B (II)	C (I)
RIF	Daily for 4 months in adults Daily for 6 months in children	RIF is used for persons who are contacts of patients with INH-resistant, RIF-susceptible TB. Some antiretroviral drugs, such as the protease inhibitors and NNRTIs, have interactions with the rifamycins. Clinicians should consult Web-based updates or experts for the latest specific recommendations. The optimal length of RIF therapy in children with LTBI is not known; however, the American Academy of Pediatrics recommends 6 months of treatment.[21]	B (II)	B (III)

Definitions of abbreviations: DOT = directly observed therapy; HIV = human immunodeficiency virus; INH = isoniazid; LTBI = latent tuberculosis infection; RIF = rifampin.

* Strength of recommendation: A = Preferred, B = Acceptable alternative, C = Offer when A and B cannot be given.

† Quality of evidence: I = Randomized clinical trial data, II = Data from clinical trials that are not randomized or were conducted in other populations, III = Expert opinion.

‡ Recommended regimen for children <18 years of age.

§ Recommended regimen for pregnant women.

Source: CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):31.

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 P ra inamide for

Treatment of Latent Tuberculosis Infection" (*MMWR* 2003;52[No. 31]:735).

Dosages

Once the appropriate regimen has been identified, refer to Table 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.

TABLE 2: RECOMMENDED DOSAGES[22,23]

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 hide the drugs in soft foods or liquids. Possible foods are 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.[24]

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

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 Montana TB Program at 406-444-0275.

Side Effects and Adverse Reactions

The patient should be monitored by a registered nurse and/or clinician or case manager at least monthly for signs and symptoms of adverse reactions until treatment is completed. If a patient is symptomatic, the provider should be consulted and the patient monitored more frequently. Chemistries and complete blood count (CBC), aspartate aminotransferase (AST)/alanine aminotransferase (ALT), or other tests based on specific drugs should be done periodically. See Table 4**: Monitoring and Interventions for Side Effects and Adverse Reactions** in this section.

As is true with all medications, combination chemotherapy for tuberculosis is associated with a predictable incidence of adverse effects, some mild, some serious.[25]

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.[26] 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.[27] In addition, proper management of more serious adverse reactions often requires expert consultation.[28]

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

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.
   - **b.** It is also important to check for guideline updates posted on the CDC’s Division of Tuberculosis Elimination home page and the list of guidelines by date .
2. While on treatment, all patients should be evaluated in person, at baseline (before starting treatment), and then at least monthly for side effects and adverse reactions.

3. The common side effects of and adverse reactions to drugs used to treat for LTBI are listed in Table 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, call the patient's provider immediately, and alert the state TB program by calling the Montana TB Program at 406-444-0275.
   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 4: **Monitoring and Interventions for Side Effects and Adverse Reactions** below.
   b. Consult with the patient's provider and contact the Montana TB program for more information by calling 406-444-0275.
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]).

6. Document the following patient information:
   a. Review of symptoms, side effects, and adverse reactions (and any labs that were drawn)
   b. Education given
   c. Refill provided
   d. Description of any problems encountered and 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 3.

If a patient reports to a healthcare worker a potentially serious adverse reaction, the healthcare worker should call the patient's provider immediately and alert the Montana TB Program by calling 406-444-0275.

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

TABLE 3: 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: ▪ 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]).	

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. 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.[30]

At present, the Division of Tuberculosis Elimination (DTBE) urges 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 404-639-8401. Also, if not done previously, please call the Montana TB Program at 406-444-0275 to report severe adverse events.

Monitoring for Side Effects and Adverse Reactions by Antituberculosis Drug

Refer to Table 4**: Monitoring and Interventions for Side Effects and Adverse Reactions** to

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

TABLE 4: MONITORING AND INTERVENTIONS FOR SIDE EFFECTS AND ADVERSE REACTIONS[31,32,33]

Antituberculosis Drug	Side Effects/ Adverse Reactions	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.

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 (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). For more information, refer to “Section 7: Drug Interactions” on page 45 in “Treatment of Tuberculosis”. Because information regarding rifamycin drug interactions is evolving rapidly, consult the CDC’s Division of Tuberculosis “News and Updates” Web page to obtain the most up-to-date information. Colors body fluids orange. May permanently discolor soft contact lenses.

Adherence

Monitor patients for adherence to self-administered latent tuberculosis infection (LTBI) treatment regimens at least monthly throughout treatment.[34] It is difficult to identify who will and who will not be adherent.[35] 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.

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 education again, 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.

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.
- 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.

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)

Completion of Therapy

Determine whether and when therapy is completed based on 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 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 the use of incentives and enablers.[36]

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.[37]

Table 5 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.

TABLE 5: RECOMMENDED REGIMENS FOR COMPLETION OF THERAPY[38]

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
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. Accessed February 1, 2007.

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, human immunodeficiency virus (HIV)-infected patients, or TB Class 4 patients) for reevaluation.[39]

For consultation regarding completion of therapy and considerations to examine when restarting treatment in noncompliant patients, contact the Montana TB Program at 406-444-0275.

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. Before treatment is initiated, contact the Montana TB Program at 406-444-0275 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. Patients with only LTBI have a 10 percent 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: HIV/AIDS" (DTBE Web site; accessed February 2007).
- ATS, CDC. "Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection" (*MMWR* 2000;49[No. RR-6]:33).
- CDC. "Prevention and Treatment of Tuberculosis among Patients Infected with Human Immunodeficiency Virus: Principles of Therapy and Revised Recommendations" (*MMWR* 1998;47(No. RR-20).
- 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).
- Francis J. Curry National Tuberculosis Center. *TB & HIV: An Online Course for Clinicians* (Francis J. Curry National Tuberculosis Center Web site; 2001). This content is no longer available online.

Alcoholism

Isoniazid (INH) (and rifampin [RIF] when used secondarily to isoniazid for the treatment of LTBI) can cause hepatitis that may result in additional liver damage in patients with preexisting liver disease. However, because of the effectiveness of isoniazid in treating LTBI in high-risk persons, it is often desirable to proceed with treatment if at all possible, even in the presence of preexisting liver disease. This is particularly true if the patient is at high risk for progression to disease (i.e., a recent contact to an infectious TB case, HIV-infected, diabetic, or otherwise immunosuppressed).

Drug-induced hepatitis, 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.

Prior to treatment, serologic testing for hepatitis viruses A, B, and C should be performed particularly if the patient uses alcohol. Close monitoring—with symptom review and repeat measurements of AST and bilirubin—is essential in managing a patient with elevated serum AST.[40]

To monitor for hepatitis:

- Conduct clinical monitoring on the first visit, and repeat monthly to check for signs of hepatitis.
- Educate patients about symptoms and signs of adverse reactions, and instruct patients to stop treatment should symptoms occur. Symptoms of adverse reactions include anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesias of hands and feet, persistent fatigue, weakness or fever lasting three or more days, abdominal tenderness (right upper quadrant), easy bruising or bleeding, and arthralgia.[41]
- If the patient is on directly observed therapy (DOT), perform a symptom review at each DOT visit to assess if there are any side effects or adverse reactions.
- Have the patient sign and keep a copy of the “Treatment of LTBI Education Form.”

For assistance with decisions on treatment candidates and/or treatment of LTBI with alcoholism, contact the Montana TB Program at 406-444-0275.

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. 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.

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.[42]

Resources and References

Resources

Whom to Treat

- CDC. “Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection” (*MMWR* 2000;49[No. RR-6]).
- CDC. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001.

Treatment Regimens and Dosages

- CDC. “Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection” (*MMWR* 2000;49[No. RR-6]).
- 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]).
- CDC. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001.

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).
- 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]; 1999:15–17, 30–32). These modules are no longer available online.

Adherence

- CDC. Module 9: "Patient Adherence to Tuberculosis Treatment" (S*elf-Study Modules on Tuberculosis.* Division of Tuberculosis Elimination Web Site; 1999). These modules are no longer available online.

  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 (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).

References

[1] CDC. Treatment of latent tuberculosis infection: maximizing adherence. *TB Fact Sheets* [Division of Tuberculosis Elimination Web site]. April 2005:1. Accessed February 1, 2007.

[2] CDC. Summary. In: Chapter 6: treatment of LTBI. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Accessed July 3, 2006.

[3] ATS, CDC, IDSA. Controlling tuberculosis in the United States: recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. *MMWR* 2005;54(No. RR-12):15.

[4] CDC. Treatment of latent tuberculosis infection: maximizing adherence. *TB Fact Sheets* [Division of Tuberculosis Elimination Web site]. April 2005:1. Accessed February 1, 2007.

[5] CDC. Treatment of latent tuberculosis infection: maximizing adherence. *TB Fact Sheets* [Division of Tuberculosis Elimination Web site]. April 2005:1. Accessed February 1, 2007.

[6] CDC. Summary. In: Chapter 6: treatment of LTBI. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Accessed July 3, 2006.

[7] CDC. Summary. In: Chapter 6: treatment of LTBI. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Accessed July 3, 2006.

[8] ATS, CDC, IDSA. Controlling tuberculosis in the United States: recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. *MMWR,*2005;54(No. RR-12):39.

[9] ATS, CDC, IDSA. Controlling tuberculosis in the United States: recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. *MMWR* 2005;54(No. RR-12):10.

[10] CDC, NTCA. Guidelines for the investigation of contacts of persons with infectious tuberculosis: recommendations from the National Tuberculosis Controllers Association and CDC. *MMWR* 2005;54(No. RR-15):13.

[11] ATS, CDC, IDSA. Controlling tuberculosis in the United States: recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. *MMWR* 2005;54(No. RR-12):38.

[12] CDC. Chapter 6: Treatment of LTBI. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Accessed July 3, 2006.

[13] CDC. Chapter 6: Treatment of LTBI. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Accessed July 3, 2006.

[14] CDC, NTCA. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *MMWR* 2005;54(No. RR-17):59; and CDC. Candidates for treatment of latent TB infection. In: Chapter 6: treatment of LTBI. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Accessed July 3, 2006.

[15] CDC, NTCA. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *MMWR* 2005;54(No. RR-17):59.

[16] CDC, NTCA. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *MMWR* 2005;54(No. RR-17):59.

[17] CDC, NTCA. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *MMWR* 2005;54(No. RR-17):59.

[18] Marsh BJ, SanVicente J, vonReyn F. Utility of dual skin tests to evaluate tuberculin skin test reactions of 10 to 14 mm in health-care workers. *Infect Control Hosp Epidemiol* 2003;24:821–4.

[19] CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):27.

[20] CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):31, 36.

[21] CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):36.

[22] ATS, CDC, IDSA. Treatment of tuberculosis. *MMWR* 2003;52(No. RR-11):4.

[23] CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):28–29.

[24] Francis J. Curry National Tuberculosis Center. *Pediatric Tuberculosis: An Online Presentation* [Francis J. Curry National Tuberculosis Center Web site]. San Francisco, CA; 2007: Slides 59–60. Accessed February 2, 2007.

[25] ATS, CDC, IDSA. Treatment of tuberculosis. *MMWR* 2003;52(No. RR-11):43.

[26] ATS, CDC, IDSA. Treatment of tuberculosis. *MMWR* 2003;52(No. RR-11):43.

[27] ATS, CDC, IDSA. Treatment of tuberculosis. *MMWR* 2003;52(No. RR-11):43.

[28] ATS, CDC, IDSA. Treatment of tuberculosis. *MMWR* 2003;52(No. RR-11):43.

[29] 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. Accessed July 11, 2006.

[30] CDC. Update: adverse event data and revised ATS/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection, United States. *MMWR* 2003;52(No. 31):735–736.

[31] CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR.* 2000;49(No. RR-6):26–29, 38–39.

[32] CDC. Module 4: treatment of tuberculosis and tuberculosis infection. *Self-Study Modules on Tuberculosis* [Division of Tuberculosis Elimination Web site]. 1999:8–9, 15–17. Available at: Accessed July 3, 2006.

[33] CDC. Update: Adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection—United States. *MMWR* 2003;52(No. 31):735–736.

[34] CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):20–21; CDC. Monitoring. In: Chapter 6: treatment of LTBI. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Accessed July 11, 2006.

[35] CDC. Module 9: patient adherence to tuberculosis treatment. *Self-Study Modules on Tuberculosis*[Division of Tuberculosis Elimination Web site].1999:6. Accessed July 3, 2006.

[36] County of Los Angeles Tuberculosis Control Program. *Tuberculosis Control Program Manual: 2003 Edition:*2-10. Accessed February 1, 2007.

[37] CDC, NTCA. Guidelines for the investigation of contacts of persons with infectious tuberculosis: recommendations from the National Tuberculosis Controllers Association and CDC. *MMWR* 2005;54(No. RR-15):19.

[38] CDC. Regimens. In: Chapter 6: treatment of LTBI. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Accessed February 1, 2007.

[39] County of Los Angeles Tuberculosis Control Program. *Tuberculosis Control Program Manual: 2003 Edition:*2.10. Accessed February 1, 2007.

[40] ATS, CDC, IDSA. Treatment of tuberculosis. *MMWR* 2003;52(No. RR-11):8.

[41] CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):39.

[42] CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):35.