

# Treatment of Latent Tuberculosis Infection

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# Quick Start Check List: Treatment of Latent Tuberculosis Infection

The tasks listed below should be performed by licensed nursing, medical, and laboratory staff according to Idaho statute.

Steps for Diagnosis of Latent Tuberculosis Infection	Instructions and Forms
Diagnose latent tuberculosis infection, ruling out tuberculosis disease	Examples of forms can be found in chapter 17. Be sure to consult your local protocols and standing orders, too.
Steps for Treatment of Latent Tuberculosis Infection	Instructions and Forms
Provide appropriate treatment in special situations. These could include: <ul style="list-style-type: none"> <li>▪ Human immunodeficiency virus (HIV) infection</li> <li>▪ Alcoholism</li> <li>▪ Pregnancy and breastfeeding</li> </ul>	Examples of forms can be found in chapter 17. Be sure to consult your local protocols and standing orders, too.
Select appropriate treatment regimens, dosages, and duration	Examples of forms can be found in chapter 17. Be sure to consult your local protocols and standing orders, too.
Monitor the patient for side effects and adverse reactions	Examples of forms can be found in chapter 17. Be sure to consult your local protocols and standing orders, too.
Assess the patient's adherence	Examples of forms can be found in chapter 17. Be sure to consult your local protocols and standing orders, too.
Verify whether treatment has been completed by the total number of doses ingested If treatment is not completed within the recommended time frame, determine whether the patient is able to continue and complete therapy or whether the patient should restart therapy	Examples of forms can be found in chapter 17. Be sure to consult your local protocols and standing orders, too.

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# Introduction

Use this section to understand and follow national and Idaho guidelines to

- determine whom to treat for latent tuberculosis infection (LTBI);
- select appropriate treatment regimens and dosages;
- monitor patients for adverse reactions;
- monitor patients' adherence to treatment;
- determine whether and when therapy is completed;
- provide treatment in special situations, such as when a patient is pregnant or 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.<sup>1</sup> LTBI is the presence of *Mycobacterium tuberculosis* organisms (tubercle bacilli), with no symptoms and no radiographic or bacteriologic evidence of TB disease.<sup>2</sup> 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 Idaho 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.<sup>3</sup>

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 U.S. LTBI treatment substantially reduces the risk that TB infection will progress to disease.<sup>4</sup> Depending upon adherence and length of treatment, completing treatment for LTBI can reduce the risk of TB disease by 65–90%.<sup>5</sup>

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## 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.<sup>6</sup>



For a list of high-risk groups by tuberculin skin test (TST) results, see the Tuberculin Skin Test Results listings below in this topic. For more information on targeted testing, see the Targeted Testing 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.<sup>7</sup>



For more information on treatment of LTBI, see the “Treatment Regimens and Dosages” topic in this section and the CDC publication “Treatment of Latent Tuberculosis Infection (LTBI)” (*TB Elimination Fact Sheet*, April 2006) at <http://www.cdc.gov/tb/pubs/tbfactsheets/treatmentLTBI.htm>.



For consultation regarding the treatment of LTBI, call the Idaho State TB Program at (208) 334-5939.

## 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.<sup>8</sup> 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.<sup>9</sup> 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 Centers for Disease Control and Prevention (CDC) recommend that the window period be estimated at eight to 10 weeks.<sup>10</sup> 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 than 5 years of age (with highest priority given to those under 3 years)
2. contacts with 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; or 3) HIV-seropositive or otherwise immunocompromised.<sup>11</sup>



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.<sup>12</sup>

# Tuberculin Skin Test Results

FIGURE 1. FACTORS AFFECTING TREATMENT DECISIONS DURING THE MEDICAL AND DIAGNOSTIC EVALUATION, BY TUBERCULIN SKIN TEST (TST) RESULT

TST result $\geq 5$ mm is positive	TST result $\geq 10$ mm is positive	TST result $\geq 15$ mm is positive*
<ul style="list-style-type: none"> <li>• Persons infected with HIV<sup>†</sup></li> <li>• Recent contacts of a person with tuberculosis (TB) disease</li> <li>• Persons with fibrotic changes on chest radiograph consistent with previous TB disease</li> <li>• Organ transplant recipients and other immunosuppressed persons (e.g., persons receiving <math>\geq 15</math> mg/day of prednisone for <math>\geq 1</math> month)<sup>§</sup></li> <li>• TB suspects<sup>¶</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Recent immigrants (i.e., within the previous 5 years) from countries with a high incidence of TB disease</li> <li>• Persons who inject illicit drugs</li> <li>• Residents and employees (including health-care workers [HCWs])** of the following congregate settings               <ul style="list-style-type: none"> <li>— hospitals and other health-care facilities</li> <li>— long-term-care facilities (e.g., hospices and skilled nursing facilities)</li> <li>— residential facilities for patients with AIDS<sup>††</sup> or other immunocompromising conditions</li> <li>— correctional facilities</li> <li>— homeless shelters</li> </ul> </li> <li>• Mycobacteriology laboratory personnel</li> <li>• Persons with any of the following clinical conditions or immunocompromising conditions that place them at high risk for TB disease               <ul style="list-style-type: none"> <li>— diabetes mellitus</li> <li>— silicosis</li> <li>— chronic renal failure</li> <li>— certain hematologic disorders (e.g., leukemias and lymphomas)</li> <li>— other specific malignancies (e.g., carcinoma of the head, neck, or lung)</li> <li>— unexplained weight loss of <math>\geq 10\%</math> of ideal body weight</li> <li>— gastrectomy</li> <li>— jejunioileal bypass</li> </ul> </li> <li>• Persons living in areas with high incidence of TB disease</li> <li>• Children aged <math>&lt;4</math> years</li> <li>• Infants, children, and adolescents exposed to adults at high risk for developing TB disease</li> <li>• Locally identified groups at high risk</li> </ul>	<ul style="list-style-type: none"> <li>• Persons with no known risk factors for TB disease</li> <li>• HCWs 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**</li> </ul>

\* TST results  $\geq 15$  mm is positive in anyone. These persons should receive a symptom screen and do not need to be tested again. They should be evaluated for TB disease, and if disease is excluded, they should be offered treatment for latent TB infection (LTBI) if they have no contraindication to treatment.

† Human immunodeficiency virus.

§ The risk for TB disease in persons treated with corticosteroids increases with higher doses and longer duration of corticosteroid use.

¶ Persons with suspected TB disease can be treated based on the medical and diagnostic evaluation, regardless of the TST results.

\*\* For 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  $\geq 15$  mm (instead of  $\geq 10$  mm) is considered to be positive. Although a result of  $\geq 10$  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. SOURCE: 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.

†† Acquired immunodeficiency syndrome.

Source: CDC. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care facilities, 2005. *MMWR* 2005;54(No. RR-17):59/

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## 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 U.S. Persons with LTBI who are considered at increased risk for TB should be offered treatment.<sup>13</sup>

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 considered for 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 persons, 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<sup>14</sup>

Drug	Interval and Duration	Comments	Rating* (evidence) <sup>†</sup>	
			HIV-	HIV+
INH	Daily for 9 months <sup>‡</sup> §	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 <sup>‡</sup> §	DOT must be used with twice-weekly dosing.	B (II)	B (II)
INH	Daily for 6 months <sup>§</sup>	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 <sup>§</sup>	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 anti-retroviral 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. <sup>15</sup>	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 Pyrazinamide for Treatment of Latent Tuberculosis Infection” (*MMWR* 2003;52[No.31]:735) at <http://www.cdc.gov/mmwr/PDF/wk/mm5231.pdf>.

## 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 national American Thoracic Society (ATS) and CDC guidelines.

TABLE 2: RECOMMENDED DOSAGES<sup>16,17</sup>

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 food 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.<sup>18</sup>



For information on 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 Idaho State TB Program at (208) 334-5939.

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## Side Effects and Adverse Reactions

The patient should be monitored by a registered nurse and/or clinician or case manager 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. (This table can also be found in chapter 6 “Treatment of Tuberculosis Disease”.)

As is true with all medications, combination chemotherapy for tuberculosis is associated with a predictable incidence of adverse effects, some mild, some serious.<sup>19</sup>

Adverse effects are fairly common and often manageable. Although it is important to be attuned to the potential for adverse effects it is at least equally important that first-line drugs not be stopped without adequate justification.<sup>20</sup> 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.<sup>21</sup> In addition, proper management of more serious adverse reactions often requires expert consultation.<sup>22</sup>

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 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/> and the list of guidelines by date at [http://www.cdc.gov/tb/pubs/mmwr/Maj\\_guide/List\\_date.htm](http://www.cdc.gov/tb/pubs/mmwr/Maj_guide/List_date.htm).
2. While on treatment, all patients should be evaluated in person, at baseline (before starting treatment), and then monthly for side effects and adverse reactions.

3. The common side effects of and adverse reactions to drugs used to treat for latent TB infection (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 Idaho State TB Program at (208) 334-5939.
  - 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 state TB program by calling the Idaho State TB Program at (208) 334-5939.
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, 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 Idaho State TB program by calling (208) 334-5939.

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<sup>23</sup>

Potentially Serious Adverse Reactions*	Less Severe Signs and Symptoms*
<p>Immediately report the following signs and symptoms or other abnormalities or unexpected events to the patient's provider. These signs and symptoms suggest side effects, including hepatotoxicity:</p> <ul style="list-style-type: none"> <li>▪ Jaundice</li> <li>▪ Dark urine</li> <li>▪ Vomiting</li> <li>▪ Abdominal pain</li> <li>▪ Fever</li> <li>▪ Visual changes</li> <li>▪ Marked clinical rash</li> </ul> <p>In consultation with the provider, instruct the patient to stop TB medications until evaluated by the provider.</p>	<p>Report the following signs and symptoms to the patient's provider within 24 hours:</p> <ul style="list-style-type: none"> <li>▪ Anorexia</li> <li>▪ Nausea</li> <li>▪ Malaise</li> <li>▪ Peripheral neuropathy: tingling or burning sensation in hands or feet</li> <li>▪ Rashes</li> </ul>
<p>* These lists are not all-inclusive. For a complete list, refer to the current guidelines for treatment of TB, "Treatment of Tuberculosis" (<i>MMWR</i> 2003;52[No. RR-11]) at <a href="http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf">http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf</a>.</p>	

Source: California Department of Health Services (CDHS)/California Tuberculosis Controllers Association (CTCA). TB case management – core components. *CDHS/CTCA Joint Guidelines*. May 11, 1998:9. Available at <http://www.ctca.org/guidelines/index.html>. Accessed July 11, 2006.

At present, the CDC 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 1-404-639-8401.

## Checking for Side Effects or 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<sup>24, 25, 26</sup>

Anti-Tuberculosis Drug	Side Effects/ Adverse Reactions	Monitoring	Comments
Isoniazid (INH)	<ul style="list-style-type: none"> <li>▪ Rash</li> <li>▪ Hepatic enzyme elevation</li> <li>▪ Hepatitis</li> <li>▪ Peripheral neuropathy</li> <li>▪ Mild central nervous system effects</li> </ul>	<p>Clinical monitoring monthly</p> <p>Liver function tests (AST, ALT and serum bilirubin) at baseline in selected cases (HIV infection, history of liver disease, alcoholism, and pregnancy)</p> <p>Repeat measurements if</p> <ul style="list-style-type: none"> <li>▪ Baseline results are abnormal</li> <li>▪ Patient is pregnant, in the immediate postpartum period, or at high risk for adverse reactions</li> <li>▪ Patient has symptoms of adverse reactions</li> </ul>	<p>Hepatitis risk increases with age and alcohol consumption</p> <p>Pyridoxine (vitamin B6, 10–25 mg/d) might prevent peripheral neuropathy and central nervous system effects</p> <p>Serum concentrations of phenytoin, disulfiram (Antabuse), and carbamazepine may be increased in persons taking INH. Measure serum concentrations of phenytoin and carbamazepine in patients receiving INH (with or without RIF) and adjust the dose if necessary</p>

Anti-Tuberculosis Drug	Side Effects/ Adverse Reactions	Monitoring	Comments
<b>Rifampin (RIF)</b>	<ul style="list-style-type: none"> <li>▪ Rash</li> <li>▪ Gastrointestinal upset</li> <li>▪ Hepatitis</li> <li>▪ Fever</li> <li>▪ Bleeding problems</li> <li>▪ Thrombocytopenia</li> <li>▪ Renal failure</li> <li>▪ Flu-like symptoms</li> <li>▪ Orange-colored body fluids (secretions, urine, tears)</li> </ul>	<p>Complete blood count, platelets, and liver function tests (AST, ALT and serum bilirubin) at baseline in selected cases (HIV infection, history of liver disease, alcoholism, and pregnancy)</p> <p>Repeat measurements if</p> <ul style="list-style-type: none"> <li>▪ Baseline results are abnormal</li> <li>▪ Patient has symptoms of adverse reactions</li> </ul>	<p>There are a number of drug interactions with potentially serious consequences. Significant interactions with methadone, birth control hormones, and many other drugs</p> <p>Contraindicated or should be used with caution when administered with PIs and NNRTIs. Reduces levels of many drugs (e.g., PIs, NNRTIs, methadone, dapsone, ketoconazole, coumadin derivatives, hormonal contraceptive, digitalis, sulfonyleureas, diazepam, <math>\beta</math>-blockers, anticonvulsants, and theophylline)</p> <p>For more information, refer to "Section 7: Drug Interactions" on page 45 in "Treatment of Tuberculosis" at <a href="http://www.cdc.gov/mmwr/PDF/rrrr5211.pdf">http://www.cdc.gov/mmwr/PDF/rrrr5211.pdf</a></p> <p>Because information regarding rifamycin drug interactions is evolving rapidly, consult the CDC's Division of Tuberculosis "News and Updates" Web page at <a href="http://www.cdc.gov/tb/">http://www.cdc.gov/tb/</a> to obtain the most up-to-date information</p> <p>Colors body fluids orange</p> <p>May permanently discolor soft contact lenses</p>

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# Adherence

Monitor patients for adherence to self-administered latent tuberculosis infection (LTBI) treatment regimens monthly throughout treatment.<sup>27</sup> It is difficult to identify who will and who will not be adherent.<sup>28</sup> 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 high-risk groups are strongly recommended for directly observed therapy (DOT).

- 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* (2004) at <http://www.umdnj.edu/globaltb/downloads/products/PediatricGuidelines.pdf>

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## 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, and evaluate the use of incentives and enablers.<sup>29</sup>

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 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.<sup>30</sup>

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<sup>31</sup>

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	4 months	120	6 months
	Child	6 months	180	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)* [DTBE Web site]. August 2003. Available at: <http://www.cdc.gov/tb/pubs/corecurr/index.htm>. 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.<sup>32</sup>



For consultation regarding completion of therapy and considerations to examine when restarting treatment in noncompliant patients, contact the Idaho State TB Program at (208) 334-5939.

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# 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 Idaho State TB Program at (208) 334-5939 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 latent TB infection. For more information on time frames, see the “Time Frames for Contact Investigation” topic in the Contact Investigation section.

### Resources

(For easy access to references, hyperlinks are provided for online references in the list below.)

- CDC. “TB Guidelines: HIV/AIDS” (DTBE Web site, accessed February 2007) at [http://www.cdc.gov/tb/pubs/mmwr/Maj\\_guide/HIV\\_AIDS.htm](http://www.cdc.gov/tb/pubs/mmwr/Maj_guide/HIV_AIDS.htm)
- ATS, CDC. “Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection” (*MMWR* 2000;49[No. RR-6]:33) at: <http://www.cdc.gov/mmwr/PDF/rr/rr4906.pdf>
- 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) at: <http://www.cdc.gov/mmwr/PDF/rr/rr4720.pdf>
- 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) at <http://www.cdc.gov/mmwr/PDF/wk/mm4909.pdf>
- Francis J. Curry National Tuberculosis Center. *TB & HIV: An Online Course for Clinicians* (2001) at [http://www.nationaltbcenter.edu/courses/course\\_details.cfm?productID=ONL-01](http://www.nationaltbcenter.edu/courses/course_details.cfm?productID=ONL-01)

## Alcoholism

Because of the effectiveness of isoniazid (INH) and rifampin (RIF), they should be used if at all possible, even in the presence of preexisting liver disease. Drug-induced hepatitis, the most serious common adverse reaction is defined as 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 absence of symptoms.

It should be noted that TB itself may involve the liver, causing abnormal liver function. Thus, not all abnormalities in liver function tests noted at baseline should be attributed to causes other than TB. Hepatic abnormalities caused by TB will improve with effective treatment.<sup>33</sup>

Prior to treatment, serologic testing for hepatitis viruses A, B, and C should be performed especially if the patient uses alcohol. Close monitoring with repeat measurements of serum AST and bilirubin and symptom review is essential in managing a patient with elevated serum AST.<sup>34</sup>

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.<sup>35</sup>
- If the patient is on directly observed therapy, perform a symptom review at each directly observed therapy visit to assess if there are any side effects or adverse reactions.

## 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 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.<sup>36</sup>

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# Resources and References

## Resources

(For easy access to references, hyperlinks are provided for online references in the list below.)

### Whom to Treat

- CDC. “Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection” (*MMWR* 2000;49[No. RR-6]) at: <http://www.cdc.gov/mmwr/PDF/rr/rr4906.pdf>
- CDC. *Core Curriculum on Tuberculosis (2000)* (November 2001) at <http://www.cdc.gov/tb/pubs/corecurr/default.htm>

### Treatment Regimens and Dosages

- CDC. “Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection” (*MMWR* 2000;49[No. RR-6]) at: <http://www.cdc.gov/mmwr/PDF/rr/rr4906.pdf>
- CDC. “Update: Adverse Event Data and Revised American Thoracic Society (ATS)/Centers for Disease Control and Prevention (CDC) Recommendations Against the Use of Rifampin and Pyrazinamide for Treatment of Latent Tuberculosis Infection” (*MMWR* 2003;52[No. 31]) at [http://www.cdc.gov/tb/pubs/mmwr/mmwr\\_updates.htm](http://www.cdc.gov/tb/pubs/mmwr/mmwr_updates.htm)
- CDC. *Core Curriculum on Tuberculosis (2000)* (November 2001) at: <http://www.cdc.gov/tb/pubs/corecurr/default.htm>

### 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) at <http://www.cdc.gov/mmwr/PDF/rr/rr4906.pdf>
- National Tuberculosis Controllers Association-National Tuberculosis Nurse Consultant Coalition. *Tuberculosis Nursing: A Comprehensive Guide to Patient Care* (Atlanta, GA;1997:47–51, 63–64)
- CDC. Module 4: “Treatment of Tuberculosis and Tuberculosis Infection (*Self-Study Modules on Tuberculosis 1999*:15–17, 30–32) at <http://www.phppo.cdc.gov/phtn/tbmodules/Default.htm>

## Adherence

- CDC. Module 9: “Patient Adherence to Tuberculosis Treatment” (*Self-Study Modules on Tuberculosis*. 1999) at <http://www.phppo.cdc.gov/phtn/tbmodules/modules6-9/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 (rewards) and enablers (things that remove barriers to patients)
  - Using DOT
- CDC. *Improving Patient Adherence to Tuberculosis Treatment*. (1994)
  - National Tuberculosis Controllers Association-National Tuberculosis Nurse Consultant Coalition. *Tuberculosis Nursing: A Comprehensive Guide to Patient Care* (Atlanta, GA; 1997:69–84)

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- <sup>2</sup> CDC. Summary. In: Chapter 6: treatment of LTBI. *Core Curriculum on Tuberculosis (2000)* [DTBE Web site]. November 2001. Available at: <http://www.cdc.gov/tb/pubs/corecurr/index.htm>. Accessed July 3, 2006.
- <sup>3</sup> 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.
- <sup>4</sup> CDC. Treatment of latent tuberculosis infection: maximizing adherence. *TB Fact Sheets* [DTBE Web site]. April 2005;1. Available at: <http://www.cdc.gov/tb/pubs/tbfactsheets/LTBIadherence.htm>. Accessed February 1, 2007.
- <sup>5</sup> CDC. Treatment of latent tuberculosis infection: maximizing adherence. *TB Fact Sheets* [DTBE Web site]. April 2005;1. Available at: <http://www.cdc.gov/tb/pubs/tbfactsheets/LTBIadherence.htm>. Accessed February 1, 2007.
- <sup>6</sup> CDC. Summary. In: Chapter 6: treatment of LTBI. *Core Curriculum on Tuberculosis (2000)* [DTBE Web site]. November 2001. Available at: <http://www.cdc.gov/tb/pubs/corecurr/index.htm>. Accessed July 3, 2006.
- <sup>7</sup> CDC. Summary. In: Chapter 6: treatment of LTBI. *Core Curriculum on Tuberculosis (2000)* [DTBE Web site]. November 2001. Available at: <http://www.cdc.gov/tb/pubs/corecurr/index.htm>. Accessed July 3, 2006.
- <sup>8</sup> 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.
- <sup>9</sup> 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.
- <sup>10</sup> 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.
- <sup>11</sup> 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.
- <sup>12</sup> CDC. Chapter 6: Treatment of LTBI. *Core Curriculum on Tuberculosis (2000)* [DTBE Web site]. November 2001. Available at: <http://www.cdc.gov/tb/pubs/corecurr/index.htm>. Accessed July 3, 2006.
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- <sup>14</sup> CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):31, 36.
- <sup>15</sup> CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):36.
- <sup>16</sup> ATS, CDC, IDSA. Treatment of tuberculosis, American Thoracic Society, CDC, and Infectious Diseases Society of America. *MMWR* 2003;52(No. RR-11):4.
- <sup>17</sup> CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection, *MMWR* 2000;49(No. RR-6):28–29.

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- <sup>25</sup> CDC. Module 4: treatment of tuberculosis and tuberculosis infection. *Self-Study Modules on Tuberculosis* [DTBE Web site]. 1999:8–9, 15–17. Available at: <http://www.cdc.gov/tb/pubs/ssmodules/default.htm> . Accessed July 3, 2006.
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- <sup>27</sup> 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)* [DTBE Web site]. November 2001. Available at: <http://www.cdc.gov/tb/pubs/corecurr/index.htm> . Accessed July 11, 2006.
- <sup>28</sup> CDC. Module 9: patient adherence to tuberculosis treatment. *Self-Study Modules on Tuberculosis* [DTBE Web site]. 1999:6. Available at: <http://www.cdc.gov/tb/pubs/ssmodules/default.htm> . Accessed July 3, 2006.
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- <sup>30</sup> 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.
- <sup>31</sup> CDC. Regimens. In: Chapter 6: treatment of LTBI. *Core Curriculum on Tuberculosis (2000)* [DTBE Web site]. August 2003. Available at: <http://www.cdc.gov/tb/pubs/corecurr/index.htm> . Accessed February 1, 2007.
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