

Treatment of Latent Tuberculosis Infection

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Introduction

Purpose

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

- Determine whom to treat for latent tuberculosis infection (LTBI);
- Select appropriate treatment regimens and dosages;
- Monitor patients for adverse reactions;
- Monitor patients' adherence to treatment;
- Determine whether and when therapy is completed;
- Provide treatment in special situations, such as when a patient is pregnant or has tuberculosis (TB)-human immunodeficiency virus (HIV) coinfection.

Prevention of TB has major public health implications, so it is essential to identify and treat all those with risk factors for TB disease.¹ LTBI is the presence of *Mycobacterium tuberculosis* organisms (tubercle bacilli), with no symptoms and no radiographic or bacteriologic evidence of TB disease.² A person with LTBI is noninfectious but can develop active TB disease. Persons with increased risk for developing TB include those who have had recent infection with *M. tuberculosis* and those who have clinical conditions associated with an increased risk for the progression of LTBI to TB disease.

Treatment of persons diagnosed with LTBI is an essential part of controlling and eliminating TB in the United States. To control and prevent TB, our healthcare resources and efforts in Nevada should be directed to meet the priorities outlined in the [most current recommendations](#) from: the American Thoracic Society, Centers for Disease Control and Prevention, and the Infectious Diseases Society of America. One of the recommended strategies to achieve the goal of reduction of TB morbidity and mortality is the identification and treatment of persons with LTBI at risk for progression to TB.³

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

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

Policy

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

Whom to Treat

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

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

<i>For Tuberculosis Infection</i>	<i>For Progression to Tuberculosis Disease</i>
<ul style="list-style-type: none">• High-priority contacts such as housemates or co-workers or contacts of persons (patients) who have smear-positive pulmonary or laryngeal tuberculosis (TB)• Infants, children, and adolescents exposed to adults in high-risk categories• Recent immigrants (<5 years) from countries with high incidence of TB. Asian, African, Latin American, and Eastern European countries have TB rates 5–30 times higher than U.S. rates, and an increasing percentage of all TB cases diagnosed in the U.S. is occurring among immigrants from those countries• Recent immigrants from Mexico• Migrant workers• Persons who have recently spent over 3 months in high-incidence countries (such as missionaries)• Native Americans• Persons with high rates of TB transmission:<ul style="list-style-type: none">- Injection (IV) drug users- Homeless persons• Persons with Human Immunodeficiency Virus (HIV) infection• Persons living or working in institutions with individuals at risk for TB such as:<ul style="list-style-type: none">- Hospitals, especially staff in nursing, emergency departments, and laboratories- Long-term care facilities- Homeless shelters- Residences for Acquired Immunodeficiency Syndrome (AIDS) patients- Correctional facilities	<ul style="list-style-type: none">• Persons with HIV infection• Infants and children aged <5 years• Persons infected with <i>Mycobacterium tuberculosis</i> within the previous 2 years• Persons with a history of untreated or inadequately treated TB disease• Persons with Chest x-ray findings consistent with previous TB disease• Persons who use alcohol or illegal drugs (such as injection drugs or crack cocaine)• Persons who have one or more of the following clinical or immunocompromising conditions:<ul style="list-style-type: none">- Silicosis- Diabetes mellitus- End-Stage Renal Disease (ESRD), chronic renal failure, or patients on hemodialysis- Some hematologic disorders (e.g., leukemias and lymphomas), and other malignancies (e.g., head, neck carcinoma, or lung cancer)- Body weight $\geq 10\%$ below ideal body weight- Prolonged corticosteroid use, and the use of other immunosuppressive treatments (e.g., prednisone or tumor necrosis factor-alpha [TNF-α] antagonists)- Organ transplantation- Gastrectomy, chronic malabsorption syndromes, and jejunio-ileal bypass



For more information on targeted testing, see the “Targeted Testing for Latent Tuberculosis Infection” at:

<http://www.cdc.gov/mmwr/PDF/rr/rr4906.pdf>



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

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



For more information on treatment of LTBI, see the “Treatment Regimens and Dosages” topic in this section (page 8) and the Centers for Disease Control and Prevention (CDC) publication “Treatment of Latent Tuberculosis Infection (LTBI)” (*TB Elimination Fact Sheet*; April 2006) at:

<http://www.cdc.gov/tb/publications/factsheets/treatment/treatmentLTBI.htm>



For consultation regarding the treatment of LTBI, contact the local or state TB program. Contact information available in the Roles, Responsibilities & Contacts section of the introduction (pages 26,27) at:

http://www.health.nv.gov/PDFs/HIV_STD_TB/Educational/TB_Protocol_Introduction.pdf



Patients should be provided with a permanent record of their tuberculin skin test, chest x-ray and treatment status. Examples and templates of LTBI cards are available at: <http://www.umdnl.edu/globaltb/products/lbcard.htm>.

Susceptible and Vulnerable Contacts

A contact is someone who has been exposed to *M. tuberculosis* infection by sharing air space with a person with infectious TB.⁸ Susceptible contacts are those who are more likely to become ill with TB disease if they are infected, and vulnerable contacts are those who could suffer severe morbidity if they progress to TB disease⁹ (These include

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

1. Contacts younger than five years of age (with highest priority given to those under three years)
2. Contacts with HIV infection or who are otherwise immunocompromised

If the second skin test or IGRA result is negative and the contact is immunocompetent (including immunocompetent young children) and no longer exposed to infectious TB, treatment for LTBI may be discontinued, and further follow-up is unnecessary. If the second test is negative but the contact is immunocompromised (e.g., with HIV infection), a full course of therapy for LTBI should be completed. If the second test result is negative but the person remains in close contact with an infectious patient, treatment for LTBI should be continued if the contact is:

1. Less than 5 years old
2. Aged 5-15 years, at the clinician's discretion
3. Those who are HIV-seropositive or otherwise immunocompromised¹¹



Persons known to be (or suspected of being) immunocompromised, such as HIV-infected persons, should be given treatment for LTBI regardless of the TST or IGRA reaction.¹²



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

Tuberculin Skin Test Results of 5 mm or More

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

- Persons with HIV infection
- Recent contacts of persons with newly diagnosed infectious TB
- Persons with fibrotic changes on their chest radiographs that are consistent with old TB
- Persons with organ transplants and other immunosuppressed patients (receiving the equivalent of 15 mg or more/day of prednisone for at least one month)¹³

Tuberculin Skin Test Results of 10 mm or More

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

- Foreign-born persons who have recently arrived (within five years) from countries with a high TB incidence or prevalence, or persons who have recently traveled to these countries (most countries in Africa, Asia, Latin America, Eastern Europe, and Russia [formerly the USSR])
- Persons who are alcoholics, who inject drugs, or who use other high-risk substances, such as crack cocaine
- Residents and employees of high-risk congregate settings, such as correctional institutions, homeless shelters, long-term residential care facilities (e.g., nursing homes, mental institutions), hospitals, and other healthcare facilities
- Mycobacteriology laboratory personnel
- Persons with medical conditions or undergoing treatments that increase the risk of TB disease (diabetes mellitus, silicosis, recent infection with *M. tuberculosis* within the past two years, bone marrow and organ transplant recipients, prolonged high-dose corticosteroid therapy and other immunosuppressive therapy, chronic renal failure, hemodialysis, some hematological disorders [e.g., leukemias and Hodgkin's disease], other specific malignancies [e.g., carcinoma of the head, neck, or lung], chronic malabsorption syndromes, weight of 10% or more below ideal body weight, and intestinal bypass or gastrectomy)
- Children less than five years of age
- Infants, children and adolescents exposed to adults at high risk for developing TB disease
- Locally identified groups at high risk¹⁴

Tuberculin Skin Test Results of 15 mm or More¹⁵

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

- Persons with no known risk factors for TB disease
- Healthcare workers* who are otherwise at low risk for TB disease and who received baseline testing at the beginning of employment as part of a TB screening program¹⁶



* For healthcare workers (HCWs) who are otherwise at low risk for LTBI and progression to TB disease if infected and who received baseline testing at the beginning of employment as part of a TB infection-control screening program, a TST result of ≥ 15 mm (instead of ≥ 10 mm) is considered to be positive. Although a result of ≥ 10 mm on baseline or follow-up testing is considered a positive result for HCWs for the purposes of referral for medical and diagnostic evaluation, if the TST result is 10–14 mm on baseline or follow-up testing, the referring clinician might not recommend treatment of LTBI.¹⁷

Treatment Regimens and Dosages

Select appropriate treatment durations, regimens, and dosages. Treatment of latent tuberculosis infection (LTBI) is an essential part of the strategy to eliminate tuberculosis (TB) in the United States. Persons with LTBI who are considered at increased risk for TB should be offered treatment.¹⁸

There are several treatment regimens available for the treatment of LTBI, and providers should discuss options with patients. Persons who are at especially high risk for TB, and either are suspected of nonadherence or are on an intermittent dosing regimen, should be treated using directly observed therapy (DOT). This method of treatment is especially appropriate when a household member is on DOT for TB disease or in institutions and facilities where a staff member can observe treatment.



The most current TB treatment guidelines state that frequent monitoring of a patient's treatment regimen and response to treatment is critical and can be accomplished through use of a drug-o-gram. This electronic resource provides an interface for entering patient data to create a drug-o-gram. It includes a user's guide with instructions and teaching points, it is available at: <http://www.umdng.edu/ntbcweb/products/drugogram.htm>



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 2 below.

Table 2: **RECOMMENDED DRUG REGIMENS FOR TREATMENT OF LATENT TUBERCULOSIS INFECTION IN ADULTS**¹⁹

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. ²⁰	B (II)	B (III)
<p>Definitions of abbreviations: DOT = directly observed therapy; HIV = human immunodeficiency virus; INH = isoniazid; LTBI = latent tuberculosis infection; RIF = rifampin.</p> <p>* Strength of recommendation: A = preferred; B = acceptable alternative; C = offer when A and B cannot be given.</p> <p>† 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.</p> <p>‡ Recommended regimen for children <18 years of age.</p> <p>§ Recommended regimen for pregnant women.</p>				

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 this hyperlink: <http://www.cdc.gov/mmwr/PDF/wk/mm5231.pdf>.

Dosages

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

Table 3: **RECOMMENDED DOSAGES**^{21,22}

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

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



The use of INH elixir is discouraged, as it commonly causes diarrhea and cramping in children. If children have difficulty taking medications, open capsules and crush tablets, and then mix the drugs into soft foods or liquids. Possible foods include yogurt, maple syrup, hot fudge, Nutella, apple sauce, jams and jellies, spinach baby food, and chocolate whipped cream, etc. Layer the food and drug on a spoon, and teach the child to take the contents of the spoon without chewing.²³

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

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

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



For 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 Francis J Curry Warm line at 415-502-4700.

Side Effects and Adverse Reactions

The patient should be monitored by a registered nurse and/or clinician or case manager at least monthly for signs and symptoms of adverse reactions until treatment is completed. If a patient is symptomatic, the provider should be consulted and the patient monitored more frequently. Blood chemistries and a complete blood count (CBC), aspartate aminotransferase (AST)/alanine aminotransferase (ALT), or other tests based on specific drugs should be done periodically. See Table 5: **Monitoring and Interventions for Side Effects and Adverse Reactions** in this section.

As is true with all medications, combination chemotherapy for tuberculosis (TB) is associated with a predictable incidence of adverse effects, some mild, some serious.²⁴

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.²⁵ 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.²⁶ In addition, proper management of more serious adverse reactions often requires expert consultation.²⁷ A comprehensive statement of Hepatotoxicity of Antituberculosis Therapy has been published by the American Thoracic Society, available at: <http://ajrccm.atsjournals.org/cgi/reprint/174/8/935.pdf>

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

Basic Monitoring Steps

1. All healthcare workers providing treatment for latent tuberculosis infection (LTBI) should be familiar with the American Thoracic Society (ATS)/Centers for Disease Control and Prevention (CDC) guidelines.
 - a. All jurisdictions should follow the national monitoring guidelines identified in the current treatment guidelines for treatment of LTBI, “Targeting Tuberculin Testing and Treatment of Latent Tuberculosis Infection,” pages 26–29 at: <http://www.cdc.gov/mmwr/PDF/rr/rr4906.pdf> .
 - b. It is also important to check for guideline updates posted on the CDC’s Division of Tuberculosis Elimination home page at : <http://www.cdc.gov/tb/default.htm> and the list of guidelines by date at: <http://www.cdc.gov/tb/publications/guidelines/default.htm>
2. While on treatment, all patients should be evaluated in person, at baseline (before starting treatment), and then at least monthly thereafter, for side effects and adverse reactions. Providing only a 30-day supply of medications at a time allows healthcare providers to conduct in person evaluations every time a prescription refill is required.
3. The common side effects of and adverse reactions to drugs used to treat for LTBI are listed in Table 4: **Reporting Reactions to Antituberculosis Medications**. Educate patients to stop the medicine and promptly report any of the symptoms or signs listed in Table 4 or any unexplained illness to the prescribing clinic immediately.
 - a. If a patient reports a potentially serious adverse reaction, call the patient’s provider immediately and take action according to the provider’s instructions.
 - 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 5: **Monitoring and Interventions for Side Effects and Adverse Reactions** below.
 - b. Consult with the patient’s medical provider, Local Health Authority or the NV State TB Program.
5. If you suspect that an antituberculosis drug may be interacting with other medications that the patient is taking, refer to pages 45–47 in the “Treatment of Tuberculosis” (*MMWR* 2003;52[No. RR-11]) at: <http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf> .
6. Document the following patient information:
 - a. Review of symptoms, test results, side effects, and adverse reactions
 - b. Education given
 - c. Refill provided
 - d. Description of any problems encountered and action taken for that visit

e. Next appointment



For more information on Assessing and Managing the Risk of Liver Disease in the Treatment of LBTI, please see the algorithm at:

http://www.heartlandntbc.org/products/assessing_and_managing_the_risk_of_liver_disease_in_the_treatment_of_lbtbi.pdf

Reporting Reactions

The table below is intended for use by a healthcare worker who performs case management services. The healthcare worker should instruct the patient to report to the provider the side effects and adverse reactions listed in Table 4.

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

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

Table 4: **REPORTING REACTIONS TO ANTITUBERCULOSIS MEDICATIONS**²⁸

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">▪ Jaundice▪ Dark urine▪ Vomiting▪ Abdominal pain▪ Fever▪ Visual changes▪ Marked clinical rash <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">▪ Anorexia▪ Nausea▪ Malaise▪ Peripheral neuropathy: tingling or burning sensation in hands or feet▪ Rashes
<p>*These lists are not all-inclusive. For a complete list, refer to the current guidelines for treatment of TB, "Treatment of Tuberculosis" (MMWR 2003;52[No. RR-11]) at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf and an Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy, available at: http://ajrcm.atsjournals.org/cgi/reprint/174/8/935.pdf</p>	

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



The two-month regimen of rifampin and pyrazinamide is no longer recommended due to serious and fatal hepatitis associated with this regimen.²⁹

The Nevada State Health Division (NSHD) would like to remind health care providers to report all adverse drug events to:

<http://www.fda.gov/Safety/MedWatch/HowToReport/ucm085568.htm>.

At present, the CDC Division of Tuberculosis Elimination (DTBE) is requesting health departments, hospices, hospitals, jails, prisons, and private medical offices to report all severe adverse events (e.g., liver injury, pancreatitis, metabolic acidosis, anaphylaxis, seizure, severe dermatitis) leading to hospitalization or death of a person receiving treatment for LTBI that occurred after January 1, 2004, to DTBE by calling 404-639-8401. Also, if not done previously, please call NSHD TB Program by calling 775-684-5982 to report severe adverse events.

Monitoring for Side Effects and Adverse Reactions by Antituberculosis Drug

Refer to Table 5: **Monitoring and Interventions for Side Effects and Adverse Reactions** to do the following:

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

Table 5: **MONITORING AND INTERVENTIONS FOR SIDE EFFECTS AND ADVERSE REACTIONS**^{30,31,32}

Antituberculosis Drug	Side Effects/ Adverse Reactions	Monitoring	Comments
Isoniazid (INH)	<ul style="list-style-type: none"> ▪ Rash ▪ Hepatic enzyme elevation ▪ Hepatitis ▪ Peripheral neuropathy ▪ Mild central nervous system effects 	<p>Clinical monitoring monthly</p> <p>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)</p> <p>Repeat measurements if</p> <ul style="list-style-type: none"> ▪ 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 	<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 rifampin), and adjust the dose if necessary.</p> <p>More information is available in the Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy, available at: http://ajrccm.atsjournals.org/cgi/reprint/174/8/935.pdf</p>

Antituberculosis Drug	Side Effects/ Adverse Reactions	Monitoring	Comments
Rifampin (RIF)	<ul style="list-style-type: none"> ▪ Rash ▪ Gastrointestinal upset ▪ Hepatitis ▪ Fever ▪ Bleeding problems ▪ Thrombocytopenia ▪ Renal failure ▪ Flu-like symptoms ▪ Orange-colored body fluids (secretions, urine, tears) 	<p>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)</p> <p>Repeat measurements if</p> <ul style="list-style-type: none"> ▪ Baseline results are abnormal ▪ Patient has symptoms of adverse reactions 	<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 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, β-blockers, anticonvulsants, and theophylline).</p> <p>Colors body fluids orange.</p> <p>May permanently discolor soft contact lenses</p> <p>For more information, refer to "Section 7: Drug Interactions" on page 45 in "Treatment of Tuberculosis" at http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf.</p> <p>Because information regarding rifamycin drug interactions is evolving rapidly, consult the CDC's Division of Tuberculosis "News and Updates" Web page at http://www.cdc.gov/tb/default.htm to obtain the most up-to-date information.</p>

Adherence

Monitor patients for adherence to self-administered latent tuberculosis infection (LTBI) treatment regimens at least monthly throughout treatment.³³ It is difficult to identify who will and who will not be adherent.³⁴ 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 TB if medicine is not taken. Provide education again, as needed.
 - d. Mutually agree upon a plan to improve adherence.
 - e. Praise patients for cooperation.
4. If adherence seems to be good, acknowledge and encourage patients’ success.



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

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



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



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

Completion of Therapy

Determine whether and when therapy is completed based upon the total number of doses administered, not on the duration of therapy. When patients have had lapses in therapy but are still able to complete the recommended number of doses in the allotted time period (see table 6), encourage them to complete therapy.

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

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

Give nonadherent patients who are at very high risk of developing TB disease every opportunity to complete treatment for LTBI. Consider these patients for intermittent therapy with DOT and evaluate the use of incentives and enablers.³⁵

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.³⁶

Table 6 describes the duration of therapy and the number of doses that patients are required to take to complete therapy as well as the time frame within which the total number of doses must be administered for completion of therapy.

Table 6: **RECOMMENDED REGIMENS FOR COMPLETION OF THERAPY**³⁷

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)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. 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, HIV-infected patients, or TB Class 4 patients) for reevaluation.³⁸

Treatment in Special Situations

Treatment of LTBI in the following situations requires special consideration:

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

Human Immunodeficiency Virus and Latent Tuberculosis Infection



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

HIV infection is the strongest known risk factor for the progression of LTBI to TB disease. HIV-infected persons with LTBI are 100 times more likely to progress to TB disease than are those patients without HIV infection. Coinfected HIV and LTBI patients have a seven to ten percent yearly risk of developing TB disease. Patients with only LTBI have a ten percent lifetime risk of developing TB disease.



High-risk contacts (less than five years of age or immunocompromised) should be started promptly on treatment for LTBI. For more information on time frames, see the “Time Frames for Contact Investigation” topic in the Contact Investigation section or see “Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis” at: <http://www.cdc.gov/mmwr/pdf/rr/rr5415.pdf>

Resources



- CDC. "TB Guidelines: HIV/AIDS" (DTBE Web site; accessed February 2007). Available at: 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). Available 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]). Available 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). Available at: <http://www.cdc.gov/mmwr/PDF/wk/mm4909.pdf>

Alcoholism

Alcohol-Related Treatment Complications

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

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

- **Immunosuppression:** Persons who use alcohol may be at increased risk for acquiring or developing TB, but given the many other potential risk factors that commonly occur among such persons, alcohol use has been difficult to identify as a separate risk factor for TB.³⁹ However, studies have shown that "alcohol consumption is a major risk factor for infection with opportunistic bacterial, viral, fungal, and parasitic pathogens."⁴⁰
- **Liver injury and death:** Drug-induced liver injury "may occur with all currently recommended regimens for the treatment of LTBI."⁴¹ In the treatment of TB disease, "the crucial efficacy of isoniazid, and particularly (INH), rifampin, warrants their use and retention, (RIF), and pyrazinamide (PZA), they should be used if at all possible, even in the face of preexisting liver disease."⁴² However, it is not fully understood yet how antituberculosis medications cause drug-induced liver injury.⁴³ For persons

taking isoniazid, an association of hepatitis was found with alcohol consumption, with rates being fourfold higher among persons consuming alcohol daily than among those who did not drink alcohol.⁴⁴ When a patient has hepatic disease, the risk of drug accumulation and drug-induced hepatitis is increased. However, with more frequent laboratory and clinical monitoring, isoniazid may be used in patients with stable hepatic disease. Transient asymptomatic hyperbilirubinemia may occur in patients taking rifampin or rifapentine, and more severe clinical hepatitis may also occur. Hepatitis is more common when rifampin is given with isoniazid than when rifampin is given alone or with drugs other than isoniazid.^{45,46} Pyrazinamide has slightly lower rates of hepatotoxicity than isoniazid or rifampin, but pyrazinamide can cause liver injury that may be severe and prolonged.⁴⁷ To prevent and manage drug-induced liver injury, the American Thoracic Society recommends the following systematic steps: consideration of benefits and risks in selecting patients and regimens, careful and thorough staff and patient education, ready access to care, good communication between providers, and clinical and biochemical monitoring.⁴⁸ The most serious common adverse reaction, is defined as a serum aspartate aminotransferase (AST) level more than three times the upper limit of normal in the presence of symptoms or five times the upper limit of normal in the absence of symptoms.

- Nonadherence to treatment:** Patients who do not complete LTBI treatment risk progression to TB disease, and those who do not complete treatment for TB disease risk relapse, development of drug-resistant TB, serious illness, and possible death. Barriers to adherence may be patient-related, such as conflicting health beliefs, alcohol or drug dependence, or mental illness, or they may be system-related, such as lack of transportation, inconvenient clinic hours, and lack of interpreters.⁴⁹ It is more difficult for patients who have an alcohol use disorder to adhere to therapy. In a prospective study of 224 patients, “noncompliance was significantly associated with homelessness and alcoholism.”⁵⁰ In a study of 237 patients in the Russian Federation undergoing DOT treatment for TB disease, “substance abuse was identified as the only factor that was strongly associated with non-adherence... These results suggest that DOT programs [sic] might be more likely to achieve TB control targets if they include interventions aimed at improving adherence by diagnosing and treating substance abuse concurrently with standard TB therapy.”⁵¹ DOTS programs that have explicitly offered substance abuse treatment have reported better outcomes than those that have not.⁵² In South Carolina, joint treatment programs to treat patients with TB who have alcohol and substance abuse problems were used in conjunction with incentives, enablers, and a process of increasing restrictions (health department warnings, then court-ordered directly observed therapy, then involuntary confinement) as needed to address noncompliance. This combination of strategies was associated with an increase in overall completion of antituberculosis therapy and a decrease in new cases between 1986-1991.⁵³

Safe Treatment Guidelines

In 2006, the American Thoracic Society (ATS) issued “An Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy.” Consult these recommendations at: <http://www.thoracic.org/sections/publications/statements/pages/mtpi/hepatotoxicity-antituberculosis-therapy.html> on pages 943-947 for guidance in the following areas for the safe treatment of LTBI and TB Disease:

- **Program Infrastructure** Adopt these standardized approaches to develop safe treatment of LTBI and TB disease.
- **Provider Education and Resources** Develop these written resources, educational programs, and referral mechanisms to assure that healthcare providers have the skills, knowledge, and resources to safely diagnose and treat patients with TB disease and LTBI.
- **Pretreatment Clinical Evaluation** Refer here for a list of what to include in the pretreatment clinical evaluation and the initial physical examination and when to screen for viral hepatitis.
- **Patient Education** Follow these suggestions to improve patients' awareness of and communication about their symptoms of liver disorders. Communicate with patients in their preferred language⁵⁴ and carefully confirm that they understand the educational points being made.
- **Medication Administration and Pharmacy** Use these tips to distribute antituberculosis medications in ways that encourage and reinforce prompt reporting by patients of adverse effects.
- **Treatment of LTBI and Treatment of TB Disease** Use these recommendations to guide treatment decisions and monitoring activities. Numbered lists of recommendations provide detailed information. Three flowcharts show key data and decisions in the following areas: LTBI pretreatment clinical evaluation and counseling, monitoring for hepatotoxicity during LTBI treatment, and monitoring for hepatotoxicity during treatment of TB disease.⁵⁵

Liver Disease

Management of LTBI in patients with unstable or advanced liver disease is difficult. The likelihood of drug-induced hepatitis may be greater in these patients. The implications of drug-induced hepatitis for patients with marginal hepatic reserve are potentially serious, even life-threatening. Also, fluctuations in the biochemical indicators of liver function (with/without symptoms) related to the preexisting liver disease confound monitoring for drug-induced hepatitis.⁵⁶



For all patients with preexisting liver disease, frequent clinical and laboratory monitoring should be performed to detect drug-induced hepatic injury.⁵⁷

Pregnancy and Breastfeeding

Pregnancy has minimal influence on the pathogenesis of TB or the likelihood of LTBI progressing to disease. Pregnant women should be targeted for testing only if they have a specific risk factor for LTBI or for progression of LTBI to TB disease. Extensive use of isoniazid (INH) during pregnancy has shown that, although it readily crosses the placental barrier, the drug is not teratogenic, even when given during the first four months of gestation. Pregnant women taking INH should receive pyridoxine supplementation.

Breastfeeding is not contraindicated when the mother is being treated for LTBI. However, infants whose breastfeeding mothers are taking INH should receive supplemental pyridoxine. Note that the amount of INH provided by breast milk is inadequate for treatment of the infant.⁵⁸



American Academy of Pediatrics. In: Pickering LK, Baker CJ, Long SS, McMillan JA, eds. *Red Book: 2006 Report of the Committee on Infectious Diseases*. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006 (Red Book® Online Web site). Available at: <http://www.aapredbook.org>.

Resources and References

Resources

Whom to Treat

- CDC. "Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection" (MMWR 2000;49[No. RR-6]). Available at: <http://www.cdc.gov/mmwr/PDF/rr/rr4906.pdf> .
- CDC. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Available at: <http://www.cdc.gov/tb/pubs/corecurr/default.htm> .
- American Academy of Pediatrics. In: Pickering LK, Baker CJ, Long SS, McMillan JA, eds. *Red Book: 2006 Report of the Committee on Infectious Diseases*. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006 (Red Book® Online Web site). Available at: <http://www.aapredbook.org> .

Treatment Regimens and Dosages

- CDC. "Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection" (MMWR 2000;49[No. RR-6]). Available at: <http://www.cdc.gov/mmwr/PDF/rr/rr4906.pdf> .
- CDC. "Update: Adverse Event Data and Revised American Thoracic Society (ATS)/Centers for Disease Control and Prevention (CDC) Recommendations Against the Use of Rifampin and Pyrazinamide for Treatment of Latent Tuberculosis Infection" (MMWR 2003;52[No. 31]). Available at: http://www.cdc.gov/tb/pubs/mmwr/mmwr_updates.htm .
- CDC. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Available 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). Available at: <http://www.cdc.gov/mmwr/PDF/rr/rr4906.pdf> .
- National Tuberculosis Controllers Association–National Tuberculosis Nurse Consultant Coalition. *Tuberculosis Nursing: A Comprehensive Guide to Patient Care* (Atlanta, GA;1997:47–51, 63–64).
- CDC. Module 4: "Treatment of Tuberculosis and Tuberculosis Infection" (*Self-Study Modules on Tuberculosis* [Division of Tuberculosis Elimination Web Site]; 1999:15–17, 30–32). Available at: <http://www.phppo.cdc.gov/phtn/tbmodules/Default.htm> .

Adherence

- CDC. Module 9: “Patient Adherence to Tuberculosis Treatment” (*Self-Study Modules on Tuberculosis*. Division of Tuberculosis Elimination Web Site; 1999). Available at: <http://www2a.cdc.gov/phn/tbmodules/modules6-9/m9/9-toc.htm> . This module is entirely devoted to assessing and promoting adherence. It covers the many areas that need to be addressed, such as:
 - Case management: assigning responsibility to the healthcare worker
 - Communication and problem-solving skills
 - Education of the patient
 - Using interpreters when needed
 - Using incentives and enablers
 - Using directly observed therapy (DOT)
- 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. Available at: <http://www.cdc.gov/tb/pubs/TBfactsheets.htm> . 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. Available at: <http://www.cdc.gov/tb/pubs/corecurr/index.htm> . 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. Available at: <http://www.cdc.gov/tb/pubs/TBfactsheets.htm> . 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. Available at: <http://www.cdc.gov/tb/pubs/TBfactsheets.htm> . 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. Available at: <http://www.cdc.gov/tb/pubs/corecurr/index.htm> . 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. Available at: <http://www.cdc.gov/tb/pubs/corecurr/index.htm> . 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. In: Chapter 6: treatment of LTBI. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Available at: <http://www.cdc.gov/tb/pubs/corecurr/index.htm> . Accessed July 3, 2006.

- ¹³ 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. Available at: <http://www.cdc.gov/tb/pubs/corecurr/index.htm> . 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.
- 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 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.
- ¹⁸ CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000; 49(No. RR-6): 27.
- ¹⁹ CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):31, 36.
- ²⁰ CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):36.
- ²¹ ATS, CDC, IDSA. Treatment of tuberculosis. *MMWR* 2003;52(No. RR-11):4.
- ²² CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):28–29.
- ²³ 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. Available at: http://www.nationaltbccenter.ucsf.edu/pediatric_tb/ . Accessed February 2, 2007.
- ²⁴ ATS, CDC, IDSA. Treatment of tuberculosis. *MMWR* 2003;52(No. RR-11):43.
- 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 California Department of Health Services(CDHS)/California Tuberculosis Controllers Association(CTCA). TB case management—core components. *CDHS/CTCA Joint Guidelines* [CTCA Web site]. 1998:9. Available at: <http://www.ctca.org/guidelines/index.html> . Accessed July 11, 2006.
- ²⁹ 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.
- ³⁰ CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):26–29, 38–39.
- ³¹ 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: <http://www.cdc.gov/tb/pubs/ssmodules/default.htm> . Accessed July 3, 2006.
- ³² 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.
- ³³ 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. Available at: <http://www.cdc.gov/tb/pubs/corecurr/index.htm> . Accessed July 11, 2006.
- ³⁴ CDC. Module 9: patient adherence to tuberculosis treatment. *Self-Study Modules on Tuberculosis* [Division of Tuberculosis Elimination Web site]. 1999:6. Available at: <http://www.phppo.cdc.gov/phtn/tbmodules/Default.htm> . Accessed July 3, 2006.
- ³⁵ County of Los Angeles Tuberculosis Control Program. *Tuberculosis Control Program Manual: 2003 Edition*:2-10. Available at: <http://www.lapublichealth.org/tb/TBManual/TBmanual.pdf> . Accessed February 1, 2007.
- ³⁶ 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.
- ³⁷ CDC. Regimens. In: Chapter 6: treatment of LTBI. *Core Curriculum on Tuberculosis (2000)*. August 2003.
- ³⁸ County of Los Angeles Tuberculosis Control Program. *Tuberculosis Control Program Manual: 2003 Edition*:2.10. Available at: <http://www.lapublichealth.org/tb/TBManual/TBmanual.pdf> . Accessed February 1, 2007.
- ³⁹ CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):10.
- ⁴⁰ Brudkey K, Dobkin J. Resurgent tuberculosis in New York City. *Am Rev Respir Dis* 1991;144:745-749; In: Isake, L. Introduction to the symposium. Alcoholism and tuberculosis: an overview. *Alcohol Clin Exp Res* February 1995;19(1):1–2.
- ⁴¹ Saukkonen, JJ, Cohn, DL, Jasmer, RM, Schenker, S, Jereb, JA, Nolan, CM, Peloquin, CA, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006;174:937.
- ⁴² Saukkonen, JJ, Cohn, DL, Jasmer, RM, Schenker, S, Jereb, JA, Nolan, CM, Peloquin, CA, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006;174:947.
- ⁴³ Saukkonen, JJ, Cohn, DL, Jasmer, RM, Schenker, S, Jereb, JA, Nolan, CM, Peloquin, CA, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006;174:935.
- ⁴⁴ CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):16-18.
- ⁴⁵ ATS, CDC, IDSA. Treatment of tuberculosis. *MMWR* 2003;52(No. RR-11):20-21.
- ⁴⁶ Saukkonen, JJ, Cohn, DL, Jasmer, RM, Schenker, S, Jereb, JA, Nolan, CM, Peloquin, CA, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006;174:937.

-
- ⁴⁷ ATS, CDC, IDSA. Treatment of tuberculosis. *MMWR* 2003;52(No. RR-11):24.
- ⁴⁸ Saukkonen, JJ, Cohn, DL, Jasmer, RM, Schenker, S, Jereb, JA, Nolan, CM, Peloquin, CA, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006;174:935.
- ⁴⁹ ATS, CDC, IDSA. Treatment of tuberculosis. *MMWR* 2003;52(No. RR-11):10.
- ⁵⁰ Brudkey K, Dobkin J. Resurgent tuberculosis in New York City. *Am Rev Respir Dis* 144:745-749, 1991. In: Isake, L. Introduction to the symposium. Alcoholism and tuberculosis: an overview. *Alcohol Clin Exp Res* February 1995;19(1):1-2.
- ⁵¹ Gelmanova, IY, Keshavjee S, Golubchikova VT, Berezina VI, Strelis AK, Yanova GV, Atwoodr S, Murray M. Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence, default and the acquisition of multidrug resistance. *Bulletin of the World Health Organization* September 2007;85(9):647-732. Accessed June 25, 2009 Available at: <http://www.who.int/bulletin/volumes/85/9/06-038331/en/index.html>
- ⁵² Gelmanova, IY, Keshavjee S, Golubchikova VT, Berezina VI, Strelis AK, Yanova GV, Atwoodr S, Murray M. Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence, default and the acquisition of multidrug resistance. *Bulletin of the World Health Organization* September 2007;85(9):647-732. Accessed June 25, 2009. Available at: <http://www.who.int/bulletin/volumes/85/9/06-038331/en/index.html>
- ⁵³ CDC. Approaches to improving adherence to antituberculosis therapy – South Carolina and New York, 1986-1991. *MMWR* 1993;42(04):74-75, 81.
- ⁵⁴ Saukkonen, JJ, Cohn, DL, Jasmer, RM, Schenker, S, Jereb, JA, Nolan, CM, Peloquin, CA, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006;174:943.
- ⁵⁵ Saukkonen, JJ, Cohn, DL, Jasmer, RM, Schenker, S, Jereb, JA, Nolan, CM, Peloquin, CA, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006;174:935.
- ⁵⁶ ATS, CDC, IDSA. Treatment of tuberculosis. *MMWR* 2003;52(No. RR-11):65.
- ⁵⁷ ATS, CDC, IDSA. Treatment of tuberculosis. *MMWR* 2003;52(No. RR-11):11.
- ⁵⁸ CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):35.