

Chapter 5 Treatment for Latent Tuberculosis Infection

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Chapter Objectives

After working through this chapter, you should be able to

- List the high-risk groups who should be given priority for latent tuberculosis infection (LTBI) treatment;
- Describe LTBI treatment regimens;
- Describe LTBI treatment regimens for specific situations; and
- Identify components of patient monitoring at baseline and during the treatment of LTBI.

Introduction

It is currently estimated that more than 11 million people in the United States have latent tuberculosis (TB) infection, which is about 4 percent of the total population. While not everyone with latent TB infection (LTBI) will develop TB disease, about 5 to 10 percent of infected people will develop TB disease if not treated. This equates to approximately 550,000 to 1,100,000 people who will develop TB at some point in their life, unless they receive adequate treatment for LTBI.

Treatment of LTBI is essential to controlling and eliminating TB disease in the United States. It substantially reduces the risk that persons infected with *M. tuberculosis* will progress to TB disease. Certain groups are at high risk of developing TB disease once infected. Targeted testing programs should be designed to identify persons who are at high risk for TB disease and who would benefit from treatment of LTBI. Targeted testing should be undertaken only if resources are identified and available to ensure full evaluation and treatment. There are two methods available for the detection of *M. tuberculosis* infection in the United States, the Mantoux tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) (see Chapter 3, Testing for Tuberculosis Infection and Disease).

Targeted testing programs should be designed to identify persons who are at high risk for TB disease and who would benefit from treatment of LTBI.

Study Question

5.1 Which statement about the purpose of LTBI treatment is true?

(choose the one best answer)

- F.** It is given to people who have LTBI to prevent them from testing positive on a subsequent TST.
- G.** It is given to people who have LTBI to prevent the progression to TB disease.
- H.** It is given to people who have TB disease to prevent the disease from getting worse.
- I.** It is given to people who have TB disease to prevent them from becoming infectious.

Candidates for the Treatment of LTBI

Persons with Positive IGRA Result, or TST Reaction ≥ 5 mm

Persons in the following high-risk groups should be given treatment for LTBI if they have either a positive IGRA result **or** if their reaction to the TST is ≥ 5 mm (Table 5.1):

- HIV-infected persons;
- Recent contacts of persons with infectious TB disease;
- Persons with fibrotic changes on chest radiograph consistent with prior TB disease (once TB disease is excluded); and
- Patients with organ transplants, and other immunosuppressed patients (including patients receiving the equivalent of 15 mg/day of prednisone for >1 month).

Persons with Positive IGRA Result, or TST Reaction ≥ 10 mm

Persons in the following high-risk groups should be considered for treatment of LTBI if they have either a positive IGRA result **or** if their reaction to the TST is ≥ 10 mm (Table 5.1):

- Recent arrivals to the United States (<5 years) from high-prevalence areas (e.g., Africa, Asia, Eastern Europe, Latin America, and Russia);
- Injection drug users;
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, and hospitals);
- Mycobacteriology laboratory personnel;
- Persons with medical conditions that increase the risk for progression to TB disease, i.e., silicosis, diabetes mellitus, chronic renal failure, certain types of cancer (e.g., leukemia and lymphomas, or cancer of the head, neck, or lung), gastrectomy or jejunioileal bypass, and weight loss of at least 10% from ideal body weight;
- Children younger than 5 years of age; and
- Infants, children, and adolescents exposed to adults in high-risk categories (see Chapter 3, Testing for Tuberculosis Disease and Infection).

Table 5.1
High-Priority Candidates for LTBI Treatment Using IGRA or TST*

Groups Who Should Be Given High Priority for LTBI Treatment	
People who have a positive IGRA result or a TST reaction of 5 or more millimeters	People who have a positive IGRA result or a TST reaction of 10 or more millimeters
<ul style="list-style-type: none"> • HIV-infected persons** • Recent contacts of persons with infectious TB disease** • Persons with fibrotic changes on chest radiograph consistent with prior TB disease • Patients with organ transplants and other immunosuppressed patients (including patients receiving the equivalent of 15 mg/day of prednisone for ≥ 1 month) 	<ul style="list-style-type: none"> • Recent arrivals to the United States (<5 years) from high-prevalence areas (e.g., Asia, Africa, Eastern Europe, Russia, or Latin America) • Injection drug users • Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, or other health-care facilities) • Mycobacteriology laboratory personnel • Persons with medical conditions that increase the risk for progression to TB disease, including silicosis, diabetes mellitus, chronic renal failure, certain types of cancer (e.g., leukemia and lymphomas, or cancer of the head, neck or lung), gastrectomy or jejunioileal bypass, and weight loss of at least 10% below body weight; • Children younger than 5 years of age; or children and adolescents exposed to adults in high-risk categories

* See Chapter 3, Testing for Tuberculosis Infection and Disease for information on interpreting a TST or IGRA result

** In certain circumstances, people in these categories may be given LTBI treatment even if they do **not** have a positive TST or IGRA result (see the Special Considerations for LTBI Treatment section in this Chapter).

Persons with No Known Risk Factors Who Have Positive IGRA Result, or TST Reaction ≥ 15 mm

People without any risk factors generally should **not** be tested for TB infection. Testing should be targeted to groups at high risk for LTBI and TB disease (see Chapter 3, Testing for Tuberculosis Infection and Disease). However, if a person without any risk factors is tested and has a positive IGRA result or TST reaction that is ≥ 15 mm, he or she should be evaluated for LTBI treatment once TB disease is excluded.

People without any risk factors generally should not be tested for TB infection.

Close Contacts Who Have a Negative IGRA or TST Result

Some contacts who have a negative IGRA or TST result should be evaluated for treatment of LTBI after TB disease has been ruled out. These contacts include:

- Children less than 5 years of age
- Immunosuppressed persons
- Those at risk for rapid progression to TB disease once infected (see Chapter 3, Testing for Tuberculosis Infection and Disease)

Any contact who is to be treated for LTBI should have a chest radiograph to exclude pulmonary TB disease before starting treatment.

Any contact who is to be treated for LTBI should have a chest radiograph to exclude pulmonary TB disease before starting treatment.

Close contacts who have a negative IGRA or TST result should be retested 8 to 10 weeks after they were last exposed to infectious TB disease. This is due to the fact that it can take 2 to 8 weeks after TB infection for the body's immune system to react to tuberculin and for the infection to be detected.

Close contacts who have a negative IGRA or TST result should be retested 8 to 10 weeks after they were last exposed to infectious TB disease.

HIV-Infected Contacts

Contacts known or suspected to be HIV infected or who have other serious immunocompromising conditions should be started on treatment for LTBI regardless of their IGRA or TST result after TB disease has been excluded. Treatment of LTBI may be discontinued if the TST or IGRA result is negative on the second test given 8 to 10 weeks after the last exposure and if the person is no longer exposed to infectious TB disease. However, because HIV-infected and other immunocompromised persons may be anergic and not be able to manifest a positive TST or IGRA result if infected, in some cases medical providers may decide to prescribe a complete course of LTBI treatment even if the second TST or IGRA result is negative, particularly if the exposure to TB is substantial (e.g., prolonged, frequent exposure to very infectious TB patient).

Contacts known or suspected to be HIV infected or who have other serious immunocompromising conditions should be started on treatment for LTBI regardless of their IGRA or TST result after TB disease has been excluded.

Infants and Young Children

Because of their age, infants and young children with LTBI are known to have been infected recently, and thus are at a high risk of their infection progressing to TB disease (Table 5.2). Infants and young children are also more likely than older children and adults to develop life-threatening forms of TB disease, especially meningeal and disseminated disease, because they do **not** have fully developed immune systems.

Because of their age, infants and young children with LTBI are known to have been infected recently, and thus are at a high risk of their infection progressing to TB disease.

Infants and young children are more likely than older children and adults to develop life-threatening forms of TB disease.

Window Prophylaxis

Children less than 5 years of age who are close contacts to an adult with infectious TB should receive treatment for LTBI even if the TST result is negative and once TB disease is excluded by chest radiograph and symptom review; this is called “window” prophylaxis. Also, infected infants may be anergic as late as 6 months of age. A second TST should be administered 8 to 10 weeks after the last exposure to infectious TB disease. Window prophylaxis can be discontinued if all of the following conditions are met:

- The infant is at least 6 months of age
- The second TST result is also negative
- The second TST was performed at least 8 weeks after the child was last exposed to an adult with infectious TB disease

Children less than 5 years of age who are close contacts to an adult with infectious TB should receive treatment for LTBI even if the TST result is negative once TB disease is excluded by chest radiograph and symptom review.

**Table 5.2
LTBI in Children**

Infants and Young Children with LTBI	Treating Children Less than 5 Years of Age Who Are Close Contacts
<ul style="list-style-type: none"> • Are known to have been infected recently (because of their age) • Are more likely than older children and adults to develop life-threatening forms of TB disease (e.g., disseminated TB, TB meningitis) 	<ul style="list-style-type: none"> • Should provide LTBI treatment even if initial TST result is negative once TB disease is excluded (infected infants may be anergic as late as 6 months of age)
	<ul style="list-style-type: none"> • Administer a second TST 8 to 10 weeks after the last exposure to infectious TB disease
	<ul style="list-style-type: none"> • Discontinue window prophylaxis if all of the following conditions are met: <ul style="list-style-type: none"> » Infant is at least 6 months of age » Second TST result is also negative » Second TST was performed at least 8 weeks after the child was last exposed to infectious TB disease

Study Questions

Match the patient with the TST reaction size that makes them a candidate for LTBI.

(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Patients	TST Reaction that Makes Them a Candidate for LTBI
___ 5.2 Peter is an injection drug user.	A. ≥ 5 mm of induration
___ 5.3 Louis is HIV positive.	B. ≥ 10 mm of induration
___ 5.4 Katrina, a 4-year-old, is a recent arrival from Mexico.	C. ≥ 15 mm of induration
___ 5.5 Edith is a resident at the DeLand Nursing Home.	
___ 5.6 Ann lives with her brother Joel, who has infectious TB disease.	
___ 5.7 Richard is the recipient of a heart transplant.	
___ 5.8 Sherry is a bank teller and has no known risk factors for TB.	
___ 5.9 Ginny is a nurse in the Dade County Correctional Facility.	
___ 5.10 Joe is diabetic.	

5.11 The following close contacts to someone with infectious TB disease have a negative IGRA result. Which patient(s) should be evaluated for treatment of LTBI?

(choose the one best answer)

- A.** Bernard is being treated for leukemia.
- B.** Sophia is 6 years old.
- C.** Kathy works in a bakery.
- D.** A, B, and C are all correct.
- E.** Only A and B are correct.

5.12 When should close contacts who have a negative IGRA or TST result be retested?

(choose the one best answer)

- A. 4 to 6 weeks after they were last exposed to infectious TB disease.
- B. 8 to 10 weeks after they were last exposed to infectious TB disease.
- C. It is **not** necessary to retest them.

5.13 Which of the following statements is true about infants and young children with LTBI?

(choose the one best answer)

- A. Because of their age, they are known to have been infected recently.
- B. They are at high risk of their infection progressing to TB disease.
- C. They are less likely than older children and adults to develop life-threatening forms of TB disease.
- D. A, B, and C are all correct.
- E. Only A and B are correct.

LTBI Treatment Regimens

There are several treatment regimens available for the treatment of LTBI. Providers should choose the appropriate regimen based on

- Drug-susceptibility results of the presumed source case (if known);
- Coexisting medical illnesses; and
- Potential for drug-drug interactions (Table 5.3).

For persons who are at especially high risk for TB disease and are either suspected of nonadherence or are given an intermittent dosing regimen, directly observed therapy (DOT) for LTBI should be considered (for more information on DOT, see Chapter 6, Treatment of Tuberculosis Disease). This method of treatment is especially appropriate if the person in need of LTBI treatment lives with a household member who is on DOT for TB disease, or lives in an institution or facility where treatment for LTBI can be observed by a staff member. It is necessary to exclude TB disease before starting LTBI treatment.

For persons who are at especially high risk for TB disease and are either suspected of nonadherence or are given an intermittent dosing regimen, directly observed therapy (DOT) for LTBI should be considered.

Isoniazid (INH) Dosage

When INH alone is given to persons with TB disease, drug resistance may develop. For this reason, persons suspected of having TB disease should receive the recommended multidrug regimen for treatment of TB disease rather than INH monotherapy until the diagnosis is confirmed or excluded.

There are two options for treatment with INH (Table 5.3):

- 9-month regimen
- 6-month regimen

INH is normally used alone for treatment of LTBI in a single daily dose of 300 mg in adults and 10–20 mg/kg body weight in children, not to exceed 300 mg per dose. INH can be given two times a week at a dosage of 20–40 mg/kg by DOT for LTBI for children, or 900 mg for adults.

The 9-month regimen is preferred because it is more efficacious. Treatment for LTBI for 6 months rather than 9 months may be more cost-effective and result in greater adherence by patients; therefore, local programs may prefer to implement the 6-month regimen rather than the 9-month regimen. Every effort should be made to ensure that patients adhere to LTBI treatment for at least 6 months.

When INH alone is given to persons with TB disease, drug resistance may develop. For this reason, persons suspected of having TB disease should receive the recommended multidrug regimen for treatment of disease rather than INH monotherapy until the diagnosis is confirmed or excluded.

9-Month INH Regimen

A 9-month INH regimen is considered optimal treatment. In order to be considered adequate treatment, the patient must receive a minimum of 270 doses administered within 12 months. The preferred regimen for children 2 to 11 years of age is 9 months of daily INH. Patients may be treated with a twice-weekly regimen as an alternative as long as they are undergoing DOT. In a twice-weekly regimen, 76 doses administered within 12 months is considered adequate therapy.

6-Month INH Regimen

A 6-month INH regimen also provides substantial protection against developing TB disease, but it is less protective than the 9-month regimen. In order to be considered adequate treatment, the patient must receive a minimum of 180 doses administered within 9 months. Patients may be treated with a twice-weekly regimen given by DOT as an alternative regimen. In the twice-weekly regimen, 52 doses administered within 9 months is considered adequate therapy. This regimen is not recommended for children, or immunosuppressed persons, or those with evidence of previous TB on chest radiograph.

Isoniazid (INH) and Rifapentine (RPT) Regimen

3-Month INH-RPT Regimen (12-Dose Regimen)

The 12-dose regimen is a combination of INH and RPT given in 12 once-weekly doses under DOT. Because missed doses, altered dosing intervals or amounts, or incomplete treatment could jeopardize the 12-dose regimen efficacy or safety, DOT is strongly recommended for this regimen. Patients using the 12-dose regimen should undergo monthly clinical monitoring, including inquiries about side effects and a physical assessment for signs of adverse effects.

The 12-dose regimen

- Is recommended as an equal option to 9 months of daily INH, but does **not** replace other recommended treatment options for LTBI (Table 5.3)
- Is recommended for treating LTBI in
 - » Otherwise healthy people, 12 years of age or older and who were recently in contact with infectious TB, or who had tuberculin skin test or positive blood test for TB infection conversions.
- Can be considered for specific groups when it offers practical advantages, such as completion of treatment within a limited timeframe.

The 12-dose regimen is **not** recommended for children younger than 2 years, HIV-infected patients taking antiretroviral therapy (ART), patients with presumed INH or RIF-resistant *M. tuberculosis*, pregnant women, or women expecting to become pregnant within the treatment period.

The dosage for a combination 12-dose regimen of INH and RPT is:

Isoniazid (INH)

- 15 mg/kg rounded up to the nearest 50 or 100 mg with a 900 mg maximum.

Rifapentine (RPT)

- 10.0–14.0 kg 300 mg
- 14.1–25.0 kg 450 mg
- 25.1–32.0 kg 600 mg
- 32.1–49.9 kg 750 mg
- ≥ 50.0 kg 900 mg maximum.

INH is formulated as 100 mg and 300 mg tablets. RPT is formulated as 150 mg tablets packed in blister packs that should be kept sealed until usage. New formulations with larger dosage per tablet and fixed-dose INH-RPT combinations are in development.

The 12-dose regimen is recommended as an equal option to 9 months of daily INH, but does not replace other recommended treatment options for LTBI.

Table 5.3
Drug Regimens for the Treatment of LTBI*

Drug	Duration	Interval	Minimum Doses	Comments
INH	9 months	Daily	270	<ul style="list-style-type: none"> The preferred regimen is daily treatment for 9 months Recommended regimen for people with HIV, for children, and for people with chest radiograph findings suggestive of previous TB disease DOT must be used with twice-weekly dosing
		Twice weekly	76	
	6 months	Daily	180	<ul style="list-style-type: none"> Not recommended for people with HIV, for children, or for people with chest radiograph findings suggestive of previous TB disease DOT must be used with twice-weekly dosing
		Twice weekly	52	
INH and RPT	3 months	Once weekly	12	<ul style="list-style-type: none"> Recommended as an equal alternative to 9 months of daily INH for otherwise healthy patients aged ≥ 12 years who were recently in contact with infectious TB, or who had tuberculin skin test or a positive blood test for TB infection conversions The 12-dose regimen can be considered for other groups when it offers practical advantages, such as completion within a limited timeframe DOT is strongly recommended Not recommended for children younger than 2 years, HIV-infected patients taking ART, patients with presumed INH or RIF-resistant <i>M. tuberculosis</i>, pregnant women, or women expecting to become pregnant within the treatment period

* For more detailed information on LTBI treatment, please refer to Targeted tuberculin testing and treatment of latent TB infection. *MMWR* 2000; 49 (No. RR-6).
http://www.cdc.gov/tb/publications/reportsarticles/mmwr/mmwr_updates.htm

* Adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection. *MMWR* 2003; 52 (31).
<http://www.cdc.gov/MMWR/preview/MMWRhtml/mm5231a4.htm>

* Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent *Mycobacterium tuberculosis* infection. *MMWR* 2011; 60 (48).
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w

Table 5.4
Adverse Drug Reactions to INH

Adverse Reaction	Comments
Peripheral neuropathy	<ul style="list-style-type: none"> • Uncommon at doses of 5 mg/kg • Those at risk may also be given pyridoxine (vitamin B₆) <ul style="list-style-type: none"> » Persons at high risk for neuropathy (e.g., diabetes, uremia, alcoholism, malnutrition, HIV infection) » Pregnant women » Persons with a seizure disorder » Patients who develop signs and symptoms of peripheral neuropathy
Fatal hepatitis	<ul style="list-style-type: none"> • Pregnant women are at increased risk • Postpartum women are at increased risk, especially during the initial 3-month postpartum period
Elevated liver enzymes	<ul style="list-style-type: none"> • 10% to 20% of persons taking INH will have some mild elevation of liver enzymes. These tend to resolve even if INH is continued. • Discontinue INH if the following occurs: <ul style="list-style-type: none"> » Measurements exceed 3 times the normal limit with symptoms present » Measurements exceed 5 times the upper limit of normal in an asymptomatic individual • Provide close clinical and laboratory monitoring if there are any signs or symptoms of hepatotoxicity or liver function test elevations less than the levels listed above

Rifampin (RIF) Regimen

For persons who **cannot** tolerate INH or have been exposed to INH-resistant TB, an alternative treatment regimen is 4 months of RIF. In order to be considered adequate treatment, the patient must receive a minimum of 120 doses administered within 6 months. RIF should not be used in HIV-infected persons being treated with some combinations of ART. In some situations where RIF **cannot** be used because of interactions with ART, another drug, rifabutin, may be used.

For persons who cannot tolerate INH or have been exposed to INH-resistant TB, an alternative treatment regimen is 4 months of RIF.

RIF should not be used in HIV-infected persons being treated with some combinations of ART.

Adverse Drug Reactions

Patients on treatment for LTBI should be instructed to report any signs and symptoms of adverse drug reactions to their health care provider, including

- Unexplained anorexia, nausea or vomiting, dark urine*, or icterus
- Persistent paresthesia of hands and feet
- Persistent weakness, fatigue, fever, or abdominal tenderness
- Easy bruising or bleeding

Peripheral neuropathy is associated with the use of INH, but is uncommon at doses of 5 mg/kg (Table 5.4). Persons with risk factors for neuropathy (e.g., diabetes, uremia, alcoholism, malnutrition, HIV infection), pregnant women, and persons with seizure disorder may be given pyridoxine (vitamin B6) 10–50 mg/day with INH, as this may prevent neuropathy. Patients who develop signs and symptoms of peripheral neuropathy may also be started on vitamin B6.

About 10% to 20% of persons taking INH will have some mild, asymptomatic elevation of liver enzymes (ALT, AST). These abnormalities tend to resolve even if INH is continued. For this reason, routine monitoring of liver enzymes is not recommended for all patients receiving INH. In persons who experience symptoms consistent with liver injury, liver enzymes should be measured to evaluate for hepatotoxicity. If any of the liver enzymes exceed three times the normal limit with symptoms present, it is generally recommended that INH be withheld. For liver enzyme elevations less than three times the upper limit of normal in symptomatic patients, at minimum close clinical and laboratory monitoring should be instituted if treatment is to be continued. Additional information on monitoring patients on LTBI treatment is provided later in this chapter.

About 10% to 20% of persons taking INH will have some mild, asymptomatic elevation of liver enzymes.

Some evidence suggests that pregnant women are at increased risk for fatal hepatitis associated with INH. This risk may also increase during the immediate postpartum period. These persons should be closely monitored for adverse reactions throughout the course of treatment.

Recommendation Against the Use of RIF/Pyrazinamide (PZA) Treatment Regimen

Recommendations for the use of a daily or a twice-weekly, 2-month regimen of RIF with PZA for LTBI treatment have changed due to associated severe liver injury. Based on the high rates of hospitalization and death from liver injury in patients treated with RIF and PZA for LTBI treatment, the American Thoracic Society (ATS) and CDC now recommend that this regimen not be offered to persons with LTBI. Alternative regimens are recommended for the treatment of LTBI (Table 5.1). RIF and PZA should continue to be administered in multidrug regimens for the treatment of persons with TB disease.

RIF and PZA should not be offered to persons with LTBI.

RIF and PZA should continue to be administered in multidrug regimens for the treatment of persons with TB disease.

Study Questions

5.14 What should an appropriate LTBI treatment regimen be based on?

(choose the one best answer)

- A. Drug-susceptibility results of the source case (if known).
- B. Coexisting medical illnesses.
- C. Potential for drug-drug interactions.
- D. A, B, and C are all correct.
- E. Only A and B are correct.

5.15 Which of the following is a recommended LTBI treatment regimen?

(choose the one best answer)

- A. INH given daily (270 doses) for 9 months.
- B. INH and RPT given once weekly (12 doses) for 3 months.
- C. INH and RIF given daily (270 doses of each drug) for 9 months.
- D. A, B, and C are all correct.
- E. Only A and B are correct.

5.16 Which of the following is an adverse reaction to INH?

(choose the one best answer)

- A. Peripheral neuropathy
- B. Fatal hepatitis
- C. Elevated liver enzymes
- D. A, B, and C are all correct.
- E. Only A and B are correct.

5.17 Which of the following statements about the use of the RIF/PZA drug combination for treating LTBI is true? (circle the one best answer)

- A. Can be used for both HIV-negative and HIV-infected patients who cannot tolerate INH.
- B. Not recommended for LTBI treatment based on high rates of hospitalization and death from liver injury.
- C. Is the recommended drug for treating pregnant women.
- D. A, B, and C are all correct.
- E. Only A and B are correct.

5.18 What LTBI treatment regimen may be recommended for people with a positive TST or IGRA result who have been exposed to INH-resistant TB disease? (circle the one best answer)

- A. RIF, at a minimum of 120 doses for 4 months.
- B. RIF, at a minimum of 180 doses for 6 months.
- C. RIF, at a minimum of 270 doses for 9 months.

LTBI Treatment Regimens for Specific Situations

HIV-Infected Persons

LTBI treatment of HIV-infected persons should be provided in consultation with an expert in the management of HIV and TB.

LTBI treatment of HIV-infected persons should be done in consultation with an expert in the management of HIV and TB.

INH

A 9-month regimen of daily INH is considered the optimal treatment for HIV-infected adults with LTBI. To be considered adequate therapy, the patient must receive a minimum of 270 doses of INH administered within 12 months. HIV-infected children should receive 9 months of INH treatment for LTBI. To be considered adequate therapy for HIV-infected persons, twice-weekly regimens of INH must be administered by DOT and consist of at least 76 doses administered within 12 months.

In HIV-infected persons, INH may be administered together with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-nucleoside reverse transcriptase inhibitors (NNRTIs). Children and adolescents who are HIV infected and/or have nutritional deficiencies should receive pyridoxine (vitamin B₆) supplementation.

INH-RPT (12-dose Regimen)

HIV-infected persons who are receiving ART should **not** take the 12-dose regimen of INH-RPT because the drug interactions have not been studied. However, HIV-infected persons who are otherwise healthy and are not receiving ART can be considered for the 12-dose regimen.

RIF

For HIV-infected patients who cannot tolerate INH or have been exposed to INH-resistant TB, an alternative treatment regimen is 4 months of RIF. To be considered adequate treatment, the patient must receive a minimum of 120 doses of RIF administered within 6 months. RIF should not be used in HIV-infected persons being treated with some combinations of ART. In some situations where RIF cannot be used because of interactions with ART, another drug, rifabutin, may be used.

Most protease inhibitors and delavirdine should not be administered together with RIF. Rifabutin with appropriate dose adjustments can be used with protease inhibitors and NNRTIs (except delavirdine). For more information, please see Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/default.htm.

Persons with Fibrotic Lesions

Persons who have a chest radiograph suggestive of old fibrotic lesions thought to represent previous TB disease should be treated for LTBI if they have the following:

- A positive IGRA result, or TST reaction (induration) of 5 mm or more;
- No symptoms of infectious TB disease; and
- No history of treatment for TB disease.

These persons should be evaluated with three sputum specimens for AFB smear and culture and only treated for LTBI once these specimens are negative by culture. Acceptable regimen options are described in Table 5.5.

Persons with evidence suggestive of healed, primary TB disease (i.e., calcified solitary pulmonary nodules, calcified hilar lymph nodes, and apical pleural capping) are **not** at increased risk for TB disease. Their risk for developing TB disease and the need for treatment of LTBI should be determined by consideration of other risk factors.

Persons with evidence suggestive of healed, primary TB disease (i.e., calcified solitary pulmonary nodules, calcified hilar lymph nodes, and apical pleural capping) are not at increased risk for TB disease.

Table 5.5
Drug Regimens for the Treatment of LTBI for Persons with Fibrotic Lesions

Drug	Duration	Interval	Minimum Doses	Comments
INH*	9 months	Daily	270	Provide LTBI treatment for patients who have a chest radiograph suggestive of old fibrotic lesions thought to represent previous TB disease and
		Twice weekly	76	
RIF	4 months	Daily	120	<ul style="list-style-type: none"> • A positive IGRA result or a TST reaction (induration of 5 mm or more) • No symptoms of infectious TB disease • No history of treatment for TB disease • Three negative sputum smears and cultures

* Preferred.

Contacts of Persons with Multidrug-Resistant TB

If a person is a contact of a patient with multidrug-resistant (MDR) TB, the risk of progressing to MDR TB disease should be considered before recommending treatment for LTBI. For persons likely to have been infected with a strain of *M. tuberculosis* resistant to both INH and RIF, alternative LTBI treatment regimens should be considered. The treatment of drug-resistant LTBI should be prescribed **in consultation with an MDR TB expert**.

If a person is a contact of a patient with multidrug-resistant (MDR) TB, the risk of progressing to MDR TB disease should be considered before recommending treatment for LTBI.

Pregnancy and Breast-feeding

INH administered either daily or twice weekly is the preferred regimen for the treatment of LTBI in pregnant women. Pregnant women taking INH should also take pyridoxine (vitamin B6) supplementation to ameliorate the side effects of the drug (Table 5.6). For pregnant women who are intolerant of INH or likely to be infected with an INH-resistant strain of *M. tuberculosis*, consultation with a TB expert is recommended.

The 12-dose regimen of INH-RPT is **not** recommended for pregnant women or women expecting to become pregnant during the treatment period because its safety in pregnancy has not yet been studied.

The 12-dose regimen of INH-RPT is not recommended for pregnant women or women expecting to become pregnant during the treatment period because its safety in pregnancy has not yet been studied.

For women who are at high risk for progression from LTBI to TB disease, especially those who are HIV infected or diabetic, LTBI treatment should **not** be delayed on the basis of pregnancy alone, even during the first trimester. TB disease must be excluded through symptom review (to see an example, go to: <http://health.state.ga.us/pdfs/tb/TB.Symp.Screen.09.Eng.pdf>) and chest radiograph prior to initiation of LTBI treatment. For these women, careful clinical monitoring and/or lab monitoring should be conducted.

For women who are at high risk for the progression of LTBI to TB disease, especially those who are HIV infected or diabetic, LTBI treatment should not be delayed on the basis of pregnancy alone, even during the first trimester.

Breast-feeding is not contraindicated when a mother is being treated for LTBI. The amount of INH in the mother's breast milk is inadequate to either harm or benefit an infant. Breast-fed infants of mothers who take INH should receive supplemental pyridoxine (vitamin B₆).

**Table 5.6
Drug Regimens for the Treatment of LTBI
for Pregnancy and Breast-Feeding**

Drug	Duration	Interval	Minimum Doses	Comments
INH	9 months	Daily	270	<ul style="list-style-type: none"> • Do not delay initiation of therapy based on pregnancy alone, even during the first trimester for women who are at high risk for progression from LTBI to TB disease, especially those who are HIV infected or diabetic
		Twice weekly	76	<ul style="list-style-type: none"> • Breast-feeding is not contraindicated when a mother is being treated for LTBI • The amount of INH provided in the mother's breast milk is inadequate to either harm or benefit an infant. • Breast-feeding infants whose mothers are taking INH should receive supplemental pyridoxine (vitamin B₆)

Study Questions

Case Study– Jesse

Jesse has fibrotic lesions representative of previous TB disease, a TST reaction of 5 mm, and no history of treatment for TB disease.

5.19 How should Jesse be evaluated?

(choose the one best answer)

- A. With a CT scan to determine the extent of lesions
- B. With three sputum specimens for AFB smear and culture
- C. With a bronchoscopy to obtain specimen samples
- D. A, B, and C are all correct.
- E. Only A and B are correct.

5.20 Once TB disease is ruled out, what should Jesse’s LTBI treatment regimen include?

(choose the one best answer)

- A. 3 months of INH or 1 month of RIF
- B. 6 months of INH or 2 months of RIF
- C. 9 months of INH or 4 months of RIF

5.21 Which of the following statements about pregnancy and breast-feeding is true?

(choose the one best answer)

- A. The preferred regimen for the treatment of LTBI in pregnant women is INH taken daily or twice weekly, with pyridoxine supplement.
- B. For pregnant women who are HIV infected, initiation of therapy should **not** be delayed on the basis of pregnancy alone even during the trimester.
- C. Breast-feeding is contraindicated when a mother is being treated for LTBI.
- D. A, B, and C are all correct.
- E. Only A and B are correct.

Patient Monitoring

Patient Medical Evaluation and Monitoring for LTBI Treatment

The components of patient monitoring for LTBI treatment include:

- Medical evaluation prior to LTBI treatment
- Baseline laboratory testing
- Monthly medical evaluation
- Routine laboratory monitoring
- Treatment follow-up

Medical Evaluation Prior to LTBI Treatment

Before treatment for LTBI is started, clinicians should conduct a medical history to:

- Exclude the possibility of TB disease, including symptom review;
- Determine if there is a history of prior treatment for LTBI or TB disease;
- Determine if there are any co-existing medical conditions that are a contraindication to LTBI treatment or are associated with an increased risk of adverse effects from treatment;
- Obtain information about current and previous drug therapy, including any previous or current adverse reactions to drugs considered for treatment of LTBI; and
- Recommend HIV testing for all TB and LTBI patients after the patient is notified that testing will be performed, unless the patient declines (opt-out screening).

In addition, conducting a medical history provides an opportunity to establish rapport with the patient and to highlight important aspects of treatment, such as:

- Benefits of treatment;
- Importance of adherence to the treatment regimen;
- Possible adverse side effects of the regimen; and
- Establishment of an optimal follow-up plan.

A chest radiograph should be performed; LTBI treatment should only be prescribed if the radiograph is normal, without evidence of any findings consistent with TB disease. If there are any abnormalities consistent with TB disease or if the patient is symptomatic, the patient should have three sputum specimens collected for AFB smear and culture, and only be given treatment for LTBI once all three cultures are negative.

A chest radiograph should be performed; LTBI treatment should only be prescribed if the radiograph is normal, without evidence of any findings consistent with TB disease.

Baseline Laboratory Testing

Baseline laboratory testing is **not** routinely indicated for all patients at the start of treatment for LTBI. Baseline hepatic measurements of serum AST (SGOT) or ALT (SGPT) and bilirubin are indicated for patients whose initial evaluation suggests a liver disorder. Baseline testing is also indicated for

- Patients with HIV infection;
- Women who are pregnant or in the immediate postpartum period (within 3 months after delivery); or
- Persons with a history of chronic liver disease (e.g., hepatitis B or C, alcoholic hepatitis or cirrhosis), persons who use alcohol regularly, and others who are at risk of chronic liver disease.

Baseline laboratory testing is **not** routinely indicated in older persons. However, testing may be considered on an individual basis, particularly for patients who are taking other medications for chronic medical conditions. Active hepatitis and end-stage liver disease are relative contraindications to the use of INH or RIF for treatment of LTBI. Use of these drugs in such patients must be undertaken with caution. Patients with baseline abnormal liver function tests should be monitored at regular intervals with clinical and laboratory evaluation.

Patients with baseline abnormal liver function tests should be monitored at regular intervals with clinical and laboratory evaluation.

Baseline laboratory testing is not routinely indicated in older persons. However, testing may be considered on an individual basis, particularly for patients who are taking other medications for chronic medical conditions.

Monthly Evaluation

At least once a month, the patient should be evaluated for

- Adherence to the prescribed regimen;
- Signs and symptoms of TB disease; and
- Signs and symptoms of adverse effects, especially hepatitis (i.e., jaundice, loss of appetite, fatigue, and/or muscle and joint aches).

Routine Laboratory Monitoring

Routine laboratory monitoring during treatment of LTBI is recommended only for those whose baseline liver function tests are abnormal and for other persons with a risk of hepatic disease. Clinicians should order laboratory testing, such as liver function studies, for patients with symptoms compatible with hepatotoxicity, to evaluate possible adverse reactions that occur during the treatment regimen. If any of the liver enzymes exceed three times the normal limit with symptoms present or five times the upper limit of normal in an asymptomatic individual, it is generally recommended that INH be withheld. For liver enzyme elevations less than three times the upper limit of normal in

symptomatic patients, at minimum close clinical and laboratory monitoring should be instituted if treatment is to be continued.

Treatment Follow-Up

Patients should receive documentation of TST or IGRA results, medication taken, treatment duration, and treatment completion dates. They should be told to present this documentation when they are required to be tested for TB. Patients should also be re-educated about the signs and symptoms of TB disease and advised to seek medical attention if these occur. They should be advised that treatment greatly reduces the risk of progression to disease, but does not entirely eliminate it.

Patients should be advised that treatment greatly reduces the risk of progression to disease but does not entirely eliminate it.

Study Questions

5.22 Why should patients receive a medical evaluation before starting treatment for LTBI?
(choose the one best answer)

- A.** To exclude the possibility of TB disease
- B.** To determine if there is a history of prior treatment for LTBI or TB disease
- C.** To determine existing medical conditions
- D.** A, B, and C are all correct.
- E.** Only A and B are correct.

Case Study– Edgar, Louise, and Samantha

Edgar was admitted to the hospital last week and diagnosed with infectious TB disease. He lives with his wife, Louise, and 1-year-old daughter Samantha. You visit their home to give both Louise and Samantha a TST. Neither one has symptoms of TB disease. You return 2 days later to read the results. You find that Louise has 14 mm of induration, but Samantha has no induration.

5.23 Why should Louise, Edgar's wife, be evaluated for LTBI treatment?
(choose the one best answer)

- A.** She is a close contact of someone with infectious TB disease.
- B.** She has a positive skin test reaction of greater than 5 mm.
- C.** She has an infant daughter.
- D.** A, B, and C are all correct.
- E.** Only A and B are correct.

5.24 After Louise is evaluated, when should she receive LTBI treatment?

(choose the one best answer)

- A. After TB disease is ruled out.
- B. After it has been determined that she has never been treated for TB infection or disease.
- C. After any medical problems that may complicate therapy have been ruled out.
- D. A, B, and C are all correct.
- E. Only A and B are correct.

5.25 Should Samantha, Edgar's daughter, receive LTBI treatment?

(choose the one best answer)

- A. Yes, she should start LTBI treatment after TB disease has been excluded because she is a close contact of a person with infectious TB disease and she is less than 4 years old.
- B. No, because she had a negative TST.

5.26 Baseline laboratory testing is routinely indicated for which of the following patients?

(choose the one best answer)

- A. HIV-infected persons
- B. Pregnant women
- C. Teenagers
- D. A, B, and C are all correct.
- E. Only A and B are correct.

5.27 Loretta is receiving LTBI treatment and is evaluated each month by her public health nurse. What should she be evaluated for?

(choose the one best answer)

- A. Adherence to the prescribed regimen
- B. Signs and symptoms of TB disease
- C. Signs and symptoms of adverse effects, especially hepatitis
- D. A, B, and C are all correct.
- E. Only A and B are correct.

5.28 Routine laboratory monitoring is recommended for which of the following patients with LTBI? (circle the one best answer)

- A. Persons whose baseline liver function tests are abnormal
- B. Persons with a risk of hepatic disease
- C. All patients receiving LTBI
- D. A, B, and C are all correct.
- E. Only A and B are correct.

Chapter Summary

Treatment of LTBI is essential to controlling and eliminating TB disease in the United States. It substantially reduces the risk that persons infected with *M. tuberculosis* will progress to TB disease. Certain groups are at high risk of developing TB disease once infected. Targeted testing programs should be designed to identify persons who are at high risk for TB disease and who would benefit from treatment of LTBI. Targeted testing should be undertaken only if resources are identified and available to ensure full evaluation and treatment. There are two methods available for the detection of *M. tuberculosis* infection in the United States, the TST and IGRAs.

Persons in the following high-risk groups should be given treatment for LTBI if they have either a positive IGRA result **or** if their reaction to the tuberculin skin test is ≥ 5 mm:

- HIV-infected persons;
- Recent contacts of persons with infectious TB disease;
- Persons with fibrotic changes on chest radiograph consistent with prior TB disease (once TB disease is excluded); and
- Patients with organ transplants, and other immunosuppressed patients (including patients receiving the equivalent of 15 mg/day of prednisone for ≥ 1 month).

Persons in the following high-risk groups should be considered for treatment of LTBI if they have either a positive IGRA result **or** if their reaction to the TST is ≥ 10 mm:

- Recent arrivals to the United States (<5 years) from high-prevalence areas (e.g. Africa, Asia, Eastern Europe, Latin America, and Russia);
- Injection drug users;
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, and hospitals);
- Mycobacteriology laboratory personnel;
- Persons with medical conditions that increase the risk for progression to TB disease, i.e., silicosis, diabetes mellitus, chronic renal failure, certain types of cancer (e.g., leukemia and lymphomas, or cancer of the head, neck, or lung), gastrectomy or jejunioileal bypass, and weight loss of at least 10% from ideal body weight;

- Children younger than 5 years of age; and
- Infants, children, and adolescents exposed to adults in high-risk categories.

People without any risk factors generally should **not** be tested for TB infection. Testing should be targeted to groups at high risk for LTBI and TB disease. However, if a person without any risk factors is tested and has a positive IGRA result or TST reaction that is ≥ 15 mm, he or she should be evaluated for LTBI treatment once TB disease is excluded.

There are several treatment regimens available for the treatment of LTBI. Providers should choose the appropriate regimen based on the susceptibility results of the presumed source case (if known), coexisting medical illnesses, and the potential for drug-drug interactions.

INH Regimens

When INH alone is given to persons with TB disease, resistance may develop. For this reason, persons suspected of having TB disease should receive the recommended multidrug regimen for treatment of TB disease rather than INH monotherapy until the diagnosis is confirmed or excluded.

There are two options for treatment with INH:

- 9-month regimen
- 6-month regimen

INH is normally used alone for treatment of LTBI in a single daily dose of 300 mg in adults and 10–20 mg/kg body weight in children, not to exceed 300 mg per dose. INH can be given two times a week at a dosage of 20–40 mg/kg by DOT for LTBI for children, or 900 mg for adults.

The 9-month regimen is the preferred because it is more efficacious. Treatment for LTBI for 6 months rather than 9 months may be more cost-effective and result in greater adherence by patients; therefore, local programs may prefer to implement the 6-month regimen rather than the 9-month regimen. Every effort should be made to ensure that patients adhere to treatment for LTBI infection for at least 6 months.

9-Month INH Regimen

A 9-month INH regimen is considered optimal treatment. In order to be considered adequate treatment, the patient must receive a minimum of 270 doses administered within 12 months. The preferred regimen for children 2 to 11 years of age is 9 months of daily INH. Patients may be treated with a twice-weekly regimen as an alternative as long as they are undergoing DOT. In a twice-weekly regimen, 76 doses administered within 12 months is considered adequate therapy.

6-Month INH Regimen

A 6-month INH regimen also provides substantial protection against developing TB disease, but it is less protective than the 9-month regimen. In order to be considered adequate treatment, the patient must receive a minimum of 180 doses administered within 9 months. Patients may be treated with a twice-weekly regimen given as DOT as an alternative. In a twice-weekly regimen, 52 doses administered within 9 months is considered adequate therapy. This regimen is not recommended for children, or immunosuppressed persons, or those with evidence of previous TB on chest radiograph.

3-Month INH-RPT Regimen (12-Dose Regimen)

The 12-dose regimen is a combination of INH and RPT given in 12 once-weekly doses under DOT. Because missed doses, altered dosing intervals or amounts, or incomplete treatment could jeopardize the 12-dose regimen efficacy or safety, DOT is strongly recommended for this regimen. Patients using the 12-dose regimen should undergo monthly clinical monitoring, including inquiries about side effects and a physical assessment for signs of adverse effects.

The 12-dose regimen does **not** replace other recommended treatment options for LTBI, but can be considered an equal option to the standard INH 9-month daily regimen for treating LTBI in otherwise healthy people, 12 years of age or older, who were recently in contact with infectious TB, or who had tuberculin skin test or blood test for TB infection conversions.

The dosage for a combination 12-dose regimen of INH and RPT is:

Isoniazid (INH)

- 15 mg/kg rounded up to the nearest 50 or 100 mg, with a 900 mg maximum.

Rifapentine (RPT)

- 10.0–14.0 kg 300 mg
- 14.1–25.0 kg 450 mg
- 25.1–32.0 kg 600 mg
- 32.1–49.9 kg 750 mg
- ≥ 50.0 kg 900 mg maximum.

INH is formulated as 100 mg and 300 mg tablets. RPT is formulated as 150 mg tablets packaged in blister packs that should be kept sealed until usage. New formulations with larger dosage per tablet and fixed-dose INH-RPT combinations are in development.

For persons who are at especially high risk for TB disease and are either suspected of nonadherence or given an intermittent dosing regimen, DOT for LTBI should be considered. This method of treatment is especially appropriate if the person in need of LTBI treatment lives with a household member who is on DOT for TB disease, or lives in an institution or facility where treatment for TB infection can be observed by a staff member. It is necessary to exclude TB disease before starting LTBI treatment.

Baseline laboratory testing is **not** routinely indicated for all patients at the start of treatment for LTBI. Baseline hepatic measurements of serum AST (SGOT) or ALT (SGPT) and bilirubin are indicated for patients whose initial evaluation suggests a liver disorder. Baseline testing is also indicated for:

- Patients with HIV infection;
- Women who are pregnant or in the immediate postpartum period (within 3 months of delivery); or
- Persons with a history of chronic liver disease (e.g., hepatitis B or C, alcoholic hepatitis or cirrhosis), persons who use alcohol regularly, and others who are at risk of chronic liver disease.

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Errata (February 3, 2012)

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