

Tuberculosis

Section XI.

Latent Tuberculosis Infection:
Evaluation, Treatment,
Monitoring and Follow-Up

Section XI.

Latent Tuberculosis Infection: Evaluation, Treatment, Monitoring and Follow-Up

Note: The term “tuberculin skin testing” (TST) is no longer used as it does not reflect the availability of blood-based tests for tuberculosis infection. A more general term, test for TB infection (TTBI), is used except in specific instances that reference the TST.

When a patient has been found to have latent TB infection (LTBI), based on the criteria detailed in Section X, the physician must make a treatment decision. Not everyone with latent infection is a candidate for treatment. However, all high-risk individuals who test positive for TB infection (see p. 174, Table X-1 and p. 180, Table X-4) should receive treatment for LTBI as soon as active TB has been ruled out.

Clinical Evaluation

Every patient who tests positive for TB infection should be examined by a physician, both to rule out TB disease and to be evaluated for treatment of LTBI. The clinical evaluation should include the elements listed below:

Medical History and Physical Examination

All patients should be asked about risk factors for the development of TB disease, including recent close contact with a person who has TB. Some patients, however, are not aware that they are contacts. For that reason, the TB Registry should also be checked to determine if the patient has been reported as a contact.

All patients should be asked about previous treatment for LTBI (the patient may refer to it as “preventive treatment”). Those who have completed a course of treatment for LTBI in the past should be asked about recent close contact with a person who has TB. In some situations, a chest X-ray (CXR) and a repeat course of treatment for LTBI may be indicated. (see p. 193).

All patients 18 years of age or older, including those without behavioral risk factors for HIV, should be counseled and offered HIV testing unless they have documentation of (1) a positive HIV antibody test or (2) a negative HIV antibody test obtained within the last 6 months.

Those younger than 18 years should be counseled and offered testing if they have behavioral risk factors for HIV and have no documented history of a positive HIV test. Parental consent for HIV testing is advised for patients younger than 18 years of age (see p. 26).

All patients should be evaluated for, and asked about, their history of alcohol ingestion, liver disease and hepatitis. See p. 190 for specific tests that should be ordered.

All patients should be assessed for contraindications to treatment for LTBI.

Chest X-ray

Everyone considered for LTBI treatment should undergo a CXR to rule out pulmonary TB disease. Children younger than 5 years of age (i.e., up to the day of their 5th birthday) should have both a posterior-anterior and a lateral CXR. All others should undergo a posterior-anterior CXR only. Additional X-rays should be done at the physician’s discretion. In general, if a CXR is done within 3 months of the medical evaluation and is documented as normal, a repeat CXR is not necessary unless the patient is currently symptomatic, immunosuppressed or a child younger than 5 years of age. In these cases the CXR should be taken within 1 month.

Patient Chest X-ray Classifications

A patient who has:

- A normal CXR, a positive test for TTBI and no signs or symptoms of TB disease should be classified as Class II.

- An abnormal CXR consistent with active TB disease should be classified as Class V (High), and should be managed according to Sections II and III of this manual.
- A CXR showing noncalcified fibrotic lesions, suggestive of old, healed TB, should be evaluated for current symptoms of TB. Physicians should take a complete blood count, chemistry panel, hepatitis screen and 3 consecutive sputum samples for smear, culture and susceptibility testing.
 - If there are no symptoms, classify the individual as Class V (Low), and follow the guidelines for treatment outlined on page 200.
 - If sputum cultures are negative for *M. tuberculosis* (*M. tb*) and the follow-up CXR at 2 months shows no change, reclassify the individual as Class IV.
 - If there are symptoms, classify the individual as Class V (High) and evaluate and treat for TB disease according to Sections II and III of this manual. If sputum cultures are positive for *M. tb*, if the follow-up CXR shows improvement, or if the patient responds clinically, reclassify the individual as Class III.

Some individuals appear at a Bureau of Tuberculosis Control (BTBC) chest center, with a report of a positive TTBI and a normal CXR, and request treatment for LTBI. In this case, the CXR report should be given to a center physician, who should decide whether a repeat CXR is indicated. In general, a repeat CXR should be obtained if:

- The original CXR was taken more than 3 months ago.
- The language in the CXR report is ambiguous, regardless of the date the CXR was taken.
- The individual currently has symptoms consistent with TB.

A CXR should be obtained immediately, even during the first trimester, for pregnant women:

- Who have symptoms that are highly suggestive of TB disease (e.g., prolonged cough, fever, night sweats, chest pain)

- Who are HIV-positive and (1) have a positive TTBI or (2) have a negative TTBI, but have been in close contact with a person who has pulmonary or laryngeal TB disease.

Other pregnant women who have a positive TTBI should be advised to obtain a CXR after the end of the first trimester.

A lead shield should be used for all pregnant women receiving CXR. Many are hesitant to receive CXR, because they fear exposing the fetus to unnecessary radiation. It should be stressed that the amount of radiation is minimal. (Explain that the patient would get the same amount of radiation by flying cross country in an airplane.) Also, the risk of untreated TB in a pregnant woman and the subsequent possibility of congenital TB in her infant far outweighs the risk from the small amount of radiation exposure.

Laboratory Tests for Individuals Being Considered for Latent Tuberculosis Infection Treatment

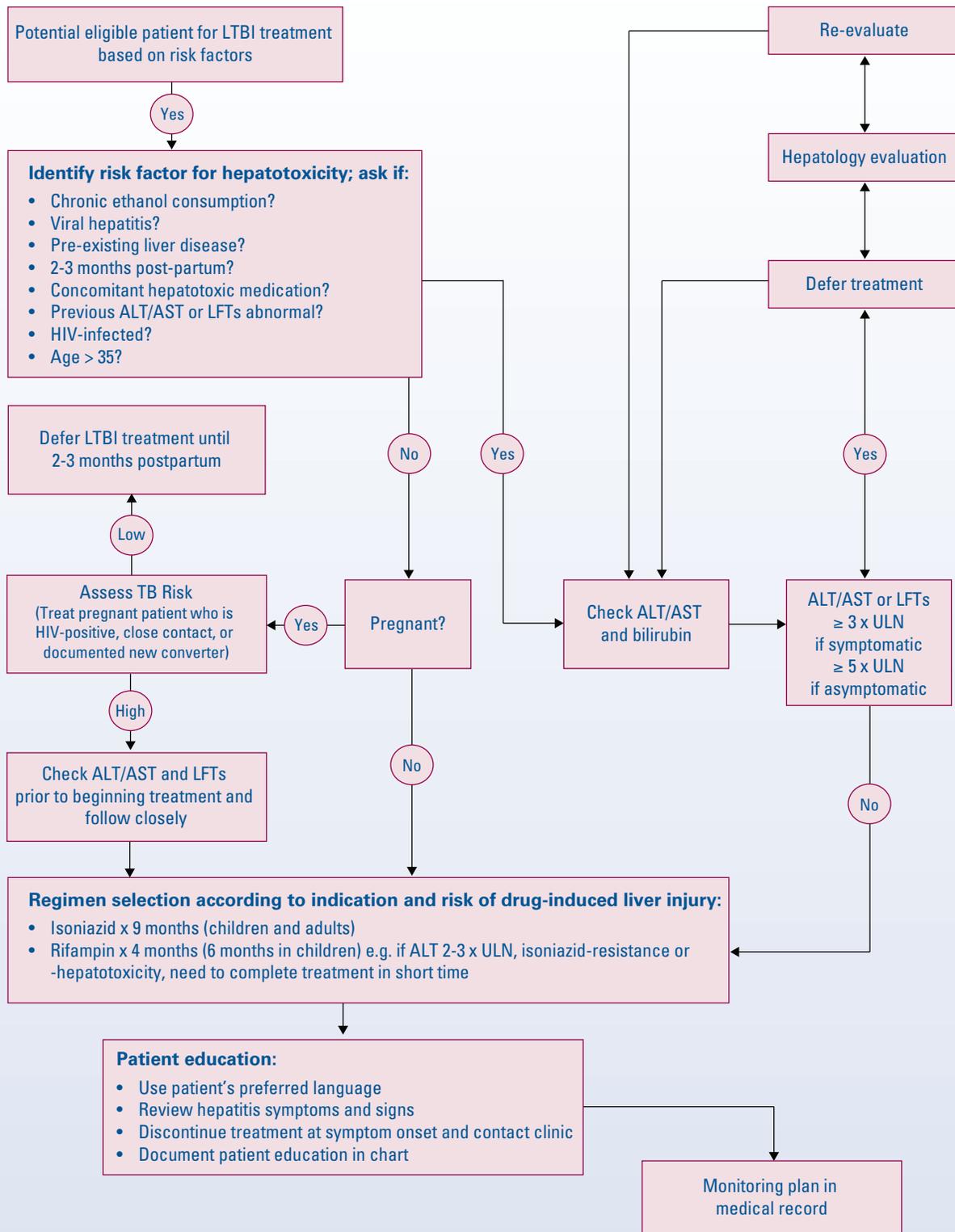
A complete blood cell count (CBC) and baseline liver function tests (LFTs) (AST/SGOT, ALT/SGPT, alkaline phosphatase, and total bilirubin), as well as a viral hepatitis screening profile, should be obtained for patients who:

- Are HIV-positive
- Have a history of heavy alcohol ingestion, liver disease or chronic hepatitis
- Are pregnant or are postpartum (up to 2-3 months after delivery)
- Have a history of drug injection
- Are older than 35 years
- Are starting treatment for LTBI with 2 or more anti-TB drugs
- Are already taking hepatotoxic drugs for other medical conditions

All abnormal test results should be evaluated by a physician as soon as possible and in all cases within 2 days of starting LTBI treatment. The physician should document follow-up in the medical record. See p. 191, Figure XI-1 for pretreatment clinical evaluation and counseling for LTBI.

Figure XI-1

Latent Tuberculosis Infection Pretreatment Clinical Evaluation and Counseling



Adapted from ATS Hepatotoxicity Statement (see Key Sources at end of section for full citation).

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, LFT = liver function test, LTBI = latent tuberculosis infection, TB = tuberculosis, ULN = upper limit of normal

XI. LATENT TB INFECTION (LTBI): EVALUATION, TREATMENT, MONITORING AND FOLLOW-UP

Candidates for Treatment For Latent Tuberculosis Infection

High-risk individuals fall into 2 categories (1) people presumed to have been recently infected, and (2) people whose underlying medical conditions substantially increase their risk of developing active TB disease. (See p. 174, Table X-1.) Routine testing of individuals at low risk for developing TB is *not* recommended.

Individuals Who May Have Been Recently Infected

- All close contacts of a person who has pulmonary or laryngeal TB (who have newly tested positive for TB infection) should be treated. See p. 163 for how to manage contacts with previously positive TTBI.
- Recent tuberculin skin test (TST) converters (who show an increase greater than or equal to 10 mm within a 2-year period) may have recent infection. When a TST-positive patient claims to have had a negative reaction to a Mantoux (not Tine) TST given in the past 2 years but cannot document it, accept the statement if the patient's history is reliable *and* if he or she is considered a recent converter. This protocol does *not* apply if the previous test was a Tine test.
- People who test positive for TB infection, or who have emigrated to the U.S. within the past 5 years from areas with high TB rates, or who have been abroad for more than 1 month in areas with high TB rates should be treated (see p. 175, Table X-2).

Patients with Clinical Conditions Associated with Progression From Latent Tuberculosis Infection to Active Tuberculosis

People who:

- Are HIV positive and those with behavioral risk factors for HIV infection who decline HIV testing
- Inject drugs, particularly those who also have HIV infection
- Show evidence of old, healed TB lesions on CXR. (See p. 200.)
- Are $\geq 10\%$ under ideal body weight

- Have clinical conditions that lead to a stressed or incompetent immune system, such as diabetes mellitus; silicosis; cancer of the head, neck or lung; hematologic and reticuloendothelial malignancies (e.g., leukemia or Hodgkin's disease); end-stage renal disease; intestinal bypass or gastrectomy; and chronic malabsorption syndromes
- Are receiving immunosuppressive therapy (i.e., prolonged corticosteroid therapy [the equivalent of greater than 15 mg/d of prednisone for 1 month or more], chemotherapy and tumor necrosis factor-alpha antagonists).
- Have diabetes mellitus and thus have an increased risk of progressing from latent infection to active TB. This is particularly true for insulin-dependent diabetics and for those with poorly controlled disease. If such individuals test positive for TB infection, they should be treated for LTBI regardless of age. Those whose diabetes is well controlled on oral agents or through diet, who do not have additional clinical conditions associated with increased risk of progression to active TB, or who do not have factors associated with recent infection should not be considered for treatment.

For guidelines on when to give a repeat course of treatment for LTBI in contacts that have already completed such treatment, see p. 193.

Persons with Immunosuppressive Conditions or Who Are Being Treated with Immunosuppressive Agents

- Evaluation and treatment for LTBI is recommended at the time the immunosuppressive condition is diagnosed or before starting treatment with immunosuppressive therapies such as prolonged corticosteroids; tumor necrosis factor-alpha antagonists (infliximab, etanercept, adalimumab) and chemotherapy.
- Patients awaiting transplant should be evaluated for LTBI.
- A TST result of greater than 5 mm should be considered indicative of TB infection in all these individuals. (See p. 180, Table X-4.) TST results in immunosuppressed individuals may be falsely negative due to drug therapy or to an underlying medical condition causing anergy. The individual may still be infected with *M. tb*. Two-step testing in these individuals

is recommended by some experts, as this may increase the yield of positive TSTs. Blood-based tests have not been studied in these individuals.

Contacts Who Should Start Treatment Regardless of Their Tuberculin Skin Test Reaction

People who have recently been exposed to TB may have a false-negative reaction to the test for TB infection. This may occur if they are tested within 8 weeks of their last exposure, even if they are truly infected. These patients should be retested 8 weeks after their last exposure. During the 8-week window between the 2 tests, the following individuals should start treatment for LTBI, even if the test is negative.

Contacts who are:

- Less than 5 years of age
- Between 5 and 15 years of age, at the physician's discretion
- HIV infected or otherwise immunosuppressed
- At behavioral risk for HIV infection who decline HIV testing

These contacts should undergo a CXR to rule out TB disease before starting treatment for LTBI.

If the second test for TB infection is negative, and the contact is not immunosuppressed, treatment may be discontinued. For most close contacts who are immunosuppressed or known to have HIV infection or who are at risk for HIV infection, a full course of treatment for LTBI is recommended—regardless of age or history of previous treatment (see p. 163.)

Pregnant Women as Candidates for Latent Tuberculosis Infection Treatment

Pregnant women should receive a TTBI only if they are in a high risk category. (See p. 174, Table X-1.) The need to treat active TB during pregnancy is unquestioned. Treatment of LTBI in pregnant women is more controversial, since the possible risk of hepatotoxicity must be weighed against the risk of developing active TB. However, for women who are HIV-positive, or have been recently infected (such as contacts of active TB cases or known recent conversions), start of therapy should not be delayed on the basis of pregnancy alone, even during the first trimester.

- Treatment should be started during the first trimester of pregnancy for:
 - TST-positive (≥ 5 mm) pregnant women who are HIV-positive or who have behavioral risk factors for HIV infection but decline HIV testing.
 - TST-positive (≥ 5 mm) pregnant women who have been in close contact with a smear-positive pulmonary TB patient. (At the physician's discretion, start of treatment can be delayed until after the second trimester but the patient should be under close observation for development of TB symptoms.)
- Treatment should be started promptly after the first trimester for pregnant women who have had a documented TST conversion in the past 2 years.
- Treatment, if indicated, should be started 2 to 3 months after delivery for all other pregnant women, including those with radiographic evidence of old, healed TB.

In pregnant women known or suspected to be infected with a TB strain resistant to at least isoniazid and rifampin, treatment for LTBI should be delayed until after delivery. This will avoid possible adverse effects of the medications on the developing fetus. A CXR should be obtained initially and again if the woman develops symptoms suggestive of TB disease. A lead shield should be used for CXRs in pregnant women. See p. 194, Figure XI-2 for evaluation of the pregnant woman at risk for TB.

See p. 196, Table XI-I for further information on LTBI treatment regimens for pregnant women.

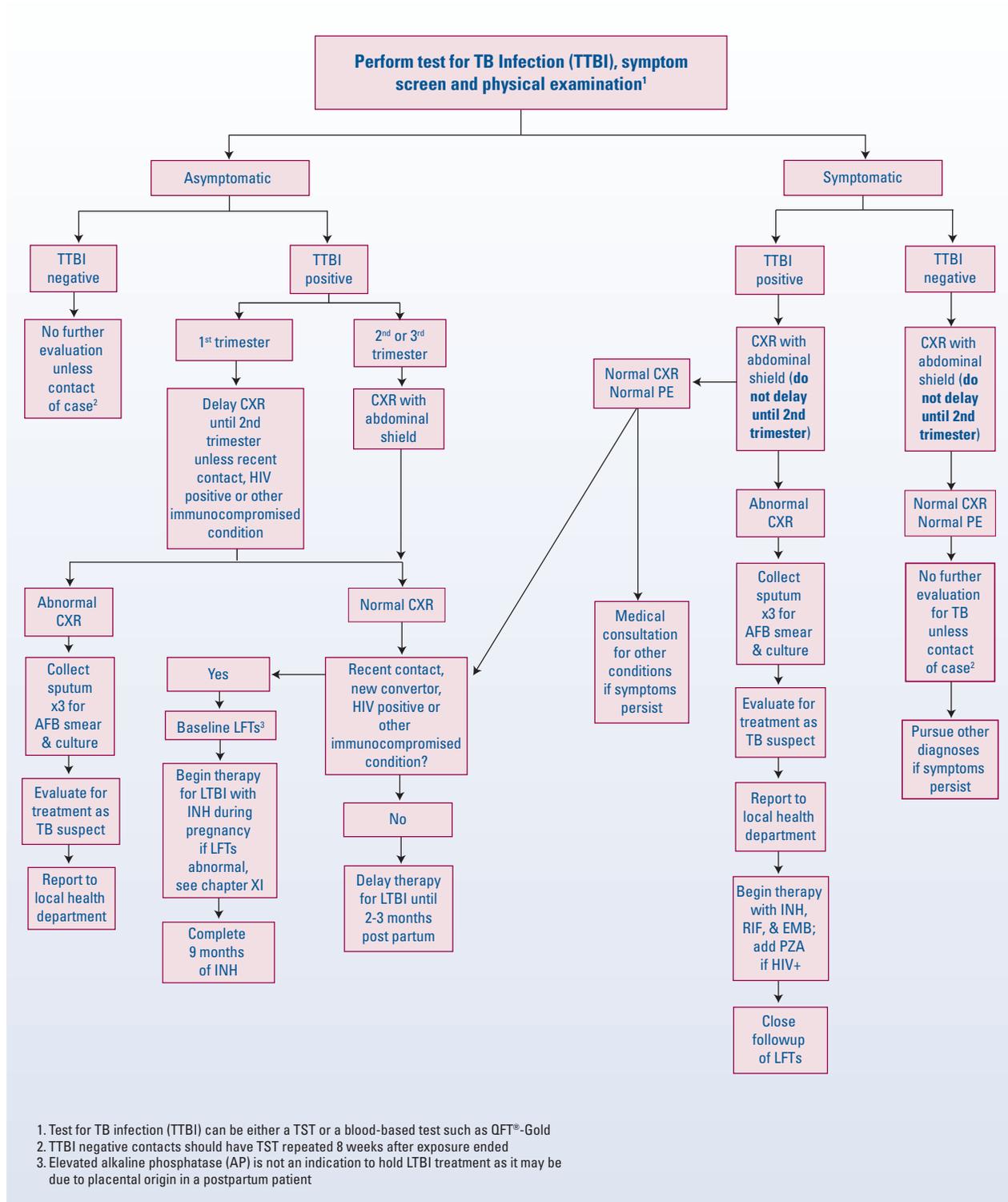
Children as Candidates for Latent Tuberculosis Infection Treatment

Children younger than 5 years old with LTBI have by definition been infected recently and are at high risk for progression to active TB. However, treatment is recommended for all children and adolescents diagnosed with LTBI because:

- The drugs used are safe in the pediatric population.
- Infection with *M. tb* is more likely to have been recent.
- Young children are at higher risk for progression to TB disease.

Figure XI-2

Evaluation of Pregnant Patients at Risk for Tuberculosis



XI. LATENT TB INFECTION (LTBI): EVALUATION, TREATMENT, MONITORING AND FOLLOW-UP

1. Test for TB infection (TTBI) can be either a TST or a blood-based test such as QFT®-Gold
 2. TTBI negative contacts should have TST repeated 8 weeks after exposure ended
 3. Elevated alkaline phosphatase (AP) is not an indication to hold LTBI treatment as it may be due to placental origin in a postpartum patient

Abbreviations: AFB = acid-fast bacilli, CXR = chest X-ray, EMB = ethambutol, INH = isoniazid, LFT = liver function test, LTBI = latent tuberculosis infection, PE = physical examination, PZA = pyrazinamide, RIF = rifampin, TTBI = test for tuberculosis infection

- Children have more years to potentially develop TB disease.

The recommended regimen for children (with or without HIV infection) is 9 months of isoniazid. The risk for isoniazid-related hepatitis is minimal in infants and children, who generally tolerate the drug better than adults. Vitamin B₆ should be given to undernourished or HIV-infected children treated with isoniazid. Children (with or without HIV infection) who have been exposed to a person with isoniazid-resistant, rifampin-susceptible TB, or who are intolerant to isoniazid, should be treated with at least 6 months of rifampin. (See p. 196, Table XI-1.)

Latent Tuberculosis Infection Treatment Regimens

Standard Regimen: Isoniazid

The optimal regimen for treatment for LTBI for all individuals is isoniazid, given daily or twice weekly for 9 months (see p. 196, Table XI-1). For adults who are HIV negative, 6 months of isoniazid is an acceptable alternative if the 9-month regimen cannot be given. However, 6 months of isoniazid is not recommended for HIV-positive persons, children younger than 18 years of age and individuals with fibrotic lesions consistent with TB on CXR. The 9-month regimen may be administered concurrently with any antiretroviral regimen used to treat HIV infection (see p. 196, Table XI-1).

Contraindications to treatment for LTBI with isoniazid are:

- A history of an isoniazid-induced reaction, including hepatic, skin or allergic reactions, or neuropathy
- Close contact with a person who has isoniazid-resistant TB
- Severe chronic liver disease
- Pregnancy, unless the woman is HIV infected, a recent TST converter or a close contact (see p. 193).

The risk of isoniazid toxicity has been shown to increase with age, in particular in persons older than 55 years of age. Those who are contacts, or who have clinical conditions associated

with increased risk of progression to active TB, should be treated regardless of age. However, the risk-benefit ratio from isoniazid may not favor treatment of patients older than 55 years whose only risk factor is recent immigration. This group should be closely monitored for isoniazid toxicity and should even possibly be excluded from treatment.

Directly Observed Therapy (DOT) for LTBI is an excellent method for promoting adherence to treatment. Because of limited resources, however, DOT cannot be offered to all patients receiving LTBI treatment through the BTBC. Currently, the principal candidates for Bureau-provided LTBI DOT are household contacts of patients with TB disease who are receiving home-based DOT. Patients receiving DOT treatment for LTBI may be candidates for intermittent therapy.

Alternative Regimen: Rifampin

An alternative regimen to isoniazid is to give adult patients (with or without HIV infection) 4 months of rifampin for treatment of LTBI (see p. 196, Table XI-1). This course is especially recommended if there are adverse reactions or resistance to isoniazid, but not to rifampin; or if the individual will not be available for more than 4 to 6 months and is thus unlikely to complete a 9-month isoniazid regimen.

If a rifampin-containing regimen is chosen for HIV-infected patients with LTBI, the drug-drug interactions and dose adjustments for antiretroviral drugs and rifamycin apply as indicated on p. 54, Figure III-2; p. 55, Table III-3; and p. 196, Table XI-1.

Children (with or without HIV infection) who have been exposed to isoniazid-resistant, rifampin-susceptible TB should be treated with at least 6 months of rifampin. Although isoniazid is the only drug that has been studied on a large scale for treatment for LTBI, rifampin is probably equally effective.

In many cases, rifabutin can be substituted for rifampin. Rifabutin may be used with regimens containing: (1) the non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz and nevirapine, or (2) many protease inhibitors (PIs). See p. 54, Figure III-2 and p. 55, Table III-3 for the recommended dosages of rifabutin, when it

Table XI-I

Treatment for Latent Tuberculosis Infection

Drug and Duration	Dosage		Major Adverse Reactions	Comments
	Daily	Twice Weekly	Recommended Monthly Monitoring ¹	
Isoniazid Children: 9 months Adults: 9 months	Children: 5-10 mg/kg (max 300 mg) Adults: 5 mg/kg (max 300 mg) Completion Criteria 270 doses within 12 months	Children: 20-30 mg/kg (max 900 mg) Adults: 15 mg/kg (max 900 mg) Completion Criteria 76 doses within 12 months	Symptoms: Unexplained anorexia, nausea, vomiting, dark urine, jaundice, persistent fatigue, weakness, abdominal tenderness (especially right upper quadrant discomfort), easy bruising or bleeding, rash, persistent paresthesias of the hands and feet, arthralgia Signs: Elevated LFTs, hepatitis, icterus, rash, peripheral neuropathy, increased phenytoin levels and possible interaction with disulfiram (Antabuse®) Clinical evaluation: LFTs (if baseline is abnormal or patient has risk factors for toxicity) ²	Preferred regimen for all individuals Vitamin B ₆ (25 mg/day) or pyridoxine may decrease peripheral and CNS effects, and should be used in patients who are: <ul style="list-style-type: none"> • Abusing alcohol • Pregnant • Breastfeeding infants on isoniazid • Malnourished Or who have: <ul style="list-style-type: none"> • HIV • Cancer • Chronic renal or liver disease • Diabetes • Pre-existing peripheral neuropathy <i>Note: aluminum-containing antacids reduce absorption.</i>
Rifampin Children: 6 months Adults: 4 months	Children: 10-20 mg/kg (max 600 mg) Completion Criteria 182 doses within 9 months Adults: 600 mg [range, 8-12 mg/kg] (max 600 mg) Completion Criteria 120 doses within 6 months	Children: Not recommended Adults ³ : 600 mg [range 8-12 mg/kg] (max 600 mg) Completion Criteria 34 doses within 6 months	Symptoms: Nausea, vomiting, loss of appetite, rash, fever or flu-like symptoms, easy bruising. Sign: Elevated LFTs, hepatitis, rash, thrombocytopenia Reduced levels of many drugs, including methadone, warfarin, hormonal contraception, oral hypoglycemic agents, theophylline, dapson, ketoconazole, PIs and NNRTIs Clinical evaluation: LFTs (if baseline is abnormal or patient has risk factors for toxicity) ² CBC, including platelets as needed	May be used to treat persons who have been exposed to isoniazid-resistant, rifampin-susceptible TB, or who have severe toxicity to isoniazid, or who are unlikely to be available for more than 4-6 months. Be aware that: <ul style="list-style-type: none"> • There will be orange discoloration of secretions, urine, tears and contact lenses. • Patients receiving methadone will need their methadone dosage increased by an average of 50% to avoid opioid withdrawal. • Interactions with many drugs can lead to decreased levels of either or both. • Rifampin may make glucose control more difficult in diabetics. • Rifampin is contraindicated for patients taking most PIs and NNRTIs.⁴ • Patients should be advised to use barrier contraceptives while on rifampin.

Abbreviations: CBC = complete blood count, CNS = central nervous system, LFTs = liver function tests, NNRTI = non-nucleoside reverse transcriptase inhibitors, PI = protease inhibitor, TB = tuberculosis

(Table XI-I cont.)

Drug and Duration	Dosage		Major Adverse Reactions	Comments
	Daily	Twice Weekly	Recommended Monthly Monitoring ¹	
Rifabutin Children: 6 months Adults: 4 months	Children: 5 mg/kg (max 300 mg) (Little data) Completion Criteria 182 doses within 9 months Adults: 5 mg/kg (max 300 mg) Completion Criteria 120 doses within 6 months	Children: Not recommended Adults ³ : 5 mg/kg (max 300 mg) Completion Criteria 34 doses within 6 months	Symptoms include: Stomach upset, chest pain, nausea, vomiting, headache, rash, muscle aches, redness and pain of the eye. Signs include: LFTs elevation, hepatitis, neutropenia, thrombocytopenia Reduced levels of many drugs including PIs, NNRTIs, dapsone, ketoconazole and hormonal contraception. However, some drugs, including PIs and some NNRTIs do increase levels of rifabutin. Clinical evaluation: LFTs (if baseline is abnormal or patient has risk factors for toxicity) ² . CBC, including platelets as needed	May be used to treat LTBI in HIV-infected patients who fit the criteria for rifampin treatment, but for whom rifampin is contraindicated, or for others who need a rifamycin but are not able to tolerate rifampin. Be aware that: <ul style="list-style-type: none"> • There will be orange discoloration of secretions, urine, tears and contact lenses. • Interaction occurs with many drugs. • For HIV-infected persons, it is necessary to adjust the daily or intermittent dose of rifabutin and monitor for decreased antiretroviral activity and for rifabutin toxicity, if taken concurrently with PIs and NNRTIs.⁴ • Methadone dosage generally does not need to be increased. • Patients should be advised to use barrier contraceptives.

Abbreviations: CBC = complete blood count, CNS = central nervous system, LFTs = liver function tests, NNRTI = non-nucleoside reverse transcriptase inhibitors, PI = protease inhibitor

1. Baseline LFTs should be done for everyone over the age of 35, all HIV-infected persons, pregnant and postpartum women (up to 2-3 months postpartum), those with history of hepatitis, liver disease or alcohol abuse, injection drug users and those on treatment with other potential hepatotoxic agents. A baseline CBC with platelets should be done on anyone prescribed a rifamycin-containing regimen.
2. Monthly LFTs should be conducted for all HIV-infected persons, pregnant and postpartum women (up to 2-3 months postpartum), those with history of hepatitis, liver disease or alcohol abuse, injection drug users and those on treatment with other potential hepatotoxic agents. Those whose baseline LFTs were abnormal should be monitored monthly, regardless of other conditions.
3. There is very little data or clinical experience on the use of intermittent treatment of latent TB infection with rifampin or rifabutin. These regimens should be used with caution.
4. Please see the NYC BTBC's HIV/TB treatment guidelines. (www.nyc.gov/html/doh/downloads/pdf/tb/tbanti.pdf).

is co-administered with these agents. There is insufficient data on the use of rifabutin in anti-retroviral regimens containing combinations of NNRTIs and PIs, or other multiple PI combinations.

Contraindications to use of rifampin for treating LTBI are:

- A history of rifampin-induced reactions, including skin and other allergic reactions, hepatitis or thrombocytopenia
- Severe chronic liver disease
- Pregnancy, unless the woman is HIV-infected, a recent TST converter, a close contact of an isoniazid-resistant case or is intolerant to isoniazid and needs to be treated (see p. 193).
- Current treatment with a PI or certain NNRTIs (an alternative is to use selected antiretroviral drugs with rifabutin, see above)

Rifampin and Pyrazinamide

The 2-month regimen containing rifampin and pyrazinamide as an option for LTBI treatment is no longer recommended due to high rates of hospitalization and death from liver injury associated with the use of a daily or twice-weekly 2-month regimen of rifampin plus pyrazinamide. As a result, this regimen should generally not be offered to HIV-negative or HIV-positive persons with LTBI.

Alternative Regimens for Contacts of Persons with Isoniazid- and Rifampin-Resistant Tuberculosis (Multidrug Resistant Contacts)

There have been no controlled trials of treatment for LTBI with drugs other than isoniazid and rifampin. Therefore, treatment protocols for contacts of patients with isoniazid- and rifampin-resistant TB (multidrug resistant TB or MDRTB) are largely empirical, and all regimens must be individualized. (See p.199, Table X1-2.) TB disease must be excluded before any therapy regimens for LTBI are initiated.

The following factors should be considered in decision-making:

- **HIV infection.** HIV infection is one of the most important risk factors for developing TB disease, and all contacts should be

strongly encouraged to undergo voluntary HIV counseling and testing.

- **The drug susceptibility pattern of the source patient.** The treatment regimen should be able to include 2 anti-TB medications that will treat the source patient's strain of TB.
- **Contact's risk factors for multidrug resistant TB (MDRTB) infection and disease.** Contacts who are not likely to be infected with MDRTB or who are at low risk of developing TB disease may not be candidates for an alternative treatment regimen.

In designing treatment, consider the following questions:

1. How likely is it that the individual is newly TB infected?

An individual with a documented prior positive test for TB infection is less likely to be newly infected and is probably not a candidate for alternative treatment for LTBI. By contrast, for example, an HIV-infected spouse of an individual with MDRTB whose 3 children have TST conversions is highly likely to be newly TB infected, even if the spouse's test for TB infection is negative.

2. How likely is it that the individual is infected with a strain of MDRTB?

- **Infectiousness of the source patient.** A source patient who is sputum acid-fast bacilli (AFB) smear positive, has cavitory disease and is coughing is much more infectious than one who is smear negative and not coughing. Also, a source patient whose contacts had TST conversions is more infectious than a source patient whose contacts did not have TST conversions.
- **Closeness and intensity of the MDRTB exposure.** Contacts are at higher risk for infection if they have (1) spent a prolonged period of time sharing air with a person who has MDRTB, (2) if they were exposed in a small, poorly ventilated area, or (3) if they were exposed during cough-inducing procedures (e.g., bronchoscopy, sputum induction, endotracheal intubation).

- **Contact’s risk of exposure to drug-susceptible TB.** Individuals who have been exposed to several sources of TB (e.g., health care workers or recent immigrants from high TB incidence areas) may be less likely to have been infected with a MDRTB strain than individuals whose only known exposure to TB was to an infectious MDRTB patient (e.g., a TST-positive infant of a mother with MDRTB).

3. How likely is an individual to develop TB disease?

Contacts are at high risk of developing TB disease if they have been recently infected, they are infants, or if they are HIV-infected or otherwise immunosuppressed (see p. 160).

4. What should be considered in making a final decision?

- **Low likelihood of infection with MDRTB.** If an individual is thought to be newly infected with non-MDRTB, contacts should be evaluated for treatment with isoniazid.
- **Intermediate or high likelihood of infection with MDRTB.** If an individual is thought to be newly infected, contacts should be evaluated for an alternative regimen for

treatment for LTBI, according to their age and immune status; specifically:

- o Those who are HIV-positive, otherwise immunosuppressed and younger than 5 years of age should be given multidrug treatment for LTBI with drugs other than isoniazid and rifampin (see p. 200, Table XI-3 for regimens).
- o Those who are HIV-negative, immunocompetent and younger than 5 years of age, should be managed according to 1 of the following 2 options:
 - Consider multidrug treatment for LTBI with anti-TB medications other than isoniazid or rifampin (see p. 200, Table XI-3 for regimens). This option is important for contacts who convert their TTBI.
 - Do not administer any treatment. Educate the patient about the symptoms of TB and evaluate by CXR and symptom review at 4, 8, 12, 18 and 24 months.

All patients starting treatment for LTBI with 2 or more drugs should have baseline LFTs, a complete blood count (CBC) and a viral hepatitis screen. The drug options for managing MDRTB patients are summarized on p. 201, Table XI-4.

Table XI-2

Likelihood of Infection with Multidrug-Resistant Tuberculosis Among Contacts Thought to Be Newly Infected*

Infectiousness of the Source MDRTB Patient	Closeness and Intensity of MDRTB Exposure	Contact’s Risk of Exposure to Drug-Susceptible TB	Estimated Likelihood of Infection with MDRTB
+	+	-	High
+	-	-	High-intermediate
-	+	-	High-intermediate
-	-	-	Intermediate
+	+	+	Intermediate
+	-	+	Low-intermediate
-	+	+	Low-intermediate
-	-	+	Low

Key: (+) = high; (-) = low

*Adapted from Centers for Disease Control and Infection. Management of persons exposed to multidrug-resistant TB. *Morb Mortal Wkly Rep.* 1992; 41:507-509.

Physicians confronted with the complexities of providing LTBI treatment to contacts of patients with MDRTB may consult with the Director of Medical Affairs for the BTBC.

Regimens for Women Who Become Pregnant while Taking Treatment for Latent Tuberculosis Infection

In general, treatment for LTBI should be discontinued in women who become pregnant while taking either isoniazid or rifampin, unless they are HIV positive or have risk factors for HIV; were a new converter when LTBI treatment was started; or are a contact to an infectious case. To reduce the risk of peripartum hepatitis, treatment for LTBI should not be restarted until 2-3 months after delivery. When treatment is restarted, a full course should be given (previous doses ignored).

However, females with a positive TTBI, and with certain risk factors, should continue therapy during pregnancy. For example:

- Women who are HIV-positive, have behavioral risk factors for HIV infection but decline HIV testing, or have been in close contact with an AFB smear-positive TB patient should continue treatment for LTBI, even during the first trimester.

- For women who have had a TTBI conversion within the past 2 years, treatment for LTBI should be discontinued during the first trimester and resumed at the beginning of the second trimester. When treatment is restarted, a full course should be given with no regard for previous doses.

Isoniazid is the preferred regimen for treatment of LTBI in pregnant women (see p. 196, Table XI-1). Extensive use of isoniazid during pregnancy indicates that it is not teratogenic, even when given during the first trimester of pregnancy. Pregnant women taking isoniazid should receive vitamin B₆. Breastfeeding is not contraindicated when the mother is being treated for LTBI. Vitamin B₆ is not indicated in nursing infants unless the baby is also being given isoniazid.

Regimens for Individuals with Radiographic Evidence of Old, Healed Tuberculosis (Classes IV and V)

- For asymptomatic individuals who have a TST reaction equal to or greater than 5 mm or a positive blood test for TB infection and a CXR that shows noncalcified fibrotic lesions suggestive of old, healed TB, treatment decision is based on clinical suspicion, prior TB treatment history, sputum results

Table XI-3
Options for Managing Contacts Likely to Be Infected with Multidrug-Resistant Tuberculosis*

Contact's Age and Immune Status	
Immunosuppressed or < 5 Years Old	Not Immunosuppressed and ≥ 5 Years Old
12 months of 2 drugs (no isoniazid or rifampin) [†]	6-12 months of 2 drugs ^{†, ‡} (no isoniazid or rifampin) Or No treatment. Medical evaluation and CXR at 4, 8, 12, 18 and 24 months

* "Likely to be infected" means an intermediate, high-intermediate or high likelihood of infection with MDRTB. (See also Table IX-1)

[†] Isoniazid may be considered for the regimen, in addition to the 2 indicated drugs, if the source patient's isolate is resistant at low concentrations (0.2 µg/ml) but is susceptible at high concentrations (1.0 µg/ml) of isoniazid. If isoniazid is added to the regimen, it should be given twice weekly at a dosage of 15 mg/kg for adults, or 20 mg/kg for children (maximum 900 mg per dose).

[‡] Suggested option for (1) recent test for TB infection converters, (2) persons with a high likelihood of infection with TB resistant to isoniazid and rifampin and (3) children 10-14 years of age who have an intermediate to high likelihood of infection with TB resistant to isoniazid and rifampin.

Table XI-4

Alternative Regimens for Preventive Treatment for Contacts Likely To Be Infected with Multidrug-Resistant Tuberculosis*

	Medications	Notes
Adults	Option I Pyrazinamide and Ethambutol	The New York City Bureau of Tuberculosis Control recommends 6-12 months of treatment with this regimen, as these drugs are bacteriostatic, not bactericidal. However, the Center for Disease Control and Prevention (CDC) recommends a 6-month course of treatment.
	Option II Pyrazinamide and a Fluoroquinolone	Treatment should last 6-12 months. Levofloxacin is the fluoroquinolone of choice. Moxifloxacin may be used in special situations.
	Option III Ethionamide and Cycloserine	Recommended for contacts of a source patient whose isolate is resistant to pyrazinamide, ethambutol and a fluoroquinolone; it should last 12 months and pyridoxine should also be given (see p. 62, Table III-4).
Children**	Option IV Pyrazinamide and Ethambutol	The preferred regimen for children if the source patient's isolate is susceptible to these drugs and if the child's vision can be monitored. Treatment should last 12 months.
	Option V Pyrazinamide and a Fluoroquinolone	Treatment should last 6-12 months. Fluoroquinolones in children should only be used if absolutely necessary.
	Option VI Pyrazinamide and Ethionamide	May be used if the source patient's isolate is resistant to ethambutol or the child's vision cannot be monitored. Treatment should last 12 months.
	Option VII Ethionamide and Cycloserine	Use if the source patient's isolate is resistant to both pyrazinamide and ethambutol; it should last 12 months and pyridoxine should also be given (see p. 62, Table III-4).

* "Likely to be infected" means an intermediate, high-intermediate or high likelihood of infection with MDRTB. (See p. 156, Table IX-1).

** For children who are receiving treatment for LTBI and are contacts to a case of MDRTB, DOT should be strongly considered.

and repeat CXR. All such patients should be evaluated for active TB with physical exam, CXR and sputa.

- If sputa are AFB smear negative and there is no evidence of adequate prior treatment for TB, treatment should be started with isoniazid and rifampin (always use Rifamate®, a combination of isoniazid and rifampin), along with pyrazinamide and ethambutol for 2 months. Prescribe pyridoxine if the patient is malnourished, alcoholic, HIV-positive or pregnant (see p. 196, Table XI-1). Ensure that the patient is followed monthly by the physician and nurse.

- This regimen has several advantages: it can be used to treat patients who may have isoniazid-resistant organisms; it may promote better adherence than the 9-month treatment regimen for LTBI; and it allows patients to start treatment at the first medical visit, rather than waiting until sputum cultures are shown to be negative for *M. tb*.

- If all cultures are negative by 2 months, repeat CXR.
 - If the CXR shows no change, the lesions were presumably inactive. Classify the patient as having old TB (class IV). In addition:

- If the patient has no prior TB treatment history, continue with 2 additional months of isoniazid and rifampin only.
 - If there is a history of prior TB treatment, continue all 4 drugs for an additional 2 months.
 - Other diagnoses should also be considered as warranted.
- If CXR shows improvement, the lesions presumably were active. Classify the person as having culture-negative active TB (class III).
- If the patient has no prior TB treatment history, continue with 2 additional months of isoniazid and rifampin only.
 - If there is a history of previous TB treatment, continue all 4 drugs for an additional 2 months.

After 4 months of therapy, the patient should receive an end-of-treatment CXR, which will serve as a baseline for future reference. Some patients classified as having old TB (Class IV or V) may show improvement on the 4-month CXR and should be reclassified as having culture-negative active TB (Class III).

Individuals who have culture-negative TB may need 6 months of therapy (i.e., for extensive fibrotic disease or HIV infection). Clinical judgment should be used to make this decision. There is little literature on the use of 4-month regimens for extrapulmonary TB.

If there is low clinical suspicion of active TB, and AFB smears are negative, there is an additional option not to treat until the cultures are finalized. If cultures are negative and a 2-month CXR shows no change, there are 2 possible regimens for LTBI therapy for individuals with evidence of old, healed TB and no history of treatment:

- 9 months of isoniazid **or**
- 4 months of rifampin (some authorities recommend using isoniazid as well)

If the 4-drug regimen cannot be used because of adverse reactions or other circumstances, isoniazid can be used alone for a total of 9 months. The physician should clearly document in the medical record the reason that a 4-drug regimen could not be used.

Treatment of Close Contacts with a Prior Positive Test for Tuberculosis Infection

Close contacts with a documented previous positive TTBI should be treated again for LTBI after active TB is ruled out, if they are HIV positive, or are sexual contacts of an HIV-infected index case, and refuse HIV testing.

Treatment should also be considered for the following individuals who have a previous positive TTBI, but who have subsequently been in close contact with a person who has AFB smear-positive pulmonary or laryngeal TB:

- Persons with immunosuppressive conditions and other medical risk factors for TB, other than HIV infection
- Children younger than 18 years of age
- Asymptomatic, HIV-negative persons who have had heavy exposure to a person with highly infectious pulmonary or laryngeal TB (i.e., the presence of secondary cases or documented conversions in the close contacts).

The regimen should depend on the susceptibility of the index case isolate. Contacts with prior positive TTBI exposed to an index case with MDRTB should be managed as per guidelines on p. 198.

Case Management of Latent Tuberculosis Infection Patients

Each patient treated for LTBI at the BTBC chest centers will be assigned a case manager (i.e., a Public Health Nurse [PHN] or Public Health Adviser [PHA]) within 1 month of the starting of therapy.

Contacts of active TB cases treated at the chest centers should preferably be case managed by a PHN. Contacts of active TB cases treated at sites other than BTBC chest centers should be case managed by a field PHA.

Monitoring Patients during Treatment

All patients receiving treatment for LTBI should be monitored on a monthly basis, with

directed clinical examinations and blood tests as needed. Patients also need to be educated about the signs and symptoms of adverse drug reactions and the need for prompt cessation of treatment and clinical evaluation should symptoms occur. Adverse effects may include unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesias of the hands and feet, persistent fatigue, weakness or fever lasting 3 days or more, abdominal tenderness (especially right upper quadrant discomfort), easy bruising or bleeding and arthralgia. Appropriate educational materials in the patient's language should be provided.

Monthly LFTs should be administered to:

- All HIV-positive patients
- Patients with a history of alcohol abuse, liver disease, chronic hepatitis
- Pregnant and postpartum women (up to 2-3 months after delivery)
- Patients currently injecting drugs
- Patients on potentially hepatotoxic agents
- Patients with baseline abnormal LFTs not due to conditions above

See p. 204, Figure XI-3 for monitoring for hepatotoxicity during treatment for LTBI.

In addition, laboratory testing should be used to evaluate specific adverse events that may occur during treatment.

Ensuring Adherence During Treatment

Many people with LTBI do not complete treatment. Most are not sick and may not feel the urgency to complete the prolonged therapy. Patients receiving treatment for LTBI must be encouraged to return for follow-up every month. Providers must educate patients about the importance of adherence to treatment and about potential side effects. Barriers to adherence should be addressed and overcome. (See Box)

How Providers Can Assess and Promote Adherence:

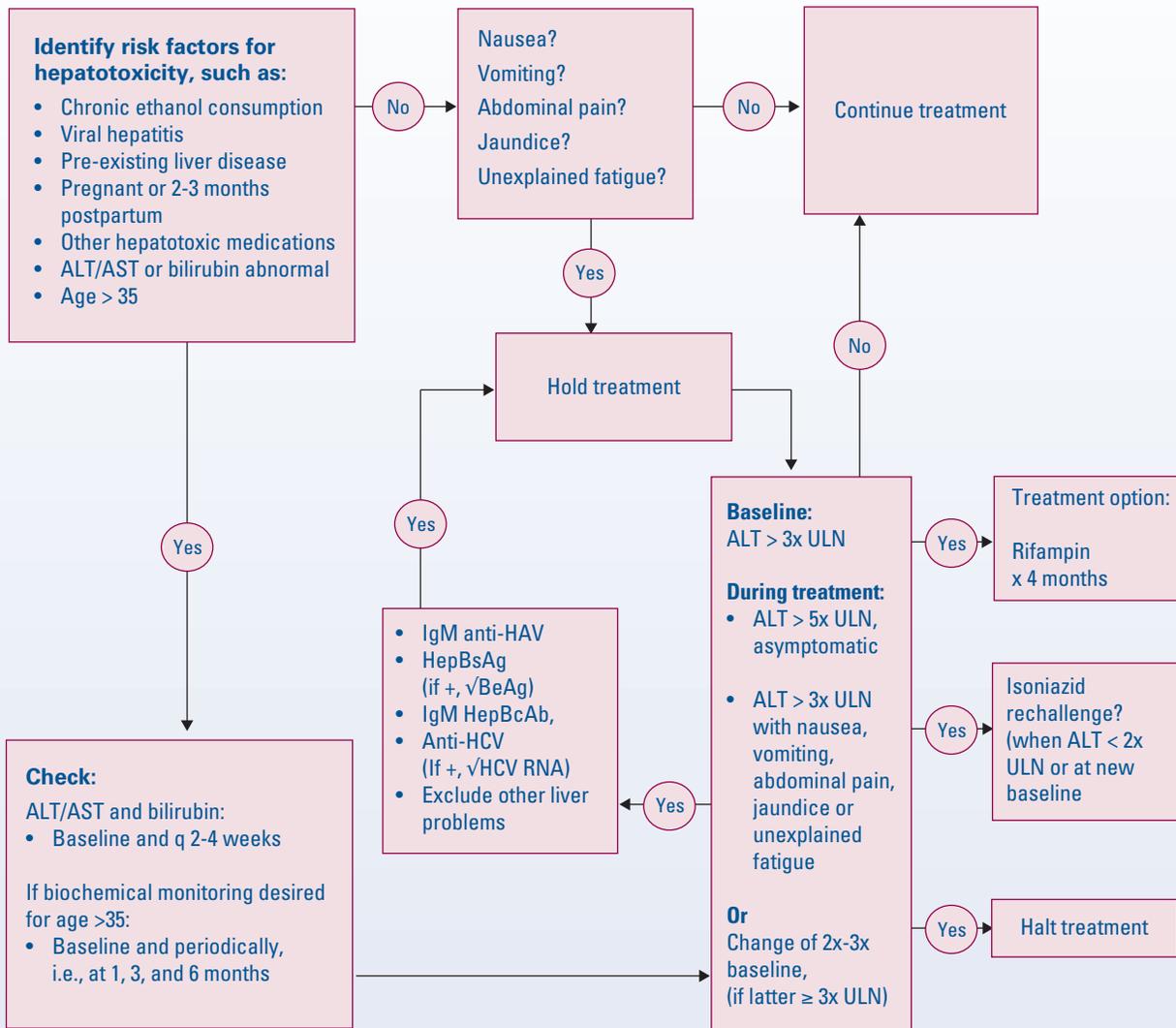
- Use DOT for LTBI when available, especially for children, contacts and HIV-infected persons. DOT can be performed at many locations such as clinics, schools, homes, work sites and day care programs.
- Provide written information about potential adverse effects of the medications at the start of treatment.
- Provide incentives such as MetroCards to help with transportation.
- Send reminder letters or call patients before appointments.
- Follow up promptly on missed appointments to prevent interruption or cessation of treatment.
- Minimize wait time at clinics.
- Ask patients at monthly visits about the number of missed pills in the past week.
- Remind patients to bring in their medication bottle(s); monitor pill counts (but not in their presence).
- During each monthly visit, stress the importance of adherence and educate patients about potential adverse effects of medication.

Managing Interruptions in Treatment

If there are interruptions in treatment, patients can be given 2 to 3 additional months to complete the regimen. The decision regarding completion of treatment should be based on the total number of medication doses administered, as well as on the duration of therapy (see p. 196, Table XI-1). For those on isoniazid, if there is a gap greater than 3 months, it may be necessary to restart treatment. However, adults with 6 or more months of treatment should be considered as having completed treatment.

Figure XI-3

Monitoring for Hepatotoxicity during Treatment for Latent Tuberculosis Infection*



*Adapted from ATS Hepatotoxicity Statement. See Key Sources at end of section for full citation.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit of normal

Completing Treatment

Patients receiving treatment for LTBI may be discharged from the chest center when they return for the final month's supply of medication (e.g., after the 8th month for patients taking a 9-month treatment regimen). The exception would be individuals being treated for LTBI as a contact to a MDRTB case.

The provider performing the monthly evaluation should note in the clinic medical record that the patient received enough medication for the last month of treatment for LTBI and was discharged from the chest center.

The patient should be advised to return to the center if either symptoms of TB or side effects to medication occur. Otherwise, further evaluation is not necessary.

The discharged patient should be informed that repeated CXRs and TTBI are not necessary. Documentation of the results of the TTBI and the LTBI treatment should be provided to the patient in writing, as repeat testing and treatment is generally not indicated except in specific circumstances as noted below.

Follow-up for Patients Who Have Completed Treatment

Follow-up care, including CXR and medical evaluations, is not necessary for patients who complete a course of treatment for LTBI unless 1) they develop symptoms of TB disease or 2) they were being treated for LTBI as a contact to an MDRTB case.

Repeat treatment for LTBI should be considered, however, for individuals who have been treated in the past, but who have subsequently been in close contact with someone who has AFB smear-positive pulmonary or laryngeal TB disease.

These individuals include:

- Persons who are HIV-positive or have another medical risk factor for developing TB disease
- Children who are younger than 18 years of age
- Persons who are HIV-negative, but have had heavy exposure to a patient with highly infectious TB (i.e., the presence of secondary cases or documented TTBI conversions in other contacts)

When treatment for LTBI is repeated, an entire course should be given (i.e., 9 months for adults, both HIV-positive and HIV-negative) on the assumption that exogenous reinfection may have occurred. This is more likely if there are TTBI conversions among other contacts who had similar exposure to the individual with TB.

Key Sources

American Thoracic Society and Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med*. 2000;161:S221-S247.

Arend SM, Breedveld FC, Dissel JT van. TNF- α blockade and tuberculosis: better look before you leap. *Neth J Med*. 2003;61:111-119.

Centers for Disease Control and Prevention. Management of Persons Exposed to Multidrug-Resistant Tuberculosis. *MMWR* 1992;41(RR-11):59-71.

Centers for Disease Control and Prevention. Tuberculosis associated with blocking agents against tumor necrosis factor-alpha – California, 2002-2003. *MMWR Morbid Mortal Wkly Rep* 2004;53:683-685.

Centers for Disease Control and Prevention. 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, 2003. *MMWR Morbid Mortal Wkly Rep* 2003;52(31):735-739.

Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? *Int J Tuberc Lung Dis*. 1999;3:847-850.

Horsburgh, RC Jr. Priorities for the treatment of latent tuberculosis infection in the United States. *N Engl J Med*. 2004;350:2060-2067.

Munsiff S, Nilsen D, King L, Dworkin F. Testing and Treatment for Latent TB Infection. *City Health Information*. 2006;25(4)21-32.

Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: A 7-year survey from a public health tuberculosis clinic. *JAMA*. 1999;1281:1014-1018.

Pediatric TB Collaborative Group. Targeted tuberculin skin testing and treatment of latent TB infection in children and adolescents. *Pediatrics*. 2004;114:1175-1201.

Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, Peloquin CA, Cordin FM, Nunes D, Strader DB, Bernardo J, Venkataramanan R, Sterling TR; American Thoracic Society Hepatotoxicity of Antituberculosis Therapy Subcommittee. An official ATS statement:hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med*. 2006 Oct 15;174(8):935-952.