

CDHS/CTCA JOINT GUIDELINES

**Targeted Testing and Treatment of
Latent Tuberculosis Infection in Adults and Children**



CTCA
CALIFORNIA TUBERCULOSIS
CONTROLLERS ASSOCIATION



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Background/About Us

The following guidelines have been developed by the California Department of Health Services, Tuberculosis Control Branch in consultation with the California Tuberculosis Controllers Association. These guidelines are official State recommendations and have been endorsed by the California Tuberculosis Controllers Association. If these guidelines are altered for local use, then the logo should be removed and adaptation from this source document acknowledged.

What's New/Overview

The latent tuberculosis infection (LTBI) guidelines published in 2000 by the American Thoracic Society and Centers for Disease Control and Prevention (CDC) recommended a change in nomenclature. The terms “chemoprophylaxis” and “preventive therapy” will no longer be used. Instead, the phrase “treatment of LTBI” is recommended because it more accurately describes the intended intervention. This change in nomenclature will hopefully promote greater understanding of the concept for both patients and providers, resulting in more informed use of this important tuberculosis (TB) control strategy.

The CDC guidelines no longer recommend using a 35 year of age cutoff for determining treatment for LTBI. Persons of any age with LTBI should be evaluated for treatment.

Due to the high incidence of hepatic failure that resulted from the 2 month regimen of PZA/Rifampin, CDC no longer recommends this LTBI regimen, with the exception of those who were started on 4 drug therapy and reclassified as TB-4.

Limited discussion of the new Food and Drug Administration (FDA)-approved in-vitro laboratory diagnostic test for LTBI, e.g., QuantiFERON-TB-Gold[®], is included in these revised guidelines.

Recommendations for using two-step testing in populations where routine testing is performed are included in this Guideline, as is a brief discussion of tuberculin skin test (TST) interpretation after Bacille Calmette-Guerin (BCG) vaccination. The subject of treating contacts to multidrug-resistant TB (MDR-TB) cases is also briefly discussed in this Guideline. Due to recent cases of individuals developing active TB while being treated for rheumatoid arthritis or other auto-immune diseases with blocking agents against tumor necrosis factor-alpha, this Guideline includes reference materials addressing this matter. These guidelines also contain and recommend use of the American Academy of Pediatrics risk assessment to guide testing decisions about which children and adolescents under 18 should receive a TST.

Target Audience

This Guideline is intended for use by local health departments and by private providers.

How to Use This Guideline

This Guideline is intended to provide the practitioner or local health department (LHD) with the standard of care for diagnosing and treating LTBI in California. LHDs are encouraged to adapt this Guideline for use in their own TB programs, and may distribute it to private providers as a written standard of care. The topics of screening, use of in-vitro laboratory diagnostic tests for LTBI, contact investigation and diagnosis of active TB are introduced here to provide context for the reader, but this Guideline does not address these issues in detail. The reader is instructed to refer to the California Department of Health Services/California TB Controllers Association Guidelines for the Treatment of Active Tuberculosis Disease and the Contact Investigation Guidelines for complete discussion. Screening will be addressed in future guidelines, and guidelines for the use of in-vitro laboratory diagnostic tests for LTBI may be found on the CDC website (www.cdc.gov).

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Targeted TB Testing

Targeted tuberculin skin testing or other in vitro laboratory diagnostic tests for LTBI aim to identify individuals at high risk for developing TB who would benefit from treatment of LTBI. High risk is defined by the CDC as risk substantially greater than that of the U.S. population.¹ A decision to test is a decision to treat, and individuals who test positive for LTBI should be offered treatment. Tuberculin skin testing of low risk populations will result in unnecessary treatment because of false-positive test results.

QuantiFERON-TB- Gold® (QFT-G), an in-vitro laboratory diagnostic test, was recently approved by the FDA for detecting infection with *M. tuberculosis* (*M. tb*). It may be used in place of the TST for screening specific populations, such as health care workers. Other in-vitro laboratory diagnostic tests are under development. Guidance for the use of QuantiFERON-TB Gold® and other in-vitro laboratory diagnostic tests is evolving at the time of writing of this guideline. Refer to the most recent CDC recommendations for guidance.²

Local health jurisdictions may use the following categories to identify and prioritize local populations that would benefit from targeted testing, as determined by local epidemiologic data and as local resources permit.

Targeted testing for LTBI is indicated for individuals at increased risk of developing TB disease. Generally, persons at high risk for developing TB disease fall into two categories: those who have been recently infected, and those with clinical conditions that increase the risk of progression from LTBI to TB disease.

Targeted testing for LTBI is indicated for individuals at increased risk of developing TB disease: those who have been recently infected, and those with clinical conditions that increase the risk of progression from LTBI to TB disease.

The following persons or groups should be tested for LTBI since they are at increased risk for being recently infected with *M. tb*:

- Close contacts of a person with infectious TB
- Persons who have immigrated within the last 5 years from areas of the world with high rates of TB (See “Candidates for treatment of LTBI – TB-2 and TB-4”, p.10, for discussion of individuals who immigrated more than 5 years ago.)
- Children and adolescents <18 years of age who have one or more positive responses to the risk assessment questionnaire.^{3,4} (See Appendix 4.)
- Groups with high rates of *M. tuberculosis* transmission as defined locally, such as homeless persons, drug users, and persons with HIV infection
- Persons who work or reside with people who are at high risk for TB in facilities or institutions such as hospitals, homeless shelters, correctional facilities, nursing homes, and residential homes for those with HIV/AIDS.
- Mycobacteriology laboratory workers

Presumed Recent Infection:

Converters: if testing identifies a recent converter (those with an increase of at least 10 mm of induration, from < 10 mm of induration to \geq 10 mm within two years), those individuals are presumed to have recent infection and are at high risk of progression from LTBI to active TB.

Children under 5 years of age with a positive TST or in-vitro laboratory diagnostic test: these individuals are presumed to be recently infected because of their age.

Persons with the following clinical conditions that increase the risk of progression from LTBI to TB disease should also be tested for LTBI⁵:

- HIV infection
- Pulmonary fibrotic lesions seen on chest radiograph consistent with prior healed TB (TB4) (see Classification System for TB p.9).
- Diabetes mellitus (especially insulin-dependent)
- Silicosis
- Chronic renal failure /hemodialysis
- Chronic immunosuppression
 - Transplant recipients
 - Prolonged corticosteroid therapy (\geq 15 mg/day prednisone for \geq 1 mo)
 - Other immunosuppressive therapy (e.g., anti-Tumor Necrosis Factor-alpha agents)⁶
- Hematological and reticuloendothelial diseases (leukemia, lymphoma)
- Malnutrition and clinical situations associated with rapid weight loss
 - Cancer of the head and neck or lung
 - Intestinal bypass or gastrectomy
 - Chronic malabsorption
 - Low body weight (\geq 15% below ideal body weight)
- Injection drug use

Drugs used for conditions such as rheumatoid arthritis can cause LTBI to progress to active TB: test and treat before using anti-TNF agents

Two-Step Testing

Two-step skin testing is used to detect individuals with TB infection acquired in the remote past who may now have diminished skin test reactivity. This procedure reduces the likelihood that a boosted reaction will later be interpreted as new infection in those persons who are serially tested. The booster phenomenon, which occurs when a second test is positive placed 1–3 weeks after initial test, may occur at any age, however, its frequency increases with age and is highest among older persons.

A two-step TST should be used for the initial skin testing of adults who will be routinely retested, such as health care workers, individuals entering congregate settings, or staff working with high risk individuals in the community (e.g., homeless shelter staff).

QFT-G does not have a boosting effect-no need to 2-step

In-vitro laboratory diagnostic tests e.g., QuantiFERON-TB-Gold®, for LTBI do not have a boosting effect. There is no need for two-step testing if using an in-vitro laboratory diagnostic test for LTBI.

- Standard two-step testing: If the result of the initial TST is negative at 48 to 72 hours, a second TST is placed 1-3 weeks after the first. A positive reaction to the second test probably represents a boosted reaction from past TB infection. On the basis of this second positive test result, the patient should be classified as previously infected and cared for accordingly. This would not be considered skin test conversion. If the second test result is negative, the person should be classified as uninfected. In these persons, a positive reaction to any subsequent test is likely to represent new infection with *M.tb*.
- Alternate Protocol for two-step testing: The first TST is read at 7 days. A positive reaction is considered valid. If the first TST is negative, the second TST is administered immediately and read at 48-72 hours.⁷

BCG Vaccination

Previous vaccination with BCG is not a contraindication to tuberculin skin testing. Because most persons who have received prior BCG vaccination are from high prevalence areas of the world, previous vaccination should generally be ignored when interpreting a TST result. It is not possible to distinguish between a tuberculin reaction that is caused by true infection and a reaction that is due to BCG.

However, QFT-G is not affected by prior BCG vaccination and is expected to be less influenced than the TST by previous infection with nontuberculous mycobacteria.⁸

Definition of a positive tuberculin skin test

The definition of a positive tuberculin skin test depends on a person's prior probability of having LTBI and the person's risk of developing active TB.

≥ 5 mm of induration*

- Persons known or suspected to have HIV infection.
- Recent contacts to an active case of pulmonary or laryngeal TB.
- Persons with fibrotic changes seen on chest radiograph consistent with TB.
- Immunosuppressed individuals (See page 7 **Targeted TB Testing/Chronic Immunosuppression**)

≥ 10 mm of induration

- All persons except those in above

NOTE: The CDC recommends using a 15 mm cutoff for low risk reactors. However, in California, this cutoff is not recognized because California is a high incidence state and the prevalence of nontuberculous mycobacterial infections is lower than in other regions of the United States.

Tuberculin skin test conversion

TST conversion is defined as an increase of at least 10 mm of induration from < 10 mm to ≥ 10 mm within two years.

Example: a TST of 4 mm that increases in size to 14 mm or more in induration within 2 years would be an example of skin test conversion.

In many cases, the exact size (in mm) of the previous tuberculin skin test may not be known. In such cases, skin test conversion is defined as a change from a negative to positive tuberculin skin test within a 2-year period.

Evaluation for TB disease and baseline evaluation for patients with LTBI

All persons who have a positive TST or other positive in vitro laboratory diagnostic test for LTBI should undergo a baseline evaluation including symptom review, physical exam and a chest radiograph. A complete list of the components of this evaluation is below.

Baseline evaluation for individuals with a positive TST or other in vitro laboratory diagnostic test for LTBI should include:

- Symptom review
- Physical exam
- Chest radiograph
- TB history, including history of prior TST results, prior TB treatment history, and TB contact history
- Evaluation of whether LTBI treatment is indicated
- Exclusion of active TB disease
- Patient education regarding:
the distinction between LTBI and TB disease; the purpose and importance of TB treatment; risk of adverse reactions; symptoms of adverse reactions; the need for prompt reporting, cessation of treatment and clinical evaluation should symptoms occur; duration of treatment; and follow-up evaluation.

Treatment for LTBI should be withheld while this evaluation is pending. Unless there is a recent radiograph within the past 6 months, a new chest radiograph should be performed at the time of evaluation. If indicated, based on clinical and radiographic findings and epidemiologic considerations (e.g., risk of transmission), treatment for suspected active TB (Class TB-5) should be considered while follow-up studies are pending (see “Classification System” below and “Treatment Regimens TB-4” p. 13).

Under no circumstances should treatment for LTBI be initiated without first ruling out active disease.

- If the radiograph is normal, and the patient has no symptoms or physical findings consistent with TB, treatment of LTBI may be indicated (see Appendix 2)
- If the radiograph is normal but the patient has a clinical presentation consistent with TB, further work-up is indicated and treatment of LTBI should be delayed until active TB has been ruled out.
- If the radiograph is abnormal and possibly consistent with TB, bacteriologic studies should be obtained, using sputum induction if necessary. When bacteriologic studies are obtained, *treatment of LTBI should not be initiated until final culture results are available. Sputa should be obtained even when the abnormalities are consistent with healed or stable lesions.* The activity of TB cannot be determined from a single chest radiograph; active disease may be present even if the radiographic findings are stable. If a radiograph is abnormal but was taken more than 3 months prior to evaluation, a new radiograph should be performed at the time of evaluation.

Radiographic findings that suggest prior TB include apical fibronodular infiltrations, often with volume loss. For further description of radiographic changes consistent with TB4, refer to American Thoracic Society, *Diagnostic Standards and Classification of Tuberculosis in Adults and Children*.⁹ If isolated, calcified granulomas (calcified solitary pulmonary nodules) or apical or basal pleural thickening are the only findings, sputum specimens need not be collected routinely.

- If the abnormality on the chest radiograph is of questionable significance, consultation with an expert is recommended.

Classification System for TB¹⁰

CLASS	TYPE	DESCRIPTION
Class TB-0	No TB exposure	Not infected: no history of exposure, negative reaction to tuberculin skin test or negative in-vitro laboratory diagnostic tests.
Class TB-1	TB exposure	No evidence of infection: history of exposure and negative reaction to TST or negative in-vitro LTBI laboratory diagnostic tests.
Class TB-2	Latent TB infection, no disease	Positive TST or positive in-vitro LTBI laboratory diagnostic tests, negative bacteriologic studies (if done) and no clinical and/or radiographic evidence of active TB. Patients with isolated calcified granulomas (calcified solitary pulmonary nodules), calcified hilar lymph nodes, or pleural thickening are generally classified as TB 2.
Class TB-3	TB, clinically active	Laboratory, clinical, bacteriologic, and/or radiographic evidence of current disease.
Class TB-4	Tuberculosis, not clinically active	History of previous episode(s) of TB, <i>or</i> Abnormal stable radiographic findings in a person with positive reaction to TST (≥5 mm) or positive in-vitro LTBI laboratory diagnostic tests and negative bacteriologic studies (if done) and no clinical and/or radiographic evidence of current disease.
Class TB-5	TB suspect	Diagnosis pending. Diagnosis of TB being considered, whether or not treatment has been started, pending completion of diagnostic procedures. Persons should not be in this class more than 3 months. When diagnostic procedures have been completed, the person should be placed in one of the preceding classes.

Candidates for Treatment of LTBI – TB-2 and TB-4 *See Appendix 2*

High-risk Individuals:

Persons in high risk categories as listed under “Targeted TB Testing” listed on pp. 4 & 5, as well as converters, should generally be treated for LTBI, after active TB disease is ruled out, if their TST or in-vitro laboratory diagnostic test is positive and they have not previously completed a course of LTBI therapy or treatment of TB disease. The CDC guidelines no longer recommend using a 35 year of age cutoff in deciding which individuals with LTBI should be treated. However, local epidemiologic circumstances and resources should determine whether a specific age cutoff is warranted.

Certain groups require special consideration:

Pregnancy is not a contraindication for treatment of LTBI in women in the following groups:

- Persons known or suspected to have HIV infection.
- Persons who have likely been recently infected.

***Do not start
LTBI treatment
until cultures, if
done, are final***

Among persons from countries with high TB prevalence, local resources and epidemiologic factors including date of immigration and age may dictate prioritization of candidates for treatment:

- Foreign-born children under 18 with LTBI should be offered treatment, given the risk of recent infection and TB progression in this group.
- Recent arrivals (arrived within the past 5 years or less) with LTBI are at increased risk of developing active TB according to some studies¹¹ and merit consideration for treatment.
- Remote arrivals (arrived over 5 years ago): the incidence of active TB in foreign-born individuals who immigrated more than 5 years ago (without medical risk factors) may remain elevated in some populations.¹² LTBI testing and treatment in this group, especially in those 18 to 35 years of age, may be carried out as local epidemiology and resources permit.

Low-risk Individuals:

Persons with LTBI who are not in high risk categories: Although persons at low risk for TB should generally not be tested for LTBI, some low risk persons are nevertheless tested, either for occupational reasons or during a contact investigation of a patient with suspected active TB (Class TB-5) in whom TB is later excluded, or from whom transmission seems unlikely. Treatment of LTBI in such persons should be considered on a case-by-case basis, in consideration of the risk of progression to active disease, the risk of treatment, the likelihood of completion of therapy, and patient and provider preference. As with all patients with LTBI, treatment should not be initiated unless there is provision for adequate patient monitoring (see p. 15). When the local health department does not provide such monitoring, it is the responsibility of the provider to do so. If adequate monitoring cannot be performed, the decision not to treat LTBI in this lower risk group may be appropriate.

Candidates for re-treatment:

In some cases, individuals may require another course of LTBI therapy if re-exposed to an infectious case. Indications for re-treatment following re-exposure include age < 5 years, HIV infection or other significant immunosuppressive conditions. Providers may also choose to retreat persons with previously treated LTBI or previous active TB who have had new exposure to a highly infectious TB case where extensive transmission has been documented, circumstances suggest a high probability of transmission, or when the new exposure occurs in a high risk setting such as a prison or other congregate facility.

Candidates for Treatment of LTBI – TB1 *(See Appendix 2)*

Close Contacts and “Window Prophylaxis”

In close contacts to an infectious TB suspect or confirmed case, the initial TST may be negative (< 5 mm) despite underlying infection with *M. tb* if the TST is placed before the contact has mounted an immune response to the tuberculin antigen. It takes 2-10 weeks after infection with *M. tb* to develop a positive TST reaction.¹³

Re-testing of TST negative contacts should be done 8-10 weeks after contact with case is broken

Close contacts to an infectious case in the following categories who have an initial TST < 5 mm should have a clinical evaluation including a chest radiograph. Once active TB disease is excluded, medical therapy with an LTBI regimen should be started.¹⁴ This is commonly called “window prophylaxis.”

- Those under 5 years of age
- Those infected with HIV or
- Those otherwise immunocompromised (see Targeted TB Testing, p. 5)
- Adults and children ≥5 years of age where circumstances suggest a high probability of transmission. Examples include situations where evaluation of other contacts with a similar degree of exposure demonstrates a high prevalence of infection, documented converters, or secondary cases.

For those individuals who are started on therapy with a TST < 5 mm, a repeat TST should be performed 8 to 10 weeks after contact with the infectious case has been broken or 8 to 10 weeks after the index case becomes non-infectious.¹⁵ Unless the patient is HIV-infected*, the decision to continue therapy should be made once the result of repeat skin testing is available. For very young children, experts recommend that the final skin test be performed after the child is 6 months of age to ensure maturity of the immune response.

***Note:** *In HIV infected contacts, empiric treatment for LTBI generally should be completed, regardless of the result of the repeat TST.*¹⁶

Treatment Regimens for TB-1 and TB-2 (See Appendix 3 for drug dosages)

1. INH alone:

- 6-9 months for immunocompetent adults. Although a 9-month regimen may provide a greater degree of protection, individual programs may choose to give 6 months of INH due to operational considerations (e.g., resources, adherence issues, etc.)
- 9 month regimen for children and adolescents (up to age 18)
- 9 month regimen for HIV-infected persons or persons suspected of having HIV infection
- Pyridoxine 25 mg. daily (Vitamin B-6) is recommended for patients with diabetes, uremia, alcoholism, malnutrition, HIV infection, seizure disorder, symptoms of peripheral neuropathy, as well as for pregnant and postpartum or breastfeeding women. It is not usually recommended for children unless they have above risk factors, eat a diet low in milk and meat or are infants who are exclusively breastfed.

- ### 2. Rifampin (RIF) alone for 4-6 months. Four months is generally recommended for adults. The American Academy of Pediatrics recommends six months for children.¹⁷ This regimen should be reserved for those individuals who cannot tolerate INH or for persons exposed to cases with resistance to INH, but susceptible to RIF.

***RIF/PZA regimen
no longer
recommended
due to fatal
hepatotoxicity***

- ### 3. Rifabutin (RFB) may be substituted for rifampin in the above regimens in situations where rifampin cannot be given, such as in HIV-infected persons taking certain protease inhibitors or non-nucleoside reverse transcriptase inhibitors. Dosage adjustments may, however, be necessary. An expert experienced with treatment of TB and HIV should be consulted. Detailed information regarding the treatment of HIV-infected individuals may be found at the following links:

http://www.cdc.gov/nchstp/tb/TB_HIV_Drugs/Table1.htm

http://www.cdc.gov/nchstp/tb/TB_HIV_Drugs/Table2.htm

- ### 4. The two drug regimen of RIF and pyrazinamide (PZA) for 2 months as treatment for LTBI is no longer recommended due to cases of severe and sometimes fatal hepatotoxicity. This regimen should generally NOT be offered as initial therapy to persons with LTBI for either HIV-negative or HIV-infected persons

However, in the unusual circumstance where the patient is initially begun on 4 drug therapy but review of the baseline and current radiographic studies reveal no abnormalities, bacteriologic studies are negative and the patient is reclassified as TB-2, therapy for LTBI is considered complete after 2 months of 4 drug therapy containing RIF and PZA.

Treatment Regimens – Contacts to Drug-Resistant Cases

1. INH resistant, RIF-susceptible source case

For contacts to cases with INH-resistant, RIF-susceptible disease in which the epidemiologic circumstances suggest recent infection, the 4-6 month regimen of RIF is recommended.

2. Multidrug-resistant source case

In contacts to cases of MDR-TB (resistant to at least INH and RIF) in which the epidemiologic circumstances suggest recent infection, the following principles apply:

- Range of options for contacts to MDR-TB include 1) treatment with 2 to 3 drugs to which the organism is sensitive, 2) INH (for those with evidence for infection likely due to INH-sensitive strain), 3) clinical monitoring for 2 years (no treatment), 4) monotherapy with a fluoroquinolone (when the isolate is also resistant to EMB and PZA or when these first-line drugs are not tolerated).
- The regimen chosen must be based on the susceptibility pattern of the source case's isolate
- Duration of treatment is 6-12 months
- Consultation with an expert familiar with the treatment of MDR-TB is highly recommended (Consider contacting the CDHS TB Control Branch MDR-TB Service or the Francis J. Curry Warmline)^{18 19}

Treatment Regimens TB-4

1. INH alone for 9 months for TB-4 (see previous section for Vitamin B-6 recommendations).
2. INH and RIF for 4 months for TB-4 (see previous section for Vitamin B-6 recommendations). Although there have been no randomized studies to document the efficacy of this regimen in persons classified as TB-4, there is a great deal of experience with this regimen.
3. Rifampin alone for 4 months (6 months for children).²⁰
4. Rifampin and PZA for 2 months for TB-5 cases begun on 4 drug therapy, and later re-classified as TB-4. There are no long term studies or clinical experience supporting regimens shorter than 3 months. However the 2000 CDC Guidelines for LTBI offer this regimen for TB5 cases begun on therapy and subsequently determined not to have active disease and reclassified as TB4. See “When to Initiate Treatment” below.
5. Rifabutin may be substituted in certain situations-see discussion in Treatment Regimens TB-1 – TB-2, above.

When to Initiate Treatment in TB-4²¹

1. High Clinical Suspicion for Active TB (TB-5 High):

If clinical suspicion for active tuberculosis is high, then empiric treatment as a TB-5 with a 4-drug regimen should be initiated promptly before acid-fast smear and culture results are known. If the smears and cultures are negative, the TST is positive (5 mm or greater induration), the initially abnormal chest radiograph remains unchanged after 2-3 months, and there is no response to treatment, then active TB is unlikely and the patient can be reclassified as TB-4 (see “Evaluation for TB Disease” & “Classification System TB-4” for discussion of radiographic findings).

There are three treatment options once the TB5 patient on standard four drug therapy has been reclassified as TB4:

- Treatment is complete once at least 2 months of treatment including rifampin and pyrazinamide has been administered.
- After negative smear and culture results are noted and chest-radiograph is unchanged, a patient reclassified as TB4 can receive a 2 month continuation phase of treatment with INH and RIF. Treatment is complete after a total of 4 months of treatment including INH and RIF. Many large TB programs report successful outcomes using this regimen.
- The patient can receive a continuation phase of treatment with INH for a total of 9 months.

2. Low Clinical Suspicion for Active TB (TB-5 Low)

If clinical suspicion for active TB is low, then empiric treatment with 4 drugs is not recommended initially. In these patients, if cultures are negative, the TST is positive (5 mm or greater induration), and the patient is determined not to have active disease, there are two treatment options for persons classified as TB-4. These options are:

- INH for 9 months or
- RIF, with or without INH, for 4 months.

Daily vs. Intermittent Dosing

INH may be given daily or intermittently (twice weekly) based on operational considerations (e.g., resources, adherence issues, etc.). When INH is given intermittently, it must be administered only by directly observed therapy (DOT).

Directly Observed Therapy

DOT for LTBI should be used when the risk of non-adherence with self-administered therapy is judged to be high, where the consequences of progression to disease are severe, or when the treatment regimens are given intermittently. Populations in which DOT may be considered include contacts (especially if HIV-infected, under the age of 5 or when the source case is MDR), very young children, the developmentally disabled, and those addicted to drug and/or alcohol. Based on local operational considerations, DOT for LTBI may or may not be possible.

Monitoring for Drug Toxicity and Adherence

1. Baseline Evaluation

- Baseline laboratory testing is not routinely indicated, even for those over 35 years of age. Such testing may, however, be considered on an individual basis.
- Persons with the following high-risk characteristics should have baseline laboratory testing:

- HIV infection
- History of, or at risk for, chronic liver disease
- Alcoholism
- Taking other hepatotoxic medications
- Pregnancy

LTBI patients on treatment should be evaluated monthly

Note: Some experts recommend that pregnant women and those in the immediate post-partum period (within 3 months of delivery) have baseline liver function tests measured. The FDA safety label for INH indicates that there may be an increased risk, particularly among black and Hispanic women, during the post partum period.

- The baseline laboratory tests will depend on which drug regimen is being used.
 - INH-containing regimen – If baseline laboratory tests are indicated, a serum AST or ALT and bilirubin should be included.
 - RIF (or RFB)-containing regimen – In persons taking a rifamycin, baseline measurements of complete blood count and platelets are recommended, in addition to liver function tests.

2. Evaluation During Treatment

- Clinical Evaluation – Patients being treated for LTBI should receive a clinical evaluation at least monthly, regardless of the regimen used. The evaluation should include a careful patient assessment for symptoms of adverse drug reactions, particularly hepatitis, e.g., anorexia, malaise, abdominal pain, fever, nausea, vomiting, dark urine, icterus. The assessment should ideally be performed face-to-face, especially when the patient may give an unreliable history. Some programs have had success with telephone monitoring protocols for selected patients based on specific criteria, thus enabling effective treatment and monitoring of expanded groups of patients. In addition, the patient should be asked about adherence to medications and educated about the possible side-effects of the medications. Counting pills and checking pharmacy records can be helpful in evaluating adherence. The clinician should reinforce patient education at each visit and provide practical suggestions to improve adherence. Patient education should include the risk of adverse reactions,

symptoms of adverse reactions as well as the need for prompt reporting of these symptoms, cessation of treatment and clinical evaluation should symptoms occur. The patient should also be instructed on the distinction between LTBI and TB disease, the purpose and importance of TB treatment, the risk of adverse reactions, the duration of treatment and the importance of follow-up evaluation

- Periodic laboratory monitoring during treatment of LTBI is indicated for persons with abnormal baseline liver function tests, for persons with history of, or at high risk for hepatic disease, or for persons with symptoms of hepatitis. The frequency of this monitoring will vary depending on the person's risk of liver disease and the severity of the liver function test abnormalities.

If a patient reports symptoms of hepatitis, TB medications should be suspended and a medical evaluation with physical exam and laboratory exam of liver function tests should be performed. Medications should be stopped if transaminase levels exceed 3-4 times the upper limit of normal in the symptomatic patient or if the transaminase levels exceed 4-5 times the upper limit of normal in the asymptomatic patient. Further evaluation and hospitalization depend on the presence of symptoms, jaundice, coagulopathy, and severity of elevation of transaminase levels.

Stop treatment if:
Symptomatic & AST/ALT >3-4x normal
Asymptomatic & AST/ALT >4-5x normal

Completion of Therapy

Completion of therapy should be based on the total number of doses administered, not on the duration of therapy. If treatment is interrupted the recommended number of doses of the regimen should be provided within a certain maximum time period (See Appendix 3). The entire regimen should be restarted if interruptions were early in the treatment course, frequent or significantly prolonged to preclude completion of doses in the time frames specified. When therapy is restarted after an interruption of more than 3 months, a medical examination should be performed to exclude active disease. In addition, consideration should be given to repeating a chest radiograph, especially in cases where there is a high risk for progression to disease (see high risk of progression section).

Note: *No set of guidelines can cover all individual treatment situations that can and will arise. Thus, when questions on individual situations not covered by this Guideline do arise, consult with the Local TB Control Program, the California Department of Health Services TB Control Branch, or the Tuberculosis Warmline at the Francis J. Curry National TB Center (www.nationaltbcenter.edu) for further information.*

Acknowledgements

LTBI Guidelines Committee: Jennifer Flood, MD, MPH; Robert Jasmer, MD; Masae Kawamura, MD; Sundari Mase, MD, MPH, TB Control Branch Co-Chair; Allyson Tabor, BSN,PHN, CTCA Executive Committee Co-Chair; .

Suggested Reading

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APPENDIX 1

High Risk Populations

Table 1

Incidence of Active TB in Persons with a Positive TST by Selected Factors

Risk Factor	TB Cases/1000 person-years
Infection < 1 year duration	12.9
Infection 1-7 year duration	1.6
HIV Infection	35.0-162.0
Injection Drug Use	
HIV seropositive	76.0
HIV seronegative or unknown	10.0
Silicosis	68
Radiographic findings consistent with old TB	2.0-13.6

Source: Modified from Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6): 1-53.
<http://www.cdc.gov/mmwr/PDF/RR/RR4906.pdf>

Table 2**Certain medical conditions associated with an increased risk of developing TB**

Medical Condition	Relative Risk
Solid organ transplant Renal Cardiac	37 20-74
Jejunioileal bypass	27-63
Silicosis	30
Chronic Renal Failure/Hemodialysis	10.0-25.3
Carcinoma of head and neck	16
Gastrectomy	2-5
Diabetes mellitus	2.0-4.1

*Source: Modified from Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 2000;49(No. RR-6): 1-53.
<http://www.cdc.gov/mmwr/PDF/RR/RR4906.pdf>*

APPENDIX 2

CANDIDATES FOR TREATMENT OF LATENT TUBERCULOSIS INFECTION (LTBI)			
(adapted from Charles P. Felton National TB Center)			
Category of person tested	TST <5 mm	TST ≥5 mm	TST ≥10 mm
(A) Recent Contact to TB Case¹			
1. Child <5 years and recent contact ²³	TREAT	TREAT	TREAT
2. HIV-infected and recent contact ²	TREAT	TREAT	TREAT
3. Immunosuppressed and recent contact ²	TREAT	TREAT	TREAT
4. Other recent contact of TB case ²⁴	Do Not Treat	TREAT	TREAT
(B) No Recent Contact to TB Case			
1. Fibrotic changes on chest-radiograph ²⁵	Do Not Treat	TREAT	TREAT
2. HIV-infected	Do Not Treat	TREAT	TREAT
3. Injection drug user with unknown HIV status	Do Not Treat	TREAT	TREAT
4. Other immunosuppressed persons ²⁶	Do Not Treat	TREAT	TREAT
5. Recent skin test converters within 2 years	Do not Treat	Do Not Treat	TREAT
6. Foreign-born persons from endemic country ²⁷	Do Not Treat	Do Not Treat	TREAT
7. Injection drug user known to be HIV negative	Do Not Treat	Do Not Treat	TREAT
8. Resident/Employee institutional setting ²⁸	Do Not Treat	Do Not Treat	TREAT
9. Mycobacteria lab personnel	Do Not Treat	Do Not Treat	TREAT
10. High-Risk clinical conditions ²⁹	Do Not Treat	Do Not Treat	TREAT
11. Children < 18 years of age exposed to adults at high risk	Do Not Treat	Do Not Treat	TREAT
12. Other persons depending on local epidemiology and resources	Do Not Treat	Do Not Treat	TREAT

Note: If a person meets more than one criteria for treatment, the lower TST cut point for therapy should be used, i.e., an immigrant from a TB endemic country who has fibrotic changes on chest radiograph should be treated if the TST is ≥ 5 mm.

APPENDIX 3

APPENDIX 4

Risk Assessment Questionnaire*

Questions

1. Was your child born outside the United States?

If yes, this question would be followed by: Where was your child born? If the child was born in Africa, Asia, Latin America, or Eastern Europe, a TST should be placed.

2. Has your child traveled outside the United States?

If yes, this question would be followed by: Where did the child travel, with whom did the child stay, and how long did the child travel? If the child stayed with friends or family members in Africa, Asia, Latin America, or Eastern Europe for a cumulative total of 1 week or more, a TST should be placed.

3. Has your child been exposed to anyone with TB disease?

If yes, this question should be followed by questions to determine if the person had TB disease or LTBI, when the exposure occurred, and what the nature of the contact was. If confirmed that the child has been exposed to someone with suspected or known TB disease, a TST should be placed.

If it is determined that a child had contact with a person with TB disease, notify the local health department per local reporting guidelines.

4. Does your child have close contact with a person who has a positive TB skin test?

If yes, see question 3 (above) for follow-up questions.

Risk-assessment questionnaires can include the following questions based on local epidemiology and priorities:

1. Does your child spend time with anyone who has been in jail (or prison) or a shelter, uses illegal drugs, or has HIV?
2. Has your child drunk raw milk or eaten unpasteurized cheese?
3. Does your child have a household member who was born outside the United States?
4. Does your child have a household member who has traveled outside the United States?

* Adolescents can be asked these questions directly.

Source: **Targeted Tuberculin Skin Testing and Treatment of Latent Tuberculosis Infection in Children and Adolescents**. Pediatric Tuberculosis Collaborative Group. *Pediatrics* 2004;114;1175-1201, p. 1178. DOI: 10.1542/peds.2004-0809.

FOOTNOTES

¹ Centers for Disease Control and Prevention. Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. *MMWR*, June 9, 2000/V49/No.RR-6, p.8.

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¹² Marks, et al. *Am J Resp Crit Care Med* 2000. 162: 1851-1854.

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²² Recent contacts to active case of pulmonary or laryngeal TB.

²³ Recent contacts who are initially TST-negative should have a TST repeated 8-10 weeks after last exposure to TB case (see Text). Treatment can usually be discontinued after negative second TST in children. HIV infected adults and children, however, should receive full course of therapy regardless of TST result.

²⁴ If circumstances suggest significant evidence of transmission, treatment is suggested in those with TST <5mm.

²⁵ Abnormal, stable, radiographic findings (parenchymal abnormalities consistent with TB, not isolated calcified granuloma or apical pleural thickening). Bacteriologic studies should be obtained for all persons with an abnormal chest radiograph consistent with TB even when the radiographic abnormalities appear stable. When bacteriologic studies are obtained, treatment of LTBI should not be initiated until final culture results are available.

²⁶ Transplant recipients, prolonged corticosteroid therapy (≥ 15 mg/day for ≥ 1 month), other immunosuppressive therapy.

²⁷ Local epidemiologic circumstances and resources should determine whether a specific age cutoff is warranted in persons who have resided in the U.S. for over 5 years.

²⁸ Residents and employees of the following high risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, residential facilities for patients with AIDS, homeless shelters; other homeless persons; employees of hospitals and health care facilities.

²⁹ Silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g. leukemias and lymphomas), other specific malignancies (e.g. carcinoma of the head and neck or lung), weight loss of $\geq 10\%$ of ideal body weight, gastrectomy, jejunioileal bypass.

Pregnancy: Treat during pregnancy if either HIV-infected or recent *M.tb* infection.