Targeted Skin Testing and Treatment of Latent Tuberculosis Infection in Adults and Children—2005

The following guidelines follow the American Thoracic Society and Centers for Disease Control and Prevention recommended change in nomenclature. The phrase "treatment of latent tuberculosis infection (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 widespread use of this important tuberculosis (TB) control strategy.

Targeted TB Skin Testing

Targeted tuberculin skin testing for LTBI aims to identify individuals at high risk for TB who would benefit from treatment of LTBI. Skin testing low risk populations will result in unnecessary testing and treatment because of false-positive test results.

High risk in San Francisco is defined as:

(1) Recent infection with *Mycobacterium tuberculosis*;
(2) The presence of clinical conditions that are associated with an increased risk of progression of LTBI to active TB (see **Appendix 1: Tables 1 and 2**); or
(3) Increased morbidity if progression to TB disease occurs.

Definition of a Positive Tuberculin Skin Test

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 be ignored when interpreting a tuberculin skin test (TST).

I. ≥ 5 mm of induration

A. Persons known or suspected to have HIV infection

B. Recent contacts with an active case of pulmonary or laryngeal TB

C. Persons with an abnormal chest radiograph consistent with TB disease

D. Immunosuppressed individuals
(See page 3 **Indications for Treatment of LTBI -TB2 and TB4**)

II. ≥ 10 mm of induration

All persons except those in I (A) above

> **Note:** The CDC recommends using a 15 mm cutoff for low risk reactors. However, in California, public health departments do not recognize this cutoff because California is a high incidence state and the prevalence of nontuberculous mycobacterial infections is lower than other regions of the United States.

III. 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 from a documented negative to positive TST.

Example: a TST of 4 mm that increases in size to 14 mm or more of induration would be considered a skin test conversion.

In some 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 - Symptom Review and Chest Radiography

I. All persons who have a positive TST or QuantiFERON-TB test (QFT) should undergo symptom review and have a chest radiograph (CXR).

A. If the radiograph is normal and the patient is asymptomatic, treatment of LTBI may be indicated (see **Appendix 2**).

B. 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.

II. Bacteriologic studies should be obtained for all persons with an abnormal chest radiograph consistent with TB even when the radiographic abnormalities appear stable. If bacteriologic studies are obtained, treatment of LTBI should not be initiated until final culture results are available.

Definition of Persons Eligible for Treatment of LTBI (TB2 and TB4)

The following classes of persons are eligible for treatment of LTBI if they have not received a prior or adequate course of treatment for active TB or LTBI. In some cases, individuals may require another course of therapy. Indications for re-treatment include persons with a new close contact to an infectious case who are < 5 years of age, or have HIV/AIDS or other significant

immunosuppression. Providers may also choose to retreat persons with previously treated LTBI or 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 in high risk settings such as prisons or other congregate facilities.

I. TB2 - TB infection, no disease:

Positive TST or QFT, negative bacteriologic studies (if done) and no clinical and/or radiographic evidence of TB. Patients with isolated calcified granulomas or apical pleural thickening are generally classified as TB 2.

II. TB4 - TB, no current disease:

A. History of previous episode(s) of TB, or

B. Abnormal*, but stable, radiographic findings in a person with a positive TST or QFT, negative bacteriologic studies, and no clinical and/or radiographic evidence of current disease.

*Abnormal refers to radiographs with parenchymal abnormalities consistent with TB, except isolated calcified granulomas.

Indications for Treatment of LTBI – TB2 and TB4 (See **Appendix 2**)

Persons in the following categories should be considered for therapy if their TST or QFT is positive and they have not previously completed a course of therapy for TB or LTBI.

I. Persons known or suspected to have HIV infection, regardless of age, including pregnant women

II. Persons with an abnormal chest radiograph suggestive of TB and classified as a TB 4, regardless of age

III. Recent close contacts to active pulmonary or laryngeal TB, regardless of age, including pregnant women

IV. TST converters within 2 years, regardless of age, including pregnant women

V. Persons from countries with high TB rates

A. Recent arrivals (arrived within the past 5 years or less), regardless of age

B. Remote arrivals (arrived over 5 years ago) under the age of 35

Note: The CDC guidelines no longer recommend using a 35 year-old cutoff in deciding which individuals with LTBI should be treated. In California, where the majority of the TB cases occur in persons born outside of the United States, it is recommended that individuals

who arrived over 5 years ago should still receive treatment for LTBI if they have a positive tuberculin skin test. Because the risk of isoniazid-induced hepatitis is greater in older individuals, an age cutoff is appropriate for this group. Local epidemiologic circumstances and resources in SF support using the 35 year-specific age cutoff.

VI. Persons with the following conditions that have been associated with an increased risk of TB (See **Appendix 1, Tables 1 and 2**), regardless of age:

A. Injection drug use, regardless of HIV serostatus

B. Diabetes mellitus (especially insulin-dependent)

C. Silicosis

D. End-stage renal disease

E. Chronic immunosuppression

1. Transplant recipients
2. Prolonged corticosteroid therapy (≥ 15 mg/day for ≥ 1mo)
3. Other immunosuppressive therapy (cancer chemotherapy, anti-TNF drugs, etc.)

F. Hematological and reticuloendothelial diseases

G. Malnutrition and clinical situations associated with rapid weight loss

1. Cancer of the head and neck
2. Intestinal bypass or gastrectomy
3. Chronic malabsorption
4. Low body weight (> 10% below ideal body weight)

VII. Children and adolescents < 18 years of age exposed to adults with the above high risk characteristics.

VIII. Residents and employees under the age of 35 years from 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, and homeless shelters; employees of hospitals and other health care facilities.

IX. Individuals who are homeless or without stable housing (includes those living in low cost hotels and supportive housing).

X. Persons with a positive TST who are less than 21 years of age and not in the above categories.

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

Close Contacts

In close contacts to infectious cases, the initial TST may be negative despite underlying infection with *M. tuberculosis* if the TST is placed before the contact has mounted an immune response to the tuberculin antigen. It takes 2 to 12 weeks after infection with *M. tuberculosis* to develop a positive TST reaction. (Duration is unknown for QFT conversion but may be similar or earlier than TST conversion.)

Close contacts (TB1) to an infectious case, who have a tuberculin skin test < 5 mm, should have a chest radiograph obtained, and once TB disease is excluded, should be started on therapy for LTBI if:

I. Circumstances suggest a high probability of infection from a highly infectious case demonstrated by a high prevalence of infection, documented converters, or secondary cases.

II. The contact is a child under 5 years of age, or is infected with HIV, or is otherwise immune-compromised.

For those individuals who are started on therapy with a TST < 5 mm, a repeat TST should be performed 10 to 12 weeks after contact with the infectious case has been broken, or the index case becomes non-infectious, to determine if the skin test has become positive. Decision on continuing therapy should be made once the result of repeat skin testing is available.

> **Note:** In HIV-infected and immunocompromised contacts, treatment should be completed, regardless of the result of the repeat skin test.

Contraindications to LTBI Treatment

Contraindications to starting isoniazid (INH) LTBI treatment include the following:

- Individuals with prior severe side effects to INH (rifampin considered as an alternative if patient at very high risk)
- Individuals with baseline liver function tests (AST/ALT) that are greater than three times normal or in patient with known unstable liver disease (rifampin considered as an alternative if patient at very high risk)

Treatment Regimens (See **Appendix 3** for drug dosages)

I. INH alone:

   A. 6 months for immune-competent adults.

B. 9-month regimen for children and adolescents up to age 15.

C. 9-month regimen for HIV-infected persons or persons suspected of having HIV infection or who are immunocompromised from other reasons

D. 9-month regimen for TB 4 (See also **below,** IV)

II. Rifampin (RIF) alone for 4-6 months. This regimen has not been studied in randomized trials, so it should be reserved for those individuals who cannot tolerate INH or are contacts to INH resistant cases.

III. INH and RIF for 4 months is the preferred regimen for TB 4.

IV. Rifabutin may be substituted for RIF in the above regimens in situations where RIF 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 should be consulted.

V. Regimens for Contacts to Multi-drug Resistant (MDR-TB) Cases

Regimens should be based on the susceptibility of the source case. First line agents such as pyrazinamide (PZA) and ethambutol (EMB) should be used whenever possible. Other options include a quinolone with or without a second line agent. There are no comprehensive studies that validate these regimens or the duration of treatment. In general, multiple drugs should be used for a minimum of 6 to 12 months. Additional 2 year, biannual follow-up (CXR and symptom review) of high-risk contacts (converters, immunocompromised and/or children under 5 years) should be considered.

Daily vs. Intermittent Dosing

INH may be given daily or intermittently. When a regimen is given intermittently, it must be administered as directly observed therapy (DOT) only.

Directly Observed Therapy

DOT for LTBI should be used in circumstances where the risk of nonadherence is judged to be high or when the treatment regimens are given intermittently. In San Francisco the following groups are placed on DOT:

- Homeless contacts, TST or QFT converters or HIV-infected
- Methadone clients
- Pediatric contacts under 5 years of age

Monitoring for Drug Toxicity and Adherence

I. Baseline Evaluation

A. All patients taking RIF or rifabutin should have a complete blood count and platelets and serum transaminase (AST or ALT) and bilirubin at baseline. With the INH regimen for LTBI, 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:

1. HIV infection
2. History of, or risk of, chronic liver disease
3. Alcoholism
4. Taking other hepatotoxic medications
5. Pregnant women or immediately postpartum

B. The baseline laboratory tests will depend on which drug regimen is being used.

II. Evaluation During Treatment

A. Clinical Evaluation – Patients being treated for LTBI should receive a clinical evaluation at least monthly, regardless of the regimen used. The evaluation should include careful, in-person questioning of the patient about side effects associated with the medications, particularly hepatitis (e.g., anorexia, malaise, abdominal pain, fever, nausea, vomiting, dark urine, icterus). In addition, the patient should be asked about adherence and educated about the possible side-effects of the medications.

B. Routine laboratory monitoring during treatment of LTBI is indicated for those whose baseline liver function tests are abnormal, for persons at high risk of hepatic disease, or 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.

C. Medications should be stopped if the transaminase levels exceed 3-4 times the upper limit of normal if associated with symptoms and 4 to 5 times the upper limit of normal if the patient is asymptomatic. Medication should be held pending clinical laboratory results.

Note: Any cases of severe liver injury (leading to hospitalization or death) in persons receiving any regimen for LTBI should be reported to the Surveillance and Epidemiology Section of the California Department of Health Services, TB Control Branch at (510) 540-2973, and will be forwarded to the Centers for Disease Control.

Completion of Therapy

Completion of therapy should be based on the total number of doses administered–not on 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 frequent or prolonged enough to preclude completion of doses in the time frames specified. When therapy is restarted after an interruption of more than 2 months, a medical examination to exclude active disease is indicated.

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 > 2 years past	**1.6**
Infection < 1 year past	**12.9**
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: American Thoracic Society/Centers for Disease Control and Prevention, 2000

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

Medical Condition	Relative Risk
Solid organ transplant	
Renal	**37**
Cardiac	**20-74**
Jejunoileal 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: American Thoracic Society/Centers for Disease Control and Prevention, 2000

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 Case			
1. Child <5 years and recent contact	TREAT	TREAT	TREAT
2. HIV-infected and recent contact	TREAT	TREAT	TREAT
3. Immunosuppressed and recent contact	TREAT	TREAT	TREAT
4. Other recent contact of TB case	Do Not Treat	TREAT	TREAT
(B) No Recent Contact to TB Case			
1. Fibrotic changes on chest X-ray	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	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 in US <5yrs	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 in institutional setting, less than 35 yrs old	Do Not Treat	Do Not Treat	TREAT
9. Homeless individuals	Do Not Treat	Do Not Treat	TREAT
10. Children < 18 years of age exposed to adults at high risk	Do Not Treat	Do Not Treat	TREAT
11. Foreign-born persons in US >5yrs and under 35 yrs old	Do Not Treat	Do Not Treat	TREAT
12. Individuals under age 21	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 induration)

Appendix 3 Recommended Drug Treatment Regimens for Treatment of LTBI

Drug	Interval & Duration	Adult Dose (max)	Pediatric Dose (max)	Criteria for Completion	Monitoring	Comments
INH	Daily for 9 mos.	5 mg/kg (300 mg)	10-20 mg/kg (300 mg)	270 doses within 12 mos.	Clinical monitoring monthly. Liver function tests at baseline in selected cases* and repeat measurements if baseline tests are abnormal, patient is at high risk for adverse reactions, or patient has symptoms of hepatitis.	Preferred regimen for all persons. In HIV-infected patients, INH may be administered concurrently with NRTIs, protease inhibitors, or NNRTIs
	Twice-weekly for 9 mos.	15 mg/kg (900 mg)	20-40 mg/kg (900 mg)	76 doses within 12 mos.		DOT must be used with twice-weekly dosing
INH	Daily for 6 mos.	5 mg/kg (300 mg)	n.r.	180 doses within 9 mos.		Alternate regimen for adults.
	Twice- weekly for 6 mos.	15 mg/kg (900 mg)	n.r .	52 doses within 9 mos.		DOT must be used with twice-weekly dosing
RIF	Daily for 4 – 6 mos.	10 mg/kg (600 mg)	10-20 mg/kg (600 mg)	120 doses within 6-8 mos.	Clinical monthly monitoring. Complete blood count, platelets, and liver function tests* at baseline in selected cases2 and repeated measurements if baseline results are abnormal or patient has symptoms of adverse reactions	Alternate regimen for adults. For persons exposed to INH resistant, RIF susceptible TB
INH plus RIF	Daily for 4 mos.	INH 5 mg/kg (300 mg) RIF 10mg/kg (600 mg)		120 doses within 6 mos.	See INH and RIF	Preferred regimen for TB Class 4 (history of previous TB or abnormal but stable radiographic findings without evidence of active TB.)

Abbreviations: INH = isoniazid, RIF = rifampin, DOT = directly observed therapy, mos.=months, n.r. = not recommended
Pregnancy: INH regimens preferred for pregnant women. **MDR-TB exposure**: For persons who are likely to be infected with INH and RIF (multi-drug) resistant TB and at high risk of reactivation, PZA and EMB or PZA and a fluoroquinolone are recommended, depending on the sensitivities of the *M. tuberculosis* isolate. (Consult expert.)

* AST or ALT and serum bilirubin HIV Infection, history of liver disease, alcoholism, and pregnancy