San Francisco Treatment Guidelines for Latent Tuberculosis Infection

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Whom To Treat

- **HIGHEST PRIORITY (Regardless of Age)**
  - **All household or other close contacts of persons with current pulmonary tuberculosis**
    - High-risk contacts including children under 5 years and immunocompromised individuals (HIV infection, chronic corticosteroids, chemotherapy, etc) should receive treatment for LTBI regardless of tuberculin skin test (TST) reaction if the index case is smear or culture (+) for M. tuberculosis.
    - Refer to Contact Investigation Guidelines for other groups
    - At 8-10 weeks following exposure, contacts with a negative IGRA or TST (<5mm) will be retested. If the non-immunocompromised contact is still negative (includes children) and the index case is on TB chemotherapy, treatment of LTBI may be discontinued. Immunocompromised close contacts should complete a full course of treatment regardless of repeat TST results since test results may be unreliable.
  - **TB test converters**
    - TST Converter: Increase in the size of the tuberculin reaction by at least 10 mm from less than 10 mm to 10 mm or more within a 2 year period.
    - IGRA Converter, Contact: Current positive test with a documented prior negative result within the past two years
    - IGRA Converter, non-Contact: Current positive test with a documented prior negative result within the past two years
  - **IGRA positive or TST reactors (5mm or greater) with <u>abnormal chest films</u>** consistent with dormant tuberculosis that have not had adequate prior therapy.
    - It is important to exclude current disease by bacteriologic evaluation and/or a review of serial x-rays.
  - **IGRA positive or TST reactors (5mm or greater) with <u>HIV infection</u>** or at high risk of HIV infection.

- **IGRA positive or TST reactors (10mm or greater) who are <u>injection drug users</u>** (HIV testing should be strongly encouraged for all individuals in this group) and have a risk factor for progression as listed in special medical conditions.
- **IGRA positive or TST reactors (10mm or greater) who are <u>homeless or have a transient living arrangement and is a TST converter, contact, or is HIV infected or immunosuppressed</u>**
  - Because of increased TB disease susceptibility and probability of TB exposure in group settings, HIV testing should be strongly encouraged for all homeless tuberculin reactors).
  - *These patients should always be placed on DOT*
- **IGRA positive or TST reactors with <u>special medical conditions</u>** that increase risk of disease progression. Prioritization of contacts, foreign-born and homeless persons with the following conditions should be made
  - HIV infection
  - Diabetes mellitus
  - Current tobacco smokers
  - Immunosuppressive therapy such as prolonged corticosteriod therapy (>15mg daily of prednisone or equivalent for 2-4 weeks), TNF-antagonists, post-transplant immunosuppressive drugs, and cancer chemotherapy.
  - Cancer of the head and neck and hematologic malignancies (leukemia or lymphoma)
  - End-stage renal disease
  - Organ transplant candidates/recipients
  - Intestinal bypass or gastrectomy (especially with weight loss)
  - Low body weight (10% or more below ideal)
  - Silicosis

  Note: *a 5 mm TST cut point is considered positive for persons who are on immunosuppressive therapy, corticosteroids, or have leukemia or lymphoma. A 10mm cut point should be used for other medical risk groups*.

- **Less than 50 years of age <u>foreign-born</u> IGRA positive or TST reactors (10 mm or greater)** who come from areas of the world with a high TB incidence (includes Central and South America, Asia, Philippines, the former Soviet Union, and Africa)

Treatment Considerations

- Known previous adverse reactions to INH or rifampin
- Unstable liver disease, with AST greater than 3 times normal. (for INH only)

Recommended Treatment Regimens

- RIF is prescribed 4 months
- RIF for 6 months is recommended for
  - children under age 15
  - immunocompromised (HIV, biologic therapy, cancer chemotherapy)
- INH is prescribed for 6 months in immunocompetent persons
  - persons who are unable to receive RIF because of a drug interaction
- <u>INH is prescribed for 9 months for</u>:
  - Children under age 15,
  - Immunocompromised reactors (especially HIV seropositive persons),

    - Alternative regimen for persons with abnormal chest films consistent with dormant tuberculosis
  - Multi-drug regimen of rifampin/INH for 4 months
  - Preferred regimen for persons with abnormal chest films consistent with dormant tuberculosis

- All patients placed on intermittent regimens will required DOT and must be under the SF TB Control DOT program
    - These regimens include biweekly INH 900 BIW
    - INH/Rifapentine 12 doses weekly
- In general, for those patients on self administered therapy, no more than one month of medication should be prescribed to ensure adequate monthly monitoring of patients
- For Dosages, see attached chart.

LTBI Treatment of Assumed Drug Resistant Strains (to be managed by TB clinic)

- Contacts of INH-resistant TB:
  - 4 to 6 months of Rifampin shall be used (longer for children and immunocompromised persons).
- Contacts of multidrug-resistant TB:
  - LTBI regimens shall be based on the drug susceptibility pattern of the index case's organism (patients on second-line drugs shall be exclusively under the care of the TB Clinic for close follow-up and monitoring).

Completion of LTBI Treatment

Definition: Completion of 100% of doses

- 4 month regimens - 120 doses within 6 months
- 6 month regimens - 180 doses within 9 months
- 9 month regimens - 270 doses within 12 months

- Managing interrupted treatment: If there is a continuous break of more than 3 months, a new medical evaluation with chest x-ray and symptom review is required. If active disease is excluded, LTBI treatment can be restarted.
- Self-administered treatment should not be restarted if 2 prior attempts to restart LTBI treatment has failed - if patient is at risk for progression to TB disease refer to TB clinic.

Use of Vitamin B6 with regimens including isoniazid

The routine use of B6 50mg-100mg is recommended only for persons at high risk of developing peripheral neuropathy: persons with diabetes, uremia, chronic alcoholism, severe malnutrition, HIV infection, pregnant women and the aged.

BCG Considerations

In healthy immunocompetent and asymptomatic children and adults, an IGRA result will be accepted over a TST result in BCG vaccinated person because of its higher specificity. BCG vaccinated patients with a positive TST refusing treatment can be offered an IGRA test. If a person has been BCG vaccinated, the preferred test is an IGRA.

Treatment Monitoring

- Standard of care: Monthly monitoring for adherence and side effects (see attached chart) is essential throughout treatment to ensure completion and safety. This can be done in person

or by phone, but monitoring in the initial stages of treatment is encouraged as a face to face encounter. A one to two week follow-up after treatment initiation is recommended to prevent early default.

- Baseline and monthly liver function tests (AST, Alkaline phosphatase and total bilirubin) are required for individuals* who:
  - Have known liver disease
  - Drink more than 2 glasses or shots of alcohol per day
  - Are injection drug users
  - Have HIV infection
  - Are placed on any multi-drug regimen (e.g. INH/RIF for 4 months)
  - Take other medications that are metabolized by the liver (e.g. statin)

**SF TB clinic routinely obtains at least one set of LFTs on patients >50 who have been on LTBI treatment and do not meet criteria for baseline LFTs*

- Complete blood count is required for those placed on rifampin or rifabutin. If baseline results are abnormal, repeat measurements should be obtained monthly until documented stable for 2 months.
- Anti-TB medication should be held if LFTS are > 3x WNL with symptoms of hepatoxicity (nausea, fatigue, anorexia, abdominal pain) or >5x WNL asymptomatic
- Monthly LFTS may be discontinued if they are WNL for > 2 months on anti-TB treatment with no new medications and monthly symptom monitoring is continued.

Treatment Not Given, Refused or Not Tolerated (if patient at risk for progression to TB disease and has refused treatment - can consider referral to TB for second opinion)

- Patients should be educated on the signs and symptoms of tuberculosis and encouraged to seek care should signs and symptoms develop.
- The current and future risk of TB disease should be explained. Possible change in risk may occur if new medical problems such as diabetes, cancer, etc. develop. If increased risk occurs, LTBI treatment should be strongly reconsidered.
- Untreated contacts and TB test converters require clinical monitoring for 2 years when the risk of progression is highest. Periodic follow-up, generally every six months, for symptom review, weight check and chest x-ray is advised.
- For immunocompromised (e.g. HIV, biologic treatment, cancer chemotherapy), refusing LTBI treatment, refer to TB clinic

Post-Treatment Monitoring

- Once LTBI treatment is completed, monitoring the patient with chest x-rays is not recommended and are considered unnecessary unless the patient develops symptoms of active TB.
- LTBI treatment reduces but does not completely eliminate the risk of reactivation TB and cannot prevent re-infection. Also, treating LTBI with INH may be ineffective when the latent infection is with an INH-resistant strain. Hence, if a patient who has completed LTBI treatment has symptoms of TB, evaluation should be performed without delay.

Drugs For LTBI

Drug	Supplied	Daily	Intermittent (must be on DOT)	Side Effects	Monitoring	Comments
Isoniazid:	Tabs: 300mg 100mg Susp: 50mg/5ml Inj: 100mg/ml	Adults: 300mg Children: ≤20kg:10-15mg/kg >20kg: 300mg	2 or 3 X weekly: 15mg/kg PO or IM (900mg max) Children: 20-30mg/kg	Hepatitis; peripheral neuropathy; mild CNS effects; skin rash; increased Dilantin levels.	LFTs (not routine) unless known or suspected liver disease or other hepatotoxic drugs used concurrently.	Give pyridoxine 25mg/day to prevent neuropathy in elderly, D.M., nutritionally deficient, renal disease, pregnancy, HIV, alcoholics.
Rifampin:	Caps: 300mg 150mg	Adults: 10mg/kg up to 600mg PO Children: 10 – 20mg/kg up to 600mg PO		Orange discoloration of secretions; cholestatic or hepatocellular hepatitis; febrile (flu-like) reaction; induces hepatic enzymes, drug interactions; thrombocytopenia; skin rash.	LFTs (not routine) unless known or suspected liver disease or other hepatotoxic drugs used concurrently. Baseline CBC.	Warn patient about orange discoloration of urine and other body secretions. Discoloration of contact lens. Induces hepatitis microsomal enzymes.
Rifabutin:	Caps: 150mg	Adults: 5 mg/kg Children: Unknown		As for rifampin except hepatic enzyme induction less; risk of uveitis when used with macrolides, PI's and azole antifungal agents.	As for rifampin.	As for rifampin. Dose adjustment often needed when using antiretroviral agents.

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