WHO TO TEST—WHO TO TREAT

Test persons at high risk for tuberculosis infection and those at high risk for progression to TB disease if infected with *M.tb*.
Before starting treatment perform initial clinical evaluation, including radiologic studies to rule out TB disease.

CATEGORY	IGRA+	TST <5 mm	TST ≥5 mm	TST ≥10 mm	TST ≥15 mm
• Contacts* <5 years of age▼ • Contacts* who are HIV-infected or otherwise immunosuppressed	T	**TREAT** using "window prophylaxis"	**TREAT**	**TREAT**	**TREAT**
• HIV-infected • Immunosuppressed persons (e.g. TNF-alpha blockers, organ transplant medications) • Contact* of TB case (not immunosuppressed) • Fibrotic changes on chest radiograph (adults)	R	Do Not Treat	**TREAT**	**TREAT**	**TREAT**
• Recent arrival from TB endemic country • Injection drug user • Resident/Employee institutional setting§ • Mycobacteria lab personnel • High-risk clinical conditions‡ • Persons <18 years exposed to high-risk adults • Child <4 years of age	E A T	Do Not Treat	Do Not Treat	**TREAT**	**TREAT**
• No known risk factors (testing discouraged)		Do Not Treat	Do Not Treat	Do Not Treat	Consider Treatment

* **All contacts** should receive an initial TST or IGRA and if test is negative should be tested again 8-10 weeks after last exposure to infectious TB case. Window prophylaxis: Start LTBI treatment even if TST or IGRA is negative in contacts who are <5 years of age, HIV-infected, or otherwise immunosuppressed and last again 8-10 weeks after last exposure. Treatment may be discontinued in a healthy child if the second test is negative. Treatment may be continued in HIV+ and other immunosuppressed individuals if exposure to TB was substantial.

§ **Institutional settings:** An increase in reaction size of ≥10 mm within 2 years should be considered a TST conversion indicative of recent infection with *M.tb*.

‡ **High-risk clinical conditions:** Silicosis, diabetes mellitus, chronic renal failure, some hemotologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinome of the head, neck or lung), weight loss of ≥10% of ideal body weight, gastrectomy, and jejunoileal bypass)

▼ **Pediatrics:** TST is the preferred method for testing children under the age of 5 years

Pregnancy: Perform shielded chest radiograph to rule out TB disease. Treat LTBI, even during first trimester, if either HIV-infected or recent *M.tb* infection. Otherwise, wait until 2-3 months post-partum.

BCG Vaccination: Disregard BCG vaccination when testing and treating for LTBI. A positive TST result indicates need to treat LTBI. IGRA result is not affected by prior BCG vaccination.

NEW JERSEY MEDICAL SCHOOL
GLOBAL TUBERCULOSIS INSTITUTE

TB INFOLINE: 1-800-4TB-DOCS www.umdnj.edu/globaltb

225 Warren Street
Newark, NJ 07101-1709
(973) 972-3270

November 2012

Diagnosis and Treatment of Latent Tuberculosis Infection (LTBI)

- **Use an interferon-gamma release assay (IGRA) or a Mantoux tuberculin skin test (TST) to detect LTBI**
- **Treat LTBI – it benefits the individual and the community**

References available at
http://www.umdnj.edu/globaltb/products/ltbidrugcardreferences.html

▶▶▶ SHORTER DRUG REGIMEN NOW AVAILABLE ◀◀◀

IGRA OR TST*

IGRAs are preferred for people who may not return for TST reading and persons who have received BCG vaccine.

TST is the preferred test for children under 5 years of age.

Routine testing with both TST and IGRA is **not** recommended. However, results from both tests might be useful in the following situations:

When the initial test is negative and:

- The risk for infection, progression to disease, and/or a poor outcome is high (e.g. HIV-infected persons or children under 5 years of age who are exposed to a person with infectious TB).
- There is clinical suspicion of TB disease (e.g. signs, symptoms, and/or radiographic evidence suggestive of TB disease) and confirmation of *M.tuberculosis* infection is desired.
- Taking a positive result from a second test as evidence of infection increases detection sensitivity.

When the initial test is positive and:

- Additional evidence of infection is required to encourage acceptance and adherence to treatment (e.g. foreign-born healthcare workers who believe their positive TST is due to BCG).
- The person has a low risk of both infection and progression from infection to TB disease. Requiring a positive result from the second test as evidence of infection increases the likelihood that the test reflects infection. An alternative is to assume, without additional testing, that the initial result is a false positive or that the risk for disease does not warrant additional evaluation or treatment, regardless of test results.

In addition, repeating an IGRA or performing a TST might be useful when the initial IGRA result is indeterminate, borderline, or invalid and a reason for testing persists.

Multiple negative results from any combination of these tests cannot exclude *M.tuberculosis* infection. Steps should be taken to minimize unnecessary and misleading testing of persons at low risk.

Selection of the most suitable test or combination of tests for detection of *M.tuberculosis* infection should be based on the reasons and the context for testing, test availability, and overall cost of testing.

*MMWR June 25, 2010/Vol. 59/No. RR-5

MANAGING PATIENTS ON TREATMENT FOR LTBI

- Rule out TB disease with an initial clinical examination, including symptom screen (for cough, fever, night sweats, weight loss, hemoptysis), chest radiograph, and other studies, as indicated, before starting LTBI treatment.
- Consider possible significant rifamycin-associated drug interactions including, but not limited to, hormonal contraceptives, antiretrovirals, methadone, oral hypoglycemics, and anticoagulants. **Women who use any form of hormonal birth control should be advised to also use a barrier method.**
- Pyridoxine (B_6) supplements are recommended for persons taking INH who are pregnant and breastfeeding women, breastfeeding infants, children and adolescents with nutritional deficiencies, persons with seizure disorder, patients who develop signs and symptoms of peripheral neuropathy while taking INH, and those with medical conditions associated with peripheral neuropathy (i.e. diabetes, malnutrition, chronic renal failure/dialysis, uremia, chronic alcohol use, HIV). Give pyridoxine 10-50 mg/day. Pyridoxine (B_6) supplements are not required for RIF-only regimen.
- Educate patients and caregivers about importance of good adherence. Emphasize possible side effects and adverse reactions. Provide patients with written instructions for adverse events. **Advise to stop treatment and promptly seek medical evaluation if these occur.** Have clients explain what they understand back to you. Use a trained interpreter if language is a barrier.
- For any regimen, support adherence to ensure successful completion by:
  - Identifying possible barriers to adherence (appointment conflicts, misinformation about TB, health beliefs and practices, limited financial resources, co-existing medical conditions, medication side effects, language barriers, real or perceived stigma)
  - Collaborating with community agencies to obtain incentives and/or enablers, case management or directly observed therapy
  - Providing effective patient education and patient-focused strategies

RECOMMENDED DRUG REGIMENS FOR LTBI TREATMENT

Determine which regimen is most appropriate for your patient and support adherence to ensure successful completion. Evidence shows that patients are more likely to complete shorter regimens.

DRUG	INTERVAL AND DURATION	ADULT DOSAGE (MAX)	PEDIATRIC DOSAGE (MAX)	COMPLETION CRITERIA	INDICATIONS	ADVERSE REACTIONS	CONSIDERATIONS WITH THIS REGIMEN
INH♦	Daily for 9 mos.	5 mg/kg (300 mg)	10–20 mg/kg (300 mg) preferred regimen for children <12 years of age	270 doses within 12 mos.	Recommended for most persons, and preferred for children aged ≤11 years. Not indicated for persons exposed to INH-resistant TB. Completion of 9 mos. regimen is >90% effective.* In HIV-infected persons, INH may be given concurrently with NRTIs, protease inhibitors, or NNRTIs.	Hepatic enzyme elevation, hepatitis (nausea, vomiting, abdominal pain, anorexia, yellow eyes/skin, light stools, dark urine), rash, peripheral neuropathy, mild CNS effects, drug interactions	Hepatitis risk increases with age, alcohol use, and concurrent use of other hepatotoxic drugs. Supplementation with pyridoxine (B_6) should be considered in certain populations. See **Managing Patients on Treatment.**
	Twice-weekly for 9 mos.	15mg/kg (900 mg)	20–40** mg/kg (900 mg)	76 doses within 12 mos.			
		DOT must be used with twice-weekly dosing					
INH♦ and RPT	Once-weekly for 12 weeks	INH:15 mg/kg rounded up to the nearest 50 or 100 mg (900 mg max) RPT: 10.0–14.0 kg (300 mg) 14.1–25.0 kg (450 mg) 25.1–32.0 kg (600 mg) 32.1–49.9 kg (750 mg) >50.0 kg (900 mg max) Rifapentine is a long acting rifamycin. **DOT must be used with 12-dose regimen**		12 doses	Recommended for otherwise healthy persons 12 years of age and older who were recently in contact with infectious TB or who recently converted their TB test from negative to positive or who have radiographic evidence of healed pulmonary TB. May be used in otherwise healthy HIV+ persons >12 years of age who are not on antiretroviral medications. May be considered for children aged 2-11 years if completion of 9 mos. INH is unlikely and hazard of TB is great. **Not recommended for:** • Children younger than 2 years old • People with HIV/AIDS who are taking antiretroviral treatment • People presumed to be infected with INH- or RIF-resistant *M.tb*. • Pregnant women or women expecting to be pregnant while taking this regimen	INH: as above RPT: Hematologic toxicity, hypersensitivity reaction (e.g. hypotension or thrombocytopenia), GI symptoms, polyarthralgia, hepatotoxicity, pseudo jaundice, flu-like symptoms, orange discoloration of bodily fluids	Hepatitis risk increases with age, alcohol use, and concurrent use of other hepatotoxic drugs. Supplementation with pyridoxine (B_6) should be considered in certain populations. See **Managing Patients on Treatment.** Vigilance for drug hypersensitivity reactions, ranging from mild reactions such as dizziness to more severe reactions including hypotension and thrombocytopenia. Consider possible rifamycin-associated drug interactions. See **Managing Patients on Treatment.** Women who use any form of hormonal birth control should be advised to also use a barrier method. Educate patients that orange discoloration of bodily fluids is expected and harmless. Train DOT provider to ask patients about adverse reactions at each DOT visit.
RIF	Daily for 4 mos.	RIF 10 mg/kg (600 mg)		120 doses within 6 mos.	For contacts of patients with INH-resistant, RIF-susceptible TB, persons with allergy/intolerance to or serious adverse effects from INH, or when shorter course treatment is preferred. In HIV-infected persons certain antiretroviral medications should not be given concurrently with RIF. An alternative with protease inhibitors is rifabutin 300 mg t/w or 150mg daily. See **www.aidsinfo.gov**.	GI intolerance, drug interactions, hepatitis, bleeding problems (from gums or other sites, easy bruising), flu-like symptoms, orange discoloration of bodily fluids	Consider possible rifamycin-associated drug interactions. See **Managing Patients on Treatment**. Women who use any form of hormonal birth control should be advised to also use a barrier method. Educate patients that orange discoloration of bodily fluids is expected and harmless.
	Daily for 6 mos.		10–20 mg/kg (600 mg)	180 doses within 9 mos.			

MONITORING FOR ALL PATIENTS

- **Evaluate at least monthly:** Include careful questioning about adherence and side effects, and a brief physical examination. Check for evidence of hepatotoxicity, RPT hypersensitivity, or other adverse reactions: fever, anorexia, dark urine, icterus, rash, persistent parasthesia of hands and feet, fatigue or weakness lasting 3 or more days, abdominal tenderness (especially in the right upper quadrant), easy bruising or bleeding, arthralgia, nausea, or vomiting.
- Routine monthly monitoring of LFTs is not generally indicated.
- **Baseline LFTs are indicated for:**
  - HIV infection
  - Regular alcohol use
  - Pregnancy or <3 months postpartum
  - History of liver disease or liver disorders
  - Risks for hepatic disease, including other potentially hepatotoxic drugs (e.g. anti-convulsants) or over-the-counter drugs (e.g. acetaminophen)
- Periodic LFTs are indicated for persons at risk for, or with a history of, hepatic disease, persons who have abnormal baseline LFTs, or those who develop symptoms consistent with hepatotoxicity.
- If side effects occur, a prompt physician's evaluation is necessary with treatment changes as indicated

Medication should be withheld and patients evaluated if:

- Transaminase levels >3 times upper limit of normal in presence of symptoms
- Transaminase levels >5 times upper limit of normal in asymptomatic patient
- If children taking LTBI treatment develop hepatitis, discontinue LTBI treatment and seek other causes, noting transaminase levels stated above.

- **When LFTs have returned to normal, consider an alternate regimen, with close clinical and laboratory monitoring. Consult with TB expert.**

Report adverse events to CDC Division of Tuberculosis Elimination by sending an email to LTBIdrugevents@cdc.gov

Abbreviations: INH = isoniazid, RIF = rifampin, RPT = rifapentine, NRTIs = nucleoside reverse transcriptase inhibitors, NNRTIs = non-nucleoside reverse transcriptase inhibitors, LFT = liver function test, DOT = directly observed therapy, mos. = months

* A 6-month regimen of daily INH is 70% effective; this is not indicated for children or persons with HIV infection or fibrotic lesions.

** American Academy of Pediatrics (AAP) Red Book recommends 20-30 mg/kg.

♦ **Breastfeeding** is not contraindicated in women taking INH. The amount of INH in breast milk is inadequate for treatment of infants with INH. Supplementation with pyridoxine (B6) is recommended for nursing women and for breastfed infants.

MDR-TB exposure: Consult TB expert. Decision to treat must consider likelihood of recent infection with MDR-TB strain, likelihood of developing TB disease, host factors, effective alternative regimen, monitoring, and follow-up.