Summary Guidelines for Testing and Treating Latent Tuberculosis Infection (LTBI) In the Primary Care Setting

Step 1: Know Whom to Test and How to Interpret the Test

Tuberculin skin testing (TST) or Interferon-Gamma Release Assay (IGRA) must be carefully targeted to high-risk individuals of all ages. Lack of targeting will lead to more false positive results. Note that a decision to test is a generally a decision to treat.

Anyone meeting the following criteria should be tested:

Individuals Who May Have Been Recently Infected	Individuals with Clinical Conditions Associated with Progression From LTBI to Active TB
• Close contacts of persons with active Tuberculosis (TB) (Refer to RISE TB Clinic 401-793-2427) • Persons who have immigrated within the last (five) 5 years from areas with high TB rates (see country list that follows) • Persons with prolonged stay (>1 month) in areas with high TB rates (see Chart that follows) • Persons who live or work in clinical or institutional settings where TB exposure may be likely (e.g., hospitals, prisons, homeless shelters, nursing homes, mycobacteriology labs, medical waste management facilities) • Children <5 years of age exposed to adults in high-risk categories	• Persons with HIV infection • Persons with evidence of old, healed TB lesions on chest X-ray • Underweight persons (<10% under ideal body weight) • Persons with certain medical conditions (e.g., silicosis, chronic renal failure, diabetes mellitus, some cancers, gastrectomy/jejunoileal bypass, organ transplant) • Persons receiving immunosuppressive therapy e.g. prolonged corticosteroid therapy (the equivalent of >15 mg/d of prednisone for one month or more], TNF-α blockers) • Injection drug users

TB Endemic Countries

Africa	**Eastern Mediterranean**	Ecuador	Nepal	Northern Mariana Islands
All countries except Seychelles	Afghanistan	El Salvador	Sri Lanka	Palau
	Bahrain	Guatemala	Thailand	Papua New Guinea
Europe	Djibouti	Guyana	Timor-Leste	Philippines
Armenia	Iraq	Haiti		Solomon Islands
Azerbaiján	Morocco	Honduras	**Western Pacific**	Vanuatu
Belarus	Pakistan	Mexico	Brunei Darussalam	Vietnam
Bosnia & Herzegovina	Qatar	Nicaragua	Cambodia	
Bulgaria	Somalia	Panama	China (including Hong Kong)	
Croatia	Sudan	Paraguay	Guam	
Estonia	Syrian Arab Republic	Peru	Kiribati	
Georgia	Yemen	Suriname	Korea, South	
Kazakhstan			Lao PDR (Laos)	
Kyrgyzstan	**North, Central, and South America**	**Southeast Asia**	Macao (China)	
Latvia	Argentina	Bangladesh	Malaysia	
Lithuania	Bahamas	Bhutan	Marshall Islands	
Portugal	Belize	India	Micronesia	
Republic of Moldova	Bolivia	Indonesia	Mongolia	
Romania	Brazil	Korea, DPR (North)	New Caledonia	
Russian Federation	Colombia	Maldives		
Tajikistan	Dominican Republic	Myanmar (formally Burma)		
Turkmenistan				
Ukraine				
Uzbekistan				

Healthcare Worker Employment

Prior to new employment, healthcare workers need to get tested with a two-step procedure to establish baseline. (If negative, first test is followed by a second test in 1-3 weeks to allow for boosting waned immune responses). See regulations: http://www.sec.state.ri.us/rules/index.php?page=details&erlid=4465

The maximum allowable interval between tests for the two-step process is 1 year or 365 days.

TST Interpretation

The reaction to tuberculin skin test (TST) is classified as positive based on the individual's risk factor(s) and the following measurements of induration:

≥5 mm for	• Persons with HIV-infection • Recent contacts of persons with active TB • Persons with evidence of old, healed TB lesions on chest X-rays • Patients with organ transplants and other immunosuppressed persons
≥10 mm for	• Persons who have immigrated within the last 5 years from areas with high TB rates • Injection drug users • Persons who live or work in institutional settings where exposure to TB may be likely (e.g., hospitals, prisons, homeless shelters, nursing homes) • Mycobacteriology laboratory personnel • Persons with clinical conditions associated with increased risk of progression to active TB, including: ▪ Silicosis ▪ Chronic renal failure ▪ Diabetes mellitus ▪ Weight loss of ≥10% of ideal body weight ▪ Gastrectomy/jejunoileal bypass ▪ Certain cancers such as carcinoma of the head or neck lung, leukemias and lymphomas ▪ Immunosuppressive agents such as corticosteroids and TNF-α blockers • Children <5 years of age or children/adolescents exposed to adults in high-risk categories • Persons with prolonged stay in areas with high TB rates (see list)
≥15 mm for	• Persons at low risk for TB disease for whom testing is not generally indicated

IGRA (Interferon Gamma Release Assay) Interpretation

Factors in selecting which test (TST or IGRA) to use include: reasons for testing, test availability, and cost.

- Populations in which IGRAs are preferred for testing:
    - Persons who have received Bacillus Calmette-Guerin (BCG) either as a vaccine or for cancer therapy; and
    - Persons from groups or individuals who are unlikely to return for TST reading.
- IGRAs can be used in place of (but not in addition to) TST in all situations in which CDC recommends TST as an aid in diagnosing *M. tuberculosis* infection.
- TST is preferred over IGRAs for testing children less than 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, the risk for progression to disease, and the risk for a poor outcome are 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 for 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 (e.g., foreign-born healthcare workers who believe their positive TST is due to BCG). A positive IGRA might prompt greater acceptance of treatment for LTBI as compared with a positive TST alone.

- 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.

Advantages of IGRAs:

- Requires a single patient visit to conduct the test
- Results can be available within 24 hours
- Does not boost responses measured by subsequent tests
- Prior BCG vaccination does not cause a false-positive IGRA test result

Disadvantages and limitations of IGRAs:

- Blood samples must be processed within 8-30 hours after collection while white blood cells are still viable
- Errors in collecting or transporting blood specimens or in running and interpreting the assay can decrease the accuracy of IGRAs
- Limited data on the use of IGRAs to predict who will progress to TB disease in the future
- Limited data on the use of IGRAs for:
    - Children younger than 5 years of age
    - Persons recently exposed to *M. tuberculosis*
    - Immunocompromised persons
    - Serial testing

Step 2: Rule Out TB Disease

Any person with a newly positive TST or IGRA result must be evaluated for active TB disease with a medical examination and a chest X-ray. An individual with TB symptoms (cough, fever, hemoptysis, weight loss, lymphadenopathy, or other extrapulmonary signs/symptoms) or an abnormal chest X-ray should be appropriately evaluated with sputum and other tests as indicated.

Active TB must be ruled out before treatment for LTBI begins.

Specialty medical consultation (see step 4) is available through the RISE TB Clinic (Miriam Hospital) at 401-793-2434.

Step 3: Decide Whether to Refer to RISE or Hasbro TB Specialty Clinics vs. Treat in Primary Care Setting

Refer the following priority case types to a specialty clinic:

- All suspect or confirmed cases of active TB disease (pulmonary or extra-pulmonary)
- All exposed household or close contacts of the above cases (any age), regardless of TST status
- Immigration and refugee physicals yielding a positive TST or abnormal chest X-ray
- LTBI in persons at high risk of progression to active disease, such as Chronic renal failure, diabetes mellitus, gastrectomy/jejunoileal bypass, injection drug use, immunosuppression from any cause
- Immunosuppressive agents, such as corticosteroids and TNF-α blockers
- HIV-positive persons
- Pregnant women when LTBI treatment is contemplated, in peripartum time frame
- Children under 5 years of age
- Undocumented/uninsured individuals from endemic countries with a positive TST or IGRA, when a primary care home cannot be assured

To Refer to RISE TB Clinic:

1. Call 401-793-2427 for an appointment.
2. Next, complete and fax this referral form: www.health.ri.gov/forms/medical/TuberculosisReferral.pdf

To Refer to Hasbro Pediatric TB Clinic:

1. Call 401-793-2427 for an appointment.
2. Next, complete and fax this referral form: www.health.ri.gov/forms/referral/HasbroChildrensTBClinicReferral.pdf

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Step 4: Start Treatment for LTBI and Monitor Adherence

People with latent TB infection have TB bacteria in their bodies, but are neither symptomatic nor contagious as bacteria are not active. People with latent TB infection do not have symptoms, and they cannot spread TB bacteria to others. Latent TB infection can become active when a person's immunity is lowered (by age or illness) and this can result in an active TB case (also called reactivation TB). For this reason, people with latent TB infection should be treated to prevent them from developing TB disease. Treatment of LTBI is easier as the bacterial load is lower than that of an active TB case. Four drugs are approved for the treatment of latent TB infection.

The medications used to treat latent TB infection include:

- Isoniazid (INH)
- Rifampin (RIF)
- Rifapentine (RPT)
- Isoniazid/Rifapentine (INH-RPT) only under clinic-based directly observed therapy

Excerpt from *The New Jersey Medical School Global Tuberculosis Institute Diagnosis and Treatment of Latent Tuberculosis Infection (LBTI), November 2012 (To view complete guidance, visit: http://globaltb.njms.rutgers.edu/downloads/products/ltbidrugcard.pdf.)*

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) **DOT must be used with twice-weekly dosing**	20–40** mg/kg (900 mg)	76 doses within 12 mos.			
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.

Step 5: Report LTBI and Active TB to HEALTH

Latent TB Infection
Latent TB Infection should be reported to the Rhode Island Department of Health (HEALTH) within four (4) days using the LTBI specific case report form. Completion of therapy should also be reported.

LTBI Case Report Form:
http://health.ri.gov/forms/reporting/cases/LatentTuberculosis.pdf

LTBI Completion of Therapy Report:
http://health.ri.gov/forms/reporting/cases/LatentTuberculosisCompletionOfTherapy.pdf

Suspected and Confirmed Active TB
Suspected and confirmed active TB disease cases (found in the course of LTBI screening or otherwise) should also be reported within 4 days, as required by regulation. To do so, call the TB Program at 401-222-2577, then submit a completed TB Case Report Form.

RI TB Case Report Form:
http://health.ri.gov/forms/reporting/cases/Tuberculosis.pdf

Instructions for completing above form:
http://health.ri.gov/forms/reporting/cases/TuberculosisInstructions.pdf

Suspect clinical findings include:

- A smear (from any anatomic site) positive for acid-fast bacilli (AFB)
- A nucleic acid amplification test result positive for *Mycobacterium tuberculosis*
- A culture positive for *Mycobacterium tuberculosis*
- Biopsy, pathology, or autopsy findings consistent with active tuberculous disease, including but not limited to, caseating granulomas in biopsies of lungs, lymph nodes or other specimens
- Having been started on two or more anti-TB medications for treatment of suspected or confirmed active TB
- Clinically suspected pulmonary or extrapulmonary tuberculosis, such that the physician or other health care provider has initiated or intends to initiate isolation or treatment for tuberculosis

When an individual has an AFB-positive smear or has started treatment for TB, reporting should never be delayed pending identification of *M. tuberculosis* with rapid diagnostic tests (e.g., nucleic acid amplification tests) or culture.

Whenever TB is suspected, the case should be reported, even if bacteriologic evidence of disease is lacking or treatment has not yet started.

Laboratories should report:

- AFB-positive smears (regardless of anatomic site), cultures positive for *M. tuberculosis*, any culture result associated with an AFB-positive smear (even if negative for *M. tuberculosis*), any nucleic acid amplification test result positive for *Mycobacterium tuberculosis*
- Results of susceptibility tests performed on *M. tuberculosis* cultures
- Pathology findings consistent with TB, including the presence of AFB and granulomas

More Information & Resources

- Latent Tuberculosis Infection: A Guide for Primary Health Care Providers
- ATS/CDC. Targeted tuberculin testing and treatment of latent TB infection. *MMWR* 2000;49(No. RR–6). (PDF)
- Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection — United States, 2010 http://www.cdc.gov/mmwr/pdf/rr/rr5905.pdf
- Interferon-Gamma Release Assays (fact sheet) http://www.cdc.gov/tb/publications/factsheets/testing/IGRA.htm
- CDC. Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection., *MMWR* 2011;60:1650-1653
- Updated Guidelines for the Use of Rifamycins for the Treatment of Tuberculosis Among HIV-Infected Patients Taking Protease Inhibitors or Nonnucleoside Reverse Transcriptase Inhibitors. *MMWR* 2004: 53 (No. 2)
- Targeted Tuberculosis (TB) Testing and Treatment of Latent TB Infection (slide set)
- Treatment of Latent Tuberculosis Infection: Maximizing Adherence

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Rhode Island Department of Health (HEALTH)

TB Program Contact: (401) 222-2577

RISE Clinic: (401) 793-2427

Hasbro Pediatric TB Clinic: (401) 444-3851

HEALTH TB Webpage:
www.health.ri.gov/diseases/tuberculosis/for/providers