

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	MONITORING FOR ALL PATIENTS
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 < 12 years of age. Not indicated for persons exposed to INH-resistant TB. 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 .	<ul style="list-style-type: none"> • 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 paresthesia 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.
	Twice-weekly for 9 mos.	15mg/kg (900 mg)	20–40 [‡] mg/kg (900 mg)	76 doses within 12 mos.				
INH ♦ and RPT	Once-weekly for 12 weeks	Adults and children ≥ 12 years of age: 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) Rifampentine is a long acting rifamycin. DOT must be used with 12-dose regimen	12 doses within 16 weeks	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 2-11 years of age if completion of 9 mos. INH is unlikely and hazard of TB is great. Not recommended for: <ul style="list-style-type: none"> • Children < 2 years of age • People with HIV/AIDS who are taking antiretroviral treatment • People presumed to be infected with INH or RIF-resistant <i>M.tb.</i> • 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.	<ul style="list-style-type: none"> – HIV infection – Regular alcohol use – Pregnancy or <3 months postpartum – History of liver disease or liver disorders <ul style="list-style-type: none"> – Risks for hepatic disease, including other potentially hepatotoxic drugs (e.g. anti-convulsants) or over-the-counter drugs (e.g. acetaminophen) <ul style="list-style-type: none"> • 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 <p style="background-color: #e0f2f1; padding: 5px;">Medication should be withheld and patients evaluated if:</p> <ul style="list-style-type: none"> • Transaminase levels >3 times upper limit of normal in presence of symptoms • Transaminase levels >5 times upper limit of normal in asymptomatic patient 	
RIF	Daily for 4 mos.	RIF 10 mg/kg (600 mg)	10–20 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 150 mg of rifabutin daily. See www.aidsinfo.nih.gov for current guidelines.	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.	<ul style="list-style-type: none"> • If children taking LTBI treatment develop hepatitis, discontinue 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 TB expert. <div style="background-color: #e0f2f1; padding: 10px; margin-top: 10px;">Report adverse events to CDC Division of Tuberculosis Elimination by sending an email to ltbidrugevents@cdc.gov</div>

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

* An additional regimen, 3 months of daily INH and RIF is included in the AAP Red Book as a possible alternative regimen, but is not currently included in CDC recommendations.

♦ **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.

§ AAP recommends 10-15 mg/kg

‡ AAP recommends 20-30 mg/kg.

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.

IGRA OR TST

CDC recommends the use of IGRA in all situations where the TST is indicated. In certain situations one test is preferred, though either is acceptable. IGRA are preferred for all persons \geq 5 years of age who have received a BCG vaccine and for those who may not return for TST reading. TST is the preferred test for children $<$ 5 years of age.*

Selection of the most suitable test or combination of tests should be based on reasons and context for testing, availability, and overall cost of testing. Routine testing with both TST and IGRA is not recommended. However, results from both tests might be useful in the following situations:

<p>When the initial test is positive and:</p> <ul style="list-style-type: none"> • Additional evidence of infection is required to encourage acceptance and adherence to treatment. • The person has a low risk of both infection and progression from infection to TB disease. Requiring a positive result from the second test reflects true infection. Unnecessary testing of persons at low risk should be avoided. 	<p>When the initial test is negative and:</p> <ul style="list-style-type: none"> • The risk for infection, progression to disease and/or a poor outcome is high (e.g. HIV-infected persons or children TB). • There is clinical suspicion of TB disease and confirmation of <i>M. tb</i> infection is desired.
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Additional considerations:

- A repeat IGRA or a TST can be useful when the initial IGRA is indeterminate, borderline or invalid and a reason for testing persists.
- Both IGRA and TST should be used when evaluating a child of any age for TB disease.**
- Some experts recommend that children with immune suppressing disease or who are about to start immunosuppressive therapy should receive both tests to increase sensitivity.**
- Consultation with an expert is suggested for complex clinical situations including patients who are on or are about to start immunosuppressive therapy or discordant results when more than one test is used.

Multiple negative results from any combination of these tests cannot exclude *M. tb* infection.

* The AAP indicates that some data support use of IGRA in children as young as 3 years of age. Some experts will use an IGRA in children 2-4 years of age, especially if they have received the BCG vaccine but have no other significant risk factors.

** Starke, J.R. & Committee on Infectious Diseases. Interferon-Gamma Release Assays for Diagnosis of Tuberculosis Infection and Disease in Children. *Pediatrics* 2014; 134: e1773.

WHO TO TEST — WHO TO TREAT

Test persons at high risk for *M. tb* 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 \geq 5 mm	TST \geq 10 mm	TST \geq 15 mm
• Contacts* <5 years of age • Contacts* who are HIV-infected or otherwise immunosuppressed • HIV-infected • Immunosuppressed persons (e.g. TNF-alpha blockers, organ transplant medications) • Contact* of TB case (not immunosuppressed) • Fibrotic changes on chest radiograph (adults)	TREAT using "window" prophylaxis	TREAT	TREAT	TREAT	TREAT
• Recent arrival from TB endemic country • Injection drug user • Resident/Employee institutional settings • Mycobacteria lab personnel • High-risk clinical conditions† • Persons > 18 exposed to adults at high risk for TB (testing discouraged) • Child <4 years of age with no other risk factors (testing discouraged)	Do Not Treat	Do Not Treat	Do Not Treat	Do Not Treat	Do Not Treat
• No known risk factors (testing discouraged)	Do Not Treat	Do Not Treat	Do Not Treat	Do Not Treat	Do Not Treat

* 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 TB treatment even if TST or IGRA is negative in contacts who are <5 years of age, HIV-infected, or otherwise immunosuppressed and test 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.

† Pediatrics: TST is the preferred method for testing children under the age of 5 years.

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

§ High-risk clinical conditions: Sillcosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head, neck or lung), gastrectomy, jejunoileal bypass, and weight loss of \geq 10% of ideal body weight.

¶ 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.

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, anticoagulants, and psychotropic medications. **Women who use any form of hormonal birth control should be advised to also use a barrier method.**
- Pyridoxine (B₆) 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 supplements are not required for RIF-only regimen.
- Educate patients and caregivers about importance of good adherence when treatment is initiated and throughout the course of treatment. 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

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2015

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Diagnosis and Treatment of Latent Tuberculosis Infection (LTBI)

Based on: the Official Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC), *Morbidity and Mortality Weekly Report (MMWR)* 2000; 49 (RR-6); *MMWR* 2010; 59 (RR-5); *MMWR* 2011; 60 (RR-48); the American Academy of Pediatrics (AAP) 2015 Red Book: Report of the Committee on Infectious Diseases.

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