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LATENT TUBERCULOSIS INFECTION (LTBI)
PART II: REVISED RECOMMENDATIONS FOR TREATMENT AND FOLLOW-UP

Treatment of latent tuberculosis infection (LTBI) is an essential part of the strategy to eliminate TB in the U.S. In April 2000, the American Thoracic Society and the U.S. Centers for Disease Control and Prevention jointly released updated recommendations for treatment of LTBI.[1] These recommendations were summarized in an earlier *Bulletin*.[2] ***In August 2001, reports of adverse reactions caused by the rifampin plus pyrazinamide (RIF&PZA) regimen resulted in revised recommendations.[3] This* Bulletin *updates and supercedes the previous* Bulletin *of June 27, 2000.***

All persons with LTBI who are at increased risk for active TB should be considered for treatment, regardless of age (See Latent Tuberculosis Infection. Part 1: Diagnosis and Evaluation. *Epidemiology Bulletin* No. 10 June 6, 2000).

Treatment of LTBI in children and adolescents ≤ 18 years**:** The only recommended treatment for LTBI in children and adolescents is 9 month of isoniazid (INH) either as daily self-administered therapy or twice weekly as directly observed therapy (DOT). The dose for daily INH is 10-20 mg/kg (maximum 300 mg); for biweekly therapy the dose is 20-40 mg/kg (maximum 900 mg).

Treatment of LTBI in adults**:** There are four treatment options for treatment of LTBI in adults (Table 1).

For non-HIV infected persons with LTBI:

- 9 months of INH remains the gold standard.
- 6 months of INH may be used, although it is less effective than 9 months.
- 4 months of daily rifampin is an acceptable alternative to INH.
- ***2 months of daily RIF&PZA may be used if it is unlikely that the patient will complete a longer regimen, does not have risk factors for hepatotoxicity, and can be carefully monitored.***

For HIV-infected persons with LTBI:

- Consider 9 months of daily INH for compliant, motivated patients.
- 6 months of INH is acceptable, and will give substantial protection.
- ***2 months RIF&PZA remains an acceptable option for HIV-infected patients; previous clinical trials did not show a high risk of severe hepatitis in this group.***
- 4 months of RIF is acceptable, especially if infection with INH-resistant *M. tuberculosis* is suspected. (RIF is generally contraindicated in persons taking protease inhibitors or nonnucleoside transcriptase inhibitors. Rifabutin can be substituted in some cases.[4])

Pyridoxine supplementation**:** Persons with conditions where neuropathy is common (diabetes, uremia, alcoholism, malnutrition and HIV infection) should receive 50 mg of pyridoxine daily when taking INH. Pregnant women, infants who are breastfeeding and persons with seizure disorders should also receive pyridoxine.

Pregnancy and lactation**:** The treatment of LTBI in pregnant women is controversial. Some experts prefer to delay treatment until after delivery, however women with HIV infection or who have recently acquired LTBI should begin treatment without delay because both of these factors increase risk of progression to TB disease. The preferred regimen for pregnant women is INH since this drug is not teratogenic, even in the first trimester. Pyridoxine supplementation should be given. Breastfeeding is not contraindicated when the mother is taking INH, however the infant should receive supplemental pyridoxine.

Monitoring treatment**:** All persons receiving LTBI treatment should be educated about adverse drug reactions and told to stop treatment immediately and contact their provider if side effects develop. Symptoms of adverse reactions include: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, paresthesias, weakness or fever lasting ≥3 days, abdominal tenderness, easy bruising or bleeding, and arthralgia.

- INH or RIF monotherapy: perform a face-to-face interview and brief physical assessment monthly during treatment. Age ≥35 years is not a criteria for routine laboratory monitoring, however monthly LFTs are indicated for persons with suspected or known liver disease, HIV infection, regular alcohol use, or women who are pregnant or <3 mo postpartum.
- ***RIF&PZA therapy: perform a face-to-face interview, a brief physical assessment, and routinely draw LFT laboratory studies for every patient at 0, 2, 4 and 6 weeks of treatment.***

Withhold LTBI treatment if transaminase levels exceed 3 times the upper limit of normal in symptomatic persons or 5 times the upper limit of normal in asymptomatic persons.

References

1. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Dis* 2000; 161:S221-S247.
2. Section of Epidemiology. Latent Tuberculosis Infection (LTBI) Part II: Treatment and Follow-up. *Epidemiology Bulletin* No. 11, June 27, 2000 (superceded by this revised Bulletin).
3. CDC. Update: Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations - United States, 2001. *MMWR* 2001; 50(34):733-5.
4. Notice to Readers: Updated guidelines for the use of rifabutin for infected persons taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. *MMWR* 2000;49:184-9

Table 1. Treatment options for latent tuberculosis infection (LTBI) in adults

Drugs	Duration	Interval	Medication dose	Monitoring
Recommended				
Isoniazid (INH) ***Dispense only 1 mo. at a time.***	9 mo.[1]	Daily or Twice weekly	***Daily*:** INH 5 mg/kg (max 300 mg) ***Twice wkly*:** INH 15 mg/kg (max 900 mg) using DOT[2]	**CLINICAL** • ***Pretreatment*:** ask about previous TB drugs, oral contraceptives (RIF) and other medications, and history of liver disease. • ***During treatment:*** monthly, check for anorexia, nausea, vomiting, abdominal pain, dark urine, icterus, rash, fatigue, fever or paresthesias. **LABORATORY** (AST & bilirubin) • ***Pretreatment:*** only necessary for suspected or known liver disease, HIV infection or women who are pregnant or <3 mo. postpartum. • ***During treatment***: repeat LFTs are only necessary when 1) they are elevated prior to treatment, 2) there are other risks for liver disease, 3) the patient is pregnant/postpartum, 4) there are adverse reactions to treatment.
	6 mo.	Daily or Twice weekly	As above	
Rifampin (RIF) ***Dispense only 1 mo. at a time.***	4 mo.	Daily	***Daily*:** RIF 10 mg/kg (max 600 mg)	
Use with caution[3]				
Rifampin (RIF) + **Pyrazinamide** (PZA) ***Dispense only 2 wks. at a time.***	2 mo. or 2-3 mo.	Daily or Twice weekly	***Daily*:** RIF 10 mg/kg (max 600 mg) + PZA 15-20 mg/kg (max 2 gm) ***Twice wkly*:** RIF 10 mg/kg (max 600 mg) + PZA 50 mg/kg (max 4 gm) using DOT[2]	**CLINICAL** • ***Pretreatment:*** Ask about history of INH toxicity, use of oral contraceptives (RIF) and other drugs and liver disease. • ***During treatment:*** Week 2, 4, 6 check for anorexia, nausea, vomiting, abdominal pain, dark urine, icterus, or fever. **LABORATORY** • Measure AST & bilirubin at 0, 2, 4, and 6 wks for each patient.

1) INH for 9 mo. is the preferred regimen for LTBI treatment.
2) DOT = directly observed therapy
3) Use RIF+PZA with caution in patients taking other hepatotoxic medications, with alcoholism (even if alcohol is stopped), or liver disease from other causes. Do not use for patients with INH hepatotoxicity.

(Contributed by Beth Funk MD, MPH and Sue Anne Jenkerson, RNC, MSN, FNP, Section of Epidemiology)