Who is Eligible for Treatment of Latent TB Infection (LTBI)?

Persons who are **close contacts to active TB** are candidates for treatment of LTBI if their skin test result is **< 5 mm <u>regardless of age</u>**, no clinical evidence of disease is present, and they have the following risk factors:

1. Investigation suggests a high probability of infection
2. Evaluation of other contacts with a similar degree of exposure demonstrates a high prevalence of infection
3. The contact is a child or adolescent in a very high-risk exposure situation
4. The contact is immunosuppressed (e.g., HIV infected, suspect HIV infected, other immunocompromised persons)

The above persons should be skin tested again in 3 months following cessation of exposure; those with skin test reactions ≥ 5 mm should continue treatment of LTBI, those with reactions < 5 mm may be discharged (except for immunosuppressed persons, who may be anergic).

Persons are candidates for treatment of LTBI if their skin test result is **<u>≥</u> 5mm regardless of age**, if they have the following risk factors:

1. Persons with HIV infection not known to be a close contact
2. Recent contacts of persons with newly diagnosed infectious tuberculosis
3. Persons with abnormal chest radiographs that show fibrotic lesions likely to represent old healed tuberculosis
4. Persons with organ transplants, and other immunosuppressed patients (receiving the equivalent of ≥ 15 mg/day of prednisone for ≥ 1 month)

Persons are candidates for treatment of LTBI if their skin test result is **≥ 10 mm regardless of age**, and they have the following risk factors:

1. Foreign-born persons who have recently arrived (within five years) from countries that have a high TB incidence or prevalence (most countries in Africa, Asia, Latin America, Eastern Europe, and Russia)
2. Foreign-born persons under the age of 35 who arrived ≥ 5 years from countries that have high TB incidence or prevalence
3. Persons who inject drugs or use other high risk substances, such as crack cocaine, and alcoholics
4. Residents and employees of high risk congregate settings such as correctional institutions, long-term residential care facilities (nursing homes, mental institutions, etc.), hospitals and other health care facilities, and homeless shelters.
5. Mycobacteriology laboratory personnel
6. Persons with medical conditions which increase the risk of TB disease (diabetes mellitus, silicosis, recent infection with *M. tuberculosis*--within the past 2 years, bone marrow and organ transplant recipients, prolonged high-dose corticosteroid therapy and other immunosuppressive therapy, chronic renal failure who are on hemodialysis, some hematological disorders--e.g., leukemias and Hodgkin's disease, other specific malignancies--e.g., carcinoma of the head or neck, chronic malabsorption syndromes, weight of 10% or more below ideal body weight, and intestinal bypass or gastrectomy)
7. children less than 4 years of age, or children and adolescents exposed to adults in high risk categories

Persons are candidates for treatment of LTBI if their skin test result is ≥**15 mm regardless of age,** if they have none of the above risk factors. This group should be given a lower priority for prevention efforts than the groups listed above. Persons in this group without high-risk factors for progression to TB will only be considered for treatment through the TB Program if they are under the age of 35 years. All other persons can be referred to a PCP for consideration of treatment of LTBI.

How to Administer Treatment for Latent TB Infection (LTBI)

Treatment of latent TB infection (LTBI) is essential to controlling and eliminating TB. Although not required, treatment of LTBI substantially reduces the risk that TB infection will progress to active TB disease. There are different treatment regimens available for the treatment of LTBI. Certain groups are at high risk for developing TB disease once infected and every effort should be made to begin appropriate treatment and ensure that the entire course of LTBI treatment is completed.

Before beginning treatment of LTBI:

- rule out the possibility of active tuberculosis
  - by CXR and medical history
  - by physical examination (it is especially important to do a physical exam of infected children because 50% of children with TB present as asymptomatic contacts to an active TB case.)
  - by bacteriology examination (for persons with signs or symptoms consistent with active TB) **Note: If sputum cultures have been obtained, await final results prior to initiating treatment for LTBI.**
- ask about previous treatment for LTBI or disease (someone with adequate previous therapy[1] may not require re-treatment; please contact the TB Program for further information)
- check for contraindications
  - previous isoniazid-associated hepatic injury
  - history of severe adverse reactions to isoniazid (INH) such as acute or unstable liver disease of any cause
  -
- check for adverse reactions to current drugs which have known interactions with drugs

[1]Adequate previous therapy is defined as documentation of a minimum of 6 months of INH treatment of LTBI within 9 months (for adults without HIV infection). Minimum therapy for adults with HIV and children may vary; please consult with CDPHE TB Program for these cases.

used for the treatment of LTBI

- recommend HIV testing, if risk factors are present
- establish rapport with patient and emphasize possible side effects (see "How to Monitor for Side Effects"), benefits of treatment, importance of adherence to the treatment, and establish an optimal follow-up plan
- for patients with HIV, see "TB and HIV"

1. CDPHE TB Program requires the following before treatment of LTBI can be provided:

    - a documented TST result (exception for patients with a history of a severe TST reaction)
    - completed "Tuberculosis Surveillance and Case Management Report" form (see "Forms") or information completed in the Colorado TB Database (TBdb)
    - CXR report (within 6 months or less of request for treatment)
    - Final sputum culture results (only if ordered)
    - appropriate physician prescription(s).

2. Results of randomized clinical research trials indicate that treatment of LTBI will reduce the risk of active TB by 68% in persons who receive 6 months of therapy and by 85% in persons who receive 9 months of therapy. Patients should be educated about the benefits of treatment, supported, influenced, and persuaded to take the medication as prescribed, and to complete treatment. In some cases, direct-observed preventive therapy may be indicated (see next page).

3. Obtain patient consent for treatment as per each agency protocol.

4. CDPHE will provide up to a 3-month supply of INH for adults and a 1-month supply for children at a time, to the health department or provider. The patient should receive only a 1-month supply of medication at a time. CDPHE will also provide a one-month supply of medications for patients who are moving out of the state.

5. Although no harmful effects of INH to the fetus have been observed, female patients and their partners should be counseled about the need for effective birth control while on treatment of LTBI. Because rifamycins (rifampin and rifabutin) may decrease the effectiveness of oral or other systemic hormonal contraceptives, use of treatment

regimens containing rifamycins necessitates use of an alternative form of birth control.

6. Special Circumstances:

   a. **Pregnancy.** Although no harmful effects of INH to the fetus have been observed, generally treatment of LTBI should be delayed until after delivery. A recent chest x-ray (within 6 months of initiation of treatment) is required before starting therapy. There does not appear to be any substantial increase in tuberculosis risk for women as a result of pregnancy. However, for pregnant women likely to have been recently infected or with high-risk medical condition, especially HIV infection, treatment for LTBI should begin when the infection is documented.

   b. **Breast-feeding.** Decisions regarding treatment for LTBI and breast-feeding should be made in conjunction with the patient's private physician.

   c. **Children**.

      - The only recommended regimen for treatment of LTBI in HIV-uninfected children and the preferred regimen for HIV-infected children is INH at a daily dose of 10-20 mg/kg (maximum 300 mg) or by directly observed preventive treatment (DOPT), twice-weekly at a dose of 20-40 mg/kg (maximum 900 mg) for 9 months.
      - When INH cannot be tolerated or the child has had contact with an active TB case who has an INH-resistant, but rifamycin-susceptible organism, rifampin alone can be used for the treatment of LTBI at a daily or dose of 10-20 mg/kg (maximum 600 mg) or by DOPT, twice-weekly at a dose of 10-20 mg/kg (maximum 600 mg) for 6 months.
      - Liquid INH is not available. To administer the INH to children, cut the pill in half and dissolve in a small amount of warm water. Then, add a small amount of apple juice to the medicine cup. Have the child drink all the liquid at one time, if possible. Administer to infants after the INH is dissolved in a small amount of warm water, via a syringe.
      - Routine administration of vitamin B6 (pyridoxine) is not recommended for children taking INH, but should be given to breastfeeding infants, children and adolescents with diets likely to be deficient in vitamin B6, HIV-infected

children taking INH, and children who experience paresthesias while taking INH.

- PA and LAT chest x-rays are recommended annually for 2 years for all children less than 5 years of age or for children/adolescents 5 years or older who are recent TST converters and refuse or cannot tolerate treatment for LTBI.

d. **Patients on Antabuse**. Although some publications recommend against the use of INH for persons taking Antabuse, there is no strong evidence that Antabuse and INH, when taken together, cause a serious health risk. Therefore, INH should be given when indicated for persons on Antabuse.

e. **Patients on Remicade (Infliximab)**. Providers should screen patients for LTBI or disease before prescribing Remicade (Infliximab). Active tuberculosis may develop soon after initiation of treatment with Remicade (Infliximab).

f. **Other drug interactions**.

- INH has been **reported to inhibit the metabolism of** the following drugs: anticonvulsants, haldoperidol, ketoconazole, theophylline and warfarin. Thus, INH may need to be introduced slowly and/or the dose of these drugs adjusted to prevent toxicity. The patient's private physician must be consulted in these situations.
- Rifamycins are known to induce certain P450 enzymes in the liver (rifampin more than rifabutin), and **may accelerate the metabolism of** certain drugs such as hormonal contraceptives, ketoconazole, fluconazole, itraconazole, beta-blockers, calcium channel blockers, cardiac glycosides, diazepam, hypoglycemic agents (sulfonylureas), some antibiotics, corticosteroids, narcotics (including methadone), anti-coagulants, anti-convulsants, tricyclic antidepressants, theophylline, and AZT.
- Rifampin is **contraindicated** in patients on all protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs). Rifabutin is **contraindicated** with ritonavir (a PI), hard-gel saquinavir (a PI), and delavirdine (a NNRTI).

g. **Heavy alcohol use.** These patients should be followed closely by a physician while on treatment of LTBI because of the increased risk of drug-induced hepatitis. They should be counseled to stop alcohol use and/or be referred for alcohol abuse treatment. Baseline hepatitis measurements of serum AST (SGOT) or ALT (SGPT) and total bilirubin **ARE** indicated. Repeat after one month of treatment for LTBI. If the tests are normal at 1 month, no further laboratory testing is necessary unless symptoms develop. If the tests are elevated at 1 month, continue monthly testing as long as levels are abnormal. If any one of the liver function tests exceeds 3-5 times the upper limit of normal at any time, consult with the patient's medical provider and strongly consider stopping therapy.

7. Patients (adults and children) failing to complete a 9-month treatment regimen within a 12-month period or a 6-month treatment regimen within a 9-month period of time **must restart** treatment of LTBI. Patients requesting to restart treatment of LTBI for the third time should **only** be allowed to restart therapy if they agree to direct observed preventive therapy (DOPT). Contact the TB Program for recommendations regarding HIV patients who have had a lapse in treatment.

8. For patients exposed to **known drug resistant tuberculosis**, contact the TB Program for treatment of LTBI regimens.

9. Pyridoxine (Vitamin B-6) is recommended for persons with conditions that may be associated with neuropathy such as nutritional deficiency, diabetes, HIV infection, renal failure, alcoholism, and pregnant and breastfeeding women.

10. Contact the CDPHE TB Program for LTBI treatment recommendations for patients who have special needs necessitating variation of the common treatment for LTBI as described above (e.g. patients intolerant to INH, patients with silicosis or a chest x-ray demonstrating old fibrotic lesions and no active TB).

RECOMMENDED DRUG REGIMENS FOR TREATMENT OF LATENT TB INFECTION IN ADULTS

Drug	Interval & Duration	Comments	Rating* (evidence)** HIV-	HIV+
Isoniazid (INH)	Daily for 9 months§¶	In human immunodeficiency virus (HIV)-infected patients, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-nucleoside reverse transcriptase inhibitors (NNRTIs).	A (II)	A (II)
	Twice weekly for 9 months§¶	Directly observed therapy (DOT) must be used with twice-weekly dosing.	B (II)	B (II)
Isoniazid	Daily for 6 months¶	Not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children.	B (I)	C (I)
	Twice weekly for 6 months¶	DOT must be used with twice-weekly dosing.	B (II)	C (I)
Rifampin	Daily for 4 months	Used for persons who are contacts of patients with INH-resistant, rifampin-susceptible TB. In HIV-infected persons, most protease inhibitors or delavirdine should not be administered concurrently with rifampin. Rifabutin with appropriate dose adjustments can be used with protease inhibitors (saquinavir should be augmented with ritonavir) and NNRTIs (except delavirdine). Clinicians should consult web-based updates for the latest specific recommendations.	B (II)	B (III)

* Strength of recommendation: A = Preferred, B = Acceptable alternative, C = Offer when A and B cannot be given.

** Quality of evidence: I = Randomized clinical trial data, II = Data from clinical trials that are not randomized or were conducted in other populations, III = Expert opinion.

§ Recommended regimen for children < 18 years of age.

¶ Recommended regimens for pregnant women.

MEDICATIONS TO TREAT LATENT TB INFECTION: DOSES, TOXICITIES, AND MONITORING REQUIREMENTS

	Oral Dose in mg/kg (maximum dose)						
	Daily		Twice Weekly*				
Drug	Adults	Children	Adults	Children	Adverse Reaction	Monitoring	Comments
Isoniazid	5 (300mg)	10-20 (300mg)	15 (900mg)	20-40 (900mg)	▪ Rash ▪ Hepatic enzyme elevation ▪ Hepatitis ▪ Peripheral neuropathy ▪ Mild central nervous system effects ▪ Drug interactions resulting in increased phenytoin (Dilantin) or Disulfiram (Antabuse) levels	Clinical monitoring monthly Liver function tests** at baseline in selected cases§ and Repeat measurements if ▪ Baseline results are abnormal ▪ Patient is pregnant, in the immediate postpartum period or at high risk for adverse reactions ▪ Patient has symptoms of adverse reactions	Hepatitis risk increases with age and alcohol consumption. Pyridoxine (Vitamin B-6), 10-25 mg/day, might prevent peripheral neuropathy and central nervous system effects.
Rifampin	10 (600mg)	10-20 (600mg)	10 (600mg)	-	▪ Rash ▪ Hepatitis ▪ Fever ▪ Thrombocytopenia ▪ Flu-like symptoms ▪ Orange-colored body fluids (secretions, urine, tears)	Complete blood count, platelets and liver function tests** at baseline in selected cases§ and Repeat measurement if ▪ Baseline results are abnormal ▪ Patient has symptoms of adverse reactions	Rifampin use contraindicated for human immunodeficiency virus (HIV)-infected patients taking protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs). Decreases levels of many drugs (e.g. methadone, coumadin derivatives, glucocorticoids, hormonal contraceptives, estrogens, oral hypoglycemic agents, digitalis, anticonvulsants, dapsone, ketoconazole, and cyclosporin). Might permanently discolor soft contact lenses.

* All intermittent dosing should be administered by directly observed therapy (DOT).
** Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and serum bilirubin.
§ HIV infection, history of liver disease, alcoholism, and pregnancy.

How to Monitor for Side Effects

1. Educate patients about possible side effects of treatment before beginning therapy and instruct them to notify the clinic if any occur (see above tables).

2. Active hepatitis and end-stage liver disease are relative contraindications to the use of INH for treatment of LTBI. Use of these drugs in such patients must be undertaken with caution.

3. Baseline laboratory testing is **NOT** routinely indicated for all patients at the start of treatment for LTBI. Baseline hepatitis measurements of serum AST (SGOT) or ALT (SGPT) and total bilirubin **ARE** indicated for:

   - Patients with an initial evaluation suggesting a liver disorder
   - Patients with HIV infection
   - Women who are pregnant or in the immediate postpartum period (within 3 months of delivery)
   - Patients with a history of chronic liver disease (e.g. hepatitis B or C, alcoholic hepatitis or cirrhosis, persons who use alcohol regularly, and others who are at risk of chronic liver disease)
   - Patients who are taking medications for chronic medical conditions (considered on an individual basis)

   If hepatic measurements are indicated as mentioned above, draw blood for liver function tests before starting therapy and at 1 month. If the tests are normal at 1 month, no further laboratory testing is necessary unless symptoms develop. If the tests are elevated at 1 month, continue monthly testing as long as levels are abnormal. If any one of the liver function tests exceeds 3-5 times the upper limit of normal at any time, consult with the patient's medical provider and strongly consider stopping therapy.

   Liver function testing may be reimbursable through the local public health agency, in compliance with state recommendations (see "TB Program Contracting and Reimbursement," Chapter 5).

4. If client is taking anti-convulsants (e.g. Dilantin), refer client to PCP for monitoring of anti-convulsant drug levels.

5. At least once a month, clinicians should evaluate patients receiving treatment of LTBI for:

   - Adherence to prescribed regimen
   - Signs and symptoms of active TB disease
   - Signs and symptoms of hepatitis

   Whenever any of these are present, consult with the patient's medical provider. Liver function tests may be indicated if signs or symptoms of hepatitis develop. In most cases, therapy should be stopped until laboratory results are reviewed.

6. Other laboratory testing (e.g. uric acid) should be considered for patients on treatment of LTBI and who develop symptoms of acute arthritis.

7. Repeat chest x-rays at 6 and 12-month intervals for no more than 2 years may be done for selected high-risk individuals such as HIV-positive persons who cannot or will not take preventive therapy or those believed to be infected with multi-drug resistant strains of TB (recently exposed).

How to Monitor for Compliance With Treatment for LTBI

Health care providers often do not realize that patients are not following recommendations. It is very important for you to determine whether your patients are taking medications as prescribed and to have a high index of suspicion of non-compliance. There are several methods for assessing compliance (see references):

- Ask the patient
- Communicate effectively
- Help the patient to remember
- Listen carefully: ask the patient to report any problem with taking the medications
- Monitor appointment keeping, medication refill, and pick-up
- Monitor pills (perform pill counts)
- Directly observe the patient swallowing each dose of medication - direct observed preventive therapy (DOPT). This is recommended for persons who are at high risk for TB and whose adherence is questionable (e.g., IV drug users, homeless, persons at high risk for progression to disease, children, contacts to drug resistant TB and persons with a history of non-compliance with treatment).

References

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Keane J., Gershon S., Wise R., et al 2001. Tuberculosis Associated With Infliximab, a Tumor Necrosis Factor α-Neutralizing Agent. The New England Journal of Medicine; 345, No. 15: 1098 – 1103.

Resources

For questions about treatment for LTBI, call the TB Program (303) 692-2638.