

Chapter V: TB Infection (formerly known as LTBI) Treatment and Follow-up

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A. Candidates for LTBI Treatment

Selecting people who should be tested and treated for TB infection (LTBI) involves assessing two different risks:

- Their risk for being infected with TB, and
- Their risk for progressing to active disease

Persons in the U.S. with the highest risk for being infected with TB are those who were born or lived in a country where TB is endemic. Others at risk for infection include persons who have lived or worked in congregate settings such as nursing homes, homeless shelters, jails, or healthcare settings, and the elderly who were likely infected during their youth when TB was more common in the U.S. Persons with a greater risk for progressing from infection to active disease are those with recent infection such as contacts of infectious TB cases, and those with an immature or suppressed immune systems such as children younger than 12 years of age and HIV-infected patients. Others at increased risk for progression to active TB include those who have certain medical conditions such as silicosis or who are taking medications that make them immunosuppressed. Persons with recent infection or evidence of old, healed TB on x-ray are also at increased risk of developing active disease.

Condition	Study	Relative Risk (95% CI)
Advanced HIV infection	Pablos-Mendez et al. ²⁷	9.9 (8.7–11.3)†
	Moss et al. ²⁶	9.4 (3.5–25.1)
Old, healed tuberculosis	Ferebee, ¹³ Ferebee et al. ²⁰	5.2 (3.4–8.0)
Chronic renal failure	Pablos-Mendez et al. ²⁷	2.4 (2.1–2.8)†
Infliximab therapy	Keane et al. ²⁸	2.0 (0.7–5.5)†
Poorly controlled diabetes	Pablos-Mendez et al. ²⁷	1.7 (1.5–2.2)†
Silicosis	Cowie ²⁹	1.7 (1.3–2.1)†
	Corbett et al. ³⁰	1.3 (1.1–1.7)†
	Kleinschmidt and Churchyard ³¹	1.2 (1.0–1.5)†
Underweight (≤ 10 percent below normal)	Palmer et al., ²² Edwards et al. ²³	1.6 (1.1–2.2)
Gastrectomy	Thorn et al. ³²	1.4 (1.1–1.9)†
	Steiger et al. ³³	1.3 (1.2–1.4)†

* CI denotes confidence interval, and HIV human immunodeficiency virus.

Horsburg, CR Priorities for the Treatment of Latent TB Infection in the United States. N Engl J Med. 2004; 350:20. www.nejm.org

Persons with LTBI diagnosed by skin testing who were not recently infected and don't have risks for progressing to active TB do not all need treatment if their likelihood of developing active TB is quite low. For person without medical risk factors and who are not likely to have been recently infected (e.g. not identified as recently exposed to an infectious TB case or document recent conversion to positive TST or IGRA) the annual risk of progression from LTBI to active TB is only 1 or 2 per 1,000 (0.1-0.2% per year). This is an ongoing risk so estimates of the life-time risk for developing active TB should be taken into account for treatment decisions (See table below).

Table 1. Annual Risk of Reactivation Tuberculosis.*

Size of Induration on Tuberculin Skin Test	Age				
	0-5 Yr	6-15 Yr	16-35 Yr	36-55 Yr	≥56 Yr
	<i>percent (95 percent confidence interval)</i>				
Persons with nonconversion positive result					
5-9 mm	0.06 (0.03-0.11)	0.04 (0.03-0.06)	0.12 (0.05-0.32)	0.07 (0.03-0.19)	0.07 (0.03-0.16)
10-14 mm	0.19 (0.12-0.28)	0.08 (0.06-0.11)	0.15 (0.08-0.29)	0.10 (0.05-0.19)	0.10 (0.06-0.17)
≥15 mm	0.24 (0.19-0.30)	0.14 (0.12-0.17)	0.19 (0.10-0.34)	0.12 (0.07-0.21)	0.12 (0.08-0.20)
Persons with recent conversion or contacts of patients with active tuberculosis					
5-9 mm	0.29 (0.08-0.74)	0.06 (0.02-0.18)	0.30 (0.18-0.50)	0.23 (0.10-0.44)	0.12 (0.02-0.44)
10-14 mm	0.37 (0.16-0.71)	0.12 (0.05-0.25)	0.37 (0.26-0.53)	0.28 (0.17-0.45)	0.15 (0.04-0.39)
≥15 mm	0.54 (0.27-0.95)	0.12 (0.07-0.23)	0.56 (0.41-0.76)	0.42 (0.28-0.62)	0.17 (0.05-0.42)

Horsburg, CR. Priorities for the Treatment of Latent TB Infection in the United States. *N Engl J Med.* 2004; 350;20. www.nejm.org

The estimated life-time risk for TB is 10% for children under 5 years of age, 6 to 7% up to age 35 years, decreases to 3% (about 1 in 33 chance) after age 35 years and to 2% at age 56. Since treatment of LTBI is believed to provide lifetime reduction in the risk for TB associated with LTBI, 9 months of treatment and particularly 3 or 4 months of treatment with a short-course regimen can be seen to provide benefit for many patients with LTBI who do not have additional risk factors.

Table 2. Lifetime Risk of Reactivation Tuberculosis.*

Size of Induration on Skin Test and Age	Nonconversion Positive Skin Test	Recent Conversion of Skin Test	Immunosuppressive Therapy	Old, Healed Tuberculosis	Advanced HIV Infection
<i>percent (95 percent confidence interval)</i>					
Induration of ≥15 mm					
0-5 Yr	13 (10-16)	17 (12-24)	25 (7-87)	66 (34-100)	100 (88-100)
6-15 Yr	7 (6-8)	8 (6-10)	14 (4-46)	37 (21-67)	70 (52-92)
16-25 Yr	8 (5-15)	13 (8-21)	17 (3-84)	44 (15-100)	83 (39-100)
26-35 Yr	7 (4-13)	12 (8-19)	15 (3-74)	39 (14-100)	73 (35-100)
36-45 Yr	4 (2-7)	7 (5-12)	8 (2-39)	21 (8-57)	40 (20-79)
46-55 Yr	3 (2-6)	6 (4-10)	6 (1-32)	17 (6-46)	32 (16-44)
56-65 Yr	3 (2-4)	3 (1-7)	5 (1-23)	13 (5-33)	25 (14-46)
≥66 Yr	2 (1-3)	2 (1-5)	4 (1-17)	9 (4-24)	18 (10-33)
Induration of 10-14 mm					
0-5 Yr	10 (6-15)	13 (8-21)	20 (4-82)	53 (22-100)	100 (56-100)
6-15 Yr	4 (3-5)	5 (3-7)	8 (2-30)	20 (10-44)	38 (24-61)
16-25 Yr	7 (3-13)	10 (6-17)	13 (2-73)	35 (12-100)	66 (30-100)
26-35 Yr	6 (3-12)	9 (5-15)	12 (2-64)	31 (10-93)	58 (26-100)
36-45 Yr	3 (2-6)	5 (3-9)	7 (1-34)	17 (6-50)	33 (15-68)
46-55 Yr	3 (1-5)	5 (3-8)	5 (1-8)	14 (5-40)	26 (12-55)
56-65 Yr	2 (1-4)	3 (1-6)	4 (1-20)	11 (4-29)	20 (11-39)
≥66 Yr	2 (1-3)	2 (1-5)	3 (1-14)	8 (3-20)	15 (8-28)
Induration of 5-9 mm					
0-5 Yr	3 (2-6)	6 (2-12)	6 (1-31)	16 (6-45)	31 (15-63)
6-15 Yr	2 (1-3)	3 (2-5)	4 (1-17)	11 (5-25)	21 (13-34)
16-25 Yr	6 (2-14)	8 (4-17)	11 (2-79)	29 (7-100)	55 (19-100)
26-35 Yr	5 (2-13)	7 (3-15)	10 (1-69)	25 (6-100)	48 (17-100)
36-45 Yr	3 (1-6)	4 (2-9)	5 (1-34)	12 (3-50)	24 (8-68)
46-55 Yr	2 (1-5)	4 (2-8)	4 (1-28)	10 (3-40)	19 (7-55)
56-65 Yr	2 (1-3)	2 (1-6)	3 (0-18)	8 (2-26)	15 (6-36)
≥66 Yr	1 (0-2)	2 (0-5)	2 (0-13)	6 (2-19)	11 (4-26)

Data on the risk associated with recent conversion are from studies of household contacts of patients with active tuberculosis and are applicable to situations in which recent infection is likely, such as among persons with recent skin-test conversion, persons living in prison or a homeless shelter, intravenous-drug users, or persons who immigrated from a country with a high incidence of tuberculosis within the previous five years. Data on the risk associated with immunosuppressive therapy are from a study involving patients who were receiving infliximab and are applicable to patients undergoing long-term therapy with other medications that are known to impair cell-mediated immunity. HIV denotes human immunodeficiency virus.

Horsburg, CR. Priorities for the Treatment of Latent TB Infection in the United States. N Engl J Med. 2004; 350; 20. www.nejm.org

Priorities for LTBI treatment remain contacts to active TB and those with additional risk factors for progression to active TB. LTBI treatment should be offered to all persons younger than 35 years of age. If resources permit we can counsel patients without additional risk factors about their cumulative risk and offer treatment to all those up to age 50 years of age, particularly when using shorter course treatment with rifampin or INH+rifapentine, regimens that are better tolerated than INH. For persons over age 50 treatment should be offered routinely for those with an additional risk factor for progressing to active

disease. The risk of infection and the risk of progression are both addressed in the table below which provides a guideline for interpreting TSTs and recommending LTBI treatment.

1. Guidelines for LTBI Treatment

If TST reaction is \geq 5 mm or greater or IGRA is positive:	Age < 50 Years	Age \geq50 Years
Radiographic evidence of old, healed TB	treat	treat
Close contact with a person who has pulmonary or laryngeal TB disease*	treat	treat
HIV infection or at risk for HIV infection but refused testing	treat	treat
Immunosuppression due to various medical treatments or other medical conditions such as TNF-alpha inhibitors, cancer chemotherapy, high-dose prednisone, etc.	treat	treat
If TST reaction is \geq 10 mm or greater or IGRA is positive:	Age < 50 Years	Age \geq50 Years
Planning to start immunosuppressants such as TNF-alpha inhibitors, cancer chemotherapy, high doses of prednisone, etc.	treat	treat
Medical risk factors for TB, other than HIV infection	treat	treat
Drug injection in HIV-seronegative persons	treat	treat
TST conversion within past 2 years (\geq 10 mm)	treat	treat
Currently living in a high-risk congregate setting (e.g., nursing home, correctional facility, homeless shelter)	treat	Don't treat - if no risk for progression*
History of living in a high-risk congregate setting (e.g., nursing home, correctional facility, homeless shelter)	treat	Don't treat - if no risk for progression*
Birth or residence in high-incidence country or region; \leq 5 years in U.S.	treat	treat
Birth or residence in high-incidence country or region; >5 years in U.S.	treat	Don't treat - if no risk for progression*
Occupational risk (e.g., employees or volunteers in health care facility, correctional facility, nursing home, mycobacteriology laboratory)	treat	Don't treat - if no risk for progression*
If TST reaction is 15 mm or greater	Age < 50 Years	Age \geq50 Years
None of the risk factors listed above and IGRA is positive	treat	Don't treat - if no risk for progression*
None of the risk factors listed above and IGRA is negative	Don't treat - if no risk for progression*	Don't treat - if no risk for progression*

NOTE: Some contacts, including children younger than 5 years old and HIV-seropositive contacts, should start LTBI treatment even if their TST reaction is <5 mm.

No need to treat unless the patient has another risk for progression to active TB

**Adapted from Moffitt MP, Wisinger DB. Tuberculosis: recommendations for screening, prevention, and treatment. Postgraduate Medicine 1996; 100:209.

2. Children and Adolescents

Because of their age, infants, young children, and adolescents with LTBI are at high risk for progressing to active disease. This is true regardless of when they were infected and particularly for those who have been recently infected. Infants and

young children are also more likely than older children and adults to develop life-threatening forms of TB. Children 5 years of age and younger who are close contacts should receive window period treatment for LTBI even if their initial TST/IGRA is negative and chest radiograph does not suggest TB because they are at risk for rapid progression and for developing severe forms of the disease. On occasion, if children less than 5 years of age and children between 5 and 12 years live in the household and are all contacts with negative TSTs, all of the children will be started on LTBI treatment to minimize confusion for the parents.

A second TST should be performed 8 to 12 weeks after the last exposure to infectious TB. If the repeat TST is positive, LTBI treatment should continue for the recommended period of time. Treatment of LTBI can be discontinued if **all** of the following conditions are met:

- The infant is at least 6 months of age (Children < 6 months of age should continue with the recommended treatment for the full 9 months, regardless of the second TST or CXR results).
- The second TST was performed at least 8 weeks after the last exposure to infectious TB and is negative.
- Repeat chest x-ray is normal (Children > 6 months of age with a negative second TST need a routine repeat chest x-ray).

A. Evaluation for LTBI Treatment

Prior to the initiation of LTBI treatment, active TB must be ruled out. All individuals found to have a positive TST/IGRA should be screened for signs, symptoms, and risk factors of TB and should have a chest x-ray to rule out pulmonary TB disease. Patients with signs or symptoms of extra-pulmonary TB will need additional studies to exclude active TB before initiating treatment for LTBI. The presence of symptoms of TB should always lead to a new clinical and/or chest x-ray evaluation.

 For more information, see *Chapter III: Evaluation for TB Infection and Disease*.

1. Timing of Chest X-Rays

Patients at high risk of progression to active disease. Children under 12 years, new immigrants, contacts to active TB, those who are immuno-compromised or have medical conditions such as diabetes should have a chest X-ray within 2 months before starting LTBI treatment.

Patients who are at low risk of progression to active disease. Older children and those without known risk factors have a risk of progression to active TB. These patients should have a chest X-ray within 6 months before starting LTBI treatment.

Pregnant women with a positive TST reaction. Pregnant women should have a shielded chest x-ray after the first trimester. A shielded chest x-ray should be done immediately, even during the 1st trimester, for pregnant women who:

- have symptoms suggestive of TB disease (cough, fever, night sweats, chest pain, etc.), or
- are TST positive and have been in close contact with a person who has pulmonary or laryngeal TB disease, or
- are HIV-positive and (1) TST/IGRA positive or (2) TST/IGRA negative, but have been in close contact with a person who has pulmonary or laryngeal TB disease.

2. Medical History and Physical Examination

The pretreatment evaluation of a person who is targeted for treatment of LTBI provides an opportunity to establish rapport with the patient, discuss details of the patient’s risk for TB, emphasize the benefits of treatment and importance of adherence to the drug regimen, and review possible adverse effects of the regimen, including interactions with other drugs.

 For more information, see *Chapter III: Evaluation for TB Infection and Disease*.

3. Baseline Laboratory Tests

Baseline laboratory testing is not routinely indicated for all patients at the start of treatment for LTBI with INH and/or rifampin. Baseline testing is also not routinely indicated in persons over 35 years of age. However, such testing may be considered on an individual basis, particularly for patients who are taking other medications that pose a potential risk for hepatotoxicity.

Diagnosis / Condition / Medication	Test
Chronic liver disorder (e.g. hepatitis, cirrhosis)*	ALT, bilirubin, albumin
Regular alcohol (ETOH) use / abuse	ALT
History of intravenous drug use (IVDU)	ALT, HepBsAg, HepCaB
HIV	ALT
Pregnant or postpartum (within 2 months after delivery)	ALT
Medications that affect the liver (e.g., metformin)	ALT

*Consultation with the patient’s medical provider recommended, if possible.

- If hepatic measurements are indicated as mentioned above, draw blood before starting therapy and again at one month.
- If the tests are normal at one month, no further lab testing is necessary unless symptoms develop.

- If the tests are elevated at one month, continue monthly testing as long as the levels are abnormal.
- If any one of the liver function test results exceed 3-5 times the upper limit of normal at any time, consult with the patient’s medical provider and strongly consider stopping therapy.

Abnormal liver function results should be evaluated by a physician as soon as possible, and certainly within 72 hours after the initiation of LTBI treatment. Other tests may be ordered later depending on the patient’s history and initial lab results. For example, a viral hepatitis profile (hepatitis B & C) should be considered for patients with a history of drug injection.

If copies of laboratory tests done within the last 60 days are obtained for the patient’s record, they may be used as a baseline.

C. Treatment of LTBI

1. RECOMMENDED DRUG REGIMENS FOR TREATMENT OF TUBERCULOSIS INFECTION IN ADULTS¹

Drug	Interval and Duration	Comments	Rating* (evidence) [†]	
			HIV–	HIV+
INH	Daily for 9 months ^{† §}	In HIV-infected patients, INH 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 ^{† §}	DOT must be used with twice-weekly dosing.	B (II)	B (II)
INH	Daily for 6 months [§]	This duration of therapy is 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)
RIF	Daily for 4 months in adults	RIF is used for persons who are contacts of patients with INH-resistant, RIF-susceptible TB. Some antiretroviral drugs, such as the protease inhibitors and NNRTIs, have interactions with the rifamycins. Clinicians should consult Web-based updates or experts for the latest specific recommendations.	B (II)	B (III)
	Daily for 6 months in children	The optimal length of RIF therapy in children with LTBI is not known; however, the American Academy of Pediatrics recommends 6 months of treatment. [¶]		
RPT + INH	One weekly for 12 weeks	DOT must be used with this regimen.		

Definitions of abbreviations: DOT = directly observed therapy; HIV = human immunodeficiency virus; INH = isoniazid; LTBI = latent tuberculosis infection; RIF = rifampin; RPT = rifapentine.

* 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 regimen for pregnant women.

2. Pregnant or Postpartum Women

Women with latent TB infection who are less than 35 years old or have risk factors for progression to active TB are candidates for LTBI treatment. Pregnancy alone is not considered a risk for developing active TB but pregnant women with LTBI need to be evaluated to exclude active TB. The evaluation should begin with a symptom review. All symptomatic patients should have a chest x-ray immediately while those who are asymptomatic should have a chest x-ray after the first trimester. Active TB must be treated during pregnancy to decrease the risk of complications to the mother and the fetus. In most pregnant and postpartum women LTBI treatment should be delayed until 2 to 3 months after delivery due to an increased risk of hepatotoxicity from isoniazid. However, in some situations LTBI treatment should begin during pregnancy:

a. During the first trimester

LTBI treatment should be started during the first trimester of pregnancy for:

- TST-positive (≥ 5 mm) pregnant women who are HIV-positive or who have behavioral risk factors for HIV infection but decline HIV testing
- TST-positive (≥ 5 mm) pregnant women who have been in close contact with a smear-positive pulmonary TB patient (at the physician's discretion)

b. Promptly after the first trimester

LTBI treatment should be started promptly after the first trimester of pregnancy for pregnant women who have had a documented TST conversion in the past 2 years.

c. Those with suspected drug-resistant TB infection

LTBI treatment should be delayed until after delivery in pregnant women known or suspected to be infected with a TB strain resistant to at least isoniazid and rifampin because of possible adverse effects on the fetus from the second-line medications for LTBI treatment. A chest x-ray should still be obtained initially and should be repeated if the woman develops symptoms to rule out active TB disease.

3. LTBI Treatment of HIV-Infected Persons

The isoniazid daily regimen for 9 months is the preferred regimen for both HIV-infected and uninfected individuals. Recommendations for HIV-infected adults parallel those for HIV-uninfected adults. LTBI treatment of HIV-infected persons requires close communication with the HIV care provider when using INH. Rifampin is generally contraindicated in persons who are taking protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs). Experts have recommended that for HIV-infected persons who are candidates for treatment of LTBI and need PI or NNRTI therapy, rifabutin may be used in some circumstances. The substitution of rifapentine for rifampin is not recommended because the safety and effectiveness of rifapentine has not been established for patients infected with HIV. Furthermore, the drug interactions between rifapentine and HIV PIs have not been studied in detail.

In TST/IGRA-negative, HIV-infected persons living in countries with a high-burden of TB, empiric treatment for LTBI has not been effective. However, most tuberculin-negative, HIV-infected patients with known contact to a case with active TB should receive treatment for presumptive LTBI, even with a non-reactive TST. Furthermore, some experts recommend treatment of possible LTBI for HIV-infected residents of institutions that pose an ongoing high risk for exposure to *M. tuberculosis* (e.g., prisons, jails, and homeless shelters).

4. Persons with Fibrotic Lesions or Suspected Disease

Patients with a positive tuberculin skin test and an abnormal chest x-ray consistent with TB require additional evaluation. While most patients with active pulmonary tuberculosis will be symptomatic, the absence of symptoms alone cannot rule out the possibility of active TB. These patients may have residual scarring from old, healed TB, but they may also have active tuberculosis. As with the symptom review, the chest x-ray findings alone cannot differentiate between prior infection and active disease. Patients with minimal abnormalities can have culture-positive TB and those with significant abnormalities may be inactive. Therefore, these patients should have 3 sputa smears and cultures collected to look for acid-fast bacilli (AFB). The decision to start treatment is then based upon the clinical suspicion for active TB. Those with a greater likelihood of active TB and/or who live or work in settings with a high risk for transmission (particularly contact to young children or immuno-suppressed persons) should be started on empiric treatment for active TB after the sputa are collected. Those considered lower risk can have medications held while waiting for the sputa cultures to grow. If the sputum remains negative, a repeat chest x-ray should be obtained after 2 months. A worsening of the x-ray suggests active TB and the patient needs further work-up, while a stable x-ray likely represents scarring from prior active TB and the patient needs treatment for latent TB/inactive TB.

Patients who begin multi-drug therapy for suspected pulmonary TB but are later determined to have inactive disease (i.e., AFB cultures are negative and chest radiographs are stable) should complete treatment with at least 2 months of a regimen containing rifampin and pyrazinamide if other causes of the radiographic abnormalities have been excluded. Patients determined to have LTBI who were not treated initially and have no history of treatment for TB should receive a course of treatment as described in the previous section (9 months of INH, 4 months of rifampin, or 4 months of rifamate).

Persons with evidence suggestive of healed, primary TB with only calcified solitary pulmonary nodules, calcified hilar lymph nodes, or apical pleural thickening are at only a two-fold increased risk for TB compared to those with a normal chest X-ray. Their risk for TB and need for treatment of LTBI should be determined by consideration of other risk factors and the size of the TST reaction.

5. Pregnancy and Lactation

To reduce the risk of peripartum hepatitis, LTBI treatment should be discontinued in women who do not have any risk factors (see below). LTBI treatment should not be restarted until 2 or 3 months after delivery for those with risk factors. When LTBI treatment is restarted, a full course of at least 6 months should be given (previous doses ignored).

INH and rifampin are both considered safe (non-teratogenic) in pregnancy. TST-positive pregnant women with certain risk factors should start or continue LTBI therapy during pregnancy (even during the 1st trimester). These women include:

- Women who are HIV-positive
- Women with behavioral risk factors for HIV infection but who decline testing
- Women who have been in close contact with a smear-positive TB patient or had a documented TST conversion within the past 2 years.

Pregnant and lactating women who are taking isoniazid should be prescribed pyridoxine (vitamin B₆), 25 mg daily. Vitamin B₆ is not needed for women taking a prenatal vitamin that contains at least 25 mg of Vitamin B₆. Breastfeeding should not be discouraged for an HIV-negative woman who is taking or planning to take any anti-TB medication(s).

6. Children and Adolescents

Infants and young children (i.e., younger than 5 years of age) with LTBI who have recently been infected are at particularly high risk for progression to active disease. Data suggest that untreated infants with LTBI have up to a 40% likelihood of developing active TB, sometimes within months. The risk for progression decreases gradually through childhood. Infants and young children are more likely than older children and adults to develop life-threatening forms of TB, especially meningeal and disseminated

disease. Timely evaluation and treatment of children less than 5 years of age is important given their high risk of progression and frequency of severe manifestations of TB.

Isoniazid therapy is widely accepted for use in children and appears to be more effective for children than adults. The only recommended regimen for treatment of LTBI in HIV-infected and uninfected children is a 9-month course of isoniazid as daily therapy or by DOPT twice-weekly. DOPT should be considered when it is unlikely that the child and family will adhere to daily self-administration. Child contacts less than 5 years of age must receive DOPT to ensure proper dosing. Children should be weighed monthly.

The risk for isoniazid-related hepatitis is minimal in infants, children, and adolescents, who generally tolerate the drug better than adults. Routine monitoring of serum liver enzyme concentrations is not necessary but should be considered in children at risk for hepatic disease or who are HIV-infected. When children taking anti-tuberculosis therapy develop hepatitis, therapy should be discontinued and a search for causes other than the LTBI treatment should be undertaken.

Routine administration of pyridoxine (Vitamin B₆) is not recommended for children taking isoniazid, but should be given in the following circumstances:

- Infants who are breastfed exclusively (dose 6.25 mg)
- Children and adolescents with diets likely to be deficient in pyridoxine (Vitamin B₆) (dose 10-15 mg/day)
- HIV-infected children (10-15 mg/day)
- Children who experience paresthesias while taking isoniazid. (10-15 mg/day).

In the United States, rifampin alone is used for the treatment of LTBI in infants, children, and adolescents when isoniazid cannot be tolerated or the child has had contact with a patient infected with an isoniazid-resistant but rifamycin-susceptible organism. The optimal length of rifampin therapy in children with LTBI is not known. The American Academy of Pediatrics recommends 6 months of treatment, but a number of U.S. TB programs have accepted a 4-month rifampin regimen as adequate in children.

D. Monitoring Patients during LTBI Treatment

1. Clinical Evaluation

Patients being treated for LTBI should receive a monthly clinical evaluation (including a brief physical assessment checking for signs of hepatitis) if receiving INH or rifampin. Clinical monitoring is indicated for all patients. This involves educating patients about the symptoms and signs that can be adverse effects of the drug(s) that are being prescribed and the need for prompt cessation of treatment and clinical evaluation should symptoms occur.

REPORTING REACTIONS TO ANTITUBERCULOSIS MEDICATIONSⁱⁱⁱ

Potentially Serious Adverse Reactions*	Less Severe Signs and Symptoms*
<p>Immediately report the following signs and symptoms or other abnormalities or unexpected events to the patient's provider. These signs and symptoms suggest side effects, including hepatotoxicity:</p> <ul style="list-style-type: none"> ▪ Jaundice ▪ Dark urine ▪ Vomiting ▪ Abdominal pain ▪ Fever ▪ Visual changes ▪ Moderate/severe rash <p>In consultation with the provider, instruct the patient to stop TB medications until evaluated by the provider.</p>	<p>Report the following signs and symptoms to the patient's provider within 24 hours:</p> <ul style="list-style-type: none"> ▪ Anorexia ▪ Nausea ▪ Malaise ▪ Peripheral neuropathy: tingling or burning sensation in hands or feet ▪ Mild rashes
<p>* These lists are not all-inclusive. For a complete list, refer to the current guidelines for treatment of TB, "Treatment of Tuberculosis" (<i>MMWR</i> 2003;52[No. RR-11]) at this hyperlink: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf .</p>	

Source: California Department of Health Services(CDHS)/California Tuberculosis Controllers Association(CTCA). TB case management—core components. *CDHS/CTCA Joint Guidelines* [CTCA Web site]. 1998:9. Available at: <http://www.ctca.org/guidelines/index.html> . Accessed July 11, 2006.

These monthly evaluations provide an opportunity to review the indications for treatment, adherence with therapy since the last visit, symptoms of adverse drug effects and drug interactions, and the agreed upon treatment plan.

Ideally, the patient should come to the public health department monthly for evaluation and refill of INH or rifampin. There are selected situations for which travel, work, or school schedules make it difficult for the patient to make monthly clinic visits for treatment of latent TB infection. Exceptions can be made on a case-by-case basis.

2. Hepatitis

Hepatitis is the most severe toxic effect of isoniazid. The risk for INH-related hepatitis is minimal in infants, children, and adolescents, who generally tolerate the drug better than adults. Young children have less than a 1% risk of hepatotoxicity. Families should be counseled at each visit to watch for the early symptoms of hepatotoxicity which may include anorexia and malaise. Later symptoms are abdominal pain, nausea, and vomiting.

Jaundice is a very late finding. Laboratory testing should be used to evaluate possible adverse effects that occur during the course of treatment. Routine, monthly laboratory monitoring during treatment of LTBI is indicated for patients who:

- have abnormal baseline LFTs
- are HIV-positive, regardless of baseline LFT results
- have a history of heavy alcohol ingestion or liver disease, or who currently inject drugs or have documented chronic hepatitis B or C, regardless of baseline LFTs
- are pregnant or postpartum (within 3 months after delivery) and who are currently taking isoniazid and/or rifampin, regardless of baseline LFT results
- are starting LTBI treatment with 2 or more drugs.

LTBI treatment should be discontinued if the individual is asymptomatic and ALT or AST values are 5 times or more the normal value. LTBI treatment should be discontinued for children if the ALT or AST values are 3 times or more the normal level. LTBI treatment should also be discontinued if an individual is symptomatic and ALT and AST values are 3 times or more the normal value. The most common cause of minor gastrointestinal symptoms is gastritis that generally improves with continuation of therapy.

In most children, LFTs will be normal. When children taking anti-TB drugs develop hepatitis, a search for causes other than LTBI treatment should be undertaken and the therapy discontinued.

3. Drug and Food Interactions

Isoniazid has been reported to inhibit the metabolism of the following drugs; as a result, dosages of these drugs may need to be adjusted to prevent toxicity:

- Haloperidol
- Ketoconazole (rarely used now)
- Theophylline (rarely used)
- Warfarin (Coumadin)
- Phenytoin (Dilantin) or other anticonvulsants: The interaction with isoniazid increases the serum concentration of both drugs. When given concomitantly, the serum level of phenytoin should be monitored.
- Disulfiram (Antabuse): Some publications recommend against the use of isoniazid for persons taking disulfiram, but a recent article showed it can be used safely in patients being treated for active TB. It appears to be safer than alcohol abuse combined with isoniazid treatment.

- Acetaminophen: It is important to caution patients or parents about excessive use of acetaminophen and to advise that ibuprofen may be a better choice while taking INH.

Monoamine (histamine/tyramine) poisoning in which some patients may complain of flushing, has been reported after eating some foods and beverages with a high monoamine content. If the patient develops symptoms of flushing, the patient should avoid the following foods or beverages: aged cheeses, aged or cured meats (e.g., air-dried sausage), any potentially spoiled meat, poultry, or fish, broad (fava) bean pods, marmite-concentrated yeast extract, sauerkraut, soy sauce and soy bean condiments, tap beer, and wine.

4. Peripheral Neuropathy

Peripheral neuropathy caused by interference with metabolism of pyridoxine (Vitamin B₆) is associated with INH administration but is uncommon in individuals on a normal diet or in adults at a dose of 5 mg/kg. In persons with diabetes, uremia, alcoholism, malnutrition, and HIV infection, neuropathy is more common and pyridoxine should be given with INH. Pregnant women and persons with seizure disorders should also take both pyridoxine and INH. Routine administration of pyridoxine (Vitamin B₆) is not necessary for children taking INH, but may be considered for:

- infants who are breastfed exclusively
- children and adolescents with diets likely to be deficient in pyridoxine (meat/milk deficient diet, malnourished)
- pregnant or breastfeeding women
- HIV-infected individuals
- individuals who experience paresthesias while taking INH.

For patients on 300 mg of INH daily, the usual dose of pyridoxine (Vitamin B₆) is 25 mg. If patients are complaining of numbness or tingling in their extremities, the dose may be increased to 50 mg daily. A new prescription will be required to increase the pyridoxine (Vitamin B₆) dose.

5. Mild Central Nervous System (CNS) Effects

Mild central nervous system (CNS) effects such as sleepiness, insomnia, or headaches are common with INH and may necessitate adjustments in the timing of administration of the drug to enhance compliance. Taking medications a few hours after eating rather than first thing in the morning on a completely empty stomach can often eliminate nausea and GI disturbances. Bedtime is also a good time to take INH.

E. DOPT and Measures to Increase Adherence

DOPT is an excellent method for promoting adherence to LTBI treatment. Because of limited resources, however, DOPT cannot be offered to all individuals receiving LTBI treatment. Patients with the highest priority for DOPT are those at the highest risk of progression from latent to active TB, including persons with HIV infection and young children who are contacts to infectious patients with pulmonary TB. Currently, the principal candidates for DOPT are household contacts less than 5 years of age to patients with TB disease who are receiving home-based DOT.

Other measures to increase adherence include an attempt to incorporate the prescribed regimen into the patients' daily routines and patient education that includes:

- Using simple, clear language to explain that LTBI is a health threat, and how it is treated
- Encouraging questions and reinforcing understanding and adherence at each visit
- Giving information about potential drug toxicity, common side effects and drug management (e.g., medications should be taken with food when gastrointestinal symptoms have occurred after medication was taken on an empty stomach.)

At each visit, the clinician/Nurse should assess adherence by doing the following:

1. Ask patients how many doses they have missed since their last refill. If patients are asked, "Did you take all your pills last month?" the natural inclination is to agree and say "yes" even if they did not.
2. Have patients bring their bottle of medicine to the refill appointment, and count how many pills are left.
3. If adherence problems are identified, include patients in the problem-solving process.
 - a. Ask patients why they think that doses are missed and what could be done better: change the time of day, the location where they keep or take their pills, etc.
 - b. Find out if there are barriers to obtaining refills in a timely manner that could be corrected.
 - c. Review with patients what they believe is their risk of developing tuberculosis (TB) if medicine is not taken. Provide education again, as needed.
 - d. Mutually agree upon a plan to improve adherence.
 - e. Praise patients for cooperation.
4. If adherence seems to be good, praise patients.

F. Interrupted or Incomplete LTBI Treatment with INH

Determine whether and when therapy is completed based upon the total number of doses administered, not on the duration of therapy. When patients have had lapses in therapy but are still able to complete the recommended number of doses in the allotted time period, encourage them to complete therapy.

Assess patients who will not complete appropriate therapy within the time frame specified to determine whether or not to restart treatment. If the decision is made to retreat the patient, then restart the entire regimen and follow the recommended treatment plan of therapy. Specific factors to consider when determining whether to restart treatment include the following:

- Individual's risk for developing tuberculosis (TB) disease
- Total number of doses of latent tuberculosis infection (LTBI) treatment administered
- Time elapsed since the last dose of treatment for LTBI
- Patient adherence issues (previous attempts at completion, willingness to continue, etc.)

Give nonadherent patients who are at very high risk of developing TB disease every opportunity to complete treatment for LTBI. Consider these patients for intermittent therapy with directly observed therapy (DOT) and evaluate the use of incentives and enablers.^{iv}

Treatment of LTBI in contacts is considered a priority in TB control activities. Make every effort to assure completion of treatment in contacts.

All contacts who are being treated for infection should be seen face-to-face by a healthcare provider monthly or more often. Incentives and enablers are recommended as aids to adherence, and the healthcare provider should educate the patient about TB, its treatment, and the signs of adverse drug effects at each patient encounter.^v

Table describes the duration of therapy and the number of doses that patients are required to take to complete therapy as well as the time frame within which the total number of doses must be administered for completion of therapy.

RECOMMENDED REGIMENS FOR COMPLETION OF THERAPY^{vi}

Regimen	Age	Duration of Therapy	Number of Doses	Must Be Administered Within
INH daily	Adult and child	9 months	270	12 months
INH daily	Adult	6 months	180	9 months
INH twice weekly	Adult and child	9 months	76	12 months
INH twice weekly	Adult	6 months	52	9 months
RIF daily	Adult	4 months	120	6 months
	Child*	4-6 months	180	6-9 months

Definitions of abbreviations: INH = isoniazid; RIF = rifampin.

Sources: CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):26–27; CDC. Regimens. In: Chapter 6: treatment of LTBI. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Available at: <http://www.cdc.gov/tb/pubs/corecurr/index.htm> . Accessed February 1, 2007.

*A number of U.S. TB programs have accepted a 4 month rifampin regimen as adequate for children as well as adults; this recommendation has been approved by Dr. Ogle, Pediatrics at Denver Public Health Department.

Make every effort to encourage patients to adhere to the LTBI treatment regimen. However, if a patient has failed three attempts to complete treatment, no further effort may be merited. The healthcare provider should contact patients who interrupt therapy and are at high risk of developing TB disease (for example, contacts of patients with infectious TB, human immunodeficiency virus (HIV)-infected patients, or TB Class 4 patients) for reevaluation.^{vii}



For consultation regarding completion of therapy and factors to consider when restarting treatment in noncompliant patients, contact the ***TB Nurse Consultant at 303-692-2656***

Ideally, patients should receive medication on a regular dosing schedule until completion of the indicated course. However, in practice, some doses may be missed, requiring the course to be lengthened. Patients who are prescribed LTBI treatment but do not complete the course of treatment should be encouraged to complete the treatment. However, if the patient has failed three attempts to complete LTBI treatment, no further efforts should be made. DOPT should strongly be considered on the third attempt.

When reinstating therapy for patients who have interrupted treatment, clinicians may need to continue the regimen originally prescribed (as long as they can complete 9 months of treatment within 12 months) or renew the entire regimen if interruptions were frequent or prolonged enough to preclude completion of treatment as recommended. When therapy is restored after an interruption of more than 6 months, the patient should have a medical examination including chest x-ray to rule out active TB disease.

1. Patients Who Should Start a New Regimen

In patients with one or more of the following conditions, the regimen should be completely renewed (i.e., disregard the previous doses):

- A lapse in treatment of 4 weeks within the first 3 months of the original regimen
- Treatment that lapsed more than 6 months ago
- Immuno-suppression, especially due to HIV infection.

The duration of the new regimen should correspond to the length of the original regimen (e.g., a new 9-month regimen in a patient originally prescribed a 9-month regimen). A prolonged regimen is not needed. Another option for the patient who has taken 3-5 months of a previous course of INH would be to recommend completion of a 6-month course. If 6 months have been completed and there is a lapse of 3 or more months, then treatment should be considered complete.

G. Completing LTBI Treatment

A physician must decide the appropriate duration of LTBI treatment for each patient. Patients taking LTBI treatment may be discharged from the clinic as having completed treatment when they return for the final month's supply of medication (e.g., after the eighth month for patients taking a 9-month LTBI treatment regimen). Since a 6-month regimen is a secondary recommendation, the patient who completes at least 6 months of a 9-month recommended regimen of INH within 9 months, should generally be considered to have completed a 6-month course.

The nurse performing the monthly evaluation should note in the public health department medical record that the patient was given enough medication for the final month of LTBI treatment and is being discharged from the public health department.

The patient should be advised to return to public health department if he or she develops symptoms of TB or side effects to the medication(s). Otherwise, further evaluation is not necessary.

The patient should be given a document stating that he or she has completed a course of LTBI treatment for __ (number) months from ____ (date) to ____ (date). Cards are available from CDPHE's TB Program to document treatment completion.

H. Follow-Up at LTBI Completion/Repeat Treatment

Follow-up care, including chest x-rays and medical evaluations, is not necessary for patients who complete a course of LTBI treatment unless they develop symptoms of TB disease or were contacts to an MDR case of TB.

A repeat course of LTBI treatment should be considered for the following individuals who have received LTBI treatment in the past but have subsequently been in close contact with a person who has infectious pulmonary or laryngeal TB disease:

- patients who are HIV-positive or have another medical risk factor for developing TB disease,
- children younger than 18 years old, and
- patients who are HIV-negative but have had heavy exposure to a patient with highly-infectious TB (i.e., the presence of secondary cases or documented TST conversions in other contacts).

When LTBI treatment is repeated, an entire course should be given on the assumption that exogenous reinfection may have occurred. Exogenous reinfection is more likely if there are TST conversions among other contacts that had similar exposure to the individual with TB disease.

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ⁱ CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):31, 36.

ⁱⁱ CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):36.

ⁱⁱⁱ California Department of Health Services(CDHS)/California Tuberculosis Controllers Association(CTCA). TB case management—core components. *CDHS/CTCA Joint Guidelines* [CTCA Web site]. 1998:9. Available at: <http://www.ctca.org/guidelines/index.html> . Accessed July 11, 2006.

^{iv} County of Los Angeles Tuberculosis Control Program. *Tuberculosis Control Program Manual: 2003 Edition*:2-10. Available at: <http://www.lapublichealth.org/tb/TBManual/TBmanual.pdf> . Accessed February 1, 2007.

^v CDC, NTCA. Guidelines for the investigation of contacts of persons with infectious tuberculosis: recommendations from the National Tuberculosis Controllers Association and CDC. *MMWR* 2005;54(No. RR-15):19.

- ^{vi} CDC. Regimens. In: Chapter 6: treatment of LTBI. *Core Curriculum on Tuberculosis (2000)*. August 2003.
- ^{vii} County of Los Angeles Tuberculosis Control Program. *Tuberculosis Control Program Manual: 2003 Edition*:2.10. Available at:
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