New York City Department of Health
Protocols for Latent TB Infection Treatment

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PROTOCOL FOR THE MEDICAL EVALUATION FOR LATENT TB INFECTION TREATMENT

All individuals found to have a positive TST reaction should be examined by a physician to rule out tuberculosis (TB) disease and to be evaluated for preventive treatment. The medical evaluation should include the following:

1. Medical history and physical examination

All patients aged 18 to 64 years, including those without behavioral risk factors for HIV, should be counseled and offered HIV testing unless they have documentation of (1) a positive HIV antibody test or (2) a negative result to an HIV antibody test given less than 6 months ago.

All patients should be asked about risk factors for the development of TB disease, including recent close contact with a person who has TB disease. Some patients, however, do not know that they are contacts. Therefore, the TB Registry should be checked for whether the patient has been reported as a contact.

All patients should be asked about previous preventive treatment for TB. Those who have completed a course of preventive treatment in the past should be asked about recent close contact with a person who has TB disease. For HIV-

seronegative patients, a chest x-ray and a repeat course of preventive treatment are not necessary. However, HIV-seropositive patients who have completed a course of preventive treatment but have been re-exposed to a person with pulmonary or laryngeal TB should be given another course of preventive treatment, regardless of their CD4+ T-lymphocyte count.

All patients should be evaluated for and asked about their history of alcohol ingestion, liver disease, and hepatitis. See "laboratory tests" for specific tests that should be ordered. All patients should be assessed for contraindications to preventive treatment. For contraindications to specific drugs used for preventive treatment, see Section C.

2. Chest X-ray

All individuals being considered for preventive treatment should undergo a chest x-ray to rule out pulmonary TB disease. Children younger than 5 years old (i.e., up to the day of the fifth birthday) should undergo both a posterior-anterior and a lateral chest x-ray. All other individuals should receive a posterior-anterior chest x-ray only; additional x-rays should be done at the physician's discretion.

Individuals with a normal chest x-ray, a positive TST reaction, and no signs or symptoms of TB disease should be classified as Class II.

Individuals with an abnormal chest x-ray consistent with active TB disease should be classified as Class V (High) and managed according to Section IV and Section V.

Individuals with a chest x-ray showing noncalcified fibrotic lesions suggestive of old, healed TB should be evaluated for current symptoms of TB and have a complete blood count, a chemistry panel, and three consecutive sputum samples for smear, culture, and susceptibility testing.

If there are no symptoms, classify the individual as Class V (Low) and follow the guidelines for treatment outlined in Section III-C(5). (If sputum cultures are

negative for *M. tuberculosis (M. tb)* and the follow-up chest x-ray shows no change, reclassify the individual as Class IV.)

If there are symptoms, classify the individual as Class V (High) and evaluate and treat for TB disease according to Sections IV and V. (If sputum cultures are positive for *M. tb* or the follow-up chest x-ray shows improvement, reclassify the individual as Class III.)

A chest x-ray should be given immediately even during the first trimester to pregnant women who:

- Have symptoms that are highly suggestive of TB disease (cough, fever, night sweats, chest pain, etc.)
- Are HIV seropositive and (1) TST positive or (2) TST negative but have been in close contact with a person who has pulmonary or laryngeal TB disease
- Are TST positive and have been in close contact with a person who has pulmonary or laryngeal TB disease
- Other pregnant women who have a positive TST reaction should be advised to obtain a chest x-ray after the end of the first trimester. An appropriate lead shield should be used for chest x-rays in pregnant women

3. Laboratory tests

Patients with a history of heavy alcohol ingestion, liver disease or hepatitis, and patients older than 35 years should have baseline liver function tests (AST/SGOT, ALT/SGPT, alkaline phosphatase, and total bilirubin). Abnormal results should be evaluated by a physician as soon as possible and certainly within 72 hours of the initiation of preventive treatment.

All patients starting preventive treatment with two or more drugs should have baseline liver function tests and a complete blood cell count.

PROTOCOL FOR IDENTIFYING CANDIDATES FOR LATENT TB INFECTION TREATMENT

1. Individuals who should receive LTBI treatment, regardless of age:

The following individuals with a positive TST reaction (Class II) are candidates for LTBI therapy, regardless of age.

- HIV-seropositive persons and persons with behavioral risk factors for HIV infection who decline HIV testing

- Persons with medical risk factors for TB other than HIV infection such as diabetes mellitus, silicosis, prolonged corticosteroid therapy, other immunosuppressive therapy, cancer of the head and neck, hematologic and reticuloendothelial disease (e.g., leukemia and Hodgkin's disease), end-stage renal disease, intestinal bypass or gastrectomy, chronic malabsorption syndromes, or low body weight (10% or more below ideal)

- Close contacts of a person who has pulmonary or laryngeal TB disease

(However, contacts older than 35 years who have documentation of a previous positive TST result are candidates for preventive therapy only if they have HIV infection or another medical risk factor, if they inject drugs, or if they have radiographic evidence of old, healed TB.)

- Persons with radiographic evidence of old, healed TB and no history of adequate treatment for TB

- Persons who inject drugs and are known to be HIV seronegative

- Recent skin test converters (10-mm or larger increase within a 2-year period)

(When a TST-positive individual claims to have had a negative reaction to a Mantoux (not Tine) TST given in the past 2 years but has no documentation of this reaction, it is necessary to accept the individual's statement. This individual should be considered a recent converter. However, this protocol does not apply if the previous test was a Tine test.)

- Children younger than 5 years old who have a reaction of 10 mm or more

For guidelines on when to give a repeat course of LTBI treatment in contacts who already completed a course of preventive treatment, see Section G.

2. Individuals who should receive LTBI treatment if younger than 35 years old

Preventive treatment is also recommended for all patients who have a positive TST reaction and are younger than 35 years old.[1, 2]

Those aged 18 to 35 years who have none of the risk factors listed above may be referred to a private primary medical provider for preventive treatment if such a provider is identified by the patient. However, the Bureau of Tuberculosis Control Chest Clinic should provide preventive treatment if the patient prefers care in the clinic or if there is no identifiable primary care provider who will accept responsibility for care.

3. Individuals who should start LTBI treatment, regardless of TST reaction

Individuals who have recently been exposed to TB may have a false-negative reaction to the TST if tested less than 12 weeks since their last exposure, even if they are truly infected. These individuals should be retested 12 weeks after their last exposure.

During the window period between the two TSTs, the following individuals should start preventive treatment even if TST negative:

- Contacts younger than 5 years old
- Contacts between 5 and 15 years old, at the physician's discretion
- Contacts with HIV infection or another medical risk factor for TB and contacts with behavioral risk factors for HIV infection who decline HIV testing

These contacts should undergo a chest x-ray to rule out TB disease before starting preventive treatment.

If the second TST result is negative and the contact is not immunosuppressed, preventive treatment may be discontinued. For most close contacts known to have HIV infection or at risk for HIV infection, a full course of preventive treatment is recommended regardless of the TST result.

4. Pregnant women as candidates for LTBI treatment

In most pregnant women, LTBI treatment should be delayed until 2 to 3 months after delivery, even though no harmful effects of INH on the fetus have been documented. In some situations, however, LTBI treatment should begin during pregnancy:

- LTBI treatment should be started during the first trimester of pregnancy for TST-positive (5 mm or more) pregnant women who are HIV seropositive or who have behavioral risk factors for HIV infection but decline HIV testing
- TST-positive (5 mm or more) pregnant women who have been in close contact with a smear-positive pulmonary TB patient (at the physician's discretion)

- 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

- LTBI treatment, if indicated, should be started 2 to 3 months after delivery for all other pregnant women including those with radiographic evidence of old, healed TB

In pregnant women known or suspected to be infected with a TB strain resistant to at least isoniazid and rifampin, LTBI treatment should be delayed until after delivery because of possible adverse effects of the medications on the developing fetus. A chest x-ray should be obtained initially and again if the woman develops symptoms suggestive of TB disease. A lead shield should be used for chest x-rays in pregnant women.

LATENT TB INFECTION TREATMENT REGIMENS PROTOCOL

1. Standard regimen: isoniazid

The standard regimen for preventive treatment is INH, given daily or twice weekly for 6 to 12 months depending on age and HIV status.

When given twice weekly, preventive treatment must be directly observed. Dosing for directly observed preventive treatment should be on Monday and Thursday or Tuesday and Friday.

The contraindications to isoniazid preventive treatment are as follows:

- History of an INH-induced reaction, including hepatic, skin, other allergic reactions, or neuropathy

- Close contact with a person who has INH-resistant TB disease

- Severe chronic liver disease

- Pregnancy, unless the woman is HIV infected, a recent TST converter, or a close contact (see Section III-B[4])

- Baseline SGOT/AST values that are 3 to 5 times the normal value, though not a contraindication for starting preventive treatment, require close serial monitoring of the patient's liver function tests (see Section VII-A[2]).

Directly observed preventive treatment (DOPT) is an excellent method for promoting adherence to preventive treatment.

2. Alternative LTBI regimen: rifampin

Patients who cannot tolerate INH or who are contacts of an individual with INH-resistant, rifampin-susceptible TB should be given rifampin for preventive treatment. Although isoniazid is the only drug that has been studied in large scale for TB preventive treatment, rifampin is probably equally effective.

When given twice weekly, preventive treatment must be directly observed. Dosing for directly observed preventive treatment should be on Monday and Thursday or Tuesday and Friday.

The contraindications to rifampin preventive treatment are as follows:

- History of a rifampin-induced reaction, including hepatic, skin and other allergic reactions, or thrombocytopenia

- Severe chronic liver disease

- Pregnancy, unless the woman is HIV infected, a recent TST converter, or a close contact (see Section B[4])

- Current treatment with a protease inhibitor (in this situation, an alternative is the use of indinavir with rifabutin)

3. Alternative LTBI regimens for contacts of patients with INH- and rifampin-resistant TB

There have been no controlled trials of LTBI treatment with drugs other than INH and rifampin. Therefore, LTBI treatment protocols for contacts of patients with INH- and rifampin-resistant TB (multidrug-resistant TB or MDR-TB) are largely empirical, and all regimens must be individualized. Five general principles apply:

- TB disease must be excluded before any therapy regimen for LTBI is initiated

Because HIV infection is one of the strongest risk factors for the development of TB disease, all contacts aged 18 to 64 years should be strongly encouraged to undergo voluntary HIV counseling and testing.

- The drug susceptibility pattern of the source patient must be considered in the selection of the medications for the preventive treatment regimen

- The LTBI treatment regimen should include two anti-TB medications to which the source patient's strain is susceptible

Before selecting an LTBI treatment regimen, clinicians should consider the contact's risk factors for MDR-TB infection and disease. Contacts who are not likely to be infected with MDR-TB or who are at low risk of developing TB disease may not be candidates for an alternative preventive treatment regimen. At least three factors should be considered:

- **How likely is it that the individual is newly TB infected?** An individual with a documented prior positive TST reaction is less likely to be newly infected and is probably not a candidate for alternative LTBI treatment. In contrast, an anergic, HIV-infected spouse of an individual with MDR-TB whose three children had TST conversions is highly likely to be newly TB infected

- **How likely is the individual to develop TB disease?** Contacts are at high risk of developing TB disease if they have been recently infected, if they are infants, or if they are HIV infected or otherwise immunosuppressed (see Section III-A). Physicians should be aggressive in prescribing multi-drug LTBI treatment for these individuals

- **How likely is it that the individual is infected with a strain of MDR-TB?**

    - *Infectiousness of the source patient*. A source patient who is sputum smear-positive, has cavitary disease, and is coughing is much more infectious than one who is smear-negative and not coughing. Also, a source patient whose contacts had TST conversions is more infectious than a source patient whose contacts did not have TST conversions

    - *Closeness and intensity of the MDR-TB exposure*. Contacts are at higher risk for infection if they have spent a prolonged period of time sharing air with a person who has MDR-TB, if they were exposed in a small enclosed, poorly ventilated area, or if they were exposed during cough-inducing procedures (bronchoscopy, sputum induction, endotracheal intubation, etc.)

    - *Contact's risk of exposure to drug-susceptible TB*. Individuals who have been exposed to several sources of TB (e.g., some health care workers) may be less likely to have been infected with a multidrug-resistant strain than individuals whose only known exposure to TB was with an infectious MDR-TB patient (e.g., a TST-positive infant of a mother with MDR-TB)

- **Low or low-intermediate likelihood of infection with MDR-TB.** If thought to be newly infected, these contacts should be evaluated for LTBI treatment with INH

- **Intermediate, high-intermediate, or high likelihood of infection with MDR-TB.** If thought to be newly infected, these contacts should evaluated for an alternative regimen for LTBI treatment according to their age and immune status:

    - Contacts who are HIV seropositive, otherwise immunosuppressed, and/or younger than 5 years old should be given multi-drug LTBI treatment with drugs other than INH and rifampin

    - Contacts who are HIV seronegative, immunocompetent, and older than 5 years old should be managed according to one of the following two options:

        1. Consider multi-drug LTBI treatment with anti-TB medications other than INH or rifampin. This option is important for recent TST converters

        2. Do not administer any LTBI treatment. Educate the contact about the symptoms of TB. Evaluate the contact with a chest x-ray and symptom review at 4, 8, 12, 18, and 24 months

All patients starting LTBI treatment with two or more drugs should have baseline liver function tests and a complete blood cell count.

4. Regimens for women who become pregnant while taking preventive treatment

In general, LTBI treatment should be discontinued in women who become pregnant while taking INH and/or rifampin for LTBI treatment. To reduce the risk of peripartum hepatitis, LTBI treatment should not be restarted until 2 or 3 months after delivery. When LTBI treatment is restarted, a full course should be given (previous doses ignored).

However, TST-positive pregnant women with certain risk factors should continue LTBI therapy during the pregnancy:

- For women who are HIV seropositive, who have behavioral risk factors for HIV infection but decline HIV testing, or who have been in close contact with a smear-positive TB patient, LTBI treatment should be continued, even during the first trimester

- For women who have had a TST conversion within the past 2 years, LTBI treatment should be discontinued during the first trimester and resumed at the beginning of the second trimester. When LTBI treatment is restarted, a full course should be given (previous doses ignored)

Pregnant women who are taking INH should be prescribed pyridoxine (vitamin B6) 25 mg daily. Additional pyridoxine is not necessary for women who are already taking a prenatal vitamin that contains at least 25 mg of pyridoxine.

Breast-feeding should not be discouraged for an HIV-seronegative woman who is taking or planning to take any anti-TB medication(s).

5. Regimens for individuals with radiographic evidence of old, healed TB

TB Classes IV and V (Low) comprise individuals who are unlikely to have TB disease at the time of the evaluation and who have all three of the following:

- A TST reaction of 5 mm or more

- A chest x-ray that shows noncalcified fibrotic lesions suggestive of old, healed TB or silicosis

- A history of untreated or incompletely treated TB

If immunocompetent, these persons should be given short-term LTBI therapy: four drugs for 2 months and two drugs for 2 months ("4 for 2, for 2"), for a total of 4 months of treatment, as described below. (Immunosuppressed individuals should receive four drugs for 4 months, as described below.) This regimen has several advantages: the risk of INH resistance is significantly lower than with a regimen of INH alone, adherence to treatment may be higher than with a 12-month regimen, and treatment can be initiated at the first medical visit rather than at a later visit after sputum cultures are shown to be negative for *M. tb*. In special instances, however, the physician may prefer to use a 12-month regimen with INH.

The protocol for the multi-drug regimen is as follows:

- For all patients, perform baseline liver function tests and a complete blood count before starting a multi-drug regimen

- Start with a four-drug regimen of INH, rifampin, pyrazinamide, and ethambutol. Prescribe pyridoxine if the patient is malnourished, alcoholic, HIV seropositive, or pregnant. Always use Rifamate® (a combination of INH and rifampin) along with pyrazinamide and ethambutol. Obtain three sputum specimens for smear and culture

- Ensure that the patient is followed monthly by the physician and nurse

- If the patient is HIV seropositive, continue all four drugs for 4 months

- If the patient is HIV seronegative, continue all four drugs for 2 months, followed by Rifamate® alone for the next 2 months

- After 4 months of treatment, obtain a second chest x-ray

    - If the chest x-ray shows no change and the sputum cultures are negative for *M. tb*, the lesion presumably was inactive. Discontinue LTBI treatment if the patient has received a total of 4 months of treatment regardless of his or her HIV status

- If the chest x-ray shows any resolution, the lesion presumably was active. Re-classify the patient as Class III even if the cultures are negative. Continue INH and rifampin for a total of 6 months of treatment in HIV-seronegative patients. Continue all four drugs for a total of 9 months of treatment in HIV-seropositive patients

If the four-drug regimen cannot be used because of adverse reactions or other reasons, use INH alone for a total of 12 months. Clearly document in the medical record the reason why a four-drug regimen could not be used.

Patients with radiographic evidence of old, healed TB who have symptoms suggestive of TB disease (cough, fever, nightsweats, weight loss, etc.) should be classified as Class V (High). The patient should be given DOT with INH, rifampin, pyrazinamide, and ethambutol, pending culture and susceptibility results. If the culture is positive for *M. tb* or the chest x-ray improves, re-classify and treat the patient as Class III. If the culture is negative and the chest x-ray does not improve, reclassify the patient as Class IV and treat as described above.

PROTOCOL FOR MONITORING PATIENTS DURING PREVENTIVE TREATMENT

After the initial clinical evaluation by the physician, an individual who is classified as TB Class II and is taking LTBI treatment should be evaluated monthly. If the patient is taking only INH or rifampin, the evaluation may be done by a registered nurse. If the patient is taking two anti-TB medications or a medication other than INH or rifampin, the evaluation should be done by a physician.

- All patients should be closely monitored for signs and symptoms of drug toxicity, especially those older than 35 years of age.

- Monthly liver function tests (LFTs) should be done only for patients whose baseline LFTs were abnormal. (Baseline LFTs should be done for patients with a history of

- heavy alcohol ingestion, liver disease or hepatitis, patients older than 35 years, and patients starting LTBI treatment with two or more drugs.)

Pregnant women taking INH and/or rifampin should have LFTs each month during pregnancy and for 4 months postpartum.

LTBI treatment should be discontinued if ALT or AST values are higher than 5 times the normal value or if there is clinical evidence of hepatitis (e.g., jaundice, pain in the right upper quadrant, etc.).

PROTOCOL FOR INTERRUPTED OR INCOMPLETE LATENT TB INFECTION TREATMENT

Interrupted or incomplete treatment is defined as the loss of at least one third of the intended LTBI treatment regimen — in other words, a lapse in treatment that lasted 2 or more consecutive months or intermittent interruptions in treatment that total 2 or more months.

Patients who are prescribed LTBI treatment but do not complete the course of treatment should be encouraged to complete the treatment. Recommendations for determining the duration of the renewed regimen are presented below. However, if the patient has failed three attempts to complete LTBI treatment, no further efforts should be made.

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., the previous doses should be disregarded):

   - A lapse in treatment within the first 3 months of the original regimen
   - Treatment that lapsed more than 6 months ago
   - Immunosuppression, 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 necessary.

2. Patients who should complete the previous regimen

In patients with none of the conditions listed in Section III-E(1) above, the regimen should last as long as needed to complete the duration of the regimen originally prescribed. For example, if treatment lapsed for 2 months after 3 months of an intended 6-month regimen, the patient should receive treatment for an additional 3 months so as to complete a total of 6 months of treatment.

PROTOCOL FOR COMPLETING LATENT TB INFECTION 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 fifth month for patients taking a 6-month preventive treatment regimen).

The nurse or physician performing the monthly evaluation should note in the clinic medical record that the individual was given enough medication for the final month of LTBI treatment and is being discharged from the clinic.

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

FOLLOW-UP FOR PATIENTS WHO HAVE COMPLETED PREVENTIVE 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. In selected instances, however, a repeat course of LTBI treatment may be indicated for these patients. For example, a repeat course of LTBI treatment should be considered for HIV-seropositive individuals and children younger than 18 years old 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.

When LTBI treatment is repeated, an entire course should be given (i.e., 12 months for HIV-seropositive individuals and 9 months for children younger than 18 years) on the assumption that exogenous re-infection may have occurred. Exogenous re-infection is more likely if there are TST conversions among other contacts who had similar exposure to the individual with TB disease.