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Patient Pretreatment Evaluation and Monitoring

Policy: Latent Tuberculosis Infection **(**LTBI) must be diagnosed and active TB Disease ruled out prior to initiating treatment. LTBI patients should be evaluated at least monthly during treatment.

Purpose: To ensure safe and appropriate treatment for LTBI.

Procedure:

1. **Rule out active TB Disease.** Ensure that the client has received a medical evaluation and chest x-ray (CXR), no more than six months ago, to rule out active TB Disease **prior to beginning treatment for LTBI.** The TB signs and symptoms checklist should be completed as soon as possible for each individual with a positive TST or Interferon Gamma Release Assay (IGRA).

   If patient is symptomatic, collect three sputums and submit to the Missouri State Public Health Lab for evaluation (see Section 3). The three sputums must be collected at least eight hours apart, with one of the three being an early morning collection. If cultures are pending, wait for results before beginning LTBI treatment, even if sputum results are smear negative.

2. **Clinical Monitoring:** Schedule a home or clinic visit with the patient at least once per month to include:
   - Brief physical assessment for signs of hepatitis (See Appendix: Urine Chart)
   - Assessment of adherence to treatment
   - Review of symptoms for possible adverse medication reactions or interactions
   - Review of signs and symptoms of TB Disease (Signs and Symptoms Checklist)

3. **Liver Function (LFT) Testing:**
   a. Baseline AST/SGOT, ALT/SGPT at the start of LTBI therapy is recommended for clients with any of the following:
      - Liver disorders
      - History of liver disease (hepatitis B or C, alcoholic hepatitis or cirrhosis)
      - Regular use of alcohol
      - Risks for chronic liver disease

- HIV infection
- Pregnancy or immediate postpartum period (within 3 months of delivery)

b. Baseline testing can be considered on an individual basis, especially for patients taking other medications for chronic medical conditions. LFT's will only be covered by the Diagnostic Services Program (DSP) on a case by case basis, with prior approval by the DHSS TB Elimination Program. (See TB Manual-DSP Program)

c. Routine periodic retesting is recommended for individuals with abnormal initial results and other persons at risk for hepatic disease.

d. Laboratory testing is recommended for any patient who has symptoms suggestive of hepatitis such as:

Fatigue, weakness, malaise, anorexia, nausea, vomiting, abdominal pain, pale stools, dark urine, chills, or signs of jaundice

e. AST level 3 or more times the upper limit of normal can be accepted if the patient is free of hepatitis symptoms and up to 3 times the upper limit of normal if there are signs and symptoms of liver toxicity.

Also see *MMWR Treatment of Tuberculosis* at:
https://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf Page 43 - Section 6.3.4. Hepatitis

4. **Patient Education:**

a. Explain the disease process and rationale for medication in the absence of symptoms or CXR abnormalities.

b. Provide patient education, written and verbal instructions, in patient's primary language, if available.

c. Advise the patient to abstain from the consumption of alcohol, to include beer and wine. The combination of alcohol and TB medications together can cause life threatening liver conditions.

d. Reinforce patient education at each visit.

e. Ensure confidentiality.

f. Review the importance of completing treatment for LTBI.

5. **Patients should be instructed to take the following steps if symptoms of hepatitis develop:**
    - **Immediately stop taking medications and contact Case Manager/clinic. Follow instruction of Case Manager/clinic personnel regarding medical attention.**
    - **If Case Manager/clinic personnel are not immediately available, leave a message notifying of the development of symptoms, then seek emergency medical attention.**
    - **Follow up with Case Manager/clinic regarding continuation or alteration of LTBI treatment regimen.**
6. **Assessing Adherence:**
    a. Many variables affect a patient's adherence to the medication regimen for treatment of LTBI. Episodes of non-adherence should be addressed as soon as possible.
    b. Adherence Questionnaire:
        - When do you take your medicines?
        - How do you remember to take your medicines?
        - How many pills did you miss?
        - How many pills do you have left in your medication bottle?
        - When was the last time you missed any of your LTBI medications?
    c. Request patient to bring medication bottles with them to each clinic visit. Count the remaining pills in each bottle.
    d. Discuss patient reminders such as pill boxes or calendars to increase adherence to medication regimen.
7. **Directly Observed Therapy (DOT)** should be considered under the following circumstances:
    a. Medication is prescribed intermittently. There are several treatment regimens available for the treatment of LTBI. Providers should choose the appropriate regimen based on:
        - Drug-susceptibility results of the presumed source case (if known);
        - Coexisting medical illnesses; and

- Potential for drug-drug interactions.

b. For persons who are at especially high risk for TB disease and are either suspected of non-adherence or are given an intermittent dosing regimen, directly observed therapy (DOT) for LTBI should be considered. (**For more information on DOT, see the; *Case Management: Disease* located at: http://health.mo.gov/living/healthcondiseases/communicable/tuberculosis/tbmanual/pdf/Chap4.pdf).**

This method of treatment is especially appropriate if the person in need of LTBI treatment lives with a household member who is on DOT for TB disease, or lives in an institution or facility where treatment for LTBI can be observed by a staff member. It is necessary to exclude TB disease before starting LTBI treatment.

c. The patient is high risk (HIV positive, TB contact or child less than 5 years of age).

8. **Dispensing TB Medications:**

a. Ensure the five rights of medication administration are followed: Right patient, right medication, right time, right dose, and right route.

b. Check patient allergies.

c. Do not issue more than a 30-day supply of medication at each monthly clinic visit.

d. Medication may be transferred to another agency that will be providing DOT for the patient i.e. long-term care facility, detention center, school or university. Notation of the transfer of medication should be documented in the patient record and DHSS's TB Elimination Program shall be notified. LPHA staff are responsible for monthly follow up of all patients receiving LTBI treatment.

9. **Documentation of Clinic Visit:**

a. If it is not documented, it did not happen.

b. Signs/symptoms of adverse reactions must be documented with actions taken in the patient record.

c. Information can be entered into the encounter page of the WebSurv program.

d. Information is to be documented on page 2 (backside) of the TBC-4.

e. Send a copy of the completed TBC-4 to the DHSS's TB Elimination Program if not entered in WebSurv.

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LTBI Treatment Regimens

Policy: All individuals taking treatment for LTBI should be on a standard treatment regimen as indicated by the CDC/ATS recommendations.

Purpose: To ensure safe and appropriate treatment for LTBI.

Drug*	Duration	Interval	Minimum Doses	Comments
INH	9 Months	**Daily** Adult: 5 mg/kg Children: 10-20 mg/kg Maximum dose 300 mg	270	• The preferred regimen is daily treatment for 9 months • Recommended regimen for people with HIV, for children, and for people with chest x-ray findings suggestive of previous TB disease • DOT **must** be used with twice-weekly dosing
		Twice weekly Adult: 15 mg/kg Children: 20-30 mg/kg Maximum dose 900 mg	76	
	6 months	**Daily** Adults: 5 mg/kg Maximum dose 300 mg	180	• **Not** recommended for people with HIV, for children, or for people with chest radiograph findings suggestive of previous TB disease • Dot **must** be used with twice-weekly dosing
		Twice weekly Adults: 15 mg/kg Maximum dose 900 mg	52	
INH And RPT	12 weeks	**Once weekly** INH: Adults: 15 mg/kg Maximum dose 900 mg RPT: 10.0 – 14.0 Kg 300 mg 14.1 – 25.0 Kg 450 mg 25.1 – 32.0 Kg 600 mg 32.1 – 49.9 Kg 750 mg ≥ 50.0 900 mg **max**	12	• Recommended as an equal alternative to 9 months of daily INH for otherwise healthy patients aged 2 years and older** who were recently in contact with infectious TB, or who had tuberculin skin test or a positive blood test for TB infection conversions • The 12-dose regimen can be considered for other groups when it offers practical advantages, such as completion within a limited timeframe • DOT is strongly recommended • **Not** recommended for children younger than 2 years, HIV-infected patients taking ART, patients with presumed INH or RIF-resistant *M. tuberculosis*, pregnant women, or women expecting to become pregnant within the treatment period
RIF	4 months	**Daily** Adults: 10 mg/kg Children: 10-20 mg/kg Maximum dose 600 mg	120	• Recommended for persons who cannot tolerate INH or exposed to INH resistant TB • Not recommended for HIV infected persons on ART therapy

Reference: *Core Curriculum on Tuberculosis: What the Clinician Should Know*. Sixth Edition 2013. Chapter 5, Treatment of LTBI. https://www.cdc.gov/tb/education/corecurr/pdf/corecurr_all.pdf

***Isoniazid (INH); Rifampin (RIF); Rifapentine (RPT)**

****updated age recommendations:** https://www.cdc.gov/tb/topic/treatment/ltbi.htm

Peripheral Neuropathy

- Uncommon at doses of 5 mg/kg
- Those at risk may also be given pyridoxine (vitamin B6)
    - ♦ Persons at high risk for neuropathy (e.g., diabetes, uremia, alcoholism, malnutrition, HIV infection)
    - ♦ Pregnant women
    - ♦ Persons with a seizure disorder
    - ♦ Patients who develop signs and symptoms of peripheral neuropathy

Medication Fact Sheets: (**see the *TB Manual; Appendices/Educational Materials* located at: http://health.mo.gov/living/healthcondiseases/communicable/tuberculosis/tbmanual/pdf/Appendices.pdf**

Checklist for Latent TB Infection – (see *TB Manual; Appendices/Other Resources* located at: http://health.mo.gov/living/healthcondiseases/communicable/tuberculosis/tbmanual/pdf/Appendices.pdf

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LTBI Medications – Adverse Effects

Policy: To educate the patient concerning the adverse effects of medications used for the treatment of LTBI.

Purpose: To ensure the patient has education concerning the adverse effects of TB medications and what action to take.

NOTE: **Patients should be instructed initially and at each monthly visit to stop taking TB medications and to seek medical attention immediately if symptoms of hepatitis (liver toxicity) develop and not to wait until a clinic visit to stop medications.**

Three of the first line anti-tuberculosis drugs, INH, Rifampin, and PZA, can cause drug-induced liver injury. If the LFT (liver function tests) AST level is three or more times the upper limit of normal in the presence of hepatic symptoms, or five or more times the upper limit of normal in the absence hepatic symptoms. The medications should be stopped immediately and the patient should be evaluated by a medical provider. If the AST is less than 5 times the upper limit of normal, toxicity can be considered mild, an AST level of 5-10 times normal defines moderate toxicity, and AST level of greater than ten times normal (i.e., greater than 500 IU) is severe. It is important to note that an asymptomatic increase in AST concentration occurs in nearly 20% of patients being treated with the standard four-drug regimen. In the absence of clinical and laboratory monitoring should be increased.

Possible adverse effects of INH:

- Risks of fulminant INH-related hepatitis appear to be greatest if INH is continued after onset of symptoms of hepatotoxicity. (In one study, 7 of 8 patients requiring INH related liver transplant continued taking INH for at least 10 days after onset of symptoms.
- In addition to clinical monitoring, it is essential to educate patients about the symptoms of hepatotoxicity and instructing them to stop treatment immediately if such symptoms occur and report to the clinician for evaluation.
- Clinical hepatitis occurs in 0.1% to 0.15% of people taking INH, and is more common when INH is combined with other agents. Factors that may increase either these rates or the severity of the hepatitis include:
    - alcohol consumption,

- underlying liver disease
- use of other medications which are metabolized in the liver such as Acetaminophen.

- Peripheral neuropathy, caused by interference with metabolism of Vitamin B6 (pyridoxine) can occur in less than 0.2% of people taking INH at regular doses (300 mg a day), and is more likely in the presence of other conditions associated with neuropathy such as diabetes, HIV, renal failure and/or alcoholism. 10-50 mg of Vitamin B6 (pyridoxine) supplementation is recommended for:

  a. Pregnant or breastfeeding women.

  b. Individuals with seizure disorders.

  c. Patients with conditions in which neuropathy is common (e.g. diabetes, uremia, alcoholism, malnutrition, HIV infection).

Recommended dosage for adults 5 mg/kg daily (300 mg per day maximum) or 15 mg/kg 2 – 3 times weekly (up to 900 mg maximum), as prescribed by the physician.

Patients unable to tolerate INH can often tolerate Rifampin.

Possible adverse effects of Rifampin:

1. Hepatotoxicity may occur in 0.6% of persons taking Rifampin. Hepatitis is more likely when combined with INH.

2. Cutaneous skin reactions, such as flushing and itching with or without a rash, may occur in 6% of persons taking Rifampin. It is generally self-limiting and may not be a true hypersensitivity; continue treatment if possible.

3. Gastrointestinal symptoms such as nausea, anorexia, diarrhea and abdominal pain are rarely severe enough to discontinue treatment.

4. Reddish orange to reddish brown discoloration of body fluids (urine, stool, saliva, sputum, sweat and tears) is expected and harmless, but patients should be advised and prepared to see this side effect. Soft contact lenses may be permanently stained.

5. Rifampin interacts with a number of drugs. It is known to reduce concentrations of oral hypoglycemic agents, methadone, warfarin, oral contraceptives and phenytoin. Women using oral or other systemic hormonal contraceptives are at greater risk of becoming pregnant during Rifampin therapy

therefore these patients should use a backup barrier form of contraception, such as condoms, to avoid pregnancy during treatment.

If patient thinks they have become pregnant during treatment, stop treatment and notify physician.

6. All drugs in treating TB can cause a rash. The response to a patient with a rash depends on its severity. Thrombocytopenia (low platelets) is a possible adverse reaction to Rifampin. A baseline complete blood count (CBC), including platelet count should be obtained for all adults. A petechial rash may suggest thrombocytopenia (dangerously low blood count) in patients taking Rifampin. If a petechial rash occurs the platelet count should be checked and, if low, Rifampin hypersensitivity should be presumed to be the cause. Rifampin should be stopped and the platelet count monitored until it returns to baseline; Rifampin should not be restarted. If the rash is generalized, especially associated with fever and/or mucous membrane involvement, all drugs should be stopped immediately and the physician should be notified. If emergency the patient should seek immediate medical attention. If the patient has been assessed by their medical provider and the rash has substantially improved, the medications can be restarted one by one, at intervals of 2-3 days. Rifampin should be restarted first, followed by INH, and EMB or PZA. If the rash recurs the last drug added should be stopped. If no rash appears after the first three drugs have been restarted, the fourth drug should not be restarted unless the rash was relatively mild and the fourth drug is considered essential for therapy.

7. Rifampin is contraindicated in HIV infected patients being treated with certain protease inhibitors (PI) or nonnucleoside reverse transcriptase inhibitors (NNRTI). In the situation, Rifabutin may be substituted for Rifampin.

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Interruption of Therapy

Policy: To provide the patient with the recommended treatment for LTBI when interruptions of therapy occur.

Purpose: To provide recommendations to ensure the patient receives the recommended doses of medication to complete therapy.

Procedure:

1. Completion of therapy is based on the total number of doses administered – not on the duration of therapy alone.
    a. The 9 month regimen of daily INH consists of 270 doses, at minimum, administered within 12 months.
    b. The 6-month regimen of INH consists of 180 doses administered, at minimum within 9 months.
    c. The twice weekly INH regimen consists of:
        - At least 76 doses administered within 12 months or *
        - At least 52 doses administered within 9 months *
    d. The 12 dose weekly regimen consists of:
        - At least 11 doses out of the recommended 12 doses within 12 weeks must be taken in order for treatment to be considered complete **
    e. All intermittent regimens must be given by directly observed therapy (DOT), including the 12 dose regimen.
2. Ideally, the patient should receive medication on a regular dosing schedule until completion of the indicated course of therapy. However, in practice some doses may be missed, requiring the course to be lengthened.
3. When restarting therapy for patients who have interrupted treatment, clinicians may need to continue the regimen originally prescribed or restart (renew the entire regimen if interruptions were frequent enough to preclude treatment doses as recommended above) the entire treatment regimen depending upon the length of the interruption and if there is sufficient time for the patient to complete the recommended doses within the recommended length of time (e.g. a 9 month regimen of INH within 12 months and complete 270 doses).

4. If greater than a 2-month interruption of therapy occurs, a medical examination to rule out active TB disease is indicated.

***Intermittent regimen should be given utilizing DOT.**

****12 dose regimen must be given by DOT.**

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Special Considerations in Treatment of LTBI

Policy: To provide appropriate treatment for LTBI for all individuals.

Purpose: To address special conditions while treating individuals for LTBI.

Contacts to Cases:

1. Contacts are those with recent, prolonged exposure to a person with known or suspected infectious TB. They should be evaluated immediately for TB disease and LTBI.

2. If TST or IGRA is positive, LTBI treatment guidelines should be followed, after ruling out active TB disease.

3. If TST or IGRA is negative, the contact should be retested in 8 – 10 weeks to allow time for the contact's immune response to TB infection to be detectable.

4. Window Treatment:

    - If a contact is a child less than 5 years of age, or an immunocompromised person of any age, they should have a TST or IGRA, medical evaluation and an anterior/posterior (AP), chest x-ray (CXR). The CXR for children should include a lateral view. If they are all negative, then treatment with daily INH should by initiated immediately until the 2nd follow up TST or IGRA is done in 8-10 weeks. (If the child is less than 6 months of age, the follow-up TST or IGRA should be done after the child is over 6 months of age, due to possible anergy). If the follow-up TST or IGRA is negative, no further treatment is needed for LTBI. If the follow-up TST or IGRA are positive, then treatment should be continued as an LTBI, until they have completed 9 months (270 doses) of INH within 12 months. If it is known that the disease case is resistant to INH, please notify the state Tb nurse for guidance.

5. DOT is recommended for infected contacts of active disease cases.

Re-Infection:

In general, TST or IGRA positive contacts with a **documented** history of prior adequate treatment for LTBI do not need to be retreated. Re-treatment may be indicated for persons at high risk of becoming infected and progressing to TB disease again, such as immunocompromised persons.

HIV-Positive Individuals:

1. HIV infected individuals should be treated with a 9-month regimen of INH.

2. Rifampin is contraindicated in HIV-infected person being treated with certain combinations of antiretroviral drugs. In those cases, rifabutin may be substituted for Rifampin. See CDC website: https://www.cdc.gov/tb/topic/treatment/tbhiv.htm.

3. If TST or IGRA is negative, treat if person has recent, prolonged exposure to infectious TB or if there is ongoing risk for exposure.

Pregnancy:

1. Consider immediate treatment for LTBI if the woman is HIV-infected or is a recent contact to TB disease case.

2. In the absence of risk factors for active TB, wait until three months post-partum to avoid administering medication during pregnancy.

3. INH daily or twice weekly by DOT is the preferred regimen.

4. Supplementation with 50 mg daily, of vitamin B6 is recommended.

Breastfeeding:

1. Breastfeeding is **NOT** contraindicated in women taking INH.

2. Supplementation with 50 mg daily, of vitamin B6 is recommended for nursing women and breastfed infants.

3. Amount of INH in breast milk is inadequate for treatment of infants exposed to TB.

Infants and Children:

1. Infants and children under 5 years of age with LTBI have been recently infected and, therefore, are at high risk for progression to disease.

2. Risk of INH-related hepatitis in infants, children and adolescents is minimal.

3. Routine monitoring of serum liver enzymes is not necessary.

4. DOT is the standard of care.

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Post-Treatment Follow-Up

Policy: All individuals completing a course of treatment for LTBI will be provided documentation of that treatment.

Purpose: To ensure that the patient has a record of LTBI treatment for any future medical care.

Procedure:

1. Patient should receive documentation of TST/IGRA results and treatment completion that includes: names and doses of medications, date of test, administered and read, date of CXR and date started treatment and completed. A copy of the TBC-18A may be given to the patient in addition to the TBC-18 skin testing record.

   See the *TB Manual; Appendices/Sample Forms* located at: http://health.mo.gov/living/healthcondiseases/communicable/tuberculosis/tbmanual/pdf/Appendices.pdf

2. The patient should be instructed to present this documentation in lieu of a TB test any time future testing is requested of the patient. See *Annual Statement for Tuberculin Reactors Form.

3. Patients should be re-educated about the signs and symptoms of TB disease and told to contact his/her medical provider or local health department should any of these symptoms develop.

4. **Routine CXRs are NOT needed, regardless of whether the client completes treatment for LTBI. An annual signs and symptom review should be done in place of a CXR. A CXR is only indicated if the patient develops signs or symptoms of TB Disease.**

*Annual Statement for Tuberculin Reactors Form: located at http://health.mo.gov/living/healthcondiseases/communicable/tuberculosis/tbmanual/pdf/Appendices.pdf

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Declining Treatment for LTBI

Policy: Treatment for latent TB infection (LTBI) is recommended to every person who is diagnosed with LTBI.

Purpose: To ensure that each person has access to education to make an informed decision about receiving treatment for LTBI.

Procedure:

1. Ensure the patient has received a medical evaluation and CXR to rule out active TB disease.
2. Educate the patient concerning the risks and benefits of receiving LTBI treatment.
3. Provide written TB educational materials for the patient, in their primary language, if available. Contact the TB Elimination Program for assistance in obtaining such materials.
4. Allow the patient an opportunity to ask questions and keep lines of communication open. It is important to build trust, so that the patient feels comfortable to ask questions or discuss concerns, which could prevent possible future issues.
5. Have the patient sign the document: "Declining Treatment for LTBI", and place this document in the patient's record. If the client agrees to take the treatment, have them sign the INH Medication Fact Sheet and keep in the patient's record also give the patient a copy to take with them.

   See the *TB Manual; Appendices/Sample Forms* located at*:*
   http://health.mo.gov/living/healthcondiseases/communicable/tuberculosis/tbmanual/pdf/Appendices.pdf

   If after starting treatment the patient decides they no longer wish to take the medication, have them sign the Declining Treatment for LTBI and attach to the signed INH Medication Fact Sheet and place in patient's record.
6. Explain to the patient that if they change their mind concerning taking treatment for LTBI, they should contact their local health department.

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References

1. Centers for Disease Control (CDC) Website: https://wwwn.cdc.gov/pubs/CDCInfoOnDemand.aspx
   - *Guide for Primary Health Care Providers: Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection*
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2. CDC. Targeted Tuberculin Testing and Treatment of Latent TB Infection. MMWR 2000; 49 (No. RR-6)
3. Adherence to Treatment for Latent Tuberculosis Infection: A Manual For Health Care Providers; Charles P Felton National Tuberculosis Center. 2005.

   Website: www.harlemtbcenter.org
4. CDC. Updated guidelines for the Use of Rifamycins for the Treatment of Tuberculosis among HIV-infected patients taking Protease inhibitors or nonnucleoside reverse transcriptase inhibitors. MMWR 2004; 53(2):37.
5. Website: National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP) | CDC