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Update on Screening and Treatment for Latent Tuberculosis Infection: Treating TB Infection to Prevent TB Disease

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OVERVIEW

- The Centers for Disease Control and Prevention (CDC) estimates that up to 13 million people in the United States are infected with *Mycobacterium tuberculosis*, and more than 80% of the tuberculosis (TB) disease is thought to be a result of longstanding, untreated latent TB infection (LTBI).

- LTBI is defined as the presence of *M. tuberculosis* in the body without signs and symptoms, or radiographic or bacteriologic evidence of TB disease.

- People with LTBI are at increased risk for developing active TB disease.

- Alaska has consistently had one of the highest rates of TB disease in the nation for decades, and the problem persists.

- The purpose of this report is to provide updated guidance to Alaska clinicians on diagnosing and treating LTBI.

- Recent advances in testing and treatment for LTBI can reduce the burden of TB disease and accelerate TB elimination in Alaska and elsewhere.

- Targeted testing focuses on testing those at increased risk for LTBI and those with conditions that increase their risk for developing active TB disease once infected.

- Interferon gamma release assays (IGRAs) are now commonly used to test for LTBI; they are especially recommended for persons with a history of BCG vaccination.

- Treating LTBI greatly reduces a person's risk for developing active TB disease. Shorter treatment regimens such as a 3-month course of once-weekly isoniazid plus rifapentine (3HP regimen) or a 4-month course of daily rifampin have equal efficacy but better treatment completion rates and fewer adverse reactions than the standard 9-month regimen of isoniazid.

- The 3HP regimen has recently been approved for most patients aged ≥2 years and can now, in many cases, be considered for self-administered therapy rather than directly-observed therapy.

- The Alaska Division of Public Health engages in TB prevention and control activities in partnership with health care providers to work toward the statewide elimination of TB.

- A major component of effective TB control involves educating and motivating patients with LTBI to begin and continue the full course of their treatment.

- The Alaska Section of Epidemiology TB Program staff are available for consultation about testing and treating TB disease and LTBI (907-269-8000).

Introduction

Approximately one-quarter of the global population is infected with *Mycobacterium tuberculosis*.[1] The Centers for Disease Control and Prevention (CDC) estimates that up to 13 million people in the U.S. are infected with *M. tuberculosis*, and more than 80% of the tuberculosis (TB) disease is thought to be a result of longstanding, untreated latent TB infection (LTBI).[2] LTBI is defined as the presence of *M. tuberculosis* bacteria in the body without signs and symptoms, or radiographic or bacteriologic evidence of TB disease (Table 1).[3]

Alaska has consistently had one of the highest rates of TB disease in the nation for decades, and the problem persists.[4] In 2017, Alaska's TB incidence rate was over double the national rate (7.0 vs 2.8 cases per 100,000 population, respectively),[5] and rates of active TB disease have been particularly high in southwestern and northern Alaska (55 and 29 per 100,000, respectively).[6]

New TB outbreaks occur in Alaska communities annually. The source of these outbreaks is often a person who develops active TB many years after becoming infected. As such, diagnosing and treating people with LTBI is essential if we are to greatly reduce the rates of active TB in Alaska.

Alaska TB Program staff collect and analyze surveillance data, provide consultation and education to health care providers and other partners, assist with community screening activities, conduct contact and outbreak investigations, and provide medications for patients with LTBI and TB disease. Alaska Section of Public Health Nursing staff, along with three grantee sites (Municipality of Anchorage, Kotzebue and North Star Boroughs), provide education and case management and conduct TB contact investigations in communities throughout Alaska. The Alaska State Public Health Laboratory (ASPHL) provides testing for *M. tuberculosis*, including nucleic acid amplification testing (NAAT), AFB (acid-fast bacilli) smears, cultures, and drug sensitivity testing. ASPHL sends all specimens to the U.S. Centers for Disease Control and Prevention (CDC) for genotyping and consults with CDC laboratories and national TB reference centers for multidrug resistance testing and antimicrobial sensitivity testing.

The purpose of this report is to provide updated guidance to Alaska clinicians on diagnosing and treating LTBI.

Table 1. The Difference between Latent TB Infection (LTBI) and TB Disease

A Person with Latent TB Infection	**A Person with TB Disease**
• Has no symptoms	• Has symptoms that may include ○ a bad cough that lasts 3 weeks or longer ○ pain in the chest ○ coughing up blood or sputum ○ weakness or fatigue ○ weight loss ○ no appetite ○ chills ○ fever ○ sweating at night
• Does not feel sick	• Usually feels sick
• Cannot spread TB bacteria to others	• May spread TB bacteria to others
• Usually has a positive skin test or blood test result indicating TB infection	• Usually has a skin test or blood test result indicating TB infection
• Has a normal chest x-ray and a negative sputum smear	• May have an abnormal chest x-ray and/or a positive sputum AFB smear or culture
• Needs treatment for latent TB infection to prevent TB disease	• Needs treatment to cure TB disease
Obtained from: https://www.cdc.gov/tb/topic/basics/tbinfectiondisease.htm	

Testing for LTBI
Identifying persons with LTBI is important because treatment can prevent these individuals from developing active TB disease and spreading it to others. "Targeted testing" focuses on screening persons at elevated risk for LTBI and those at elevated risk for developing active TB disease once infected (Box 1).

Box 1. Persons Who Should be Tested for Tuberculosis Infection

- People who have spent time with a person who has infectious TB disease.
- People born in or who frequently travel to countries where TB disease is common, including Mexico, the Philippines, Vietnam, India, China, Haiti, and Guatemala, or other countries with high rates of TB.
    - People born in Canada, Australia, New Zealand, or Western and Northern Europe are not considered at high risk for TB infection, unless they spent time in a country with a high TB rate.
- People who currently, or used to, live in large group settings, such as homeless shelters or prisons and jails where TB is more common.
- Health care workers and others who work in places at high risk for TB transmission, such as hospitals, homeless shelters, correctional facilities, nursing homes, and residential homes for those with HIV.
- People with current or planned immunosuppression, including persons with HIV infection, organ transplant recipients, and persons taking immunosuppressant medications such as TNF-alpha antagonist (e.g., infliximab, etanercept, others) or steroids (equivalent of prednisone ≥15 mg/day for ≥1 month).
- People with radiographic evidence of prior healed TB.
- Persons with other medical conditions associated with increased risk for progression to TB disease if infected, such as silicosis, diabetes mellitus, severe kidney disease, substance abuse (such as smoking, alcohol abuse, or injection drug use), low body weight, gastrectomy, jejunoileal bypass, organ transplants, and head or neck cancer.
- Children, especially those aged <5 years, have a higher risk of developing TB disease once infected; therefore, testing for TB infection in children is important if they are in one of the risk groups noted above.

From: CDC Latent TB Infection Testing and Treatment: Summary of U.S. Recommendations

The Mantoux Tuberculin Skin Test
The Mantoux tuberculin skin test (TST) has long been the standard method of determining whether a person is infected with *M. tuberculosis*. The skin test requires reading by a trained healthcare worker 48–72 hours after administration. Its interpretation depends on the size of induration (not redness) in millimeters, the positive predictive value of the TST, and the person's risk of TB infection and progression. A false-positive TST result can be caused by previous BCG vaccination, infection with nontuberculous mycobacteria, incorrect TST administration, or incorrect interpretation of the TST reaction.

In Alaska, a TST reaction of ≥10 mm is considered to indicate TB infection in all persons (Table 2). While this is also the case in California and Canada, [7,8] it is different from CDC's national guidance, where the cut-point for people with no TB risk factors is ≥15 mm induration.[9] The rationale for Alaska's lower cut-point is based on three factors: an increased risk for TB infection associated with Alaska's ongoing high rate of TB disease, a low rate of nontuberculous mycobacterial infection,[10,11] and studies which show that previous BCG vaccination in infancy is unlikely to cause a TST of ≥10 mm.[12]

Table 2. Classification of the Tuberculin Skin Test Reaction in Alaska

≥5 mm induration is considered positive in • HIV-infected persons • A recent contact of a person with TB disease • Persons with fibrotic changes on chest radiograph consistent with prior TB • Patients with organ transplants • Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF-α antagonists)
≥10 mm induration is considered positive in • All persons other than those listed above

Interferon Gamma Release Assays
In light of the TST's limitations, many TB programs and clinicians now use interferon gamma release assays (IGRAs) such as the QuantiFERON®-TB Gold Plus or the T-SPOT® TB test (T-Spot) in place of TST testing. IGRAs offer similar sensitivity to TSTs but have much higher specificity and positive predictive value for TB infection.[13,14] Since IGRAs are unaffected by prior BCG vaccination, the U.S. Citizenship and Immigration Services now requires IGRA testing for all applicants aged ≥2 years who are being evaluated for adjustment of status for permanent residency in the United States.[15] A comparison of IGRAs and TST tests is provided below (Table 3).

Table 3. Comparison of Interferon Gamma Release Assays (IGRAs) and the Tuberculin Skin Test (TST)

IGRAs	TST
• Currently recommended for adults and children aged ≥2 years. Some pediatric TB specialists use IGRAs for children aged ≥1 year. • Requires a single patient visit to conduct the test. • Results can be available within 24 hours. • Does not boost responses measured by subsequent tests.	• May be done at any age. Young infants aged <6 months may lack the immunologic maturity to manifest a positive TST reaction if infected. • Requires two patient visits 48–72 hours apart to conduct the test. • Repeated testing may boost responses measured by subsequent tests.
• Preferred test for persons with history of BCG vaccination, as prior BCG vaccination does not cause a false-positive IGRA test result.	• Prior BCG vaccination may cause a false-positive TST result. If a person with history of BCG vaccination has a positive TST, follow-up testing with an IGRA is recommended to help determine whether the TST reaction is attributable to TB infection or to the previous BCG vaccine.
• Requires a blood test.	• No blood test required.
• Blood samples must be processed within 16–32 hours after collection (depending on the test) while white blood cells are still viable. • Specimens must be shipped to the laboratory at room temperature 17–27 °C. • Errors in collecting or transporting blood specimens or in running and interpreting the assay can decrease the accuracy of IGRAs.	• Errors in reading and interpreting the TST can decrease the accuracy.
• Tests may be expensive.	• Test material is inexpensive, but labor costs can be expensive.
• Currently not available in all areas of Alaska.	• Available throughout Alaska.
Please note: • *For persons with immunosuppression and persons with household contact to a person with infectious TB, any positive test (IGRA or TST) indicates TB infection.* • *A negative IGRA or TST does not rule out active TB. As such, persons with symptoms or radiographic findings of possible active TB need further evaluation.* • *A positive IGRA or TST indicates a person is infected with TB. Additional clinical evaluation starting with screening for symptoms of active TB (e.g., protracted cough, fevers, night sweats, unexplained weight loss, or bloody cough) and a chest radiograph is needed to better determine if the person has LTBI or TB disease. If TB disease has been excluded, patients with LTBI should be treated, regardless of their age, unless treatment is medically contraindicated.* • *Live virus vaccines like measles, mumps, rubella; rotavirus; varicella; yellow fever; and live attenuated influenza vaccines may temporarily suppress tuberculin and presumably IGRA reactivity for 4–6 weeks. A TST can be applied or blood can be drawn for an IGRA at the same visit during which these vaccines are administered (i.e., before substantial replication of the vaccine virus); otherwise, the test should be done 4–6 weeks after vaccination.*	

Treatment of LTBI

Treatment of LTBI greatly reduces the risk for subsequent development of active TB disease and is essential to control and eliminate TB in Alaska. Up to 10% of LTBI patients will go on to develop TB disease if not treated, and the risk is much higher for persons with HIV and other forms of immunosuppression. For many years, the recommended treatment regimen for LTBI has been daily isoniazid for 9 months (or daily rifampin for 4 months in cases with suspected isoniazid resistance). A completed 9-month course of isoniazid reduces the risk for developing active disease by ≥90%.[16]

Shorter-course treatment regimens are now an option for many patients. The benefits of the shorter-course regimens include equal protective efficacy, fewer side effects, and higher completion rates when compared with the 9-month isoniazid regimen.[14,17,18] Once-weekly isoniazid and rifapentine for 12 weeks (3HP regimen) can now be used in persons aged ≥2 years. Moreover, new recommendations recently published in the MMWR endorse self- or parent-administered treatment for this regimen, as opposed to the previous recommendation for directly-observed therapy.[17] These changes further reduce barriers to treatment completion. CDC has a very useful Medication Tracker and Symptom Checklist to assist patients with self-administration of this regimen.

Directly-observed therapy remains an option for persons who may have difficulty with self-administration and persons who are at elevated risk for progression to severe forms of TB disease, including young children and immunosuppressed patients. Preferred LTBI treatment *regimens* and LTBI treatment *considerations* are summarized below (Table 4 and Box 2).

Table 4. Preferred* Treatment Regimens for Latent Tuberculosis Infection[18-21]

<table>
<tr><th colspan="2">Isoniazid and Rifapentine (3HP) Once Weekly for 12 Weeks, for Persons Aged ≥2 Years</th></tr>
<tr><td colspan="2">Not recommended for:
Children aged <2 years,
Persons living with HIV/AIDS and taking antiretroviral medications with clinically significant or unknown drug interactions with rifapentine,
Persons presumed to be infected with INH- or RIF-resistant M. tuberculosis, or
Women who are pregnant or expect to become pregnant during the 12-week regimen.
Isoniazid is available in 100 mg and 300 mg scored tablets. Rifapentine is available in 150 mg tablets.</td></tr>
<tr><th>Once Weekly Dosage</th><th>Most Common Adverse Reactions</th></tr>
<tr><td>a. Isoniazid
Adults and children aged ≥12 years: 15 mg/kg
Children aged 2–11 years: 20–30 mg/kg
Round dose up to nearest 50 or 100 mg
Maximum Dose 900 mg once weekly</td><td>Hepatitis
Peripheral neuritis
Hypersensitivity reaction</td></tr>
<tr><td>b. Rifapentine
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 kg = 900 mg
Maximum Dose 900 mg once weekly</td><td>Orange discoloration of body fluids, staining of contact lenses, hypersensitivity reaction, hepatitis, hematologic abnormalities, rash, and pruritus.
Rifapentine may interact with many other drugs.
Hormonal contraceptives may be ineffective.</td></tr>
<tr><th colspan="2">Rifampin Once Daily for 4 Months</th></tr>
<tr><td colspan="2">Not recommended for persons who are:
Living with HIV/AIDS and taking antiretroviral medications with clinically significant or unknown drug interactions with rifampin (rifabutin may sometimes be used as a substitute),
Presumed infected with RIF-resistant M. tuberculosis, and
Women who are pregnant or expect to become pregnant within the 4 month regimen.
Rifampin is available in 150 mg and 300 mg capsules.</td></tr>
<tr><th>Once Daily Dosage</th><th>Most Common Adverse Reactions</th></tr>
<tr><td>Adults: 10 mg/kg
Children aged ≥2 years : 15–20 mg/kg
Children aged <2 years: 20–30 mg/kg
Maximum Dose: 600 mg once daily</td><td>Orange discoloration of body fluids, staining of contact lenses, hypersensitivity reaction, hepatitis, hematologic abnormalities, rash and pruritus.
Rifampin may interact with many other drugs.
Hormonal contraceptives may be ineffective.</td></tr>
<tr><th colspan="2">Isoniazid Once Daily for 9 Months</th></tr>
<tr><td colspan="2">Not recommended for persons who are presumed infected with INH-resistant M. tuberculosis.

Preferred treatment for:
Persons living with HIV AIDS and taking antiretroviral medications with clinically significant or unknown drug interactions with once-weekly rifapentine or daily rifampin,
Pregnant women (with pyridoxine/vitamin B6 supplements)
Isoniazid is available in 100 mg and 300 mg scored tablets.</td></tr>
<tr><th>Once Daily Dosage</th><th>Most Common Adverse Reactions</th></tr>
<tr><td>Adults: 5 mg/kg
Children aged <15 years: 10–15 mg/kg
Maximum dose: 300 mg once daily</td><td>Hepatitis
Peripheral neuritis
Hypersensitivity reaction</td></tr>
</table>

**Note that other regimens exist; however, those listed in Table 4 are preferred by the Alaska Section of Epidemiology. When adherence with LTBI treatment cannot be ensured, DOT can be considered. The Section of Epidemiology TB Program is available to discuss tailoring regimens for specific situations (call: 907-269-8000).*

Box 2. Important LTBI Treatment Considerations

1. **Rule out active TB disease prior to initiating treatment for LTBI.**
   - TB disease is diagnosed by medical history, physical examination, chest x-ray, and other laboratory tests.
   - TB disease should be suspected in persons who have any of the following symptoms:
     - Prolonged cough
     - Hemoptysis
     - Unexplained weight loss
     - Loss of appetite
     - Night sweats
     - Fever
     - Fatigue
   - If TB disease is in the lungs (pulmonary), symptoms may include:
     - Coughing for longer than 3 weeks
     - Hemoptysis (coughing up blood)
     - Chest pain
   - If TB disease is in other parts of the body (extrapulmonary), symptoms will depend on the area affected.
   - People suspected of having TB disease should be referred for a complete medical evaluation before starting treatment.

2. **Rifampin and rifapentine can induce the metabolism of many other medications.**
   In some cases, careful monitoring and dosage adjustment of other patient medications may allow treatment with one of the short-course regimens. In other cases, treatment with isoniazid for 9 months is preferable to avoid adverse interactions with other critical medications.

3. **Rifampin and rifapentine can reduce the effectiveness of hormonal contraceptives**, **potentially leading to contraceptive failure and unintended pregnancy.**
   Women who use hormonal birth control should be advised of this risk and of the need to add, or switch to, a barrier method if they choose treatment with one of the short-course regimens. Women should be advised to inform their health care provider if they decide to try to become pregnant or become pregnant during one of the short-course treatment regimens.

4. **Patients on LTBI treatment should be monitored closely for possible adverse drug reactions.**
   Gastrointestinal effects, hepatic inflammation with elevation of liver transaminases, and skin rashes are the most frequent reactions. Often these reactions are minor and do not preclude continuing treatment, but in some cases reactions are more severe and require stopping treatment.

5. **Nine months of INH is better than 6 months.**
   Isoniazid for 9 months is preferred over isoniazid for 6 months as the 9-month regimen has shown greater efficacy in preventing TB disease.[13,15,16]

Summary Recommendations

1. Targeted testing guidelines should be used to screen at-risk persons for LTBI.
2. When available, IGRA testing should be considered over traditional TST, especially in persons with a history of BCG vaccination.
3. Persons diagnosed with LTBI need education about their infection and their risk for developing TB disease. They should be strongly encouraged to start and complete treatment.
4. Shorter-course LTBI treatment regimens should be encouraged, if clinically appropriate.
5. Self-administered therapy for the 3HP regimen should be considered for appropriate patients.
6. Active TB disease should be ruled out prior to initiating treatment for LTBI.
7. *All cases of suspected active TB disease should be reported promptly to Section of Epidemiology TB Program* by calling 907-269-8000.
8. For consultation regarding LTBI treatment, call the Alaska TB Program at 907-269-8000.
9. For more information, including an LTBI Medication Request form, please visit the Alaska TB Program website at: http://dhss.alaska.gov/dph/Epi/id/Pages/tb.aspx

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