LATENT TUBERCULOSIS INFECTION:

A Quick Guide to Case Management for Public Health Nurses

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Introduction

This guide is intended for public health nurses (PHN) who care for individuals who have or may be at risk for latent tuberculosis infection (LTBI). LTBI is the presence of *Mycobacterium tuberculosis* in the body without signs, symptoms, radiographic or bacteriologic evidence of tuberculosis (TB) disease.

In the United States, an estimated 9-14 million people have LTBI. Without treatment, approximately 5-10% of persons with LTBI will progress to TB disease at some point in their lifetime unless LTBI therapy is initiated. Identifying and treating those at highest risk for TB disease will help move toward elimination of the disease.

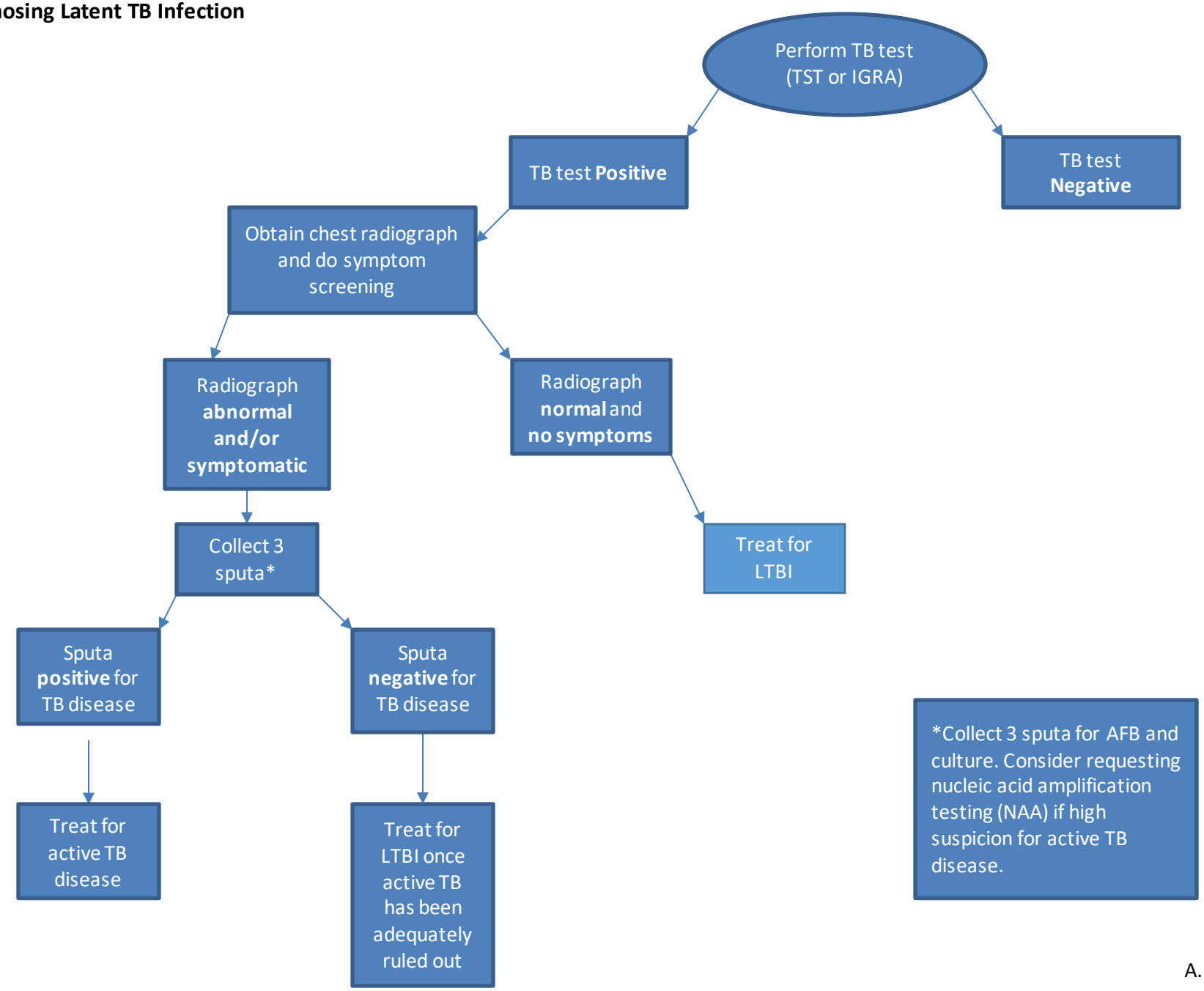
This document is not meant to be used as a substitute for the comprehensive guidelines published by the Centers for Disease Control and Prevention (CDC) and by Alaska TB Program, but rather as a ready and useful reference that highlights the main points of those guidelines.

In this document you will find summaries of the main topics related to LTBI diagnosis and case management, links to useful tools and resources, as well as current forms used by the Alaska TB Program.

Many thanks to the Washington State Department of Health, Tuberculosis Program for allowing the Alaska TB Program to use their *Latent Tuberculosis Infection A Quick Guide to Case Management 2014* as a template for this document.

We also gratefully acknowledge the contributions made by Section of Public Health Nursing staff including Evelina Achee, Susi Peterson, Tammy Kaboord and Donna Bean, as well as Dr. Bruce Chandler.

Diagnosing Latent TB Infection



Section One: Diagnosing TB Infection

Tests for TB Infection

Tuberculin Skin Test (TST)

The tuberculin skin test is administered intradermally using the Mantoux technique by injecting 0.1 ml of 5 TU purified protein derivative (PPD) solution. If a person is infected and has an intact immune system, a delayed-type hypersensitivity reaction should be detectable 2-8 weeks after infection. The reading and interpretation of TST reactions should be conducted within 48 to 72 hours of administration by a trained health care professional.

Online training on administration of the TST using the Mantoux method is available at:
http://www2c.cdc.gov/podcasts/player.asp?f=3739

Key Points

- TST remains the most widely available test used for TB screening in Alaska.
- Almost everyone can receive a TST, including infants, children, pregnant women, people living with HIV, and people who have had a bacille Calmette-Guerin (BCG) vaccination. People who had a severe vesicular reaction to a previous TST should not receive another TST.
- The TST should not be performed on a person who has written documentation of either a previous positive TST result or treatment for TB disease. Once positive, a TST will likely remain positive on subsequent testing.
- Interpretation of the TST result is the same for persons who have a history of BCG vaccination.
- A positive TB test indicates that a person has been infected with TB but does not differentiate between latent and active TB.[i]
- A negative TB test alone is not sufficient to rule out TB infection or disease. Test results must be taken in context of level of risk and other clinical factors. For persons who are immunosuppressed or high risk, additional clinical evaluation may be indicated.

How to Interpret a Tuberculin Skin Test Reaction

Induration Size	Considered Positive In:
5 mm or more	• HIV-infected persons • Recent contacts of a person with infectious TB disease • Persons with fibrotic changes on chest radiograph consistent with prior TB • Organ transplant recipients • Persons who are immunocompromised for other reasons (e.g., taking equivalent of ≥ 15 mg/day of prednisone for 1 month or more or those taking TNF-alpha antagonists)
10 mm or more	• All others in Alaska

BCG Vaccine

The BCG vaccine is currently used in many parts of the world where TB is common in order to protect infants and young children from serious, life-threatening disease. BCG vaccination is not recommended in the U.S. The question of the effect of BCG vaccine on TST results often causes confusion. TST reactivity caused by BCG vaccine generally wanes with the passage of time, but periodic skin testing may prolong (boost) reactivity in vaccinated persons. A history of BCG vaccination is not a contraindication for tuberculin skin testing or treatment for LTBI in persons with positive TST results. TST reactions should be interpreted regardless of BCG vaccination history.

Vaccination with BCG may cause a false positive reaction to a TB skin test. A positive reaction to a TB skin test may be due to the BCG vaccine itself or due to infection with TB bacteria. TB blood tests (IGRAs), unlike the TB skin test, are not affected by prior BCG vaccination and are not expected to give a false-positive result in people who have received BCG. Interferon-Gamma Release Assays (IGRAs) use *M. tuberculosis* specific antigens that do not cross react with BCG and therefore, do not cause false positive reactions in BCG recipients.[i] TB blood tests are the preferred method of TB testing for people who have received the BCG vaccine, although "a TST is an acceptable alternative, especially in situations where an IGRA is not available, too costly, or too burdensome."[ii]

Interferon –Gamma Release Assays (IGRAs)

Like the TST, IGRAs are used to determine if a person is infected with *M. tuberculosis.* The QuantiFERON®- TB Gold In-Tube test (QFT-GIT), and T-SPOT.®- *TB* are the two available IGRA tests. The advantages of IGRAs include that they are unaffected by BCG and most environmental non-tuberculous mycobacteria, and that a positive and negative control is built into the test which minimizes false positive and negative results. For more information on QFT-Plus see: https://www.quantiferon.com/us/products/quantiferon-tb-gold-plus-us/

Key Points

- Blood samples must be processed within 8-16 hours.
- Blood samples must be collected using specific tubes and collection technique.
- Limited data exist on use in children younger than 5 years of age.
- IGRAs do not cross react with BCG vaccine.[i]
- Once positive, an IGRA will likely always react positive on subsequent testing.
- In Alaska, IGRA access and availability varies by community. The Alaska TB Program does not provide or routinely pay for IGRA testing without preauthorization from PHNs.[iii] Testing is available through reference laboratories or facilities in many communities. Additionally, eligible persons may receive testing through the Municipality of Anchorage TB Program and regional native corporations such as Yukon Kuskokwim and Norton Sound Health Corporations.

Selecting a Test to Detect TB Infection

- **IGRAs are the preferred method of testing for**:
  --Groups of people who have poor rates of returning to have the TST read
  --Persons who have received BCG vaccine
- **TST is the preferred method for testing for**:
  --Children under the age of 5 years
  --Communities in Alaska without access to IGRAs

Either TST or IGRA may be used without preference for other groups that are tested for LTBI. For more information on selecting a test for TB infection and identifying medical or social risks please see: https://www.cdc.gov/mmwr/pdf/rr/rr5905.pdf?_sm_au_=iVVN1vwSWZqfw3DRjk7tvK06K81Qp

For more information on past and current BCG vaccination practices of countries outside of the U.S., see: BCG World Atlas (bcgatlas.org)

Key Points

- Routine testing with *both* TST and IGRAs is **NOT** recommended.
- IGRAs may not be readily available in all communities statewide

At the time of testing the person should be evaluated for risk of TB infection and disease, symptoms of TB disease, and any TB history such as prior positive TB tests or completion of treatment for LTBI or TB. A thorough risk assessment will help in choosing a testing method, interpreting TB test results, and provide useful information regarding potential treatment options.

Assessing TB Risk

The following should be considered when assessing risk for LTBI or active TB disease. Persons with these risks are more likely to become infected if exposed to TB and may progress more rapidly from LTBI to active TB disease:

- Recent close or prolonged contact with someone with infectious TB disease
- Age $\leq$ 5 years of age
- Chest radiographs with fibrotic changes suggesting inactive or past TB
- HIV infection
- Organ transplant recipient
- Immunosuppression secondary to use of prednisone (equivalent of ≥15 mg/day for ≥1 month) or other immunosuppressive medication such as TNF-α antagonists
- Injection drug user
- Resident or employee of high-risk congregate setting (e.g., prison, long term care facility, hospital, homeless shelter)
- Medical conditions associated with risk of progressing to TB disease if infected (e.g., diabetes mellitus, silicosis, cancer of head or neck, Hodgkin's disease, leukemia, and end-stage renal disease, intestinal bypass or gastrectomy, chronic malabsorption syndrome, low body weight [10% or more below ideal for given population])
- Foreign-born person from, or recent traveler to, high-prevalence area
- Signs and symptoms of TB

Follow-up for Positive TB Test – TST or IGRA

Chest Radiograph

All persons with a positive TB test should receive a chest radiograph. Chest radiographs help differentiate between LTBI and active pulmonary TB disease.[i]

Key Points

- Persons ≥ 5 years of age should have a posterior-anterior view radiograph.
- Children under 5 years of age should have both posterior-anterior and lateral views.
- Periodic follow-up radiographs are not indicated regardless of whether treatment is completed except in unusual circumstances (e.g., contacts to patients with drug resistant TB).[i]

Radiographic findings suggestive of active TB include:

- Air-space opacity or consolidation, often referred to as air-space disease
- Interstitial opacity
- Nodules or masses
- Thoracic lymphadenopathy
- Pulmonary cysts or cavities
- Pleural space abnormalities

For more information on TB Chest Radiology see:
http://www.currytbcenter.ucsf.edu/products/product_details.cfm?productID=ONL-15

Symptom Screening

Symptom screening is recommended for all persons with a newly positive TB test. Common symptoms of pulmonary TB include:

- Productive cough of 2 or more weeks duration
- Hemoptysis (cough productive of bloody sputum)
- Chest pain
- Unintended weight loss
- Loss of appetite
- Night sweats
- Fatigue
- Fever/chills
- Failure to thrive in young children

Any person with symptoms should be evaluated by a provider and sputa should be collected. Use the *Tuberculosis (TB) Disease Symptom Screening Form.*
http://dhss.alaska.gov/dph/Epi/id/SiteAssets/Pages/TB/AK%20TB%20Disease%20symptom%20screening%20form%202019.pdf

Sputum Examination

Sputum examination is indicated for persons with positive TB test results and either an abnormal chest radiograph or the presence of respiratory symptoms (even when the chest radiograph is normal).

Key Points

- Three consecutive sputa should be collected 8-24 hours apart with at least one being an early morning sputum.
- Specimens should be refrigerated until sent to the laboratory.
- Order an Acid-Fast Bacilli (AFB) smear and culture on each specimen.
- Nucleic Acid Amplification testing (NAAT) may be ordered through the Alaska State Public Health Laboratory (ASPHL) or the Alaska TB Program. Contact the Alaska TB Program at 907-269-8000 for assistance
- See the Alaska TB Manual Laboratory Section for information about available TB laboratory services: https://go.dhss.ak.local/pub/home/dph/Epi/id/SiteAssets/Pages/Alaska-TB-Manual/12Lab%20Services%2004-05-21.pdf

Section Two: Initiating Treatment

Decision to Treat

The decision to initiate or forego treatment for LTBI should be made by weighing a person's risk for progression to active TB disease, risk for potentially harmful side effects from the medication, and likelihood of patient adherence. Treatment of LTBI is a very important TB elimination strategy for Alaska and the US. The following tool may help you estimate the risk of active TB for persons with a TST reaction ≥ 5mm and/or a positive IGRA: http://tstin3d.com/en/calc.html

Key Points

- There is no age cutoff for LTBI treatment
- Never begin treatment for LTBI until active TB disease is ruled out

Choosing an LTBI Treatment Regimen

Each LTBI treatment regimen differs regarding risk for side effects, drug-drug interactions, and length of treatment. With this in mind, an appropriate regimen should be chosen after considering a person's health status, other medications prescribed, and life circumstances.[iv]

Latent Tuberculosis Infection (LTBI) Treatment Regimens

Regimens	Dosages	Advantages	Disadvantages	Comments
Shorter-course (preferred)		**In comparison to 6H/9H:**		
Rifampin Daily x 4 months [4R]	**Preparation:** 150 mg or 300 mg capsules **Adults:** Generally 600 mg. Consider 450 mg once daily for adults who weigh less than 50 kg **Children:** 15-20 mg/kg once daily (600 mg maximum) **Target Duration:** 120 doses within 180 days	• Higher rate of treatment completion • Lower rate of side effects, especially drug-induced hepatitis	• **Caution:** drug-drug interactions – hormonal contraceptives, anticoagulants, antiretrovirals, etc.	• **Note:** this regimen is recommended instead of Isoniazid for children of all ages including those < 2 years of age
Isoniazid (INH) + Rifapentine Once weekly x 12 weeks [3HP]	**Isoniazid Adults and Children (age 12 and older):** 15 mg/kg per dose once weekly, rounded up to the nearest 50 or 100 mg (max 900 mg) **Children (age 2-11):** INH 25 mg/kg per dose once weekly, rounded up to the nearest 50 or 100 mg (max 900 mg) **Rifapentine Adults and Children:** once weekly dosage by weight Preparation: 150 mg tablets. 300 mg for 10.0 – 14.0 kg, 450 mg for 14.1 – 25.0 kg, 600 mg for 25.1 – 32.0 kg, 750 mg for 32.1 – 49.9 kg, 900 mg for ≥50.0 kg **Target Duration:** 12 doses within 16 weeks	• Higher rate of treatment completion • Lower rates of side effects, especially drug-induced hepatitis • May be self-administered in low-risk persons > 2 years of age	• Higher rate of treatment discontinuation due to adverse events • Not indicated when pregnant or planning to become pregnant during treatment • **Caution:** drug-drug interactions due to rifapentine	• If patient has diabetes, HIV, renal failure, alcoholism or poor nutrition, use vitamin B6 50 mg once weekly • **Note:** this regimen is NOT recommended for children < 2 years of age
Isoniazid (INH) + Rifampin Daily x 3 months [3HR]	**Isoniazid** **Preparation:** 100 mg or 300 mg tablets **Adults:** 5 mg/kg per dose (300 mg max) Consider 200 mg once daily for adults 40 kg or less **Children:** 10-15 mg/kg per dose (300 mg max) **Rifampin** See the dosages for **"Rifampin Daily x 4 months"** **Target Duration:** 90 doses within 4 months	• Higher rate of treatment completion • Similar rate of drug-induced hepatitis	• Higher rate of treatment discontinuation due to adverse events • **Caution**: drug-drug interactions due to rifampin	• If patient has diabetes, HIV, renal failure, alcoholism or poor nutrition, use vitamin B6, 25-50 mg daily
Alternative				
Isoniazid Daily x 6 – 9 months [6H/9H]	**Preparation:** 100 mg or 300 mg tablets **Adults:** 5 mg/kg per dose (300 mg max) Consider 200 mg once daily for adults 40 kg or less **Children:** 10-15 mg/kg per dose (300 mg max) **Target duration:** 180 doses within 9 months; 270 doses within 12 months		• Lowest rates of treatment completion due to longer duration • Suspension is poorly tolerated; crush tablets for those who cannot swallow pills (e.g., younger children)	• If patient has diabetes, HIV, renal failure, alcoholism or poor nutrition, use vitamin B6, 25-50 mg daily

• Monthly symptom review to assess side effects for any regimen

• Pyridoxine: If the patient has diabetes, HIV, renal failure, alcoholism, poor nutrition, or is pregnant/breast-feeding, give pyridoxine 25-50 mg daily for 3HR and 6H/9H, or 50 mg once weekly for 3HP

This Table was adapted from Washington State LTBI Treatment Guidance available at: Microsoft Word - 343-157-LTBI Treatment Options One Pager_Dec2020 (wa.gov)

Key Points

- Intermittent therapy (such as INH biweekly) should be administered by directly observed therapy (DOT), meaning a trained health care provider observes the person swallowing each dose of medication. The only exception is 3HP, which may be self-administered by low-risk individuals.
- HIV+ persons on antiretroviral (ARV) therapy should not be dosed intermittently. Potential drug interactions with ARV, especially with rifampin and rifapentine, should be carefully reviewed when selecting a regimen.
- Use of liquid Isoniazid in children may cause diarrhea. Crushing the tablets is a common alternative.

For additional information on TB drugs, side effects, and contraindications see:
http://www.currytbcenter.ucsf.edu/tbdruginfo/

Baseline Laboratory Monitoring

Baseline laboratory testing (measurements of serum AST, ALT and bilirubin) are not routinely necessary unless the provider orders or patient has any of the following factors:

- 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 within immediate postpartum period (within 3 months of delivery)
- Use of other hepatotoxic medications[i]

Patient Education

Upon initiating treatment, it is important that the patient fully understand the benefits and risks of LTBI therapy. Patient education should include:

- basic disease process (LTBI vs. TB disease)
- basis for their LTBI diagnosis (TB test result, x-ray result, etc.)
- rationale for medication in the absence of symptoms or radiographic abnormalities
- possible side effects of the medication
- instructions to stop taking treatment and seek medical attention immediately if symptoms of hepatitis or other serious side effect develop

Patients on self-administered (SA) regimens, especially 3HP, should be aware of side effects, importance of notifying the case manager of any concerns, and the need to document doses. Guidelines for PHNs whose patients are taking SA 3HP are available at: http://dhss.alaska.gov/dph/Epi/id/SiteAssets/Pages/TB/GuidelinesforPHNs.pdf. Using the CDC tracker and checklist is advised. See:
https://www.cdc.gov/tb/publications/pamphlets/LTBI_Medication_Tracker.pdf

For resources and additional information on TB patient education see: http://ethnomed.org/patient-education/tuberculosis or https://findtbresources.cdc.gov/

Once the patient has been informed of the benefits and risks of LTBI therapy and agrees to start treatment, it is important to document the patient's agreement on your encounter form.

Special Situations

HIV-Infected Individuals

- 3HP and 4R regimens may be used as long as no significant drug interactions are present https://www.cdc.gov/tb/topic/treatment/tbhiv.htmhttp://www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/recommendations03.htm and http://www.currytbcenter.ucsf.edu/ltbihiv/

Pregnancy

- Use a shield when performing a chest radiograph to rule out TB disease. Chest radiography may be delayed until after the first trimester if desired but should not be delayed until after pregnancy.
- After TB disease is excluded, wait until 2-3 months postpartum to initiate treatment for LTBI unless the woman is high-risk, HIV-infected, or a recent contact to an infectious case
- If treatment is delayed 3 or more months from the initial evaluation, symptom screening and chest radiograph should be repeated before initiating treatment.
- 4R, 3HR, or isoniazid regimens may be used in pregnancy. If INH is used, supplementation with 10-25mg/d of pyridoxine (vitamin B6) is recommended. The 3HP regimen is NOT recommended for women who are or plan to become pregnant during the course of treatment.

https://www.cdc.gov/tb/topic/treatment/pregnancy.htm

Breastfeeding

- Supplementation with 10-25 mg/d of pyridoxine (vitamin B6) is recommended for nursing women and breastfed infants treated with an INH-containing regimen

Infants and Children

- Infants and children under 5 years of age with LTBI have been recently infected and, therefore, are at high risk for progression to disease
- Risk of INH-related hepatitis in infants and children is minimal
- Directly observed therapy (DOT) should be considered

Section Three: Case Management

Patient Monitoring

In Alaska, to ensure safe and efficacious treatment for LTBI, the PHN case manager should have monthly contact with the patient. The encounter should include monitoring for any adverse reactions or symptoms of active TB disease, number of doses taken to date, discussion of any follow up laboratory or medical appointments, and ongoing patient education. The encounter can occur face-to-face or by phone.

Clinical Monitoring

Routine periodic laboratory retesting is only recommended for persons with abnormal baseline results or those who have, or are at risk for, hepatic disease. Laboratory testing is also recommended if patients develop symptoms suggestive of hepatitis (abdominal pain, nausea, vomiting, loss of appetite, fatigue, jaundice, fever, dark urine, etc.). Treatment should be immediately discontinued if the patient develops AST or ALT elevations greater than 5 times the upper limit of normal without hepatitis symptoms, or elevations greater than 3 times the upper limit of normal if hepatitis symptoms are present. Elevated liver function tests (LFTs) should be discussed with the primary care provider and/or the Alaska TB Program.

Section Four: Dispositioning the Patient

Determining Treatment Completion

When determining treatment completion, both the number of doses and duration of treatment should be considered. If the patient cannot complete the required number of doses within the maximum amount of time, treatment is not considered complete and should be restarted or discontinued.

The following chart is a tool to assist in determining treatment completion:

Drug(s)	Typical Duration	Frequency	Total doses required	Maximum time to complete
Isoniazid (INH) + Rifapentine Once weekly x 12 weeks (3HP)	3 months	Once weekly	11-12	4 months (16 weeks)
Rifampin (RIF) daily x 4 months (4R)	4 months	Daily	120	6 months
Isoniazid (INH) + Rifampin (RIF) daily x 3 month (3HR)	3 months	Daily	90	4 months
Isoniazid (INH) (9R or 6R)	9 months	Daily	270	12 months
		Twice weekly	76	12 months
	6 months	Daily	180	9 months
		Twice weekly	52	9 months

Documentation

Patients should receive documentation of TST or IGRA results and treatment completion that includes name, dates, chest radiograph results, medication and dosage, number of doses and duration of medication. The patient should be instructed that he or she should present this documentation any time future testing is required.

Complete the LTBI *Treatment Completion Letter* and LTBI *Treatment Completion Form* for the patient. Use the *Latent Tuberculosis Infection (LTBI) Treatment Report* to document the course of treatment and submit it to the SOE TB Program. They are available at:
http://dhss.alaska.gov/dph/Epi/id/SiteAssets/Pages/TB/TB_Manual_Forms.pdf

Education

Providers should re-educate patients about the signs and symptoms of TB disease and advise them to contact the medical provider if they develop any of these signs or symptoms. Patients should also be reminded that their TB test will likely always be positive despite completing treatment and to avoid additional TB testing by showing documentation of treatment completion.

Section Five: Additional Resources

State
Contact us: (907) 269-8000 or tb@alaska.gov

References
Alaska TB Manual
http://dhss.alaska.gov/dph/Epi/id/Pages/Alaska-TB-Manual.aspx

Alaska TB Program webpage
http://dhss.alaska.gov/dph/Epi/id/Pages/tb.aspx

CDC LTBI Resources
https://www.cdc.gov/tb/publications/ltbi/ltbiresources.htm

References:

[i] Testing for Tuberculosis (TB) (cdc.gov)
[ii] Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children | Clinical Infectious Diseases | Oxford Academic (oup.com)
[iii] The *Referral and Authorization for TB Screening and Follow-up Services* Form is available in the Forms Section of the Alaska TB Manual 18Forms 5_14_20.pdf (alaska.gov)
[iv] Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020