TB Control
Yukon Communicable Disease Control
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January 2019

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CHAPTER 8: TREATMENT OF LATENT TB INFECTION (LTBI)

8.1 Background and Rationale

Treatment of LTBI contributes to TB control in Yukon by preventing people who are infected with TB bacteria from developing active TB disease.

Overall, only about 10% of people who become infected with TB bacteria will go on to develop active TB disease. However, there are a number of risk factors that can substantially increase the risk (see Table 4-3), most related to reduced or suppressed immune function. HIV infection is the strongest risk factor.

Clients must be carefully evaluated to rule out active TB disease before LTBI treatment is started.

The treatment regimen for LTBI is long (typically 9 months), but it is usually tolerated well by most clients. Clients with LTBI in Yukon are supported to complete LTBI treatment with directly observed therapy (DOT). Medications for LTBI treatment are provided without cost to clients.

Treatment of LTBI is not mandatory; clients (or parents/guardians) may decline treatment or choose to discontinue treatment at any point after it is initiated.

8.2 Indications

Treatment of LTBI is generally indicated for:

- Clients who were recently infected with TB bacteria (e.g., TB contacts whose TST or IGRA results change from negative to positive).

  NOTE: Treatment of contacts for *presumed* recent infection is discussed in Chapter 10.

- Clients with LTBI **and** risk factors for development of active TB disease (Chapter 4, Table 4-3).

Although treatment might be indicated for some clients, it might not always be appropriate. For example, LTBI treatment might not be recommended for some clients if their risk for drug-induced hepatotoxicity is thought to be greater than their risk for development of TB disease (e.g., clients with abnormal baseline bilirubin and/or transaminases [AST/ALT]).

8.3 LTBI Treatment Regimens

Recommendations for LTBI therapy include:

- 4 months daily, rifampin (4R)
- 9 months daily or twice weekly isoniazid (9H)
  Supplemental pyridoxine (vitamin B6) is added to the treatment regimen for clients (usually those greater than 16 years of age)
- 12 doses, once weekly, isoniazid/rifapentine (3HP)
  Isoniazid and rifapentine is not recommended for some clients: children less than 2 years; people living with HIV/AIDS taking anti-retroviral treatment with unacceptable drug interactions with rifapentine; pregnant or planning pregnancy during treatment; hypersensitivity to rifamycins.

The decision related to which regimen is best for the client is based on many factors. Providers should engage clients in conversation to best understand which LTBI treatment regimens may be most appropriate. This dialogue may include co-morbidities, risk factors, medication regime, including drug-drug interactions, lifestyle, timing of therapy as well as what supports may be needed to facilitate adherence. When there is preference for specific LTBI regime, these details should be provided YCDC TB nurses and communication to BC CDC TB Services for LTBI assessment and/or prescription as per routine Panorama processes.

Supplementary pyridoxine (vitamin B6) is prescribed for clients 16 years of age and older taking isoniazid to prevent peripheral neuropathy. Vitamin B6 is not included in LTBI treatment regimens for otherwise healthy children. Exceptions include children on meat and milk-deficient diets, breastfed infants, those with nutritional deficient diets, and pregnant or breastfeeding adolescents.

Individualized LTBI treatment regimens are recommended for clients thought to be infected with drug-resistant TB bacteria.

Duration of therapy is determined by how long it takes for the client to complete the prescribed number of doses. Generally, the number of doses required to complete standard LTBI treatment regimen are as follows:

- INH, Once daily, prescribed for nine months: 270 doses
- INH, Two-times-a-week, prescribed for nine months: 76 doses
- Rifampin, Once daily, prescribed for four months: 120 doses
- INH/Rifapentine (3HP), Once weekly, prescribed for 12 weeks: 12 doses

8.4 LTBI Medications and Dosages

8.4.1 LTBI Medications

Common and uncommon but important side effects associated with isoniazid, rifampin and rifapentine are outlined in Table 8-1. Information on interactions between isoniazid and food is included in Appendix H.

It is important to note that there are a number of important drug interaction associated with rifampin and rifapentine.

Table 8-1, Medications used for treatment of LTBI and associated side effects[1]

Medication	Common side effects	Uncommon but important side effects
Isoniazid	rash drug induced hepatitis† peripheral neuropathy nausea/vomiting* fatigue, drowsiness, diarrhea flushing reaction with tyramine or histamine containing foods	central nervous system toxicity anemia headache mild hair loss acne
Rifampin**	rash nausea/vomiting* dizziness diarrhea (liquid formation containing sorbitol only) drug induced hepatitis† and/or hyperbilirubinemia rash nausea/vomiting* dizziness diarrhea	'flu-like' illness with fever hypotension leukopenia thrombocytopenia
Rifapentine**	Rash, itching nausea/vomiting* diarrhea dizziness headache conjunctivitis drug induced hepatitis† and/or hyperbilirubinemia	hypersensitivity reactions (flu-like symptoms) angioedema, hypotension or shock shortness of breath, bronchospasm, wheezing neutropenia thrombocytopenia

† Symptoms can include anorexia (loss of appetite), nausea and/or vomiting, abdominal discomfort, unexplained fatigue, dark-coloured urine, scleral icterus or jaundice

* Especially with intermittent regimens administered in combination with rifampin. This symptom can also be associated with drug-induced hepatitis

** Saliva, urine, tears may become orange/red in colour (harmless but could permanently stain soft contact lenses)

8.4.2 Dosages

Dosages of isoniazid and rifampin are determined by age, weight, and dosing frequency (Table 8-2).

Table 8-2, Summary of medications used in LTBI treatment regimens for children and adults[2,3,4]

Medication	Formulations	Daily Dose		Two-Times-A-Week Dose		Once Weekly Combination Regime	
		Child	Adult	Child	Adult	Child	Adult
Rifampin[Φ]	**Capsules(PO):** 300 mg; 150 mg **Injection[Ψ]:** 600 mg/10 mL	15 mg/kg (10–20 mg/kg) Maximum: 600 mg	10 mg/kg Maximum: 600 mg				
Rifapentine[Ψ]	**Tablets (PO):** 150 mg					For persons: > 50kg = 900mg 32.1–49.9kg =750mg 25.1–32.0kg = 600mg	
Isoniazid	**Tablets (PO):** 100 mg; 300 mg **Suspension (PO):** 10 mg/mL **Injection[Ψ](IM):** 100 mg/mL	10 mg/kg (10-15 mg/kg) Maximum: 300 mg	5 mg/kg Maximum: 300 mg	20-30 mg/kg Maximum: 600-900 mg	15 mg/kg Maximum: 900 mg	15 mg/kg Maximum: 900 mg	15 mg/kg Maximum: 900 mg
Vitamin B6 (pyridoxin)	**Tablets (PO):** 25 mg; 50 mg; 100 mg	As indicated[§]	25 mg	As indicated[§]	50 mg	As indicated	50 mg

[Ψ] Available through Health Canada's Access to Drugs in Exceptional Circumstances

[§] Indicated for children on meat and milk-deficient diets, breastfed infants, those with nutritional deficiencies, children with symptomatic HIV infection and adolescents who are pregnant or breast feeding

[Φ] Recipes are available for pharmacies to compound oral capsules or tablets into liquid suspension

8.5 Procedure for Initiating LTBI Treatment

Procedure for Initiating LTBI Treatment: Communities Outside of Whitehorse

- **YCDC TB Control Nurse** forwards the recommendation to the Nurse-in-Charge of the Health Centre where the clients lives. It is important to note that depending on how LTBI is discovered (ie converter during contact tracing), all steps prior to request for treatment should be completed **prior to** a documented recommendation from the BCCDC TB Services physician. This approach helps minimize delays and supports LTBI conversations and treatment as soon as possible post identification of LTBI.

- **Health Centre Nurse:**
  - Notifies the client of the recommendation
  - Collaborates with YCDC TB Control Nurse to provide education and counseling on LTBI and LTBI treatment (including monitoring requirements) to the client.
  - Collects information on medication and current prescriptions, allergies, over-the-counter medications, and herbal/homeopathic/naturopathic/alternative supplements, and communicates this information to the YCDC TB Control Nurse.

Upon acceptance of LTBI treatment by the client or parent/guardian:

- **Community Health Nurse:**
  - Coordinates baseline blood tests (see 8.6.1) and engagement with the client's most responsible health care provider.
  - **YCDC TB Control should be included as copies to.**

- **Primary Health Care Nurse:**
  - Coordinates baseline blood tests (see 8.6.1) and engagement with the client's most responsible health care provider. In situations where the health centre is the most responsible health care provider no additional engagement is required.
  - **YCDC TB Control should be included as copies to.**

After the client has been seen by their most responsible health care provider and they are supportive of Tx:

- **Health Centre Nurse:**
  - Coordinates completion of a "Request for Preventive Therapy" form (see Appendix K-4 for sample), indicating whether or not the client accepts the offer for treatment. Once completed, the form should be faxed to **YCDC TB Control at (867) 667-8349. DO NOT FAX THE FORM TO BCCDC TB SERVICES.**

- **YCDC TB Control Nurse:**
  - Coordinates referral through Panorama and completion of all required fields as per Panorama TB standards including documentation of consent for or against the offer for treatment.
  - Once received, forwards a copy of the prescription from BCCDC TB Services physician specialist to the Community Health Centre.
  - Prepares an electronic copy of a client-specific DOT checklist (see sample, Appendix K-5). This checklist is used to accurately track the number of doses taken and upcoming laboratory testing dates

NOTE: Treatment administration will be tailored to meet client needs. This may include: directly observed therapy (DOT) with assistance of a nurse, TB worker, or capable designate; modified DOT, or self-administration.

Procedure for Initiating LTBI Treatment: Whitehorse

- Recommendation for LTBI treatment received by YCDC TB Control Nurse from BCCDC TB Services physician specialist through Panorama. It is important to note that depending on how LTBI is discovered (ie converter during contact tracing), all steps prior to request for treatment should be completed **prior to** a documented recommendation from the BCCDC TB Services physician. This approach helps minimize delays and supports LTBI conversations and treatment as soon as possible post identification of LTBI.
- **YCDC TB Control Nurse** forwards the recommendation to the client's physician and notifies the client of the recommendation with a letter (see Appendix K-3)

Upon acceptance of LTBI treatment by the client (or parent/guardian):

- **YCDC TB Control Nurse**
  - Arranges for baseline blood work to be done (see 8.6.1) and engagement with the client's most responsible health care provider.

After the client has been seen by their most responsible health care provider for medical clearance:

- **YCDC TB Control Nurse**
  - Coordinates referral through Panorama and completion of all required fields as per Panorama TB standards including documentation of consent for or against the offer for treatment.
  - Prepares an electronic copy of a client-specific DOT checklist (see sample, Appendix K-5). This checklist is used to accurately track the number of doses taken and upcoming laboratory testing dates.

NOTE: Treatment administration will be tailored to meet client needs, which may include: directly observed therapy (DOT) with assistance of a nurse, TB worker, or capable designate; modified DOT, or self-administration.

8.6 Monitoring and Education during LTBI Treatment

Although LTBI treatment is usually well tolerated, isoniazid and rifampin can cause side effects (see Table 8-1). Baseline testing and ongoing monitoring is important for early detection and management of side effects, drug-to-drug interactions, and adverse reactions.

To help identify clients at increased risk, clients' medical history and use of other prescription medications, over-the-counter medications and traditional / herbal / homeopathic / naturopathic / alternative supplements should be documented prior to the start of treatment and updated regularly over the course of LTBI treatment. **This information should be communicated to YCDC TB Control, along with updates/changes when they occur.**

YCDC TB Control submits information on clients' medication use through Panorama. A pharmacist will confirm the prescription with YCDC TB Control or notify the BCCDC TB Services physician specialist when adjustments to the prescription are indicated. When adjustments are made, and a new prescription will be issued. When a physician narrative accompanies a prescription change, this will be provided to the primary health care provider by YCDC TB Control.

Clients taking anticonvulsants and either INH or rifampin should be monitored closely because both of these drugs can affect the metabolism and serum levels of anticonvulsants.[5] Other important drug-to-drug interactions associated with rifampin include:

- Estrogens -- **women using hormonal contraceptives should be advised to use alternate forms of birth control while taking rifampin and rifapentin**
- Anticonvulsants
- Coumadin
- Glucocorticoids
- Digoxin
- Antiarrhythmics
- Sulfonylureas
- Theophylline
- Cyclosporine
- Methadone
- Ketoconazole

Consult with YCDC TB Control if there are concerns about potential side effects or drug-drug interactions.

Health care providers should educate clients on:

- Potential side effects of the TB medication(s) they are taking.
- The client's role in identifying and preventing potential side effects, with special attention to hepatotoxicity.
- The importance of consulting with their health care provider immediately if any potential side effects, drug-to-drug interactions, or adverse effects occur. **In some circumstances, it might be necessary to stop LTBI treatment.**

8.6.1 Most Responsible Health Care Provider Engagement

All clients are carefully assessed for LTBI eligibility and suitability, through multiple providers including physicians in BC associated with the Yukon TB program, BC CDC pharmacy services, YCDC TB nurses as well as Community and/or Primary Health Care Nurses. As such medical clearance is no longer required by a primary care physician prior to commencement of LTBI. However, it is important to engage with the client's most responsible health care provider prior to initiation of LTBI treatment.

A clients most responsible health care provider can provide additional insight and understanding related to additional client health history including, readiness of start treatment, additional management of existing co-morbidities, current medication profile

and planned medication changes that may result in potential for drug interactions, as well as additional information related to medication intolerances and allergies. The engagement and support of the client's most responsible health care provider to initiate LTBI treatment is also important so there is a health care provider to address any non-TB/LTBI related health changes that occur during the treatment period.

8.6.2 Baseline Testing

Blood Testing

Baseline blood tests should be completed prior to clients seeing their most responsible health care provider. Where scope of practice permits, test should be ordered by the facility with copies of the test results should be cc'ed to the clients' most responsible health care provider and YCDC TB Control.

Refer to Appendix G for baseline blood testing requirements.

In general, otherwise healthy children are less likely than adolescents or adults to have pre-existing conditions or liver disease. Therefore, baseline blood testing for clients less than 16 years of age is not routinely required. Baseline testing may be requested by the BCCDC TB Services physician specialist for clients less than 16 years of age at risk for liver toxicity.

AST is the transaminase preferred by TB Services for monitoring liver function during treatment with TB drugs. When existing blood work includes an ALT and no AST, the ALT value may be accepted in place of repeating the blood draw to obtain an AST.

Results from blood tests done within the prior 6 months can be used as baseline results provided they are within normal limits and the client does not have any of the following risk factors for hepatotoxicity:

- 65 years or older
- Pregnant or within first three months postpartum
- History of previous drug-induced hepatitis
- Current cirrhosis or chronic active hepatitis of any cause
- Pre-exisiting liver disease, particularly Hepatitis B or C with prior with abnormal transaminases
- Daily alcohol consumption
- Concomitant use of other hepatotoxic drugs (e.g., methotrexate)

YCDC TB Control must be notified is the client has **any** of the above risk factors for liver toxicity.

Existing blood test results for clients with any of the above risk factors should not be used as baseline results beyond 30 days from when the tests were performed.

Risk factors for drug-induced hepatotoxicity can include: pregnancy or first 3 months postpartum; history of previous drug-induced hepatitis; current cirrhosis or chronic active hepatitis of any cause; hepatitis C; hepatitis B with abnormal transaminases; daily alcohol consumption or concomitant treatment with other hepatotoxic drugs (e.g., methotrexate). HIV is not an independent risk for drug-induced hepatitis. See 8.6.3 and Appendix G for monitoring recommendations.

8.6.3 Monitoring

Baseline and ongoing monitoring includes updating clients' medical history and medication/supplement use, and communicating changes to YCDC TB Control.

Clients in Whitehorse are monitored by YCDC TB Control Nurses. Clients in communities outside of Whitehorse are monitored by nurses at the health centre, with all relevant information being provided to YCDC TB Control. Refer to Appendix G for a summary of monitoring requirements.

8.6.3.1 Clinical Monitoring

Weight

Document weight at baseline for all clients starting TB treatment. Weight is especially important for pediatric clients, whose prescriptions may need to be adjusted as they grow and gain weight.

Monthly monitoring of weight is indicated for all clients less than 5 years of age, low weight adults and adults who lost a significant amount of weight prior to starting or during treatment.

Weight loss or failure to gain weight in growing children could be a significant finding and should be reported to YCDC TB Control.

Baseline weight is generally sufficient for many adults. However, consideration should be given to regular weights on adults for whom a small weight fluctuation would result in a change in medication dosing.

Side Effects

Clients on LTBI treatment should be assessed for hepatotoxicity and other side effects (described in Table 8.1) with each visit (see sample DOT checklist, Appendix K-5).

Emphasis should be placed on identifying signs/symptoms of hepatotoxicity. Signs/symptoms of hepatotoxicity can include:

- Anorexia (loss of appetite)
- Nausea and/or vomiting
- Abdominal discomfort

- Unexplained fatigue
- Dark-coloured urine
- Scleral icterus or jaundice

Any side effects should be reported to YCDC TB Control immediately.

8.6.3.2 Adherence

TB medications must be taken as prescribed to be effective. Non-adherence to LTBI treatment can put clients at risk for developing active TB disease and increase the risk of drug resistance.

Nurses are responsible to maintain accurate counts of doses taken each month. These counts are to be communicated to YCDC TB Control every 2 weeks by faxing the completed DOT checklist, attention to YCDC TB Control, to **(867) 667-8349**.

YCDC TB Control should be consulted as soon as possible when adherence issues arise.

Clients (or their parents/guardians) have the right to refuse or to discontinue LTBI treatment. Providers should consult with YCDC TB Services and/or review the indications for LTBI treatment with the client. Exploring clients' perceptions about LTBI treatment and adherence challenges can provide important insights for potential solutions (e.g., use of alternate regimens). Manage clients whose LTBI treatment is discontinued prior to completion (either by their choice or on the recommendation of TB Services) as described in Section 8.10.

8.6.3.3 Laboratory Testing

Refer to Appendix G for ongoing blood testing requirements. Direction on periodic testing for people with abnormal baseline results and people at increased risk for hepatotoxicity is provided in consultation with the BCCDC TB Services physician specialist.

Any abnormal test results should be reported to YCDC TB Control immediately.

Additional and/or more frequent blood testing may be requested by the client's specialist or TB Services physician, based upon:

- Results of blood tests
- TB drugs included in the treatment regimen
- Whether there is increased risk for adverse reactions related to co-morbidities and/or other treatments/drugs a client is taking.
- Whether the client reports potential side effects/adverse reactions (e.g., signs/symptoms of hepatotoxicity).

Abnormal AST Levels

Any abnormal test results should be reported to YCDC TB Control immediately for

required follow-up.

Signs and symptoms of hepatotoxicity should be assessed in combination with AST levels. The following may also contribute to an abnormal AST level, and should be assessed

whenever the AST is greater than 45:

- Changes in medications or supplements
- Alcohol consumption
- Acetaminophen use

When the AST level is greater than 45, the patient should be contacted within 24 hours for a symptom assessment. It is recommended to allow for sufficient resulting and follow-up time during business hours.

8.7 Medication Supplies

An initial 2-month supply of medications is sent from BCCDC Vaccine and Pharmacy Services when TB treatment prescriptions are initiated, with the exception of Rifapentine. For clients in communities outside of Whitehorse, medication supplies are shipped directly from BC CDC Vaccine and Pharmacy Services to the local community health centre. Supplies for Whitehorse clients are shipped to YCDC TB Control.

Canadian jurisdictions accessing Rifapentine are accessing this medication through the *Access to Drugs in Exceptional Circumstances* regulatory pathway developed and administered by Health Canada. As a result of this pathway, this medication cannot be accessed through BC CDC for use in Yukon and stock managed directly by YCDC. When Rifapentine is prescribed, an initial 8 week supply of Rifapentine is sent from YCDC to the local community health centre via registered mail. In contrast INH and B6 used in this regime, is shipped from BC CDC TB services. YCDC TB Control coordinates medication reorders for **all clients** on TB treatment.

8.8 Supporting Adherence to LTBI Treatment

Poor adherence to LTBI treatment can lead to treatment failure and development of active TB disease. Refer to Appendix H for some tips on administering TB medications.

Adherence to LTBI treatment is supported with directly observed therapy (DOT) for some clients in Yukon. The use of DOT for LTBI is generally focused on clients at higher risk for progressing to active TB disease and for non-adherence, such as children and adolescents, and clients with previous non-adherence, unstable housing, injection drug use/other substance abuse, or major mental illness.

DOT ensures that clients:

- Ingest each dose of their prescribed treatment.
- Receive careful monitoring for side effects.
- Have regular access to encouragement and TB education from program staff.

In the community, DOT is administered by nurses, TB workers, or capable delegates and usually take place in clients' homes, or in the health centre or clinic. Health care providers and delegates responsible for administering DOT must be properly trained in the delivery of TB medications and in recording/reporting practices.

Modified DOT might be used with some clients. The decision to implement modified DOT for LTBI is made by YCDC TB Control and the BCCDC TB Services physician specialist.

8.9 Treatment Completion

Duration of LTBI treatment using isoniazid and vitamin B6 is 9 months if taken regularly. For treatment to be considered complete, 80% of the prescribed doses must be taken within 12 months of treatment start. Duration of LTBI treatment using rifampin is 120 daily doses (roughly equivalent to 4 months if taken regularly), to be completed within 6 months of treatment start.

As clients near their anticipated completion date, YCDC TB Control consults with the BCCDC TB Services through Panorama to determine whether additional tests or doses are necessary prior to treatment being discontinued (e.g., AST, chest x-rays).

Routine follow-up after completion of LTBI is not required except for contacts to source cases with multi-drug resistant TB disease (refer to 10.4.5).

Although the risk of developing active TB disease is usually negligible for most cases that complete LTBI treatment, clients (or the parents / guardians of children) should be reminded to seek evaluation promptly to rule out active TB disease should any TB signs/symptoms occur.

8.10 Management of Clients that Discontinue LTBI Treatment Prior to Completion

YCDC TB Control must be advised when LTBI treatment is discontinued or interrupted prior to completion. YCDC TB Control will communicate with BCCDC TB Services. In some circumstances, follow-up testing and/or monitoring for active TB disease might be requested.

Clients that discontinue LTBI treatment early should be educated about:

- Their risk for future development of active TB disease.
- TB signs/symptoms, and the need to seek evaluation for active TB disease promptly should TB signs/symptoms occur.

- The importance of re-evaluating treatment to prevent TB should their health status/immune function become compromised in the future.

Clients with LTBI that discontinue LTBI treatment should be counselled to reconsider LTBI treatment, including trialing a different LTBI regimen, if there is an opportunity to do so in the future or when barriers to successful treatment completion have been mitigated.

8.11 Management of Clients that Decline or Cannot Take LTBI Treatment

Clients who decline or cannot take LTBI treatment are generally followed for 2 years with assessments for signs/symptoms of active TB disease and chest x-rays at 6, 12, and 24 months. Clients found to have signs or symptoms of TB disease at reassessment should be managed as described in 7.1.1.

Clients with untreated LTBI treatment should be educated about:

- Their risk for future development of active TB disease.
- TB signs/symptoms, and the need to seek evaluation for active TB disease promptly should TB signs/symptoms occur.
- The importance of re-evaluating treatment to prevent TB should their health status/immune function become compromised in the future.

Clients with LTBI that decline LTBI treatment initially should be counselled to reconsider LTBI treatment, including trialing a different LTBI regimen, if there is an opportunity to do so (e.g., when TB screening is sought in the future).

8.12 Isoniazid Overdose

Isoniazid overdose can be fatal; large quantities should not be kept in the home.

Isoniazid should be used only as prescribed and by the person to whom it was prescribed. It should be stored safely, in the original pharmacy-dispensed container, and out of the reach of children.

Treatment of isoniazid overdose typically requires the administration of intravenous pyridoxine (Vitamin B6). Emergency care of acute isoniazid toxicity is beyond the scope of this manual; refer to external guidelines as appropriate.

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