Communicable Disease Control Manual
Chapter 4: Tuberculosis

Treatment of Latent TB Infection (LTBI)
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6.0 TREATMENT OF LATENT TB INFECTION (LTBI)

Treatment of LTBI can prevent development of active TB disease for those infected with TB bacteria. In BC, an emphasis is placed on treating LTBI in the following:

- Those infected within the previous two years (e.g., close contacts to infectious cases, people with demonstrated TST conversions or new positive IGRA).
- Immigrants and refugees from high-TB prevalence countries
- Contacts under 5 and those with substantial immune suppression requiring presumptive LTBI treatment (see Section 8.3.2).
- Those with LTBI and risk factors that substantially increase the likelihood of progression to active TB disease, including but not limited to:
  - HIV infection or AIDS
  - Chronic kidney disease on dialysis or end-stage
  - Organ transplant (related to immune suppressing treatment)
  - Treatment with TNF alpha inhibitors and/or other immune suppressing drugs/therapies such as chemotherapy or systemic corticosteroids (equivalent of ≥ 15 mg/day of prednisone for 2 weeks or longer)
  - Abnormal chest x-ray consistent with prior TB (e.g., fibronodular disease)
  - Carcinoma of head and neck
  - Silicosis

Unlike treatment of active TB disease, treatment of LTBI is voluntary. Clients, or their parents/guardians, may decline treatment or elect to discontinue treatment at any time.

It is essential that active TB disease be ruled out before LTBI treatment is initiated. LTBI is usually treated with a single anti-TB drug (monotherapy) but a combination regimen may be an option for some clients (see Section 6.1). Treating for LTBI in the presence of active TB disease can result in:

- Development of TB drug resistance (acquired drug resistance).
- Delayed cure, and increased risk for morbidity/mortality.
- Delayed diagnosis leading to prolonged infectiousness and transmission from cases with active respiratory TB disease.

6.1 Overview

Recommendations for LTBI treatment regimens are individualized to ensure the benefit (prevention of active TB disease) outweighs the risks for potential adverse effects and that treatment completion is achievable. Some medical considerations include:

- Potential for serious drug-drug interactions or complications to co-morbidities.
- **Risk for hepatotoxicity**: may occur with both isoniazid and rifampin (lower rate). Adjusting treatment regimens and/or enhanced monitoring may be used with clients at increased risk for hepatotoxicity when the risk of progression to TB disease is very high.
- **Drug sensitivity of the organism and likelihood that the client is infected with a drug-resistant strain of TB bacteria.** For example, contacts of cases with isoniazid-resistant TB disease would likely be treated with rifampin instead of isoniazid and vice-versa.
- **Adherence: shorter course regimens** may be prescribed to support completion of LTBI treatment. Also, directly observed preventative treatment (DOPT) may be recommended to improve adherence (see Section 6.11).
Alignment with comorbidity care plan: shorter course regimens may be prescribed to support completion of LTBI treatment in a timely manner to facilitate moving forward with other medical care (e.g. organ transplant, TNF-alpha inhibitor therapy).

There are also client-centred considerations such as stigma, transportation issues, and/or time absent from work that are factors in determining appropriate treatment regimens.

Recommendations for LTBI therapy in BC include:

- 4 months daily, self-administered rifampin
- 9 months daily, self-administered isoniazid
- 12 doses, once weekly, directly observed isoniazid/rifapentine

The current first line regimen for LTBI treatment in BC is 4 months of daily, self-administered rifampin. Further details on recommended LTBI treatment regimens are described in Section 6.3. Refer to Section 8.3.2 for information on management of contacts taking presumptive LTBI treatment (e.g. window period prophylaxis).

When LTBI is diagnosed during pregnancy, treatment is usually deferred until at least three months post-partum (see Section 6.15).

Monitoring for medication side effects and other adverse reactions is done throughout LTBI care. Routine baseline and ongoing monitoring requirements are described in Section 6.8 and Section 6.9. For some clients, monitoring will also include chest x-rays at the end of LTBI treatment (see Section 6.13).

Duration of treatment and determination of treatment completion are dependent upon:

- TB drugs used; treatment schedule and whether treatment was self-administered or directly observed.
- Adherence and treatment interval.

Clients with untreated or incompletely treated LTBI remain at risk for active TB disease. Some are followed periodically, typically for a period of 2 years from the time of diagnosis, when known to be a recent TB contact or evidence of recent TST conversion or IGRA conversion (see Section 6.14). Periodic follow-up may also be recommended for clients thought to be infected with drug-resistant TB bacteria and for those with significant immune suppression, regardless of whether LTBI treatment was completed (see Section 6.13).

LTBI treatment is rarely repeated but may be considered for clients with severe immune compromise following significant re-exposure to infectious TB.
6.2 Procedure for Initiation of LTBI Treatment

Figure 6-1, Flowchart for initiation of LTBI treatment

- Send completed TB Screening form, TST/GRA results and chest x-ray to TB Services.
- TB Services physician reviews clinical information and prepares narration containing treatment and monitoring requirements and/or follow-up recommendations. Narration sent to Health Authority CD Services and/or primary health-care provider.

LTBI treatment recommended

<table>
<thead>
<tr>
<th>Decision on LTBI treatment made during discussion between MRP/PHN/CHN and client.</th>
</tr>
</thead>
</table>

LTBI treatment NOT recommended

| Chest x-ray surveillance and/or signs/symptoms monitoring might be recommended. If LTBI treatment was recommended but declined, revisit recommendation with client at subsequent appointments. |

LTBI treatment accepted

| LTBI treatment declined |

- Order baseline bloodwork (AST +/- bilirubin, CBC) when indicated (see Sections 6.8 and 6.9).
- Complete TB Treatment Initiation form with client (consent and current chest x-ray, baseline blood test results, medications and weight) and forward to TB Services.

- TB Services physician reviews information, writes prescription, and sends to BCCDC Vaccine and Pharmacy Services. Copy forwarded to dispensing health care provider.
- 2-month supply of TB drugs shipped by BCCDC Vaccine and Pharmacy Services to provider responsible for dispensing medication and for monitoring client *.

Provider responsible for dispensing medication and for monitoring client (e.g. PHN/CHN):
- Prior to dispensing first dose or supply of TB drugs, consults with TB Services when:
  - baseline blood test results are abnormal or beyond recommended timeframe for use
  - client’s current weight does not correspond to prescribed dosages (see Table 6-1)
- Educates client on potential side effects/adverse reactions associated with the prescribed regimen
- Follows guidelines for abnormal AST results and consults with TB Services as indicated (see Section 5.9.2)
- Consults with MRP when other blood tests are abnormal. Notifies TB Services as indicated (see Section 6.9)
- Advise client to STOP treatment immediately if there are any adverse reactions. Consults with TB Services and/or the client’s physician or NP for further direction.
- For clients on self-administered therapy: dispenses 1-month supply of TB drugs to client, along with a requisition for repeat blood tests and/or chest x-rays (see Section 6.9). Confirm date/time of next appointment.
- For clients on directly observed treatment: administers initial dose. Confirms plan for next scheduled dose.
- Complete the TB Medication Reorder Form and submit to TB Services promptly after 2nd month supply of rifampicin or isoniazid regimen is started or after 1st month supply of isoniazid and rifampicin regimen is started.

* Blister packing can be requested on the medication re-order form.

Doses for self-administration on weekends and statutory holidays (closures) are encouraged, and may be given at the discretion of the provider once confirmed with TB services.
6.3 Recommended LTBI Treatment Regimens

Recommendations for LTBI therapy in BC include:

- 4 months daily, self-administered (or daily directly observed) rifampin. Rifabutin may be substituted for rifampin for clients with HIV infection, transplant clients, or those on medications known to interact as rifabutin has fewer drug interactions than rifampin.

- 9 months daily, self-administered (or twice weekly directly observed) isoniazid. Supplemental pyridoxine (vitamin B6) is added to the treatment regimen for clients (usually those greater than 16 years of age) who are at an increased risk for TB medication-induced neuropathies\(^1\).

- 12 doses, once weekly, directly observed isoniazid/rifapentine. Supplemental pyridoxine (vitamin B6) is added to the treatment regimen for clients (usually those greater than 16 years of age) who are at an increased risk for TB medication-induced neuropathies.

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; clients with drug interactions (eg. warfarin, digoxin, and methadone); pregnant or planning pregnancy during treatment; presumed to be infected with isoniazid or rifampin-resistant organism; hypersensitivity or adverse reaction to rifapentine.

There are medical and client considerations to review that guide determination of the best LTBI treatment option for clients (Section 6.1). Additionally, alternate LTBI treatment regimens are used for clients likely infected with drug-resistant TB bacteria (see Section 6.16).

The actual duration of LTBI treatment is determined by how long it takes for the client to complete the prescribed number of doses (see Table 6.1 below)

Table 6-1: Number of doses required to complete LTBI treatment regimen

<table>
<thead>
<tr>
<th>Medications</th>
<th>Dosing Frequency</th>
<th>Required number of doses to complete LTBI therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>Once daily for four months</td>
<td>120 doses</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Once daily for nine months</td>
<td>270 doses</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Twice weekly for nine months(^\Omega)</td>
<td>76 doses, directly observed</td>
</tr>
<tr>
<td>Isoniazid and Rifapentine</td>
<td>Once weekly for 12 weeks</td>
<td>12 doses, directly observed</td>
</tr>
</tbody>
</table>

\(^\Omega\) Twice weekly DOPT should only be used if daily self-administered regimens or the isoniazid/rifapentine regimen are not feasible or successful

Practitioner Alert!
Confirm the dosages against the client’s weight at the time of treatment start. Consult with TB Services prior to dispensing the initial supply of TB drugs or administering the initial DOPT doses when there appears to be discrepancies between prescriptions and recommended doses in Table 6-2.

\(^1\)Breastfed infants; children with nutritionally deficient diets (including meat and/or milk deficiencies); clients with risk factors for pyridoxine deficiency, such as: HIV; pregnancy/breastfeeding; diabetes; renal failure; malnutrition; substance abuse; seizure disorder.
## 6.4 Drugs and Dosages

### Table 6-2: Summary of drugs and dosing for LTBI treatment regimens (1, 2, 3, 4, 5)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Formulations</th>
<th>Daily Dose</th>
<th>Twice Weekly Dose</th>
<th>Once-Weekly Combination Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Child</td>
<td>Adult</td>
<td>Child</td>
</tr>
<tr>
<td>Rifampin Φ</td>
<td>Capsules (PO): 150 mg</td>
<td>15 mg/kg</td>
<td>10 mg/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>300 mg</td>
<td>(10–20 mg/kg)</td>
<td>Maximum: 600 mg</td>
<td>Maximum: 600 mg</td>
</tr>
<tr>
<td></td>
<td>Injection ψ (IV): 600 mg</td>
<td>Maximum: 600 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin Φ</td>
<td>Capsules (PO): 150 mg</td>
<td>Consult with TB physician as</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>depends on other medications*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifapentine Ω</td>
<td>Tablets (PO): 150 mg</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Tablets (PO): 100 mg</td>
<td>10 mg/kg</td>
<td>5 mg/kg</td>
<td>20-40 mg/kg</td>
</tr>
<tr>
<td></td>
<td>300 mg</td>
<td>(10-15 mg/kg)</td>
<td>Maximum: 300 mg</td>
<td>Maximum: 900 mg</td>
</tr>
<tr>
<td></td>
<td>Syrup (PO): 10 mg/mL</td>
<td>Maximum: 300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Injection (IM) ψ</td>
<td>Maximum: 300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 mg per mL</td>
<td>Maximum: 300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B6 (pyridoxine)</td>
<td>Tablets (PO): 25 mg 25 mg</td>
<td>As indicated §</td>
<td>25 mg</td>
<td>As indicated § 50 mg</td>
</tr>
<tr>
<td></td>
<td>100 mg</td>
<td>As indicated §</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Φ Formulas are available for compounding oral capsules or tablets into liquid suspension.

Ψ Daily doses can be divided to reduce gastrointestinal upsets.

Ω Rifapentine tablets are crushed and given with semi-solid food for children who are not able to swallow pills.

§ Breastfed infants; children with nutritionally deficient diets (including meat and/or milk deficiencies)
### 6.5 Drug Side Effects / Adverse Reactions, and Drug-Drug Interactions

**Table 6-3: Drugs included in LTBI treatment regimens and associated side effects**

<table>
<thead>
<tr>
<th>TB drug</th>
<th>Common side effects/adverse reactions</th>
<th>Uncommon but important side effects/adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>rash, drug-induced hepatitis †, peripheral neuropathy, nausea/vomiting †, fatigue, drowsiness †, diarrhea †, flushing reaction with tyramine or histamine containing foods</td>
<td>central nervous system toxicity, anemia, headache, mild hair loss, acne</td>
</tr>
<tr>
<td>Rifampin</td>
<td>rash, nausea/vomiting †, diarrhea †, dizziness, saliva, sweat, urine, feces, tears can become orange/red in colour (harmless but could permanently stain soft contact lenses, dentures), drug-induced hepatitis † and/or hyperbilirubinemia</td>
<td>‘flu-like’ illness with fever, hypotension, leukopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>rash, nausea †, diarrhea †, taste disturbances, saliva, sweat, urine, feces, tears can become brown/orange in colour (harmless but could permanently stain soft contact lenses or dentures), drug-induced hepatitis † and/or hyperbilirubinemia</td>
<td>leukopenias, thrombocytopenia, uveitis (eye pain, change in vision, or sensitivity to light), arthralgias</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>rash, itching, nausea/vomiting †, diarrhea, dizziness, conjunctivitis, saliva, sweat, urine, feces, tears can become orange/red in colour (harmless but could permanently stain soft contact lenses or dentures), drug-induced hepatitis † and/or hyperbilirubinemia</td>
<td>hypersensitivity reactions (flu-like symptoms), angioedema, hypotension or shock, shortness of breath, bronchospasm, wheezing, neutropenia, platelet disorders</td>
</tr>
</tbody>
</table>

† Symptoms can include anorexia (loss of appetite), nausea and/or vomiting, abdominal discomfort (especially over right upper quadrant), unexplained fatigue, dark-coloured urine, scleral icterus or jaundice.
Ψ Can also be a symptom of drug-induced hepatitis.
▲ Liquid preparations containing sorbitol may be associated with diarrhea.
Φ There are a number of important drug interactions associated with rifamycins. Refer to Micromedex or Lexicomp.
6.5.1 Drug-Drug Interactions

Refer to Section 5.6.1

6.6 Client Education

Refer to Section 5.8.1

6.7 Drug Supplies

Refer to Section 5.8.3

6.8 Baseline Testing

6.8.1 Blood Testing

Refer to Table 6-4 for routine baseline blood testing requirements for clients taking rifampin or rifabutin, to Table 6-5 for clients taking isoniazid and to Table 6-6 for clients taking rifapentine.

Baseline blood testing for clients less than 16 years of age taking rifampin or isoniazid is generally not required unless there is risk for liver toxicity (e.g., those with pre-existing liver disease or taking concurrent hepatotoxic medications). Baseline blood testing is required for all clients taking both isoniazid and rifapentine.

Baseline blood tests should be completed prior to LTBI treatment requests being submitted to TB Services (see Section 6.2). Additional blood tests and/or alternate treatment regimens may be recommended by the client’s MRP or a TB Services physician.

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-existing liver disease, particularly Hepatitis C, or hepatitis B with abnormal transaminases in the past
- Daily alcohol consumption
- Concomitant use of other hepatotoxic drugs (e.g., methotrexate)

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. See Section 5.9.2 for guidelines for monitoring AST levels.
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 Table 6-4, Table 6-5 and Table 6-6 for monitoring recommendations.

6.8.2 Weight

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

For clients less than 16 years of age, confirm the prescribed dose against the calculated weight-based dose at the time of treatment start (see Table 6-2). Consult TB Services clinicians prior to dispensing the initial supply of TB drugs or administering the initial DOPT dose when there appears to be discrepancies between the prescribed and recommended doses in Table 6-2.
## 6.9 Monitoring

Table 6-4: Rifampin or rifabutin- Summary of baseline testing and ongoing monitoring for clients taking rifampin or rifabutin for LTBI treatment

<table>
<thead>
<tr>
<th>Actions</th>
<th>Baseline</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
<th>Month 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical evaluation Ω</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical assessment ▲</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherence assessment</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Chest x-ray Θ</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight§</td>
<td>✓</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Note:** Indicated for clients with liver toxicity, thrombocytopenia and/or signs/symptoms of TB or for clients who require chest x-ray at treatment completion.

### Actions
- Medical evaluation: Defined as a physical examination and investigation of liver transaminase values and bilirubin levels by the MRP.
- Clinical assessment: For clients taking rifabutin, monitor for eye pain and/or changes in vision.
- Chest x-ray: A CXR done within the last 6 months may be used for baseline assessment, unless the client is immune compromised, then a CXR within the last 3 months is required.
- Any age with risk factors for drug-induced hepatitis: Generally only required for clients with TB-related abnormalities noted on their initial chest x-rays.

### Monitoring
- Baseline weights are required for all LTBI clients.
- Total Bilirubin and CBC results are to be managed by the MRP. Forward abnormal results to TB Services.
- See Section 5.9.1
### Table 6-5: Isoniazid - Summary of baseline testing and ongoing monitoring for clients taking isoniazid for LTBI treatment

<table>
<thead>
<tr>
<th>Actions</th>
<th>Baseline</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
<th>Month 4</th>
<th>Month 5</th>
<th>Month 6</th>
<th>Month 7</th>
<th>Month 8</th>
<th>Month 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical evaluation Ω</td>
<td>✔</td>
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<tr>
<td>NOTE: Indicated for clients with liver toxicity and/or signs/symptoms of TB or for clients who require chest x-ray at treatment completion.</td>
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<tr>
<td>Clinical assessment</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Adherence assessment</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Chest x-ray ❋</td>
<td>✔</td>
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<tr>
<td>**Defined as a physical examination and investigation of liver transaminase values and bilirubin levels by the MRP.</td>
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<tr>
<td>Weight §</td>
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<tr>
<td>Monthly monitoring of weight for clients &lt; 5 years old.</td>
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<tr>
<td>AST (NOTE: Testing of clients under 16 is only indicated when recommended by TB Services)</td>
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<tr>
<td>16 to 34</td>
<td>✔</td>
<td>✔</td>
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<td></td>
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<tr>
<td>35 to 50</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Any age with risk factors for drug-induced hepatitis Ψ</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<td>ψ Defined as a physical examination and investigation of liver transaminase values and bilirubin levels by the MRP.</td>
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<td>** Generally only required for clients with TB-related abnormalities noted on their initial chest x-rays.</td>
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<td>❋ A CXR done within the last 6 months may be used for baseline assessment, unless the client is immune compromised, then a CXR within the last 3 months is required.</td>
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<td>§ Baseline weights are required for all LTBI clients.</td>
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<td>Ψ See Section 5.9.1.</td>
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### Table 6-6: Isoniazid and rifapentine - Summary of baseline testing and ongoing monitoring for clients taking isoniazid and rifapentine for LTBI treatment

<table>
<thead>
<tr>
<th>Actions</th>
<th>Baseline</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
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<tr>
<td>Medical evaluation Ω</td>
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<td>If needed, NOTE: Indicated for clients with liver toxicity, thrombocytopenia, and/or signs/symptoms of TB or for clients who require chest x-ray at treatment completion.</td>
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<td>Clinical assessment</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
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<td>Adherence assessment</td>
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<td>Chest x-ray Ø</td>
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<td>Weight §</td>
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<td>Monthly monitoring of weight for clients &lt; 5 years old.</td>
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<td>Bloodwork: AST, Total Bilirubin &amp; CBC Φ</td>
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<td>Φ Total Bilirubin and CBC results to be managed by the MRP. Forward abnormal results to TB Services.</td>
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6.9.1 Side Effects / Adverse Reactions and Drug-Drug Interactions

Common and/or important side effects and adverse reactions associated with isoniazid, rifabutin, rifampin and rifapentine are described in Table 6-3.

Question clients (or their parents/guardians) about side effects/adverse reactions and current medication use at least monthly during self-administered treatment (i.e. with each TB drug supply refill). Question clients on DOPT prior to each dose.

Place emphasis on identifying signs/symptoms of hepatotoxicity (see Section 5.9.1).

Ensure TB Services and BCCDC Vaccine and Pharmacy Services are notified of any new or changes to prescriptions, over-the-counter medications, or alternative/recreational therapies prior to initiating therapy.

Consult TB Services and/or the client’s primary care provider immediately when potential adverse reactions to LTBI treatment are identified. In some circumstances, it may be necessary to temporarily hold treatment until the client can be assessed by a physician/NP and/or undergo blood testing.

6.9.2 Blood Testing

Refer to Table 6-4 for routine blood testing requirements for clients taking rifampin or rifabutin, Table 6-5 for clients taking isoniazid, and Table 6-6 for clients taking isoniazid and rifapentine. Additional and/or more frequent blood testing may be requested for some clients based on:

- Results from baseline (and subsequent) blood tests.
- TB drugs included in the treatment regimen (i.e. when alternate LTBI treatment regimens are used).
- 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 or symptoms of hepatotoxicity).

Consult with TB Services when there is uncertainty about testing requirements for individual clients. See Section 5.9.2 for guidelines for monitoring AST levels.

6.9.3 Weight

Weigh clients under five years of age monthly to ensure appropriate dosing is maintained.

Practitioner Alert!

Report weight loss or failure to gain weight in growing children during TB treatment to TB Services as this may be a sign of progression to active TB disease.

6.9.4 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.
Asking clients on self-administered treatment about their adherence and encouraging clients to bring medications to each visit provides opportunities to offer support/suggestions for maintaining or improving adherence. When monitoring adherence, it is important to ensure a client-centred approach, assess barriers to adherence, offer close follow-up with frequent reminders of the importance of therapy and provide consistent encouragement to complete therapy.

Practitioners should document adherence information monthly in the client record and on the TB Medication Reorder Form. This form should be faxed to TB Services bi-monthly and upon treatment completion to ensure adequate adherence information is documented in Panorama. Refer to Section 6.11 for information on directly observed preventive treatment (DOPT) to support adherence.

Management of Non-Adherence to LTBI Treatment

Clients (or their parents/guardians) have the right to refuse or to discontinue LTBI treatment. Providers may find it helpful to consult with 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 6.14.

6.10 Management of Adverse Reactions to LTBI Treatment

Adverse reactions to LTBI treatment can range from mild fatigue or subtle, asymptomatic, and transient elevations in liver enzymes to acute liver failure. Comprehensive information on the management of all potential adverse reactions to TB treatment is beyond the scope of this document. TB Services should be consulted when issues of adverse events arise.

Health care professionals:
An adverse reaction is a noxious and unintended effect to a health product. HCPs should report adverse reactions to medications to the Canada Vigilance Program of Health Canada [7].

Hospitals: mandatory reporting of serious adverse drug reactions
A serious adverse reaction is defined in general terms as one which requires hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death. Adverse reactions that require significant medical intervention to prevent one of these outcomes are also considered to be serious (7).

On December 16, 2019, there will be new mandatory reporting requirements for hospitals. The mandatory reporting requirement applies to the facility (hospital) rather than individual health care professionals working in the hospital. For more information, see the Mandatory reporting of serious adverse drug reactions.
6.11 Supporting Adherence to LTBI Treatment – Directly Observed Preventive Treatment (DOPT)

Directly observed preventative treatment (DOPT) may be recommended to support adherence to LTBI treatment in some situations. All intermittent dosing must be DOPT by a health care provider or trained lay worker.

Daily DOPT can be given Monday to Friday. Doses for self-administration on weekends and statutory holidays (‘carries’) are recommended, and may be given at the discretion of health care providers once confirmed with TB Services. For clients prescribed DOPT, self-administered doses do not count towards the number of doses required to complete treatment. The Record of Supervised TB Medication form may be used to document adherence.

6.12 LTBI Treatment Completion

Where there have been periods when treatment was not taken (e.g., due to side effects or non-adherence), the duration of treatment is generally extended until treatment reaches the required number of doses. For example, in some situations, clients may be given up to 12 months to complete nine months’ worth of LTBI treatment with isoniazid, up to 6 months to complete 4 months’ worth of LTBI treatment with rifampin and up to 16 weeks to complete 12 weeks of isoniazid and rifapentine treatment. Where there was an extended break in treatment, TB Services may recommend treatment be restarted from the beginning.

Completion of treatment for clients on DOPT is achieved once all prescribed doses have been observed as taken. See Section 6.3 for total number of doses and recommended timelines for the completion of LTBI therapies.

Consult TB Services prior to dispensing the last month of medications to the client, to review the total number of doses taken, adherence, need for any further follow-up (e.g., chest x-ray) and to confirm when treatment can be stopped. An exit chest x-ray is generally required if the initial chest x-ray is abnormal, or may be required upon recommendation by a TB Services physician, as indicated in a prior narrative.

Health care providers are responsible for completing the Treatment Completion Form at the end of treatment and faxing it to TB Services or ensuring the appropriate details, such as treatment start/end dates; major mode of treatment; adherence; and if indicated, reason treatment not completed; are documented in Panorama. This information supports effective client care and provides surveillance and epidemiological data for program evaluation.
6.13 Follow-up after Completion of LTBI Treatment

Routine follow-up after completion of LTBI treatment is generally not required, but will be outlined in prior narratives provided by a TB Services physician if recommended. Exceptions can include contacts to source cases with multi-drug resistant TB disease and clients with significant immune-suppression.

Clients, who have completed LTBI treatment and/or their families, should be reminded to promptly seek evaluation should any TB signs/symptoms occur in the future. They should be advised NOT to have TST or IGRA in future evaluations. When TB screening is required (e.g., for work or school) a risk assessment including evaluation of TB signs/symptoms and TB risk factors is completed. Further TB screening tests will depend on results of risk assessment and reason for screening (see Section 4.3).

6.14 Management of Clients with LTBI that Decline or Cannot Take Treatment, or Discontinue LTBI Treatment Prior to Completion

Certain clients with LTBI who decline or cannot take treatment, or who discontinue treatment prior to completion will be followed for a period of two years from the time of diagnosis. Examples include:

- TST-positive or IGRA-reactive contacts.
- Clients with specific chest x-ray findings consistent with prior TB (e.g., granulomas, fibronodular changes, fibrocalcific scarring).
- Recent contacts (e.g., within past two years) with HIV infection or immune suppressive treatment who received recommendations for LTBI treatment but did not take or complete.
- Recent TST conversions.

For clients that decline LTBI therapy, health care providers should document this decision in their clinical record and/or submit the Treatment Initiation Form to TB Services indicating their client’s decision.

Follow-up recommendations will be noted in a TB Services physician narrative, and typically includes assessments for TB signs/symptoms and chest x-rays every six months for two years. An updated TB Screening form can be used as a chest x-ray requisition on subsequent visits to ensure that TB Services receives a copy of the report. Please note on the form that the client is on radiological surveillance.

For clients found to have TB signs/symptoms or chest x-ray results suggestive of or consistent with active TB disease at reassessment, see Section 4(b) Symptomatic Screening.

Clients with untreated (or partially treated) LTBI remain at risk for development of active TB disease. Provide these clients with information on:

- 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 the risks/benefits of LTBI treatment should their health status/immune function become compromised in the future.
- When appropriate, counsel clients 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).
6.15 Treatment of LTBI during Pregnancy or Breastfeeding

LTBI treatment is usually deferred for pregnant women until at least three months post-partum unless they are at very high risk for active TB disease development (e.g., contacts with HIV infection). When treatment is not deferred, enhanced monitoring for drug-induced hepatotoxicity is required. See Table 6-4 (rifampin) and Table 6-5 (isoniazid).

Very small amounts of maternal doses of TB drugs are excreted in breast milk. The amount is not sufficient to produce toxic effects in breastfeeding children, nor is it adequate for treating active TB disease, or preventing active TB disease in children with LTBI. Information on the effects of TB drugs in breastfed children is available from the Drugs and Lactation Database (LactMed).

6.16 Management of Clients with Presumed Drug-Resistant LTBI

LTBI treatment regimens for clients infected with presumed drug-resistant TB bacteria are individualized based on which TB medications are likely to provide effective treatment. For clients exposed to an infectious drug-resistant source case, the LTBI treatment regimen is based on the source case’s drug susceptibility test results.

Duration of LTBI treatment is determined by how long it takes for the client to complete the prescribed number of months of treatment (or doses) (see Section 6.11).

Clients who have completed LTBI treatment should be reminded to promptly seek evaluation should any TB signs/symptoms occur in the future. Periodic follow-up after completion of treatment for presumed drug-resistant LTBI may be recommended in some situations (e.g., clients with abnormal baseline chest x-rays or intermittent adherence, contacts to infectious multi-drug resistant TB disease).

Manage clients as described in Section 6.14 when treatment is not taken, or started but not completed. For clients who are contacts to drug resistant source cases, see Section 8.8.
6.17 Isoniazid Overdose

**Practitioner Alert!**

Isoniazid overdose can be fatal.

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.

**Should an overdose of isoniazid occur, call the 24-hour line at the BC Drug and Poison Information Centre (DPIC) to speak to a Poison Information Specialist.**

**BC Lower Mainland:** (604) 682-5050

**Outside BC Lower Mainland (toll-free):** 1-800-567-8911

**Telephone interpreting is available in over 150 languages.**
If the client is unconscious, or having a seizure, difficulty breathing or chest pain, immediately call 9-1-1. In an acute situation where prompt referral to an Emergency Department (ED) is needed, consulting with DPIC will initiate a process in which DPIC will contact the ED and provide information to facilitate appropriate care for the client when s/he arrives.

Remote dispensing locations should ensure pyridoxine, the antidote for isoniazid poisoning, is available. For stocking recommendations, see the [Antidote Stocking Guidelines for BC Hospitals](#) and call DPIC for further information.
REFERENCES


