Communicable Disease Control Manual
Chapter 4: Tuberculosis

Section 6: TB Preventive Treatment
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6.0 TB PREVENTIVE TREATMENT

TB preventive treatment (TPT) can prevent development of TB disease for those with TB infection. In BC, an emphasis is placed on offering TPT for people at higher risk for progressing to TB disease. This includes:

- People diagnosed with TB infection within the previous two years such as close contacts to infectious cases and people with demonstrated TST conversions or new positive IGRA. The development of TB disease occurs with greatest frequency in the first 2 years after infection with 50% of the total lifetime risk of reactivation occurring in this period.
- Contacts under 5 years of age and those with untreated HIV requiring presumptive TPT, also known as window period prophylaxis (see Section 8).
- Newcomers from a country with a high TB incidence
- Those with TB infection and medical risk factors (see TB DST - Table 2) which impact their immune status or lung health, including but not limited to:
  - HIV infection
  - Silicosis
  - Chronic kidney disease on dialysis or end-stage
  - Solid organ or hematopoietic transplant recipient
  - Fibronodular disease
  - Receiving treatment with TNF alpha inhibitors and/or other immune suppressing drugs/therapies such as chemotherapy or systemic steroid treatments equivalent to 15 mg per day or more for 1 month or longer
  - Abnormal chest x-ray (e.g., granuloma, fibronodular or fibrocalcific disease)
  - Cancer (lung, sarcoma, leukemia, lymphoma or gastrointestinal)

Unlike treatment of TB disease, treatment of TB infection is voluntary. Clients, or their parents/guardians, may decline treatment or elect to discontinue treatment at any time. For clients with untreated TB infection and ongoing risk for developing TB disease, revisiting TPT should be a part of their care plan. In BC, short, safe and effective regimens are available.

It is essential that TB disease be ruled out before TPT is initiated. TPT may include a single anti-TB drug (monotherapy) or a combination regimen may be an option for some clients (see Section 6.1). Treating for TB infection in the presence of 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 respiratory TB disease.
6.1 Overview

Recommendations for TPT regimens are individualized to ensure the benefit (prevention of 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 (e.g., worsening diabetic control, increase opioid needs, change in anticoagulation).
- **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 of infection with a drug-resistant strain of TB bacteria. For example, contacts of cases with rifampin-resistant TB disease would likely be treated with isoniazid instead of rifampin and vice-versa.
- **Adherence**: shorter course regimens are now available as first-line therapy to support completion of TPT. Also, directly observed preventive treatment (DOPT) may be recommended to improve adherence (see Section 6.11).
- **Alignment with co-morbidity care plan**: shorter course regimens may be prescribed to support completion of TPT in a timely manner to facilitate moving forward with other medical care (e.g., organ transplant, TNF-alpha inhibitor therapy). See Section 6.14 TPT in Select Populations.

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. Additionally, for families making decisions about TPT for children, the total pill burden and availability of liquid suspensions; need for treatment support and available local public or community health supports are important considerations (1).

Refer to Section 8 for information on management of contacts taking window period prophylaxis (WPP).
6.2 Procedure for Initiation of TB Preventive Treatment

Figure 6-1, Flowchart for initiation of TPT

Local HCP sends TB Screening notification with TST/IGRA results and CXR to TBS.

TBS reviews clinical information and provides recommendations on treatment, monitoring requirements and/or further follow-up. Sends recommendations to local HCP. (E.g. CD Unit, PHN, CHN, GP, NP)

TPT recommended

Local HCP and client discuss TBS recommendations and client makes decision.

TPT accepted

CXR surveillance and/or signs and symptoms monitoring might be recommended.

TPT NOT recommended

Revisit TPT with client at subsequent visit.

Local HCP orders baseline bloodwork including: AST, bilirubin, CBC (see Sections 6.8 and 6.9). TB Treatment Initiation request sent to TBS, including ALL of the following: client consent, current CXR results*, baseline blood test results♦, allergies, prescription and over-the-counter medications and weight.

TBS reviews information, writes prescription, and sends to BCCDC Pharmacy. Notification sent to local HCP dispensing and monitoring treatment. One or two month supply of TB medications shipped by BCCDC Pharmacy to local HCP dispensing and monitoring treatment.†

Local HCP:
- Prior to dispensing first dose or supply of TB medication, consult with TBS when (1) baseline blood test results are abnormal or beyond recommended timeframe for use AND/OR (2) client’s current weight does not correspond to prescription dosage (see Table 6-1).
- Educate client on potential side effects/adverse reactions associated with the regimen prescribed.
- Follow guidelines for abnormal AST results and CBC results and consult with TBS as indicated (Section 6.8).
- MRP manages CBC results and other blood tests if abnormal. Local HCP notify TBS as indicated (Section 6.8).
- Advise client to contact PHN/CHN immediately if there are any adverse reactions. PHN/CHN consult with TBS and/or the client’s MRP for further direction.

For client’s on self-administered therapy: dispense one-month supply of TB medications to client, along with a requisition for repeat blood tests. If TBS recommends end of treatment CXR, ensure requisition provided prior to dispensing last month or weekly supply of TB drugs (see Section 6.11). Confirm date and time of next appointment.

For client’s on Directly Observed Preventive Treatment: administer initial dose. Confirm plan for next scheduled doseΩ.

Complete the TB Medication Reorder Form and submit to TBS promptly after second month supply of TB medications has been started.

* A CXR completed within the last six months is valid.
♦ Blood work results completed in the past six months may be used provided they are within normal limits and the client does not have any risk factors for hepatotoxicity (see Section 6.8).
† Standard supplies are provided in vials. Blister packaging is available if requested and if adherence is a concern for treatment.
Ω Doses for self-administration on weekends and statutory holidays (‘carries’) are encouraged, and may be given at the discretion of the HCP once confirmed with TBS.
6.3 Recommended TB Preventive Treatment Regimens

There are medical and client considerations to review to determine the best TPT option for clients (Section 6.1). Additionally, alternate TPT regimens are used for clients likely infected with drug-resistant TB bacteria (see Section 6.14.1). The actual duration of TPT is determined by how long it takes for the client to complete the prescribed number of doses (see Table 6.1).

TB preventive therapy recommendations in BC:

First-line regimens:
- 4 months daily, self-administered (or daily directly observed) rifampin (4R)
- 12 doses, once weekly, directly observed isoniazid/rifapentine (3HP).
  - Supplemental pyridoxine (vitamin B6) 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.
  - Not recommended for children less than 2 years of age; people living with HIV taking antiretroviral treatment with unacceptable drug interactions with rifapentine; clients with drug interactions (e.g., 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.

Alternative regimen:
- 9 months daily, self-administered isoniazid (9H)
  - Supplemental pyridoxine (vitamin B6) 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 neuropathies¹.
- 9 months, twice weekly, directly observed isoniazid (if other options not feasible or contraindicated).

Table 6-1: Number of doses required to complete TPT treatment regimens

<table>
<thead>
<tr>
<th>Medications</th>
<th>Dosing Frequency</th>
<th>Required number of doses to complete TPT</th>
<th>Acceptable Timeframe to complete TPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>Once daily for 4 months</td>
<td>120 doses</td>
<td>Up to 6 months</td>
</tr>
<tr>
<td>Isoniazid and Rifapentine</td>
<td>Once weekly for 12 weeks</td>
<td>12 doses, directly observed</td>
<td>Up to 16 weeks</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Once daily for 9 months</td>
<td>270 doses</td>
<td>Up to 12 months</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Twice weekly for 9 months *</td>
<td>76 doses, directly observed</td>
<td></td>
</tr>
</tbody>
</table>

* Twice weekly directly-observed isoniazid should only be used if daily self-administered regimens or the isoniazid/rifapentine regimens are not feasible or successful.

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

#### Table 6-2: Summary of drugs and dosing for TB preventive treatment regimens (2–6)

<table>
<thead>
<tr>
<th>Medication *</th>
<th>Formulations</th>
<th>Daily Dose</th>
<th>Twice Weekly Dose</th>
<th>Once-Weekly Combination of Rifapentine and Isoniazid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rifampin</strong></td>
<td>Capsules (PO): 150 mg or 300 mg</td>
<td>Child: 15 mg/kg (10-20 mg/kg) Maximum: 600 mg</td>
<td>Adult: 10 mg/kg Maximum: 600 mg</td>
<td>50 kg or more = 900 mg (Maximum) 32.1-49.9 kg = 750 mg 25.1-32.0 kg = 600 mg 14.1-25.0 kg = 450 mg 10.0-14.0 kg = 300 mg</td>
</tr>
<tr>
<td></td>
<td>Injection† (IV): 600 mg reconstituted = 60 mg per mL Powder requires reconstitution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rifapentine</strong></td>
<td>Tablets (PO): 150 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tablets (PO): 100 mg or 300 mg Syrup (PO): 10 mg/mL Injection* (IM): 100 mg per mL</td>
<td>10 mg/kg (10-15 mg/kg) Maximum: 300 mg</td>
<td>5 mg/kg Maximum: 300 mg 20-30 mg/kg Maximum: 900 mg 15 mg/kg Maximum: 900 mg</td>
<td>25 mg/kg in clients 2 to 11 years 15 mg/kg in clients 12 years or older (rounded to the nearest 50 mg or 100 mg) Maximum: 900 mg</td>
</tr>
<tr>
<td><strong>Isoniazid</strong></td>
<td>Tablets (PO): 100 mg or 300 mg</td>
<td>10 mg/kg (10-15 mg/kg) Maximum: 300 mg</td>
<td>5 mg/kg Maximum: 300 mg 20-30 mg/kg Maximum: 900 mg 15 mg/kg Maximum: 900 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Syrup (PO): 10 mg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vitamin B6 § (pyridoxine)</strong></td>
<td>Tablets (PO): 25 mg or 100 mg</td>
<td>As indicated ø</td>
<td>25 mg</td>
<td>50 mg</td>
</tr>
</tbody>
</table>

---

* Rifabutin (capsules) is an option in special circumstances but rarely used. Dosing varies based on client’s other medications.

† Formulas are available for compounding oral capsules into liquid suspension.

‡ Available through Health Canada’s Special Access Program.

Ω Rifapentine tablets may be crushed and mixed with semi-solid food and given within 30 minutes to children who are not able to swallow pills.

§ Given as an adjunct to isoniazid.

Ø Breast/chest-fed infants; children with nutritionally deficient diets (including meat and/or milk deficiencies).
6.5 Drug Side Effects / Adverse Reactions, Drug-Drug Interactions

Contact BCCDC Provincial TB Services (TBS) and/or the Most Responsible Provider (MRP) immediately with concerns about TB drug side effects or adverse reactions (Table 6-3).

The first-line TPT regimens include drugs from the rifamycin family, however, rifampin and rifapentine are not interchangeable (7). It is important to note that there are a number of important drug interactions associated with rifamycins. Refer to clinical drug interaction databases (e.g., Micromedex, Lexicomp), the Rifamycin Drug-Drug Interactions – A Guide for Primary Care Providers Treating Latent Tuberculosis Infection, and Section 5 for further guidance on drug interactions.

Table 6-3: Drugs included in TB preventive treatment regimens and associated side effects (4,8)

<table>
<thead>
<tr>
<th>TB drug</th>
<th>Side effects or adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Uncommon but Important</td>
</tr>
<tr>
<td>Rifampin</td>
<td>rash and/or itching</td>
</tr>
<tr>
<td></td>
<td>nausea/vomiting*</td>
</tr>
<tr>
<td></td>
<td>diarrhea*</td>
</tr>
<tr>
<td></td>
<td>dizziness</td>
</tr>
<tr>
<td></td>
<td>discoloration† of saliva, sputum, sweat, urine, feces, tears and teeth</td>
</tr>
<tr>
<td></td>
<td>drug-induced hepatitis† and/or hyperbilirubinemia</td>
</tr>
<tr>
<td></td>
<td>flushing and itching of face, with/without rash (self-limiting)</td>
</tr>
<tr>
<td></td>
<td>flu-like illness with fever</td>
</tr>
<tr>
<td></td>
<td>decreased blood pressure</td>
</tr>
<tr>
<td></td>
<td>leukopenia</td>
</tr>
<tr>
<td></td>
<td>thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>acute interstitial nephritis</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>rash, itching</td>
</tr>
<tr>
<td></td>
<td>nausea/vomiting*</td>
</tr>
<tr>
<td></td>
<td>diarrhea</td>
</tr>
<tr>
<td></td>
<td>dizziness</td>
</tr>
<tr>
<td></td>
<td>headache</td>
</tr>
<tr>
<td></td>
<td>conjunctivitis</td>
</tr>
<tr>
<td></td>
<td>discoloration† of saliva, sputum, sweat, urine, feces, tears and teeth</td>
</tr>
<tr>
<td></td>
<td>drug-induced hepatitis† and/or hyperbilirubinemia</td>
</tr>
<tr>
<td></td>
<td>-hypersensitivity reactions (flu-like symptoms)</td>
</tr>
<tr>
<td></td>
<td>-angioedema, hypotension or shock</td>
</tr>
<tr>
<td></td>
<td>-shortness of breath, bronchospasm, wheezing</td>
</tr>
<tr>
<td></td>
<td>neutropenia</td>
</tr>
<tr>
<td></td>
<td>platelet disorders</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>rash</td>
</tr>
<tr>
<td></td>
<td>drug-induced hepatitis†</td>
</tr>
<tr>
<td></td>
<td>peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td>nausea/vomiting*</td>
</tr>
<tr>
<td></td>
<td>fatigue, drowsiness*</td>
</tr>
<tr>
<td></td>
<td>diarrhea</td>
</tr>
<tr>
<td></td>
<td>flushing reaction with tyramine or histamine-containing foods</td>
</tr>
<tr>
<td></td>
<td>central nervous system toxicity</td>
</tr>
<tr>
<td></td>
<td>anemia</td>
</tr>
<tr>
<td></td>
<td>headache</td>
</tr>
<tr>
<td></td>
<td>mild hair loss</td>
</tr>
<tr>
<td></td>
<td>acne</td>
</tr>
<tr>
<td>Rifabutin §</td>
<td>rash</td>
</tr>
<tr>
<td></td>
<td>nausea*</td>
</tr>
<tr>
<td></td>
<td>diarrhea</td>
</tr>
<tr>
<td></td>
<td>taste disturbances</td>
</tr>
<tr>
<td></td>
<td>discoloration† of saliva, sputum, sweat, urine, feces, tears and teeth</td>
</tr>
<tr>
<td></td>
<td>drug-induced hepatitis† and/or hyperbilirubinemia</td>
</tr>
<tr>
<td></td>
<td>leukopenia</td>
</tr>
<tr>
<td></td>
<td>thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>uveitis Ø</td>
</tr>
<tr>
<td></td>
<td>arthralgia</td>
</tr>
</tbody>
</table>

* Side effect can also be a symptom of drug-induced hepatitis.
† Liquid preparations containing sorbitol may be associated with diarrhea.
‡ Harmsless brown/orange discoloration may occur. This could permanently stain soft contact lenses or dentures.
Ω 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.
§ Rifabutin (capsules) is an option in special circumstances but rarely used.
Ø Eye pain, change in vision, or sensitivity to light.
6.6 Client Education
Refer to Section 5 - Client Education

6.7 Drug Supplies
The BCCDC Pharmacy provides all routine TB medications in BC without cost to the client. If a Health Care Provider (HCP) determines that a client is on TPT with medications dispensed by a local pharmacy or other external source, the HCP should notify TBS to facilitate medication distribution from BCCDC Pharmacy.

Follow your agency’s policy or process for ordering TB medications. Some areas use the TB Medication Adherence and Reorder Form. For further details, refer to Section 5 - Drug Supplies.

6.8 Baseline and Ongoing Testing and Monitoring
Baseline testing of blood work and weight is routine for most clients taking TPT as well as ongoing monitoring of medication side effects and other adverse reactions for all clients.

Blood Testing
- Table 6-5 for routine baseline and ongoing blood testing requirements for clients taking rifampin or rifabutin.
- Table 6-6 for clients taking rifapentine.
- Table 6-7 for clients taking isoniazid.

Baseline blood testing
- Generally not required for clients less than 16 years of age taking rifampin or isoniazid is unless there is risk for liver toxicity (e.g., those with pre-existing liver disease or taking concurrent hepatotoxic medications).
- Required for all clients taking both isoniazid and rifapentine.
- Complete prior to TPT requests being submitted to TBS (see Section 6.2).

Additional and/or more frequent blood testing may be requested for some clients based on:
- Results from baseline (and subsequent) blood tests.
- The combination of TB drugs included in the treatment regimen (i.e. when alternate TPT regimens are used).
- Whether there is increased risk for adverse reactions related to co-morbidities and/or other treatments/drugs a client is taking (e.g., HCV, alcohol use).
- Whether the client reports potential side effects/adverse reactions (e.g., signs or symptoms of hepatotoxicity).

Consult with TBS when there is uncertainty about testing requirements for individual clients.
Monitoring

Recommendations for monitoring for hepatotoxicity
AST is the transaminase preferred by TBS 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 six 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)

HIV is not an independent risk for drug-induced hepatitis. 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 - Monitoring Treatment for guidelines for monitoring AST levels. See Table 6-5, Table 6-6 and Table 6-7 for TPT monitoring recommendations.

Recommendations for monitoring hematology
A complete blood count (CBC) is monitored for medication-induced adverse events such as rifampin-induced neutropenia or thrombocytopenia. Generally, clients are asymptomatic and changes in lab values may be identified when reviewing monthly blood work results (see Table 6-4).

Appropriate nursing assessment and CBC monitoring includes:

- a review of prior results (e.g., to identify trends such as if the current results are new, better, worse, or stable);
- an assessment of signs and symptoms including bleeding (nose bleeds, bruising), petechial rash or fever;
- a review of other or new medications/conditions that could contribute to any changes in lab values.

Following completion of the nursing assessment, consult as appropriate:

- MRP – CBC results are managed by the local MRP. Although TB medications may cause abnormal hematology results, many clients on TPT have co-morbid conditions and/or other medications that can also affect their hematology results (e.g., chemotherapy, transplant).
- TBS – If the MRP recommends holding a dose of TPT to manage abnormal hematology results, consult TBS. If TPT is interrupted, it is important to ensure a plan is in place to determine when it is safe to restart treatment.
- Emergency - Send client to emergency department and notify MRP and TBS if:
  - Fever with Neutrophils count of $1.5 \times 10^9/L$
  - Bleeding with Platelets count of $50 \times 10^9/L$
Table 6-4: CBC Grading Severity and Management Guideline

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Range*</th>
<th>Grade 1</th>
<th>Grade 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>4.0-11.0 x 10^9/L</td>
<td>3.0 x 10^9/L or more and less than LLN*</td>
<td>Less than 3.0 x 10^9/L</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>135-170 g/L</td>
<td>90 g/L or more and less than LLN* or 10% to 25% drop from pre-treatment</td>
<td>Less than 90 g/L or 25% or more drop from pre-treatment</td>
</tr>
<tr>
<td>Platelets</td>
<td>150-400 x 10^9/L</td>
<td>75.0 x 10^9/L or more and less than LLN*</td>
<td>Less than 75.0 x 10^9/L or 50% or more drop from pre-treatment</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>2.0-8.0 x 10^9/L</td>
<td>1.5 x 10^9/L or more and less than LLN*</td>
<td>Less than 1.5 x 10^9/L</td>
</tr>
</tbody>
</table>

Grade 1 Management

An assessment of signs and symptoms includes bleeding (nose bleeds, bruising), petechial rash or fever

Complete a nursing assessment
- Consult MRP
- Follow MRP recommendations (e.g. continue to closely monitor; repeat blood work)
- Consult TBS if MRP recommends interruption in TPT

Complete a nursing assessment

IF an emergency, defined by:
- Fever with Neutrophil count of 1.5 x 10^9/L or less
- Bleeding with Platelet count of 50 x 10^9/L or less

Send client to emergency department and notify MRP and TBS

IF no emergency:
- Consult MRP in one to two business days
- Follow MRP recommendations
- Consult TBS if interruption in TPT

* Reference ranges vary depending on the laboratory assay used. Clinical decision-making should be based on ranges on lab report versus what is listed in this table.
♦ Lower limit of normal (LLN): Refers to the low-value of the reference range.

Practitioner Alert!

Neutropenic fever is an emergency. Cancer and cancer treatments are the most common causes of neutropenic fever (8). If your client is neutropenic (neutrophils less than 1.5 x 10^9/L) and has a fever (temperature over 38°C) direct them to go to their nearest emergency department.
Weight

Document weight at baseline for all clients starting TPT. Baseline weight is especially important for pediatric clients, whose dosages may need to be adjusted as they grow and gain weight. Weigh clients under five years of age monthly to ensure appropriate dosing is maintained.

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 TBS 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.

**Practitioner Alert!**

Report to TBS any weight loss or failure to gain weight in growing children receiving TPT, as this may be a sign of progression to TB disease.
Baseline and Ongoing Monitoring Tables

Table 6-5: Rifampin* - Summary of baseline testing and ongoing monitoring for clients

<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 *</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>If needed. NOTE: Indicated for clients with liver toxicity, thrombocytopenia and/or signs/symptoms of TB or for clients who require CXR at treatment completion.</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>CXR Ω</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>§</td>
</tr>
<tr>
<td>A CXR done within the last six months may be used for baseline assessment.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Ø</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>§</td>
</tr>
<tr>
<td>Monthly monitoring of weight for clients under 5 years of age.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**AST, Total Bilirubin Ψ, CBC Ψ Ø (NOTE: Testing of clients under 16 years of age is done as recommended by TBS)**

<table>
<thead>
<tr>
<th>Age Group</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>16 to 34 years</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35 to 50 years</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 years and older</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any age with risk factors for drug-induced hepatitis ^</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

* For client prescribed rifabutin, follow the same monitoring actions as rifampin.

† Defined as a physical examination and investigation of liver transaminase values and bilirubin levels by the MRP.

‡ For clients taking rifabutin, monitor for eye pain and/or changes in vision.

Ω A CXR done within the last six months may be used for baseline assessment.

§ Generally only required for clients with TB-related abnormalities noted on their initial CXR.

Ø Baseline weights are required for all clients starting TPT.

Ψ Total Bilirubin and CBC results to be managed by the MRP. Forward abnormal results to TBS. See Section 6.8 for CBC monitoring guidance.

^ See Section 5.
Table 6-6: Isoniazid and rifapentine - Summary of baseline testing and ongoing monitoring for clients

<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>
<th>Week 8</th>
<th>Week 9</th>
<th>Week 10</th>
<th>Week 11</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical evaluation ♦</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<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>
<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>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CXR †</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ω</td>
</tr>
<tr>
<td>Weight §</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloodwork: AST, Total</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin &amp; CBC</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

♦ Review flu-like symptoms prior to Week 3 and 4 doses since when this side effect occurs, it is most likely at this point in treatment. Reactions are usually mild and resolved within 24 hours.

† Defined as a physical examination and investigation of liver transaminase values and bilirubin levels by the MRP.

† A CXR done within the last six months may be used for baseline assessment.

Ω Generally, only required for clients with TB-related abnormalities noted on their initial CXR.

§ Baseline weights are required for all clients starting TPT.

Ø Total Bilirubin and CBC results to be managed by the MRP. Forward abnormal results to TBS. See Section 6.8 for CBC monitoring guidance.
### Table 6-7: Isoniazid - Summary of baseline testing and ongoing monitoring for clients (6)

<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 *</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td></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>
<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>CXR ♦</td>
<td></td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Weight Ω</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AST (NOTE: Testing of clients under 16 is only indicated when recommended by TBS)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 to 34</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>51 and older</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Any age with risk factors for drug-induced hepatitis §</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

* Defined as a physical examination and investigation of liver transaminase values and bilirubin levels by the MRP.

♦ A CXR done within the last 6 months may be used for baseline assessment.

† Generally only required for clients with TB-related abnormalities noted on their initial CXR.

Ω Baseline weights are required for all clients starting TPT.

§ See Section 5.
6.9 Evaluating for Side Effects / Adverse Reactions, Drug-Drug Interactions

Common and/or important side effects and adverse reactions associated with rifampin, rifabutin, rifapentine and isoniazid are described in Table 6-3. All rifamycin-based regimens have important drug-drug interactions, including but not limited to these categories: antihypertensives, anticoagulants, antifungals, methadone and other opioids, some immunosuppressive agents, hormonal contraceptives, and antiretrovirals.

Remind and ask clients (or their parents/guardians) about side effects/adverse reactions and current medication use at least monthly during self-administered therapy (SAT) (i.e. with each TB drug supply refill). Ask clients on Directly Observed Preventive Therapy (DOPT) prior to each dose. Place emphasis on identifying new or worsening signs/symptoms of hepatotoxicity (see Section 5). Ensure TBS and BCCDC Pharmacy are notified of any new or changes to prescriptions, over-the-counter medications, or alternative/recreational therapies prior to initiating or adjusting therapy.

Practitioner Alert!
Consult TBS and/or the client’s MRP immediately when potential adverse reactions to TPT are identified. In some circumstances, it may be necessary to temporarily stop treatment until the client can be assessed by an MRP, and/or undergo blood testing.

6.9.1 Management of Adverse Reactions to TB Preventive Treatment

Adverse reactions to TPT 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. TBS should be consulted when issues of adverse events arise.

Health care professionals (HCP):
An adverse reaction is a noxious and unintended effect to a health product. In BC, HCPs should report adverse reactions to medications via the BC Patient Safety and Learning System (BCPSLS), which reviews and forwards adverse drug reactions (ADR) to Health Canada on behalf of the health authorities (9).

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.

Mandatory reporting for hospitals is required under the Protecting Canadians from Unsafe Drugs Act, known as Vanessa’s Law (10). The mandatory reporting requirement applies to the facility (hospital) rather than individual health care professionals working in the hospital. For more information, go to BCPSLS Central, Vanessa’s Law. (9)
6.10 Adherence

TB medications must be taken as prescribed to be effective. Non-adherence to TPT can put clients at risk for developing TB disease. **Adherence to treatment in the first month strongly predicts treatment completion highlighting the importance of encouraging and facilitating adherence at the start of treatment.**

Practitioner Alert!

Consult TBS in a timely manner when adherence issues arise, as TPT may need to be extended or restarted to complete the required number of doses.

6.10.1 Supporting Adherence

Offering comprehensive, client-centred incentives and enablers should be provided during TPT to promote successful adherence and completion of treatment. When monitoring adherence, it is important to ensure:

- A client-centred approach.
- An assessment of barriers to adherence.
- Close follow-up with frequent reminders of the importance of therapy.
- Consistent encouragement to complete therapy.

Self-administered treatment (SAT)

Asking clients on SAT about their adherence and encouraging clients to bring medications to each visit provides opportunities to offer support/suggestions for maintaining or improving adherence.

Directly observed preventative treatment (DOPT)

May be recommended to support adherence to TPT in some situations whether it be people on short-course treatments such as a 12 week course of Isoniazid and Rifapentine or people requiring complex medical care. This may include but is not limited to people living with HIV, people experiencing homelessness or underhoused, people with substance use or mental health disorders and others with significant barriers to successful TPT completion.

Consideration of DOPT requires an informed discussion with the client to ensure autonomy and trust are maintained. Table 6-8 offers a summary of potential advantages and disadvantages of DOPT to help guide the conversation. Depending on local resources and policies, DOPT may be offered as community-based, facility-based or virtual. If DOPT is not a feasible option, a daily or regular supportive care plan tailored to the client’s needs should be developed.

All intermittent dosing must be DOPT by a HCP or trained lay worker.

Daily DOPT can be given Monday to Friday. Doses for SAT on weekends and statutory holidays (‘carries’) are recommended, and may be given at the discretion of HCP once confirmed with TBS. Additionally, observing one dose of a weekly dosette is not DOPT rather, this is supportive therapy.
Table 6-8: Potential advantages and disadvantages of providing directly observed preventive treatment (DOPT) (2)

<table>
<thead>
<tr>
<th>Potential advantages of DOPT</th>
<th>Potential disadvantages of DOPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Allows for clients to ask questions to providers with each dose</td>
<td>• Requires substantial additional healthcare worker time</td>
</tr>
<tr>
<td>• Allows providers more frequent opportunities to detect potential adverse effects and to detect them earlier, which may enhance safety</td>
<td>• Less convenient for clients</td>
</tr>
<tr>
<td>• Increased treatment completion rates</td>
<td>• Less flexibility in timing of doses</td>
</tr>
<tr>
<td>• Ensures treatment is going according to plan</td>
<td>• Clients may perceive DOPT as an infringement on their autonomy</td>
</tr>
<tr>
<td>• Allows the team to offer incentives and enablers when barriers identified, so that clients can achieve improved adherence</td>
<td></td>
</tr>
<tr>
<td>• Allows for an opportunity for the healthcare team to identify others who might need testing in the client’s environment</td>
<td></td>
</tr>
</tbody>
</table>

6.10.2 Documenting Adherence
Regularly documenting adherence supports improved client outcomes. HCPs should document adherence information by doses (see Table 6-1) in the client record. The TB Medication Adherence and Reorder Form may be used in your area to support this process. Upon treatment completion, ensure accurate adherence information is documented in Panorama.

For clients prescribed DOPT, the Record of Supervised TB Medication form may be used to document adherence. If “carries” are provided on weekends, self-administered doses should be documented as SAT.

6.10.3 Management of Non-Adherence
Clients (or their parents/guardians) have the right to refuse or to discontinue TPT. Providers may find it helpful to consult with TBS and/or review the indications for TPT with the client. Exploring clients’ perceptions about TPT and adherence challenges can provide important insights for potential solutions (e.g., use of alternate regimens). In some scenarios, the timing of treatment may not work for the client. The option to reoffer TPT in the future (e.g., diabetes clinic, chemotherapy clinic) should be part of the client’s overall care plan. Manage clients whose TPT is discontinued prior to completion (either by their choice or on the recommendation of TBS) as described in Section 6.13.
6.11 TB Preventive Treatment Completion

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

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

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. See Table 6-1 for preferred and acceptable timeframes. When there is an extended break early in treatment, TBS may recommend treatment be restarted from the beginning.

Consult TBS prior to dispensing (SAT) or administering (DOPT) 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 CXR is generally required if the initial CXR is abnormal, or may be required upon recommendation by a TBS provider, as indicated in a prior narrative. Most persons completing TPT do not need an exit CXR.

HCPs are responsible for completing the Treatment Completion Form at the end of treatment and faxing it to TBS 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.

6.12 Follow-up after Completion of TB Preventive Treatment

Routine follow-up after completion of TPT is generally not required. Exceptions can include contacts to source cases with multi-drug resistant TB disease and clients with significant immune-suppression. A TBS provider will make such recommendations, as appropriate, in their narrative.

End of treatment counselling

Clients, who have completed TPT and/or their families, should be:

- Reminded to promptly seek evaluation should any TB signs/symptoms occur in the future.
- 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 should be completed.
- Advised that further TB screening tests (e.g., sputum or CXR) will depend on results of risk assessment and reason for screening (see Section 4(b) TB Screening DST).
6.13 Follow-up if TB Preventive Treatment Declined or Incomplete
For client’s that decline TPT, HCPs should document this decision in their clinical record and/or submit the Treatment Initiation Form to TBS indicating their decision.

Counselling for Clients with Declined or Incomplete TPT
Clients with untreated (or partially treated) TB infection remain at risk for development of TB disease. Provide these clients with information on:

- Risk for future development of TB disease.
- TB signs/symptoms, and the need to seek evaluation for TB disease promptly should TB signs/symptoms occur.
- The importance of re-evaluating the risks/benefits of TPT should their health status/immune function become compromised in the future.
- When appropriate, counsel clients to reconsider TPT, including trialing a different TPT regimen, if there is an opportunity to do so (e.g., when TB screening is sought in the future).

6.13.1 Follow-up of Contacts with Declined or Incomplete TPT
Contacts with TB infection 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 since they remain at risk for TB disease. For example:

- A TB contact with a documented new TST-positive or IGRA-reactive result should be offered symptom assessment and CXR every 6 months for 2 years after their last date of exposure. This scheduled follow-up allows for additional opportunities to discuss TPT.
- If at a follow-up visit, a client is found to have TB signs/symptoms or chest x-ray results suggestive of or consistent with TB disease refer to Section 4(b) TB DST, Symptomatic Screening.

6.14 TB Preventive Treatment in Select Populations

6.14.1 Clients with Presumed Drug-Resistant TB Infection
TPT 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 TPT regimen is based on the source case’s drug susceptibility test results.

Duration of TPT 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 TPT 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 TB infection 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 6.13 when treatment is not taken, or started but not completed. For clients who are contacts to drug resistant source cases, see Section 8.
6.14.2 Clients who are Pregnant or Breast/chest-feeding

TPT is usually deferred during pregnancy until at least three months postpartum unless a person is at very high risk for developing TB disease (e.g., a person of contact also with HIV infection). When treatment is not deferred due to the high risk of progression to active TB, four months of daily rifampin is the preferred option and enhanced monitoring for drug-induced hepatotoxicity is required. (See Table 6-5, rifampin). Isoniazid-based regimens should be avoided until 3 months postpartum in all but exceptional circumstances (e.g., a person of contact of a rifampin-resistant TB case who has a very high risk of reactivation). See Table 6-7 (isoniazid).

Very small amounts of TB drugs are excreted in breast/chest milk. The amount is not sufficient to produce toxic effects in breast/chest-feeding children, nor is it adequate for treating TB disease, or preventing TB disease in children with TB infection. Information on the effects of TB drugs in breast/chest-fed children is available from the Drugs and Lactation Database (LactMed).

6.14.3 Clients with specific co-morbidities

The BC Renal and BC Transplant programs work closely with TBS to determine appropriate screening and TPT regimens.

- For most transplant recipients, if possible, TPT should be completed prior to transplantation. If TPT is provided post-transplant, the person should receive 9-months of isoniazid due to the altered drug-drug interactions with rifamycins and risk for organ rejection.
- For clients with end-stage kidney disease, close monitoring of treatment is important due to the risk of drug-related adverse reactions in this population for all TPT regimens.
- For clients with end-stage liver disease, TPT is most often delayed until after transplant but discussion between TBS and the transplant team is strongly recommended to decide timing and regimen.

For people living with HIV (PLWH), some anti-retrovirals (ARVs) have significant drug-drug interactions with TPT regimens. An HIV specialist should be involved in determining the best TPT regimen.

Clients receiving ARVs for Hepatitis C can also have significant drug-drug interactions with rifamycin-based regimens. TPT will be managed on a case-by-case basis.

6.14.4 Clients with immune-mediated inflammatory diseases starting biologics

Limited information exists on the ideal duration of TPT prior to starting biologic therapy. When a person requires urgent biologic treatment for an underlying medical condition, this is prioritized and TPT may be initiated as soon as clinically safe.

Generally, at a minimum, TPT should be provided for at least 1-2 months prior to initiating biologic therapy (11,12). In a person requiring biologics less urgently, a full course of TPT is ideal (13).
6.15 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 [BC Drug and Poison Information Centre](#) (DPIC).** Interpretation services are available in over 150 languages.

- **Lower Mainland:** (604) 682-5050
- **Outside Lower Mainland** (toll-free): 1-800-567-8911

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 they arrive.

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


