Communicable Disease Control Manual
Chapter 4: Tuberculosis

Treatment of Active TB Disease
# TABLE OF CONTENTS

5.0  **TREATMENT OF ACTIVE TB DISEASE** ................................................................................................................................. 2

5.1  Objectives and Principles .......................................................................................................................................................... 2

5.2  Overview .................................................................................................................................................................................. 2

5.3  Flowchart for Initiation of Active TB Treatment .................................................................................................................. 4

5.4  Standard TB Treatment Regimen .......................................................................................................................................... 5

5.5  Drugs and Dosages ................................................................................................................................................................... 7

5.6  Drug Side Effects / Adverse Reactions, and Drug-Drug Interactions ................................................................................... 9

5.7  TB Treatment in Special Circumstances ............................................................................................................................. 10

5.8  Initiating Treatment ............................................................................................................................................................... 13

5.9  Monitoring TB Treatment ....................................................................................................................................................... 15

5.10 Treatment Completion ............................................................................................................................................................. 21

5.11 Follow-up after Completion of TB Treatment ....................................................................................................................... 21

5.12 Management of Adverse Reactions to TB Treatment ............................................................................................................ 22

**REFERENCES** ........................................................................................................................................................................... 23
5.0 TREATMENT OF ACTIVE TB DISEASE

The diagnosis and treatment of people with active tuberculosis (TB) disease is the first priority of TB prevention and control programs. Timely diagnosis and prompt initiation of appropriate treatment improves client outcomes and prevents transmission.

5.1 Objectives and Principles

The objectives of TB treatment are to:
- Reduce the number of TB bacteria as rapidly as possibly, to reduce morbidity and mortality, and to stop transmission.
- Prevent development of drug resistance (or prevent worsening of existing drug resistance).
- Prevent relapse of TB disease after completion of treatment.

A number of principles must be followed to meet these objectives, including:
- Use of a standardized approach to TB treatment.
- Use of drug susceptibility testing results to guide treatment whenever possible.
- Use of at least two effective drugs at all times during treatment and at least three effective drugs during the intensive phase.
- Commitment to:
  - Ensuring treatment is not interrupted or irregular at any time.
  - Providing client-centered support, monitoring and supervision throughout treatment.
  - Initiating alternative treatment promptly when adverse reactions are experienced.

5.2 Overview

Most clients with uncomplicated, fully drug-susceptible TB disease will be treated with the standard TB treatment regimen (see Section 5.4). Others, such as those with drug-resistant TB disease and those with severe liver disease, require individualized treatment regimens (see Section 5.7).

5.2.1 Phases of TB Treatment

TB treatment is divided into two phases:
1. **Intensive Phase.** During the intensive phase (when bacillary load is highest), multiple TB drugs are taken in combination to rapidly reduce the number of TB bacteria.
2. **Continuation Phase.** Fewer TB drugs are taken during the continuation phase, when emphasis is on eliminating any remaining TB bacteria.

Monitoring throughout TB treatment may include (see Section 5.9):
- Medication side effects and other adverse reactions
- Response to treatment
- Adherence to treatment
Monitoring TB drug levels (therapeutic drug monitoring) may be considered for select clients, in consultation with TB Services.

Consistent adherence to TB treatment is critical. Directly observed treatment (DOT) may be recommended to support adherence in some situations (see Section 5.9.3). Statutes within the British Columbia Public Health Act are available to assist local Medical Health Officers when treatment adherence becomes an issue.

Follow-up after completion of TB treatment is not usually necessary but may be recommended for some clients (see Section 5.11).
5.3 Flowchart for Initiation of Active TB Treatment

Figure 5-1: Flowchart for Initiation of Active TB Treatment

- Complete the Treatment Initiation form with client (consent, allergies, current chest x-rays, blood test results, medications and weight) and forward to TB Services, along with any other relevant clinical documents.
- A TB Services physician will review the Treatment Initiation form and supporting clinical information to prepare a narration, detailing any monitoring recommendations, and TB drugs prescription.*

Narration including prescription received by health care provider (HCP) responsible for dispensing medication and monitoring client

TB drug starter pack on-hand for ALL prescribed medications? **

YES

NO

Initiate treatment using TB drug starter pack ♦

Initiate treatment once supply of TB drugs has been received from BCCDC Vaccine and Pharmacy Services

- Consult with TB Services prior to dispensing first dose or TB drugs, if the client's:
  - baseline blood test results are abnormal or beyond recommended timeframe for use
  - current weight does not correspond to prescription dosage (see Table 5.3)
  - vision testing is abnormal (if taking ethambutol)
- Educate the client on potential side effects and adverse reactions with prescribed regimen.
- Follow guidelines for abnormal AST results and consults with TB Services as indicated (see Section 5.9.2).
- Consult with most responsible provider (MRP) and notify TB Services of any abnormal results (see Section 5.9).
- Advise client to STOP treatment immediately if there are any adverse reactions. Consult with TB Services and/or the client's MRP for further direction.
- Self-administered therapy (SAT): dispense one month supply of TB drugs to client, along with a requisition for blood tests, sputum collection and/or chest x-ray(s) (see Section 5.9). Confirm date and time of next appointment with client.
- DOT: administer initial dose client. Confirm plan for next scheduled dose. Carries (doses for self-administration on weekends and statutory holidays) are recommended. Carries are given at the discretion of the HCP responsible for dispensing medication and monitoring client once confirmed with TB Services.
- Complete the TB Medication Reorder Form and submit to TB Services promptly after second month supply of TB drugs started.

* TB Services physician may adjust existing TB prescribed medications after consultation with the client's MRP (e.g., clients discharged from acute care or other institutions or those arriving on treatment from areas outside of B.C.).
** Do NOT initiate partial treatment. When on-hand TB drug starter pack is inadequate to cover all medications included in the prescription, initiate treatment once client's TB drugs have been received from BCCDC Vaccine and Pharmacy Services.
♦ Blister packing can be requested on the TB Medication Reorder Form.
5.4 Standard TB Treatment Regimen

The standard TB treatment regimen is used for clients with uncomplicated, fully drug-susceptible TB disease.

5.4.1 Standard Intensive Phase (first two months of TB treatment)

The treatment regimen for standard intensive phase includes:

- Isoniazid
- Rifampin
- Pyrazinamide
- Ethambutol

Supplemental pyridoxine (vitamin B6) is added to the treatment regimen for clients at increased risk for TB medication-induced neuropathies, most commonly seen with isoniazid, prescribed to those 16 years of age and older.

Isoniazid, rifampin and pyrazinamide (and pyridoxine [vitamin B6], if indicated) are taken together throughout the intensive phase. Ethambutol can generally be discontinued once the drug susceptibility tests have confirmed that there is not resistance to isoniazid, rifampin or pyrazinamide. Additional considerations for discontinuing ethambutol should include whether the client is on adequate treatment (i.e., taking medication as prescribed, tolerating medications, no staggering of treatment) and in some cases, clinical improvement.

Dosing frequency is:

- Daily for clients on SAT.
- At least five days a week (Monday-Friday) for clients on DOT. Carries (doses for self-administration on weekends and statutory holidays) are recommended, and may be provided to clients on treatment in the community at the discretion of HCPs once confirmed with TB Services.
- Intermittent dosing (i.e., three days a week: Monday, Wednesday, Friday) is prescribed for some clients after a period of daily treatment.
- All intermittent dosing must be DOT by a HCP or trained lay worker.
- The duration of the intensive phase is at least two calendar months, during which a set number of doses must be completed (see Table 5-1). The duration of the intensive phase can extend beyond two months when doses are missed or if the disease is extensive. A prolonged break in treatment during the intensive phase could result in having to restart treatment entirely.

---

a Breastfed infants, children with nutritionally deficient diets (including meat and/or milk deficiencies), clients with risk factors for pyridoxine (vitamin B6) deficiency, such as HIV, diabetes, renal failure, malnutrition, substance abuse (including alcohol) seizure disorders, pregnant or breastfeeding women, and those of advanced aged (1, 2).

b Drug susceptibility testing results are often available within two weeks of a positive mycobacterial culture.

c TB treatment for clients residing in institutions (e.g., long-term care facilities, correctional facilities) with access to daily medication support should be provided as seven days a week DOT.
Table 5-1: Doses required to complete intensive phase of standard TB treatment regimen

<table>
<thead>
<tr>
<th>Method of Administration</th>
<th>Frequency of Dosing</th>
<th>Intensive Phase Required Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Options for Two Month Intensive Phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAT</td>
<td>Once daily, seven days a week</td>
<td>60 doses</td>
</tr>
<tr>
<td>DOT</td>
<td>Once daily, seven days a week</td>
<td>60 observed doses</td>
</tr>
<tr>
<td>DOT</td>
<td>Daily, five days a week* (Monday-Friday)</td>
<td>40 observed doses**</td>
</tr>
<tr>
<td>DOT</td>
<td>Daily, three days a week (Monday, Wednesday, Friday)</td>
<td>Variable as dependent on number of daily doses taken prior to start of intermittent dosing; consult with TB Services when clarification is required.</td>
</tr>
</tbody>
</table>

* Carries (doses for self-administration on weekends and statutory holidays) are recommended and may be given at the discretion of HCP once confirmed with TB Services.

** For clients prescribed DOT, self-administered doses do not count towards the number of observed doses required to complete the intensive phase.

TB Services can be consulted to confirm the number of doses required to complete the intensive phase of treatment for clients whose TB treatment began in acute care or other institutions, or outside of B.C.

5.4.2 Standard Continuation Phase

At least two TB drugs (usually isoniazid and rifampin) are taken during the continuation phase. If supplemental pyridoxine (vitamin B6) was taken during the intensive phase, it is usually continued.

Dosing frequency is:
- Daily for clients on SAT
- Five days a week for clients on daily DOT (e.g., Monday–Friday)
- Three days a week for clients on intermittent DOT (e.g., Monday, Wednesday, Friday)

For adherent clients with uncomplicated, drug-susceptible TB disease, the continuation phase is typically four calendar months, during which a set number of doses must be completed (see Table 5-2). For others, a longer period of treatment and higher number of doses are necessary to ensure cure. This can include having more extensive disease and/or cavities on a chest x-ray or being persistently smear and/or culture–positive after two months of therapy.

As in the intensive phase, missed doses and breaks in treatment can substantially extend the continuation phase and could result in having to restart treatment entirely.
Table 5-2: Doses required to complete continuation phase of standard TB treatment regimen

<table>
<thead>
<tr>
<th>Method of Administration</th>
<th>Frequency of Dosing</th>
<th>Continuation Phase Required Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four Month Continuation Phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAT</td>
<td>Once daily, seven days a week</td>
<td>120 doses</td>
</tr>
<tr>
<td>DOT</td>
<td>Once daily, seven days a week</td>
<td>120 observed doses</td>
</tr>
<tr>
<td>DOT</td>
<td>Daily, five days a week (Monday-Friday)</td>
<td>80 observed doses**</td>
</tr>
<tr>
<td>DOT</td>
<td>Daily, three days a week (Monday, Wednesday, Friday)</td>
<td>48 observed doses</td>
</tr>
</tbody>
</table>

| Seven Month Continuation Phase |                                                         |                                  |
| SAT                      | Once daily, seven days a week                           | 210 doses                        |
| DOT                      | Once daily, seven days a week                           | 210 observed doses               |
| DOT                      | Daily, five days a week (Monday-Friday)                 | 140 observed doses**             |
| DOT                      | Daily, three days a week (Monday, Wednesday, Friday)    | 84 observed doses                |

* Carries (doses for self-administration on weekends and statutory holidays) are recommended and may be given at the discretion of HCP once confirmed with TB Services.
** For clients prescribed DOT, self-administered doses do not count towards the number of observed doses required to complete the continuation phase.

5.5 Drugs and Dosages

Dosages of TB drugs are determined by age, weight, and dosing frequency (see Table 5-3). Adjusted doses of pyrazinamide and ethambutol are needed for clients with creatinine clearance of less than 30 per cent of normal (see Section 5.7.2). Decisions on whether to include pyrazinamide in TB treatment regimens are individualized for pregnant clients and clients at increased risk for hepatotoxicity. Refer to Section 5.7 and the BCCDC’s Medication Counselling Sheets, which are available in different languages.
Table 5-3: Summary of drugs and dosing for the standard active TB disease treatment regimen (1, 3)

<table>
<thead>
<tr>
<th>TB Medication</th>
<th>Formulations</th>
<th>Daily Dose</th>
<th>Three Days a Week Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Child</td>
<td>Adult</td>
<td>Child</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Tablets 100 mg</td>
<td>300 mg Liquid</td>
<td>10 mg/kg (10-15 mg/kg)</td>
</tr>
<tr>
<td></td>
<td>Max: 300 mg</td>
<td></td>
<td>Max: 300 mg</td>
</tr>
<tr>
<td>Rifampin*</td>
<td>Tablets 150 mg</td>
<td>300 mg Injection**</td>
<td>15 mg/kg (10–20 mg/kg)</td>
</tr>
<tr>
<td></td>
<td>Max: 600 mg</td>
<td></td>
<td>Max: 600 mg</td>
</tr>
<tr>
<td>Pyrazinamide*♦†</td>
<td>Tablets 500 mg</td>
<td>35 mg/kg (30-40 mg/kg)</td>
<td>20-25 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Max: 2000 mg</td>
<td></td>
<td>Max: 2000 mg</td>
</tr>
<tr>
<td>Ethambutol*♦</td>
<td>Tablets 100 mg</td>
<td>400 mg</td>
<td>20 mg/kg (15-25 mg/kg)</td>
</tr>
<tr>
<td></td>
<td>Max †</td>
<td></td>
<td>Max: 1600 mg</td>
</tr>
</tbody>
</table>

* Formulas are available for compounding oral capsules or tablets into liquid suspension.
** Available through Health Canada’s Special Access Program.
♦ Adjustment of drug dosing for pyrazinamide and ethambutol are needed for clients with creatinine clearance of less than 30% of normal or on dialysis (see Section 5.7.2).
† Use during pregnancy and with clients at increased risk for hepatotoxicity is individualized.
Ω Varies by clinical resource and expert opinion. 50mg/kg (2), 50mg/kg/dose and max: 2000mg (4, 5).
§ The Canadian TB Standards (3) and B.C. Children’s Hospital Pediatric Drug Dosage Guidelines (5) vary in the recommended mg/kg dosing for pediatric cases on three days per week TB regimens.
† Varies by clinical resource and expert opinion. Max: 1000mg (4) and max: 2500mg (5).
Ψ Varies by clinical resource and expert opinion. 50mg/kg (2), 50mg/kg/dose and max: 2500mg (4, 5).

<table>
<thead>
<tr>
<th>Adjunct Medication</th>
<th>Formulations</th>
<th>Daily Dose</th>
<th>Three Days a week Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Child</td>
<td>Adult</td>
<td>Child</td>
</tr>
<tr>
<td>Pyridoxine (Vitamin B6)</td>
<td>Tablets 25 mg</td>
<td>50 mg</td>
<td>100 mg</td>
</tr>
</tbody>
</table>

* Breastfed infants and children with nutritionally deficient diets (including meat and/or milk deficiencies).
5.6 Drug Side Effects / Adverse Reactions, and Drug-Drug Interactions

Contact TB Services and/or the client’s MRP immediately with concerns about TB drug side effects or adverse reactions. Refer to Section 5.12 for more information.

Table 5-4: Drugs included in the standard TB treatment regimen and associated side effects (1)

<table>
<thead>
<tr>
<th>TB drug</th>
<th>Common side effects / adverse reactions</th>
<th>Uncommon side effects / adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid ♦,</td>
<td>rash</td>
<td>central nervous system toxicity</td>
</tr>
<tr>
<td></td>
<td>drug-induced hepatitis *</td>
<td>anemia</td>
</tr>
<tr>
<td></td>
<td>peripheral neuropathy</td>
<td>headache</td>
</tr>
<tr>
<td></td>
<td>nausea/vomiting **, †</td>
<td>mild hair loss</td>
</tr>
<tr>
<td></td>
<td>fatigue, drowsiness †</td>
<td>acne</td>
</tr>
<tr>
<td></td>
<td>diarrhea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>flushing reactions with tyramine or histamine containing foods</td>
<td></td>
</tr>
<tr>
<td>Rifampin ♦, Ψ</td>
<td>• rash</td>
<td>‘flu-like’ illness with fever</td>
</tr>
<tr>
<td></td>
<td>• nausea/vomiting **, †</td>
<td>hypotension</td>
</tr>
<tr>
<td></td>
<td>• diarrhea</td>
<td>leukopenia</td>
</tr>
<tr>
<td></td>
<td>• dizziness</td>
<td>thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>• saliva, sweat, urine, feces, tears can become orange/red in colour (harmless but could permanently stain soft contact lenses or dentures)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• drug-induced hepatitis * and/or hyperbilirubinemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• flushing and itching, with or without rash</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide ♦</td>
<td>rash</td>
<td>gout Ω</td>
</tr>
<tr>
<td></td>
<td>nausea/vomiting **, †</td>
<td></td>
</tr>
<tr>
<td></td>
<td>diarrhea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>drug-induced hepatitis *</td>
<td></td>
</tr>
<tr>
<td></td>
<td>arthralgia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>photosensitivity</td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>visual toxicity (retrobulbar neuritis) §</td>
<td>rash</td>
</tr>
<tr>
<td></td>
<td>nausea/vomiting **, †</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dizziness</td>
<td></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 (see Section 5.9.1).

** Especially with intermittent regimens administered in combination with rifampin.

♦ Monitor AST levels and assess for signs/symptoms of hepatotoxicity (see Table 5-5a).

† Can also be a symptom of drug-induced hepatitis.

Ω Although elevation in serum uric acid levels are common with pyrazinamide use, acute gout is rarely seen except in those with pre-existing gout.

§ Manifested by decreases in visual acuity, visual fields, or colour vision (red/green discrimination) and more common with higher doses. E.g., 25 mg/kg, older age, and renal impairment (see Appendix E).

¥ Liquid preparations containing sorbitol may be associated with diarrhea.

Ψ There is a number of important drug interactions associated with rifampin (see Micromedex or Lexicomp).
5.6.1 Drug-Drug Interactions

There is potential for drug-drug interactions. For example, both isoniazid and rifampin can affect the metabolism and serum levels of anticonvulsants. There are also a number of important interactions associated with rifampin, including hormonal contraceptives, warfarin, digoxin, and methadone. Use online resources to check for drug interactions. Some HCPs may have access to Micromedex or Lexicomp.

Ensure TB Services and the BCCDC Vaccine and Pharmacy Services are aware of all prescription and over-the-counter drugs and supplements that clients are taking during TB treatment, or when there are any changes. For example, changes to rifampin use or dosing during TB treatment may affect a client’s warfarin or methadone needs.

5.6.2 TB Drug Intolerances

Any possible adverse reaction should be carefully evaluated to identify other potential causes and the responsible drug. Doing so can be difficult when clients are taking many different medications and/or have co-morbidities.

Adverse reactions to TB drugs can occur, with some requiring temporary or permanent adjustments to the treatment regimen. In some situations, the offending TB drug can be discontinued and duration of treatment may be extended. Close collaboration among the client, their HCPs and TB Services is important for ensuring safe and effective care for the remainder of the treatment period.

Refer to Section 5.12 for information on management of adverse reactions to TB treatment.

5.7 TB Treatment in Special Circumstances

There are some circumstances in which adjustments to the standard TB treatment regimen may be made, including:

- Hepatic disease/Severe Liver Disease
- Renal insufficiency or on dialysis
- Pregnancy or breastfeeding
- HIV infection
- Pediatric TB disease
- TB disease in those 65 years of age and older
- Drug-resistant TB disease

When such adjustments are necessary, the duration of treatment, frequency of dosing, and number of doses required to complete treatment is largely dependent on which TB drugs can be included in the treatment regimen.
5.7.1 Hepatic disease/Severe Liver Disease (1)

Isoniazid, rifampin/rifabutin, and pyrazinamide are hepatotoxic, so alternate treatment regimens are often required for people with severe liver disease. Therapeutic drug monitoring may be considered for some clients with hepatic insufficiency (see Section 5.9.5). Education and careful monitoring for hepatotoxicity is especially important for clients at increased risk for drug-induced hepatotoxicity and/or with pre-existing liver disease.

Practitioner Alert!

Notify TB Services if the client has any of the following risk factors for drug-induced hepatotoxicity which includes clients:
- 65 years of age or older
- Pregnant or within first three months postpartum
- With a history of previous drug-induced hepatitis
- With current liver cirrhosis or chronic active hepatitis of any cause
- With pre-existing liver disease, particularly hepatitis B or C with prior with abnormal transaminases
- With daily alcohol consumption
- With concomitant use of other hepatotoxic drugs (e.g., methotrexate)

5.7.2 Renal Insufficiency and Dialysis (1, 2)

Clients with renal insufficiency or end-stage renal disease are immunocompromised. TB clients with renal failure have worse clinical outcomes than those without. Adjusted doses of ethambutol and pyrazinamide are usually necessary for clients with creatinine clearance less than 30% of normal. Isoniazid and rifampin can be given at the usual doses.

Standard doses of isoniazid, rifampin, ethambutol, and pyrazinamide can be used with clients when given by DOT three days a week (e.g., Monday, Wednesday, Friday) in the renal unit after dialysis. Therapeutic drug monitoring may be considered for some clients with renal insufficiency (see Section 5.9.5).

Practitioner Alert!

Clients with renal insufficiency treated with ethambutol are at increased risk for visual toxicity. Refer to Appendix E for information on vision monitoring during treatment with ethambutol.

Peritoneal Dialysis

Adjustments to dosing, scheduling, and monitoring of TB treatment may be necessary and additional monitoring may be recommended by the client’s specialist or a TB Services physician.
5.7.3 Pregnancy and Breastfeeding (1, 2)

The risk of untreated active TB to a pregnant woman and her fetus is far greater than the risk of the toxic effects of drugs used in TB treatment. Although anti-TB drugs cross the placenta, they do not appear to have teratogenic effects in humans. Therefore, isoniazid, rifampin, and ethambutol are considered safe for use during pregnancy. Supplemental pyridoxine (vitamin B6) is added to regimens that include isoniazid for pregnant or breastfeeding women.

Use of pyrazinamide during pregnancy is individualized and the risks and benefits of the medication should be discussed with the client. TB treatment is extended to at least nine months when pyrazinamide is not included throughout the intensive phase of treatment (see Section 5.10).

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

5.7.4 HIV Infection (1, 5)

Close collaboration among HCPs is important for ensuring safe and effective care of clients with HIV infection on TB treatment. Treatment of TB in clients with HIV should be guided by a physician with expertise in the management of both diseases or in close collaboration with a physician expert in HIV care. Common issues include:

- Immune reconstitution reactions after initiation of antiretroviral therapy (ART).
- ART and/or paradoxical reactions to anti-TB treatment.
- Decreased absorption of TB drugs.d
- Interactions between TB drugs and antiretroviral drugs.
- Increased risk for TB drug-associated neuropathy.

HIV is not an independent risk factor for drug-induced hepatitis. TB treatment is taken daily throughout the intensive phase. Daily treatment is also preferred during the continuation phase.

Therapeutic drug monitoring is often considered for clients with HIV infection (see Section 5.9.5). Clients that do not take ART require extended TB treatment (see Section 5.10). For information on timing of initiation of ART, refer to the Canadian Tuberculosis Standards TB and HIV chapter (6).

Follow-up after completion of treatment may be recommended for clients with HIV infection and substantial immune suppression (see Section 5.11).

5.7.5 Pediatric TB Disease (3)

Treatment of active TB disease in children is very similar to treatment of active TB disease in adults. Active TB in children is a sentinel event that should prompt a search for the source case (also known as reverse contact tracing).

d Measurement and monitoring of serum concentrations of TB drugs may be recommended for some clients, including those with chronic diarrhoea and advanced HIV disease, in whom drug interactions are suspected to be lowering TB medication levels or who are demonstrating a suboptimal response to TB treatment (1). Refer to Section 5.9.5 for more information.
Ensuring adherence to treatment can be challenging. Consult with TB services if the child and their family need support with medication administration. Routine blood work is not recommended for every pediatric TB case. Many pediatric TB cases are best managed by care providers with expertise in TB and in pediatrics. A collaborative care-model exists for children between Pediatric Infectious Disease Specialists at BCCH and TB Services.

Age-appropriate visual assessment is needed for children starting treatment with ethambutol; however, treatment start should not be delayed pending visual assessment. While ethambutol is in use, visual assessments should be completed monthly or more often if issues arise.

A child’s weight should be documented at baseline and at least monthly during treatment (see Table 5-5). Dose increases are usually required in growing children to ensure appropriate dosing is maintained. Follow-up after completion of treatment is usually recommended (see Section 5.11).

Practitioner Alert!
During treatment, report a weight loss or failure to gain weight in growing children to TB Services.

5.7.6 TB Treatment in Clients 65 Years of age and Older
Pyrazinamide may not be recommended in some clients 65 years of age and older due to an increased risk for drug-induced hepatotoxicity. TB treatment is extended to at least nine months when pyrazinamide is not included throughout the intensive phase of treatment (see Section 5.10).

5.7.7 Drug-Resistant TB Disease
Treatment regimens for cases that are confirmed or suspected to be TB drug-resistant are guided by Drug Susceptibility Results when available (or based on source case information), to ensure an adequate number of effective drugs are used.

The length of treatment for drug-resistant TB disease can be substantially longer than for drug-susceptible TB disease. Decisions on duration of treatment are guided by the drug susceptibility testing results, response to treatment, and adherence (see Section 5.10). Clients on treatment for drug-resistant TB often require additional support (e.g., DOT) and more frequent monitoring.

Therapeutic drug monitoring may be considered for some clients with drug-resistant TB (see Section 5.9.5). Follow-up after completion of treatment is recommended for some cases (see Section 5.11).

5.8 Initiating Treatment
Client centred care is an essential part of TB treatment and requires collaboration between the client, their family, community supports, and HCP team (2). It is important for the client to be an active participant in their own care. The client or their family may identify strengths, supports, needs or barriers to TB treatment success. HCPs can advocate to address client identified needs and/or barriers to care. Interventions may include: client reminders, follow-up for missed appointments, incentives or enablers, home visits and coordination between involved HCPs and community based organizations.
5.8.1 Client Education (2)

Assessing the client’s learning needs and their understanding of provided education is an essential part of client centered care. Improving health literacy for the client and their family includes use of plain language (whenever possible) that is appropriate to the culture, language, age and reading level of the client. For clients who speak English as a second language, the use of a medical interpreter is preferred over using family or friends.

The client and their family should know:

- What is TB, how it is spread and that it is treatable and curable.
- Isolation precautions (if applicable).
- Who is involved in their care, contact information and after-hours plan of care.
- Their roles in identifying and preventing potential side effects of the TB drugs they are taking, adverse reactions (especially hepatotoxicity), adherence, and any scheduled follow-up, including clinical visits and blood tests.
- The importance of notifying their HCP immediately about any new over-the-counter or prescribed medications or alternative therapies, or any changes to the medications noted prior to initiating therapy. If treatment is interrupted, to restart TB treatment as advised by their HCP.
- The importance of consulting their HCP immediately about:
  - Potential side effects
  - Drug-to-drug interactions
  - Adverse reactions

Complete the TB Treatment Initiation form and refer to Appendix G for client education resources.

5.8.2 Baseline Testing

Blood Testing

Refer to Table 5-5 for baseline blood testing requirements. 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 previous 30 days can be used as baseline results provided they are within normal limits. Notify TB Services if the client has risk factors for hepatotoxicity (see Section 5.7.1).

Weight

At baseline, document the weight of 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. Dose adjustments may also be required for low weight adults.
Vision

Document visual acuity and red/green colour discrimination for clients prescribed ethambutol (see Appendix E). Referral to an ophthalmologist (not an optometrist) is indicated if there is evidence of visual abnormality at baseline or if ongoing use of ethambutol is expected beyond the intensive phase. Consult TB Services for guidance when necessary.

5.8.3 Drug Supplies

TB drugs are supplied through the BCCDC Vaccine and Pharmacy Services for clients outside of acute care facilities and federal correctional institutions. TB drugs are provided without cost to the client and a B.C. Services Card (personal health number) is not required.

TB drugs are sent from the BCCDC Vaccine and Pharmacy Services to the HCP or program responsible for dispensing them to the client (e.g., health unit, health centre, TB clinic). Although TB drugs are supplied in two-month batches, clients who are self-administering their TB treatment should be provided no more than one month of TB drugs at a time.

Write requests for blister packs on the TB Medication Reorder form and fax to TB Services promptly after dispensing the first of the two-month batches of TB drugs.

When necessary, consult TB Services for clarification on when and how to reorder TB drugs from the BCCDC Vaccine and Pharmacy Services.

5.9 Monitoring TB Treatment

The duration of standard TB treatment is six months minimum. For client’s requiring TB treatment longer than six months, continue with the monitoring schedule (Table 5-5). For respiratory cases with longer TB treatment, the chest x-ray is at the end of treatment (not at six months) unless otherwise specified by a TB Services physician.

Ask clients about TB drug side effects and adverse reactions at each clinic visit, medication refill, and prior to every DOT dose of TB drugs. Confirm monitoring requirements for clients with abnormal baseline blood test results, clients at increased risk for side effects (including hepatotoxicity), clients that develop side effects, and clients whose treatment will exceed six months.

The absolute minimum course of active TB treatment is six months. Consult TB Services prior to dispensing the last month of medications to the client, to review the total number of doses taken, the need for any further follow-up (e.g., sputum, chest x-rays) and to confirm when treatment can be stopped. A prescription discontinuation is generated by a TB Services physician upon receipt and review of the Treatment Completion form.
Table 5-5: Summary of baseline testing - ongoing monitoring requirements for clients taking standard TB treatment

<table>
<thead>
<tr>
<th></th>
<th>At Baseline *</th>
<th>End week 1</th>
<th>End week 2</th>
<th>End month 1</th>
<th>End month 2</th>
<th>End month 3</th>
<th>End month 4</th>
<th>End month 5</th>
<th>End month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV serology</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST ** Total Bilirubin ♦</td>
<td>✓</td>
<td></td>
<td>16+</td>
<td>16+</td>
<td>16+</td>
<td>16+</td>
<td>16+</td>
<td>16+</td>
<td>16+</td>
</tr>
<tr>
<td>Serum creatinine †</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CBC Ω</td>
<td>16+</td>
<td>16+</td>
<td>16+</td>
<td>16+</td>
<td>16+</td>
<td>16+</td>
<td>16+</td>
<td>16+</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B Hepatitis C HgbA1C §</td>
<td>16+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uric Acid</td>
<td>Not routinely required at baseline or during treatment. Consult TB Services if taking pyrazinamide and symptomatic for gout.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg) †</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Check dosing against current weight (kg) †</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snellen chart and Ishihara colour tests If includes ethambutol</td>
<td>Repeat monthly while regimen includes ethambutol (see Appendix E). Consult TB Services and refer to ophthalmology if evidence of visual abnormality or ongoing use of ethambutol.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum for TB testing Ψ</td>
<td>3 sputum (all cases)</td>
<td>3 sputum samples every two weeks until AFB smear is negative Φ</td>
<td>3 sputum Φ, ⊘</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest x-ray ^</td>
<td>✓ (all cases)</td>
<td></td>
<td></td>
<td>✓ Φ</td>
<td></td>
<td>✓ ⊘</td>
<td></td>
<td></td>
<td>✓ Φ</td>
</tr>
</tbody>
</table>
Table 5-5: Summary of baseline testing - ongoing monitoring requirements for clients taking standard TB treatment (footnotes):

* Results from blood tests done within 30 days prior to treatment start date can be used as baseline measurements provided they are within normal limits (see Section 5.9.2). Notify TB Services for clients with risk factors for hepatotoxicity (see Section 5.7).

** When existing blood test results include ALT and no AST, ALT may be used at baseline. Indicate if result is outside of local reference range. Refer to Section 5.9.2 for monitoring abnormal AST levels.

16+ Routinely required only for cases 16 years of age or older.

♦ Total Bilirubin results to be managed by MRP. Forward abnormal results to TB Services.

† Routinely monitor for serum creatinine due to rare reports of kidney injury associated with active TB treatment.

Ω CBC results to be managed by MRP. Forward abnormal results to TB Services.

§ Not required if already documented positive, or in the case of HbgA1C, identified.

✝ Monthly monitoring of weight is indicated for pediatric clients, low weight adults or those adults who lost a significant amount of weight prior to starting or during treatment.

Ψ Consult TB Services for guidance on the management of children unable to spontaneously produce sputum. Gastric lavage is typically recommended in young children. Refer to Appendix C for collection of specimens for TB testing.

▲ A chest x-ray in the past two weeks can be used for baseline assessment.

Φ Respiratory cases only.

✂ Consult TB Services if AFB smear-positive or culture-positive after two months of treatment. End of treatment specimens should be submitted if possible (i.e., it is not necessary for clients to undergo sputum induction for this purpose).
5.9.1 Side Effects / Adverse Reactions and Drug-Drug Interactions

Common and/or important side effects and adverse reactions associated with standard TB treatment regimen are described in Table 5-4. Refer to Section 5.7.1 for list of risk factors for drug-induced hepatotoxicity.

<table>
<thead>
<tr>
<th>Practitioner Alert!</th>
</tr>
</thead>
<tbody>
<tr>
<td>Place emphasis on identifying signs/symptoms of hepatotoxicity, which can include:</td>
</tr>
<tr>
<td>• Rash</td>
</tr>
<tr>
<td>• Malaise, or unexplained fatigue</td>
</tr>
<tr>
<td>• Headache</td>
</tr>
<tr>
<td>• Diarrhea</td>
</tr>
<tr>
<td>• Fever</td>
</tr>
<tr>
<td>• Anorexia (loss of appetite)</td>
</tr>
<tr>
<td>• Nausea and/or vomiting</td>
</tr>
<tr>
<td>• Dark-coloured urine</td>
</tr>
<tr>
<td>• Scleral icterus or jaundice</td>
</tr>
<tr>
<td>• Abdominal pain, especially over right upper quadrant</td>
</tr>
</tbody>
</table>

Refer to Section 5.9.2 for guidelines on managing abnormal AST levels.

Ensure TB Services and the BCCDC Vaccine and Pharmacy Services are aware of any new over-the-counter or prescribed medications or alternative therapies, or any changes to the medications noted prior to initiating therapy.

5.9.2 Blood Testing

Refer to Table 5-5 for routine blood testing requirements. Consult with TB Services if there is uncertainty about testing requirements for an individual client. Additional and/or more frequent blood testing may be requested by the client’s specialist or TB Services physician, based upon:

- The 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 or drugs a client is taking.
- Whether the client reports potential side effects and adverse reactions (e.g., signs/symptoms of hepatotoxicity).

Abnormal AST Levels

The following guidelines are recommended when monitoring AST levels. Signs/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 client 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. Fax a Notification of Abnormal AST form to TB Services for all AST levels greater than 45, after consulting with TB Services as indicated in the table below.

### Table 5-5a: Guidelines for monitoring AST levels

<table>
<thead>
<tr>
<th>AST Level</th>
<th>Symptoms*</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST greater than 45 and less</td>
<td>NO</td>
<td>• Continue treatment</td>
</tr>
<tr>
<td>100</td>
<td></td>
<td>• Repeat bloodwork in one-two weeks**</td>
</tr>
<tr>
<td>AST greater than 45 and less</td>
<td>YES</td>
<td>• Consult with TB Services</td>
</tr>
<tr>
<td>100</td>
<td></td>
<td>• Repeat bloodwork in one week or as directed by TB Services</td>
</tr>
<tr>
<td>100 or higher</td>
<td>NO/YES</td>
<td>• STOP TREATMENT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Consult with TB Services</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Repeat bloodwork weekly until AST reaches baseline or as directed by</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TB Services</td>
</tr>
</tbody>
</table>

* For signs/symptoms of hepatotoxicity refer to Section 5.9.1.

** For clients with AST levels closer to 100, bloodwork may be repeated at one week or earlier.

### 5.9.3 Adherence: SAT & DOT

TB drugs must be taken as prescribed to be effective. In addition to poorer outcomes for clients, non-adherence can lead to TB transmission and to the development (or worsening) of drug resistance.

**Practitioner Alert!**

Consult TB Services and/or the local Medical Health Officer in a timely manner when adherence issues arise, as treatment may need to be extended.

Asking clients on SAT about their adherence provides opportunities to offer support/suggestions for maintaining or improving adherence. DOT may be recommended to support adherence to TB treatment in some situations. All intermittent dosing (e.g., three days a week dosing) must be DOT by a HCP or trained lay worker (see Section 5.4).

Daily DOT can be given Monday to Friday (1). Carries (doses for SAT on weekends and statutory holidays) are recommended and may be given at the discretion of HCP once confirmed with TB Services. For clients prescribed DOT, self-administered doses do not count towards the number of observed doses required to complete the intensive or continuation phase.

### 5.9.4 Response to Treatment

Most clients will begin to notice a reduction in their symptoms within the first few weeks of treatment, such as resolution of fever and night sweats, improvements in cough, energy levels and appetite. Weight can be an important indicator of response to TB treatment. Weigh clients at least monthly to ensure appropriate dosing is maintained.
For clients with respiratory TB disease, various results can be used to gauge clinical improvement including symptoms, sputum specimen AFB smears, mycobacterial cultures, and repeat chest x-rays. These results guide decisions on when airborne precautions can be discontinued (i.e., when clients can return to work or school, or travel). In some situations, it may be necessary to induce sputum specimens for these purposes (see Appendix D).

Results from sputum tests and chest x-rays done after two months of treatment guide decisions on how long treatment should continue. For example, extended treatment is often recommended for clients with persistent or new cavities on their chest x-rays and clients whose sputum cultures remain positive after two months of treatment (see Section 5.10). Consult TB Services if AFB smear-positive or culture-positive after two months of treatment (culture results available six to eight weeks after collection). This consultation allows for an in-depth review of the client’s status by TB Services, including their current sputum, chest x-ray, medication adherence and other signs of clinical improvement. Consultation may also include a discussion of the client’s isolation status and the effectiveness of current therapy and drug levels.

Some cases will continue to produce AFB smear-positive sputum specimens for several weeks and sometimes months into treatment. Consult TB Services if isolates from active cases remain culture positive after four months of treatment, or whose cultures become positive after a period of negative results, as repeat drug susceptibility testing or other interventions should be done. Sputum tests and chest x-rays are usually done during the last month of treatment for cases with respiratory disease to document cure and to guide decisions on whether post-treatment follow-up is necessary (see Section 5.11).

### Practitioner Alert!

**Respiratory cases:** Collect three sputum for AFB smear every two weeks until AFB smear is negative and collect three sputum for AFB smear every two months until cultures are negative.

Consult TB Services if AFB smear-positive or culture-positive after two months of treatment.

### 5.9.5 Therapeutic Drug Monitoring

Monitoring of serum concentrations of TB drugs may be useful in situations where there are risk factors for altered drug absorption or malabsorption and excretion, such as clients with:

- Gastrointestinal disease or HIV infection due to potential for malabsorption of drugs.
- Liver or renal disease, due to reduced drug excretion.
- Drug resistant TB disease, to optimize every available drug.
- Diabetes.

Access to therapeutic drug monitoring (TDM) is extremely limited in Canada. When indicated, TB Services will provide guidance on how to facilitate TDM.
5.10 Treatment Completion

Treatment of active TB disease requires at least six months of multiple drugs. The actual length of treatment for individual clients is influenced by:

- **Site(s) and clinical presentation of TB disease**: some forms of active TB disease may require an extended continuation phase (e.g., cavitory pulmonary TB disease, TB meningitis, bone TB, lymph node TB).

- **Response to treatment**: an extended continuation phase is required for some cases, such as:
  - Cases with sputum specimens that are AFB smear or culture-positive after two months of treatment and/or that have persistent cavities on chest x-ray.
  - Cases unable to take the standard TB treatment regimen, including when the intensive phase of the treatment regimen did not include pyrazinamide throughout and/or either phase of treatment did not include isoniazid and rifampin (or rifabutin) throughout.

- **Drug Susceptibility Testing results**: extended treatment is usually required for drug-resistant TB disease.

- **Adherence and/or Treatment interruptions**: treatment is usually considered complete once all prescribed doses have been taken. Where there was an extended break in treatment (e.g., where a client begins treatment and then becomes lost to follow-up) TB Services may recommend that treatment be extended or restarted from the beginning.

- **HIV status**: extended treatment may be recommended for clients with HIV infection that declined or for other reasons, did not take ART (6).

Sputum specimen testing and chest x-rays at completion of TB treatment are generally required only for clients with respiratory forms of TB disease and those with TB-related abnormalities noted on their initial chest x-rays. 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., sputum, chest x-ray) and to confirm when treatment can be stopped.

Upon completion of TB treatment, clients (or the parents/guardians of children) should be reminded about TB signs/symptoms and the need to promptly seek evaluation to rule out active TB disease in the future. HCPs are responsible to complete the Treatment Completion Form and fax to TB Services.

5.11 Follow-up after Completion of TB Treatment

Routine follow-up after completion of treatment for active TB disease is not usually required. Exceptions include:

- Cases on non-standard treatment regimens (e.g., cases with drug-resistant TB disease).
- Pediatric cases.
- Cases with substantial immune suppression.
- Cases with questionable adherence (especially when combined with suboptimal end of treatment chest x-ray findings or extensive, persistent radiographic abnormalities).
- Cases with suboptimal end of treatment chest x-ray findings.
Follow-up after completion of treatment for active respiratory TB disease may include assessments for TB signs/symptoms and chest x-rays at three months post-treatment completion and then every six months for two years, or at the treating physician’s discretion. Assessments for TB signs/symptoms and repeat imaging (e.g., ultrasound, CT, MRI) may be recommended for cases whose TB disease involved other organs.

Pediatric cases should be followed for at least one year after treatment completion. Assessment should be done every three to six months, and include a general exam by their MRP, and a review of TB signs/symptoms. The need for chest x-ray should be reviewed with TB services or the MRP on a case-by-case basis. Refer to Section 4(b) for information on management of clients found to have or with signs/symptoms consistent with active TB disease post-treatment.

### 5.12 Management of Adverse Reactions to TB Treatment

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 immediately in the event of an adverse reaction.**

**Practitioner Alert!**

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

### 5.12.1 Reporting of Adverse Reactions to TB Treatment (7)

**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](https://www.canada.ca/en/health-canada/services/medications-safety/vigilance-program.html) of Health Canada.

**Hospital 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.

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 HCPs working in the hospital. For more information, go to [Mandatory reporting of serious adverse drug reactions](https://www.canada.ca/en/health-canada/services/medications-safety/vigilance-program.html).
REFERENCES


