Yukon Communicable Disease Control – TB Control
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CHAPTER 9: TREATMENT OF ACTIVE TB DISEASE

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CHAPTER 9: TREATMENT OF ACTIVE TB DISEASE

Identification and treatment of people with active TB disease is the most important TB prevention and control strategy. Prompt and appropriate treatment ensures the best possible outcomes for those with active TB disease and also protects others from TB by preventing ongoing transmission of TB bacteria from infectious cases.

Treatment for people diagnosed with active TB disease in Yukon is usually initiated in hospital, in consultation with the BCCDC TB Services physician specialist. Ongoing treatment and monitoring, and public health management occurs through YCDC TB Control in consultation with the BCCDC TB Services TB physician. YCDC TB Control disseminates recommendations from the BCCDC TB Services physician specialist to appropriate health care team members, such as clients' family physicians and community Health Centres/agencies.

In Yukon, all people with active TB disease are supported to complete treatment with directly observed therapy (DOT). Medications for TB treatment are provided without cost to clients.

Clinical and public health management of people with active TB disease often involves a period of airborne precautions (see Chapter 11), and contact investigation (contact tracing). When young children are diagnosed with active TB disease, efforts are made to identify the person their infection came from (a source case investigation). Information on contact investigations and source case investigations is provided in Chapter 10.

9.1 TB Treatment Regimens

9.1.1 Standard TB Treatment Regimen

In Yukon, the standard regimen used to treat active TB disease is isoniazid, rifampin, and pyrazinamide given for 2 months followed by isoniazid and rifampin given for at least 4 more months. A fourth TB medication, ethambutol, is included in TB treatment regimens for select cases. Within Yukon, ethambutol is often not recommended by the TB physician specialists at BCCDC TB Services, due to comprehensive local epidemiology supporting a high sensitivity to isoniazid, and virtually no TB drug resistance in TB acquired within Yukon.

Supplementary pyridoxine (vitamin B6) is prescribed for clients 16 years of age and older taking isoniazid to prevent peripheral neuropathy. Vitamin B6 is not included in TB treatment regimens for otherwise healthy children. Exceptions include breastfed infants, and pregnant or breastfeeding adolescents.

9.1.2 Alternate TB Treatment Regimens

Alternate TB treatment regimens are sometimes required, for example with clients that:

- Have drug-resistant TB disease.
- Have conditions or comorbidities that influence which TB medications can be used (such as pre-existing significant liver disease).
- Cannot take or tolerate one or more of the medications in the standard TB regimen.

Section 9.4 provides information on some situations in which alternate regimens might be prescribed.

9.2 Phases of TB Treatment

Treatment of active TB disease is divided into two phases:

1. **Initial Phase** (also known as the intensive phase)

   During the initial phase, a combination of several TB medications (usually isoniazid, rifampin, and pyrazinamide, along with vitamin B6) are used to rapidly reduce numbers of TB bacteria and prevent:

   - Complications (reduce morbidity)
   - Death (reduce mortality)
   - Transmission (reduce contagiousness)
   - Emergence or worsening of, TB drug resistance

   The duration of the initial phase is roughly 2 months. Treatment is typically given daily, in a hospital setting. If ethambutol was

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included in the initial treatment regimen, it is usually discontinued after consultation with the BCCDC TB Services physician specialist once drug susceptibility testing confirms the case does not have drug-resistant TB disease (usually 4-6 weeks into treatment).

2. Continuation Phase

The emphasis during the continuation phase is on preventing relapse of TB disease. Treatment regimens for cases with drug-susceptible TB disease typically include fewer TB medications during the continuation phase (usually isoniazid and rifampin, along with vitamin B6). If ethambutol was included in the initial treatment regimen, it will often have been stopped prior to the start of the continuation phase. Pyrazinamide is usually discontinued in consultation with the BCCDC TB Services physician specialist after 2 months of treatment have been completed.

The duration of the continuation phase is determined by the BCCDC TB Services physician specialist. It is typically 4 months for adherent clients with uncomplicated, drug-susceptible TB disease.

Some forms of TB disease require a longer continuation phase, such as TB meningitis. Extended treatment is also usually recommended for cases with:

- TB drug resistance.
- Interruptions in treatment (e.g., from side effects or non-adherence).
- Treatment regimens that did not include both isoniazid and rifampin throughout, or regimens that did not include pyrazinamide for the first 2 months.
- Risk factors for relapse of TB disease such as:
  - Having extensive disease and/or cavities on chest x-ray in the first 2 months of treatment;
  - Remaining culture-positive after 2 months of treatment;
  - Having cavities on chest x-ray at the end of treatment.

Treatment during the continuation phases can be given daily or intermittently. Intermittent regimens can only be done as directly observed therapy (DOT).

The Canadian Thoracic Society recently updated recommendations on the frequency of intermittent dosing during treatment for active TB disease from twice-a-week to three-times-a-week. Three-times-weekly is recommended over twice-weekly because if clients miss a dose while on three-times-weekly dosing, it has less of an impact than missing a twice-weekly dose. HIV-negative clients with minimal disease (e.g., initially smear-negative but culture-positive) or clients that have been reliable with DOT may be considered for twice-weekly DOT in the continuation phase, as recommended by BCCDC TB Services physician specialist (i.e., after completing 2 months of daily treatment).

9.3 TB Medications and Dosages

9.3.1 TB Medications

Determinations on which TB medications are included in individual client treatment regimens are made by the BCCDC TB Services physician specialist.

Medications included in the standard TB treatment regimen, and common and uncommon but important side effects associated with them are outlined in Table 9-1. Information on interactions between isoniazid and food is included in Appendix H.

Table 9-1, TB medications included in the standard TB treatment regimen and associated side effects[1]

Medication	Common side effects	Uncommon but important side effects
Isoniazid	rash hepatitis† neuropathy nausea/vomiting* fatigue, drowsiness, headache mild hair loss	central nervous system toxicity anemia
Rifampin**	drug interactions rash	hepatitis† 'flu-like' illness neutropenia thrombocytopenia
Pyrazinamide	rash nausea/vomiting hepatitis† arthralgia	gout❑ photosensitivity
Ethambutol	visual toxicity (retrobulbar neuritis)^	rash

† Symptoms can include anorexia (loss of appetite), nausea and/or vomiting, abdominal discomfort, unexplained fatigue, dark-coloured urine, scleral icterus or jaundice
*** Especially with intermittent regimens administered in combination with rifampin**
**** Saliva, urine, tears may become orange/red in colour**
❑Although elevation in serum uric acid levels is 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. More common with higher doses (e.g., 25 mg/kg), older age, and renal impairment

9.3.2 Dosages

Dosages of TB medications are determined by age, weight, and dosing frequency (Table 9-2). Adjusted doses of pyrazinamide and ethambutol are needed for clients with creatinine clearance of less than 30% of normal (see 9.4.2). Use of pyrazinamide during pregnancy is individualized (see 9.4.4).

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Table 9-2, Summary of medications and dosing for the standard active TB disease treatment regimen for children and adults[2,3]

Medication	Formulations	Daily Dose		Three-Times-A-Week Dose	
		Child	Adult	Child	Adult
Isoniazid	**Tablets:** • 100 mg • 300 mg **Suspension** • 10 mg/mL **Injection$^{\Psi}$** • 100 mg/mL	10 mg/kg (10-15 mg/kg) Maximum: 300 mg	5 mg/kg Maximum: 300 mg	20-30 mg/kg Maximum: 600-900 mg	10 mg/kg Maximum: 600 mg
Vitamin B6 (pyridoxine)	**Tablets** • 25 mg • 50 mg • 100 mg	1 mg/kg§ Maximum: 25 mg	As ordered	As ordered	As ordered
Rifampin $^{\Phi}$	**Capsules** • 300 mg • 150 mg **Injection$^{\Psi}$** • 600 mg/10 mL	15 mg/kg (10–20 mg/kg) Maximum: 600 mg	10 mg/kg Maximum: 600 mg	10–20 mg/kg Maximum: 600 mg	10 mg/kg Maximum: 600 mg
Pyrazinamide $^{\wedge,\square,\Phi}$	**Tablets** • 500 mg	35 mg/kg (30-40 mg/kg) Maximum: 2000 mg	20-25 mg/kg Maximum: 2000 mg	70 mg/kg (60-80 mg/kg) Maximum: *	30-40 mg/kg Maximum: 4000 mg
Ethambutol $^{\wedge,\Phi}$	**Tablets** • 400 mg • 100 mg	20 mg/kg (15-25 mg/kg) Maximum: **	15-20 mg/kg Maximum: 1600 mg	40 mg/kg (30-50 mg/kg) Maximum: ***	25-40 mg/kg Maximum: 2400 mg

$^{\Psi}$ Available through Health Canada's Special Access Program

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

$^{\Phi}$ Recipes are available for compounding oral capsules or tablets into liquid suspension

$^{\wedge}$ Adjustment of drug dosing for pyrazinamide and ethambutol are needed for clients with creatinine clearance of less than 30% of normal or on hemodialysis

$^{\square}$ Use during pregnancy is individualized

*** For pyrazinamide: maximum three-times-a-week dose for children is 3000 mg according to the American Thoracic Society (ATS)[4], 2000 mg according to the Red Book[5]**

**** For ethambutol: maximum daily dose for children is 1600 mg according to the ATS[4], 2500 mg according to the Red Book[5]**

***** For EMB: maximum three-times-a-week dose for children is 2400 mg according to the ATS[4], 2500 mg according to the Red Book[5]**

9.4 TB Treatment in Special Circumstances

9.4.1 Hepatic Disease

Isoniazid, rifampin, and pyrazinamide can cause drug-induced hepatotoxicity. Alternate regimens are usually prescribed for people with severe liver disease, along with careful monitoring of liver enzymes during treatment if any hepatotoxic TB medications are used.

9.4.2 Renal Insufficiency and Dialysis

Ethambutol and pyrazinamide are excreted by the kidneys, so reduced doses of these two TB medications are usually given to cases with creatinine clearance less than 30% of normal. Isoniazid and rifampin can be given at the usual doses as they are metabolized by the liver.

Ideal management of cases on dialysis is standard doses of isoniazid, rifampin, ethambutol, and pyrazinamide given three times a week **after dialysis**.

NOTE: Visual toxicity from ethambutol is more common in clients with renal insufficiency. Refer to Section 9.6 for information on baseline and ongoing monitoring of vision during treatment with ethambutol.

9.4.3 Peritoneal Dialysis

Standard dosing and scheduling of TB treatment is used, with close monitoring as directed by the BCCDC TB Services physician specialist.

9.4.4 Pregnancy and Breastfeeding

Isoniazid, rifampin, and ethambutol are considered safe for use in pregnancy and breastfeeding. Supplemental vitamin B6 should be given. Individualized recommendations are made for the use of pyrazinamide during pregnancy.

Very small amounts (3%, at most) of maternal doses of TB medications are excreted in breast milk. This amount will not produce toxic effects in breast feeding children, nor will it provide an effective dose for treatment of active TB disease or LTBI.

Yukon Communicable Disease Control – TB Control
4 Hospital Road, Whitehorse, YT Y1A 3H8
Phone: 667-8323 Fax: 667-8349

9.4.5 HIV Infection

Treatment of active TB disease in people with HIV infection requires collaboration between health care providers involved in the specialized management of these two conditions.

Some considerations in TB treatment for HIV-infected people include:

- Interactions between TB medications and antiretroviral drugs
- Immune reconstitution reactions after initiation of antiretroviral therapy (ART)
- Need for extended TB treatment for cases that do not take ART
- Potential for decreased absorption of TB medications
- Potential for increased risk of isoniazid-associated neuropathy

Treatment of TB disease in HIV-infected clients should be given daily during the initial phase. Treatment during the continuation phase should be given, at minimum, as three-times-a-week DOT (i.e., Monday/Wednesday/Friday), particularly in those with CD4 cell counts $\leq 100 \times 10^6$/L.

9.4.6 Pediatric TB Disease

Treatment of pediatric TB disease is very similar to treatment of TB disease in adults. Children tend to tolerate TB medications better than adults. For providers, the greatest challenge can be ensuring adherence to treatment. Some tips for supporting adherence to TB treatment are provided in Appendix H.

When possible, opthalmological assessment should be obtained in younger children before starting ethambutol and repeated regularly while ethambutol is being used.[6]

Monthly monitoring of weight for pediatric cases is important for monitoring response to treatment, and ensuring appropriate dosing is maintained throughout treatment. **Weight loss or failure to gain weight in a growing child during TB treatment could indicate treatment failure and should be reported to YCDC TB Control immediately.**

9.4.7 TB Treatment in the Elderly

Pyrazinamide is the most common cause of drug-induced hepatotoxicity in people receiving treatment for active TB disease. For this reason, pyrazinamide might not be prescribed for elderly clients, whose risk for drug-induced hepatotoxicity can be higher than that of younger clients. When pyrazinamide is not included in the initial phase (i.e., for the first 2 months), TB treatment is usually extended to 9 months.

9.4.8 Drug-Resistant TB Disease (DR-TB)

There are growing numbers of cases with DR-TB disease globally. DR-TB disease is most likely to occur in people who have been previously treated for active TB disease, who are from or have spent substantial time in a country where DR-TB disease is prevalent, or who were exposed to someone with infectious DR-TB disease. DR-TB disease continues to be uncommon in Canada and is rarely seen in Canadian-born cases. Nevertheless, drug susceptibility testing (DST) is routinely performed on initial isolates (positive mycobacterial cultures) from all TB cases.

TB treatment regimens for cases with confirmed or suspected DR-TB disease are tailored (based on DST results, when available) to ensure they include an adequate number of effective medications.

The treatment of cases with DR-TB disease can be challenging. The medications available for the treatment of DR-TB disease can cause more side effects. The length of treatment for DR-TB disease can also be substantially longer than for drug-susceptible TB disease. Careful monitoring and additional support is often required.

Decisions on duration of treatment are guided by the DST results, response to treatment, and adherence.

Treatment regimens for contacts to infectious DR-TB disease are based on source cases' DST results (see 10.4.5).

9.5 Roles and Responsibilities during TB Treatment

The YCDC TB Control Nurses are responsible for medication administration (DOT) and monitoring of clients living in Whitehorse during treatment for active

TB disease. Roles and responsibilities during TB treatment for clients living outside of Whitehorse are outlined in Table 9-3.

Table 9-3, Roles and Responsibilities during TB Treatment for Cases Living Outside of Whitehorse

YCDC TB Control Nurses
• Coordinate internal and external consultations (e.g., CMOH, BCCDC TB Services physician specialist) • Manage medication supplies from BCCDC Vaccine and Pharmacy Services • Forward copies of prescriptions to Community Health Centres • Prepare electronic copies of client-specific DOT checklists (see sample, Appendix K-5). The DOT checklist is used to help track the number of doses taken and upcoming laboratory testing dates. • Support health care providers in the field as necessary
Community Health Nurses, Health Centre Nurses

• Check new supplies of medications when they arrive from BCCDC Vaccine and Pharmacy Services to ensure that they are correct and match clients' current prescriptions
• Interview clients (or parents/guardians) regarding side effects
• Administers and records DOT and clinical monitoring on the DOT checklist, or supervises TB workers, or capable delegates to administer/record DOT
• Complete/facilitate ongoing monitoring. **Indicate on blood and sputum test requisitions that copies of the results are to be sent to YCDC TB Control and to clients' physicians**.
• Provide ongoing support and TB education to clients/families
• Follow-up with YCDC TB Control to:
  ○ Report/discuss any side effects, adherence issues, or other concerns
  ○ Maintain medication supplies
  ○ Ensure adjustments to the treatment regimen are made when necessary (e.g., when weight gain necessitates dosage adjustments)
  ○ Communicate adherence (total doses given/month)
  ○ Ensure blood work and other monitoring is completed
  ○ Collaborate to identify and implement strategies to support or improve adherence as needed
• Support TB Workers/capable designates as necessary

TB Workers / Capable Designates
• Observe clients swallowing each dose of TB medications • Interview clients (or parents/guardians) regarding side effects • Documenting administration of TB medications and clinical monitoring on the DOT checklist and in field notes • Consult immediately with supervising nurse about any side effects, adherence issues, or other concerns

9.6 Monitoring and Education during TB Treatment

Although TB treatment is usually well tolerated, all TB medications can cause side events (see Table 9-1). Baseline testing and ongoing monitoring is important

for early detection and management of side effects, drug-to-drug interactions, and adverse reactions.

To help identify clients at increased risk, health care providers should update clients' medical history and use of other prescription medications, over-the-counter medications and herbal / homeopathic / naturopathic / alternative supplements regularly over the course of TB treatment.

Clients taking anticonvulsants and either isoniazid or rifampin should be monitored closely because both of these drugs can affect the metabolism and serum levels of anticonvulsants.[7] Other important drug-to-drug interactions associated with rifampin include:

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

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

Health care providers should educate clients (or parents/guardians of children on TB treatment) on:

- TB disease process
- TB transmission (to help reduce/prevent ongoing transmission from contagious cases)
- The importance of adhering to and completing, TB treatment
- Potential side effects of the TB medication(s) they are taking
- The client's role in identifying and preventing potential side effects, with special attention to hepatotoxicity

Yukon Communicable Disease Control – TB Control
4 Hospital Road, Whitehorse, YT Y1A 3H8
Phone: 667-8323 Fax: 667-8349

- The importance of consulting with their health care provider immediately if any side effects, drug-to-drug interactions, or adverse events occur

9.6.1 Baseline Testing

Weight should be recorded for all clients at the start of treatment.

Visual acuity and red/green colour discrimination should be documented for clients prescribed ethambutol.

In general, otherwise healthy children are less likely than adolescents or adults to have pre-existing conditions or liver disease. Therefore, less comprehensive baseline blood testing is usually required. Baseline blood testing for cases **less than 16 years of age** should be done as ordered by the BCCDC TB Services physician specialist.

Baseline blood testing for cases **16 years of age and older** should include:

- Complete blood count (CBC) including platelets
- Total and direct bilirubin
- Transaminases (AST/ALT)
- Electrolytes
- HIV serology
- Hepatitis B and hepatitis C
- Random glucose
- Haemaglobin A1C
- Serum creatinine

Copies of test results should be requested on laboratory requisitions for clients' physicians and YCDC TB Control. Consult YCDC TB Control about abnormal baseline blood test results.

9.6.2 Ongoing Monitoring

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

9.6.2.1 Clinical Monitoring

Weight

Monthly monitoring of weight during TB treatment is important for monitoring response to treatment and ensuring appropriate dosing is maintained throughout treatment.

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

Side Effects

Clients on TB treatment should be assessed for hepatotoxicity and other potential side effects with each visit (see DOT record, sample Appendix K-5).

Signs/symptoms of hepatotoxicity can include:

- Anorexia (loss of appetite)
- Nausea and/or vomiting
- Abdominal discomfort
- Unexplained fatigue
- Dark-coloured urine
- Scleral icterus or jaundice

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

Clinical Improvement

Symptoms of active TB disease usually begin to resolve within the first few weeks of treatment.

Results from repeat sputum tests are used to guide decisions on discontinuation of isolation and airborne precautions, in consultation with the BCCDC TB Services physician specialist and in accordance with facility/program internal policies. It might be

necessary to induce sputum specimens for this purpose (see Appendix F).
Results from sputum tests and chest x-rays done after 2 months of treatment are used by the BCCDC TB Services physician specialist to guide decisions on length of treatment.

Sputum tests and chest x-rays are done at treatment completion to document cure and results are used by the BCCDC TB Services physician to guide decisions on whether any follow-up is necessary.

The need for additional or more frequent sputum tests or chest x-rays is determined in consultation with the BCCDC TB Services physician specialist.

9.6.2.2 Adherence

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

YCDC TB Control should be consulted when adherence issues arise. In some situations, additional supports might be required and/or it might become necessary for the Chief Medical Officer of Health (CMOH) to intervene (see 2.2).

9.6.2.3 Laboratory Testing

Direction on periodic testing for people with abnormal baseline results and people at increased risk for hepatotoxicity is provided in consultation with the BCCDC TB Services physician specialist. Other clients 16 years of age and older should have AST repeated every month for the first 3 months of treatment, and then every 2 months until treatment has been completed.

Consult YCDC TB Control about any abnormal blood test results.

Yukon Communicable Disease Control – TB Control
4 Hospital Road, Whitehorse, YT Y1A 3H8
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9.7 Medication Supplies

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

YCDC TB Control coordinates medication reorders for **all clients** on TB treatment.

9.8 Supporting Adherence to TB Treatment

Poor adherence to TB treatment is the most common cause of treatment failure. Refer to Appendix H for some tips for administering TB medications.

In Yukon, adherence to treatment for active TB disease is supported with directly observed therapy (DOT).

DOT ensures clients:

- Ingest each dose of their prescribed treatment.
- Receive careful monitoring for side effects.
- Do not develop drug resistance.
- Have regular access to encouragement and TB education from program staff.
- Are more likely to be cured.

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

Yukon Communicable Disease Control – TB Control
4 Hospital Road, Whitehorse, YT Y1A 3H8
Phone: 667-8323 Fax: 667-8349

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

Refer to Appendix H for some tips for administering TB treatment.

9.9 Treatment Completion

Duration of TB treatment is determined by the BCCDC TB Services physician specialist, and informed by:

- Type of TB disease
- Risk factors for relapse
- Interruptions in treatment
- Which TB medications were used
- Whether there is drug resistance

As clients near their anticipated completion date, YCDC TB Control Nurses consult with the BCCDC TB Services physician specialist to determine whether additional tests are necessary prior to treatment being discontinued (e.g., AST/ALT, sputum testing for TB, chest x-rays).

9.10 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 with multi-drug resistant TB disease
- Pediatric cases

Requirements for follow-up after completion of treatment for active TB disease are determined in consultation with the BCCDC TB Services physician specialist.

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

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