

Use of rifapentine and isoniazid combination therapy for the treatment of latent tuberculosis infection in Ontario



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Public Health Ontario

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This document is intended to assist Ontario health care providers and public health units in clinical decision-making by describing a range of generally acceptable approaches for the use of rifapentine and isoniazid combination therapy for the treatment of latent tuberculosis infection in eligible individuals. This document should not be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the same results. The ultimate judgment regarding care of a particular patient must be made by the prescribing health care provider in light of the individual circumstances presented by the patient. The application and use of this document is the responsibility of the user. PHO assumes no liability resulting from any such application or use.

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Abbreviations

ALP: alkaline phosphatase

ALT: alanine aminotransferase

AST: aspartate aminotransferase

CBC: complete blood count

CDC: Centers for Disease Control and Prevention

DOPT: directly observed preventive therapy

FDA: Food and Drug Administration

HIV: human immunodeficiency virus

INR: international normalized ratio

LTBI: latent tuberculosis infection

MOHLTC: Ministry of Health and Long-Term Care

PHO: Public Health Ontario

PHOL: Public Health Ontario Laboratory

PHU: public health unit

TB: tuberculosis

ULN: upper limit of normal

US: United States

WRHA: Winnipeg Regional Health Authority

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Key practice points

Background

- Rifapentine and isoniazid administered in combination once weekly for 12 weeks by direct observation (directly observed preventive therapy [DOPT]) is an effective alternative to nine months of daily isoniazid for the treatment of latent tuberculosis infection (LTBI).
- In Ontario, the Ministry of Health and Long-Term Care requires public health units (i.e., Medical Officers of Health) to request approval for rifapentine use in their jurisdiction from the provincial Chief Medical Officer of Health. Local health care providers can contact their local [public health unit](#) to discuss access to rifapentine.

Initial assessment

- To be considered eligible for rifapentine and isoniazid combination therapy patients **must** meet all of the following minimum clinical criteria:
 - Be two years of age or older;
 - Have a positive LTBI test result (tuberculin skin test or interferon gamma release assay);
 - **Active tuberculosis (TB) disease has been ruled out;**
 - **NOT** pregnant or expecting to become pregnant during treatment;
 - **NOT** known to have had a previous adverse reaction to rifampin (e.g., hepatotoxicity, hypersensitivity or thrombocytopenia);
 - **NOT** contacts of an active TB case known to have resistance to isoniazid or rifampin.

Warnings and precautions

- Rifapentine is an inducer of cytochrome P-450 oxidative enzymes as well as the P-glycoprotein transport system, and this will affect the levels of many drugs. Check for and carefully consider potential drug interactions. For example:
 - Rifapentine decreases the effectiveness of hormonal contraceptives.
 - Rifapentine is contraindicated with the use of most antiretrovirals used to treat human immunodeficiency virus (HIV) infection.
- Rifapentine may cause hepatotoxicity, hypersensitivity and/or thrombocytopenia. If concerns arise, timely communication is required between prescribers and DOPT providers.

- Prior to starting LTBI treatment, baseline alanine aminotransferase (ALT) and complete blood count (CBC) tests are recommended, as well as HIV testing (which is recommended as a routine part of the TB/LTBI work-up).

Patient monitoring

- During treatment, patients over 35 years of age or with risk factors for acute liver injury should have monthly ALT and CBC tests; monthly bilirubin testing is optional.
- If pregnancy is suspected, rifapentine treatment should be discontinued.
- Rifapentine should be taken orally with food to prevent gastrointestinal upset.

Introduction

Purpose

The purpose of this guide is to provide direction on the administration and monitoring of rifapentine and isoniazid combination therapy to treat latent tuberculosis infection (LTBI) in adults and children two years of age and over. It also includes guidance for follow-up on potential adverse events. It is intended for Ontario health care providers and public health unit staff.

For information on access to rifapentine, see the [Availability and use in Canada and Ontario](#) section of this document.

Background

An alternative, shorter-course therapy for LTBI

Individuals with LTBI serve as an important reservoir of future active tuberculosis (TB) disease.¹ Studies have estimated that in low incidence settings such as Canada, 80% to 85% of active TB cases could be attributable to reactivation of LTBI.²⁻⁴ For this reason, the identification and treatment of individuals with LTBI is an important strategy for preventing and eliminating TB.

The [Canadian tuberculosis standards](#) recommend nine months of self-administered isoniazid as the standard, first choice treatment regimen for LTBI.⁵ However, isoniazid-associated hepatotoxicity and long duration of therapy are both well recognized barriers to treatment acceptance and completion.⁶ For this reason, alternative, shorter-course LTBI treatment regimens have been evaluated, including isoniazid in combination with rifapentine. Due to its long half-life, rifapentine can be administered once weekly and when given in combination with isoniazid, shortens the duration of LTBI treatment from nine months of daily treatment to 12 weeks of once-weekly treatment.^{5,7}

Evidence from multi-centre randomized control trials and systematic reviews have demonstrated the efficacy, acceptability, and safety of 12 weeks of rifapentine and isoniazid combination therapy for LTBI, compared to nine months of daily isoniazid.⁷⁻¹²

Availability and use in the United States

In 1998, the United States (US) Food and Drug Administration (FDA) approved the use of rifapentine (Priftin®) for use, in combination with one or more antituberculosis drugs, in the treatment of active TB caused by *Mycobacterium tuberculosis*.¹³ In 2014, the US FDA expanded its approval for the use of rifapentine to include the treatment of LTBI for patients two years of age and older at increased risk of progression to TB disease (e.g., those in close contact with active TB patients, recent conversion to a positive tuberculin skin test, HIV-infected patients, or those with pulmonary fibrosis on radiograph).¹⁴

Since 2011, the US Centers for Disease Control and Prevention (CDC) have recommended rifapentine and isoniazid combination therapy administered weekly with direct observation as an “equal alternative to the nine month isoniazid regimen for otherwise healthy patients aged ≥ 12 years who have LTBI and factors that are predictive of TB developing (e.g., recent exposure to contagious TB).”¹⁵ However, the US CDC continued to recommend nine months of isoniazid as the preferred regimen for children aged two to 11 years.¹⁵

In 2018, following the US FDA approval for use of rifapentine and isoniazid to treat LTBI in patients two years of age or older in 2014, the US CDC recommendations were also updated, expanding the recommended use of 12 weekly doses of rifapentine and isoniazid combination therapy to include children aged two to 11 years of age and adding the option of weekly self-administration as an alternative to direct observation.¹⁶

Availability and use in Canada and Ontario

CANADIAN CONTEXT

In Ontario, the MOHLTC requires public health units (i.e., Medical Officers of Health) to request approval for the use of rifapentine in their jurisdiction from the provincial Chief Medical Officer of Health.

At present, rifapentine is not licensed for use in Canada. However, as it is licensed for LTBI treatment by the US FDA, it can be accessed through two mechanisms administered by Health Canada: 1) the [Special Access Programme](#)¹⁷ (for individual practitioners and patients); and 2) the [Access to Drugs in Exceptional Circumstances Regulations](#)¹⁸ via the [List of Drugs for an Urgent Public Health Need](#)¹⁹ (for public health jurisdictions).

In the past in Ontario, rifapentine has been obtained through the Special Access Programme, for use in combination with isoniazid to treat LTBI in a small number of contacts in a Toronto congregate setting outbreak.²⁰ Rifapentine and isoniazid combination therapy for LTBI is also being used elsewhere in Ontario in the context of clinical research.²¹

Through the Drugs for an Urgent Public Health Need pathway, provincial/territorial Chief Medical Officers of Health may make a request to the federal Minister of Health to enable importation and sale of rifapentine in the requesting jurisdiction for up to one year, to address an urgent public health need.¹⁹ Of note, the rifapentine product manufacturer has indicated that for jurisdictions for whom rifapentine is on the list of Drugs for an Urgent Public Health Need, the Special Access Programme route for accessing rifapentine will **not** be available (i.e., the Drugs for an Urgent Public Health Need route becomes the sole route for accessing rifapentine) (March 28, 2018 letter from Sanofi-Aventis Canada Inc. to the MOHLTC).

Since June 2017, British Columbia, Alberta, Manitoba, Newfoundland and Labrador, Yukon, Northwest Territories, and Nunavut, as well as two federal departments (Health Canada’s First Nations and Inuit

Health Branch, and Public Health Agency of Canada [for use in Correctional Services Canada facilities]) have notified the federal Minister of Health of an urgent public health need to use rifapentine within their jurisdictions for the “treatment of LTBI caused by *Mycobacterium tuberculosis* in combination with isoniazid in patients at high risk of progression to TB disease”.¹⁹

ONTARIO CONTEXT

On June 15, 2018, rifapentine was added to the [List of Drugs for an Urgent Public Health Need](#) for Ontario for a period of one year. As a result, the Chief Medical Officer of Health is able to procure rifapentine directly from the supplier for use, in selected circumstances, as part of an alternative regimen to treat LTBI in combination with isoniazid. As noted above, this route for accessing rifapentine from the product manufacturer is now the sole route for accessing rifapentine in Ontario (i.e., per the product manufacturer, rifapentine will no longer be available via the Special Access Programme route) (March 28, 2018 letter from Sanofi-Aventis Canada Inc. to the MOHLTC).

The Ontario MOHLTC requires public health units (i.e., Medical Officers of Health) to request approval for the use of rifapentine in their jurisdiction from the provincial Chief Medical Officer of Health. Public health units may contact the Office of the Chief Medical Officer of Health for further information on rifapentine access, use, and monitoring requirements (see [Appendix B](#)). Local health care providers considering use of this LTBI treatment regimen can contact their local public health unit to discuss access to rifapentine.

Guide

Initial assessment: clinical criteria for use

Rifapentine and isoniazid combination therapy is recommended solely for the treatment of latent TB infection (i.e., it is not recommended for the treatment of active TB disease). Active TB disease **must** be ruled out prior to initiation of treatment.

To be considered eligible for rifapentine and isoniazid combination therapy patients **must** meet all of the following minimum criteria:

- Be two years of age or older;
- Have a positive LTBI test result (i.e., tuberculin skin test or interferon gamma release assay);
- Active TB disease has been ruled out** (see *Ruling out active TB* below);
- NOT** pregnant or expecting to become pregnant during treatment;
- NOT** known to have had a previous adverse reaction to rifampin (e.g., hepatotoxicity, hypersensitivity or thrombocytopenia);
- NOT** contacts of an active TB case known to have resistance to isoniazid or rifampin.

Ruling out active TB

Patients confirmed as having LTBI require further evaluation to rule out active TB disease. This should include the following:^{22,23}

- Clinical evaluation including a history, review of risk factors, and physical examination for signs and symptoms of active pulmonary *and* extrapulmonary TB disease (e.g., enlarged lymph nodes);
- Chest x-rays (anteroposterior and lateral views);
- Microbiological examination of sputum (if symptomatic and/or abnormal chest x-ray findings*).

For detailed guidance on the clinical evaluation for and diagnosis of active pulmonary and extrapulmonary TB disease, please refer to the 2014 [Canadian tuberculosis standards](#).^{23,24} For further assistance, please contact your local [public health unit](#) and/or PHO.

*Note: In an outbreak setting, and in consultation with the local public health unit and Public Health Ontario Laboratory (PHOL) *prior to any specimen collection activities*, consideration may be given to collecting sputum from all close contacts of the index case, regardless of clinical and/or radiographic findings.

For further information on laboratory specimen collection, handling, and turnaround times, please refer to the PHOL [test directory for Mycobacterium](#). The PHOL Customer Service Centre can be reached at 416-235-6556 or 1-877-604-4567 (toll-free), or by email at: CustomerServiceCentre@oahpp.ca.



Do NOT proceed with administration of rifapentine and isoniazid combination therapy for the treatment of LTBI until active TB disease has been ruled out.

Warnings and precautions

Hepatotoxicity

Both isoniazid and rifapentine may cause elevations in liver transaminases.¹³ Patients should be monitored for signs and symptoms and advised to discontinue medication and contact their health care provider if nausea, vomiting, anorexia, abdominal pain, or jaundice occur (see *Patient monitoring and follow-up* for more information).

Hypersensitivity

Rifapentine may cause hypersensitivity reactions, including (rarely) anaphylaxis;¹³ patients should be monitored for signs and symptoms of such reactions.

Signs and symptoms of hypersensitivity reactions include: hypotension, urticaria, angioedema, acute bronchospasm, conjunctivitis, thrombocytopenia, or a syndrome that may include: weakness, fatigue, nausea, vomiting, headache, fever/chills, myalgia/arthralgia, shortness of breath, cough, chest pain, syncope, and palpitations.¹³

A recent analysis of adverse events (i.e., systemic drug reactions) observed in a large clinical trial found that while systemic drug reactions (particularly a flu-like syndrome) were more common in the rifapentine and isoniazid combination therapy arm than in the nine months of daily isoniazid arm of the trial, severe reactions were rare (0.3%) with no reported anaphylaxis or death.²⁵

Discolouration of body fluids

Rifapentine may cause a reddish-orange discolouration of body fluids and/or tissues (e.g., tears, sweat, saliva, urine, teeth, tongue, etc.);¹³ patients should be advised to wear glasses instead of contact lenses, if necessary, for the duration of treatment as this discolouration may be permanent.

Drug interactions

Rifapentine is an inducer of cytochrome P-450 oxidative enzymes as well as the P-glycoprotein transport system and this will affect the levels of many drugs. Check for and carefully consider potential drug interactions.

Rifapentine decreases the effectiveness of hormonal contraceptives.

Rifapentine is contraindicated with the use of most antiretrovirals used to treat HIV infection.

Rifapentine is an inducer of cytochrome P-450 oxidative enzymes as well as the P-glycoprotein transport system.¹³ As a result, concomitant use of rifapentine with other drugs that are metabolized via these mechanisms may cause a significant decrease in plasma concentrations and subsequent loss of therapeutic effect of the concurrently administered drug.¹³

[Table 1](#) provides a list of the most common drug classes known to interact with rifapentine. However, this list is not exhaustive and health care providers should verify potential interactions of any drug which will be prescribed concurrently with rifapentine.

The decision to use rifapentine concomitantly with any of these drugs should be made only after careful consideration of the potential benefits and risks and with very close monitoring, following consultation with all prescribing health care providers (and a TB specialist, if indicated). In some situations (e.g., a patient receiving methadone treatment) it may be possible to continue treatment with the drug by raising and very closely monitoring therapeutic drug dosages during rifapentine/isoniazid therapy and then lowering to the usual dosage after rifapentine/isoniazid treatment completion with close monitoring.²⁶

HORMONAL CONTRACEPTIVES AND ANTIRETROVIRALS

Rifapentine decreases the effectiveness of hormonal contraceptives.¹³ Women using oral, transdermal patch, or other systemic hormonal contraceptives (e.g., hormone-releasing intrauterine devices) should be advised to add a barrier method for the duration of treatment.^{13,15}

Because the potential drug interactions have not yet been comprehensively studied, rifapentine is contraindicated with the use of most antiretrovirals with the exception of efavirenz and raltegravir.^{16,27} Treatment decisions in HIV-infected patients taking antiretrovirals other than these two medications require consultation with the health care provider treating the patient's HIV infection (i.e., primary care provider or HIV specialist).

Pregnancy

If pregnancy is suspected, rifapentine treatment should be discontinued.

Because safety in pregnancy has not yet been established, rifapentine is contraindicated in pregnancy and for women planning to become pregnant during the course of treatment.¹⁵ If pregnancy is suspected, treatment should be discontinued and the prescribing clinician should be notified.

Note: Among 126 pregnancies reported among participants inadvertently exposed to rifapentine and isoniazid combination therapy during two clinical trials, no unexpected fetal loss or congenital anomalies were reported.²⁸

Table 1. Common drug interactions with rifapentine (adapted from reference 13)

Drug class	Examples of drugs within class
Antiarrhythmics	Disopyramide, mexiletine, quinidine, tocainide
Antibiotics	Chloramphenicol, clarithromycin, dapson, doxycycline; fluoroquinolones (such as ciprofloxacin)
Anticoagulants (including novel oral anticoagulants)	Warfarin, apixaban, dabigatran, rivaroxaban
Anticonvulsants	Phenytoin
Antimalarials	Quinine
Azole antifungals	Fluconazole, itraconazole, ketoconazole
Antipsychotics	Haloperidol
Barbiturates	Phenobarbital
Benzodiazepines	Diazepam
Beta-blockers	Propranolol
Calcium channel blockers	Diltiazem, nifedipine, verapamil
Cardiac glycoside preparations	Digoxin
Corticosteroids	Prednisone
Fibrates	Clofibrate
Hormonal contraceptives/progestins	Ethinyl estradiol, levonorgestrel
Immunosuppressants	Cyclosporine, tacrolimus
Methylxanthines	Theophylline
Narcotic analgesics	Methadone
Oral hypoglycemics	Sulfonylureas (e.g., glyburide, glipizide)

Drug class	Examples of drugs within class
Phosphodiesterase-5 inhibitors	Sildenafil
Thyroid preparations	Levothyroxine
Tricyclic antidepressants	Amitriptyline, nortriptyline

Note: This table is not exhaustive. The mechanism of action of any drug prescribed concurrently with rifapentine should be reviewed prior to use.

Medication dosage, administration, and storage

Dosage

Table 2. Dosage for combination regimen of rifapentine and isoniazid in 12 once-weekly doses along with daily pyridoxine (vitamin B6)

Medication	Dosage (kilograms [kg], milligrams [mg])
Rifapentine¹³ (available in 150 mg tablets)	<u>Weight-based (i.e., regardless of age):</u> 10.0 kg – 14.0 kg = 300 mg (2 tablets) 14.1 kg – 25.0 kg = 450 mg (3 tablets) 25.1 kg – 32.0 kg = 600 mg (4 tablets) 32.1 kg – 49.9 kg = 750 mg (5 tablets) ≥50.0 kg = 900 mg (6 tablets) (maximum)
Isoniazid¹³ (available in 100 mg and 300 mg tablets)	<u>Children two to 11 years of age:</u> 25.0 mg/kg (rounded to nearest 50 mg or 100 mg) up to 900 mg maximum <u>Adults and children ≥12 years of age:</u> 15.0 mg/kg (rounded to nearest 50 mg or 100 mg) up to 900 mg maximum
Pyridoxine (Vitamin B6)^{29,30} (to prevent potential peripheral neuropathies associated with isoniazid)	In some individuals receiving isoniazid, the Canadian Tuberculosis Standards recommend pyridoxine (vitamin B6) to prevent neuropathy, at a suggested dose of 1 mg/kg/day for children, ²⁹ or 25.0 mg per day for adults. ³⁰ An additional possible pediatric dosing approach, for consideration by the prescribing health care provider, is as follows: <u>Children weighing 10 to 20 kg:</u> 12.5 mg/day <u>Children weighing >20 kg:</u> 25.0 mg/day

Administration and storage

- Rifapentine and isoniazid combination therapy must be administered orally once weekly for 12 weeks by directly observed preventive therapy (DOPT).⁵
- As with other drugs, there is a rare but potential risk of anaphylaxis associated with the administration of rifapentine.
- Treatment completion is defined as at least 11 weekly doses administered within 16 weeks of treatment start; doses must be separated by >72 hours.⁷
- Rifapentine should be taken orally with food to prevent gastrointestinal upset. If patients are unable to swallow tablets, they can be crushed and added to a small amount of semi-solid food (e.g., pudding, applesauce).¹³
- Both rifapentine and isoniazid should be stored at room temperature (15°C to 30°C) and protected from freezing, excessive heat, and humidity.¹³
- Rifapentine tablets are supplied in blister packs that should be kept sealed until usage.¹³

Patient monitoring and follow-up

PRIOR TO INITIATING TREATMENT:

Baseline alanine aminotransferase (ALT) and complete blood count (CBC) tests are recommended for all patients, as well as HIV testing (which is recommended as a routine part of the TB/LTBI work-up).

DURING TREATMENT:

Patients should be asked at each visit about signs or symptoms of hepatotoxicity, hypersensitivity and thrombocytopenia (e.g., fever, jaundice, purpuric rash, myalgia/arthralgia, syncope, or >1 day of nausea, vomiting, anorexia, or abdominal pain). An ALT and bilirubin should be checked if symptoms of hepatotoxicity are present and the medication held until results are available. Platelets (i.e., CBC) should be checked if signs or symptoms of thrombocytopenia are present.

Patients over 35 years of age or with risk factors for acute liver injury (e.g., pre-existing liver disease, regular alcohol use, or use of potentially hepatotoxic medications) should have routine monthly ALT and CBC tests; monthly bilirubin testing is optional.

If concerns arise, timely communication is required between prescribing health care providers and DOPT providers.

Collaboration between prescribers and DOPT providers

A collaborative and coordinated approach to patient monitoring and follow-up between the prescribing health care provider and public health unit (PHU) staff is essential to the patient's adherence to and completion of LTBI treatment. This is particularly important in the context of a regimen that is administered by weekly DOPT.

The general roles and responsibilities of both the prescribing health care provider and the public health unit staff (or delegate) providing DOPT are detailed below and summarized in [Table 3](#).

Health care provider

INITIAL ASSESSMENT (WEEK 0)

IF NOT YET COMPLETED (SEE [INITIAL ASSESSMENT](#)):

- Confirm diagnosis of LTBI (i.e., positive tuberculin skin test or interferon gamma release assay).
- Evaluate patient to rule out active TB (i.e., clinical examination and chest x-rays, plus sputum specimens if symptomatic and/or abnormal chest x-ray findings).
- Determine if patient meets eligibility criteria and has no known contraindications for treatment with rifampine and isoniazid combination therapy; this includes determining that female patients are not pregnant or planning on becoming pregnant in the next three months.
- Contact your local [public health unit](#) to discuss access to rifampine and DOPT resources.

WHEN ALL OF THE ABOVE STEPS HAVE BEEN COMPLETED, PROCEED WITH THE FOLLOWING:

- Discuss the risks and benefits of LTBI treatment, including potential risk of hepatotoxicity, hypersensitivity reactions and thrombocytopenia associated with rifampine and isoniazid combination therapy.
- Assess the patient's understanding of treatment and the likelihood of adherence, including:
 - Availability for 12 consecutive weekly doses administered by DOPT (i.e., patient is not planning on moving or travelling within the next three months and is willing to accommodate visits with public health unit staff [or delegate]).
 - Availability for baseline and monthly follow-up appointments with health care provider (including blood work as necessary).
- If patient consents to LTBI treatment with rifampine and isoniazid combination therapy:
 - Provide education and counselling regarding:
 - The need to stop treatment and seek medical attention/contact health care provider if they develop any of the following symptoms: fever, jaundice, purpuric rash, myalgia/arthralgia, syncope, or >1 day of nausea, vomiting, anorexia, or abdominal pain.
 - The need to stop treatment and contact health care provider if pregnancy is suspected.
 - The need for women to add a barrier method of birth control if using oral, transdermal patch, or systemic hormonal contraceptives.
 - The potential discolouration of body fluids and the need to switch from contact lenses to glasses if necessary.

- Perform baseline laboratory testing:
 - The following tests are recommended at baseline for all individuals starting on rifapentine and isoniazid combination therapy:
 - Baseline alanine aminotransferase (ALT)
 - Complete blood count (CBC)
 - HIV testing (which is recommended as a routine part of the TB/LTBI work-up).
 - Note: As needed, based on the results of baseline testing, consider and discuss the possible benefits and risks of proceeding with LTBI treatment. For patients with baseline ALT elevation of more than 2.5 to 3 times the upper limit of normal, chronic alcohol consumption, or severe liver disease manifested by low albumin and coagulopathy or encephalopathy, the risks of LTBI treatment may outweigh benefits. If LTBI treatment is undertaken, close monitoring is needed.³¹

ONGOING ASSESSMENT (WEEKS 4, 8, AND 12)

- Perform clinical assessment for signs and symptoms of treatment-associated adverse events. Specifically inquire about symptoms suggestive of hepatotoxicity, hypersensitivity and thrombocytopenia (e.g., fever, jaundice, purpuric rash, myalgia/arthralgia, syncope, or >1 day of nausea, vomiting, anorexia, or abdominal pain).
 - Reinforce patient education and counselling (see above).
 - Perform follow-up laboratory testing:
 - The following tests are recommended on a monthly basis for patients over 35 years of age or with risk factors for acute liver injury including daily alcohol consumption, concomitant treatment with other potentially hepatotoxic drugs, chronic liver disease, or baseline elevation of ALT to >2 times the upper limit of normal [ULN]):
 - Testing of liver enzymes (ALT; bilirubin is optional)
 - CBC
- If hepatotoxicity or thrombocytopenia is suspected, consider expert consultation as needed. For reference, the [American Thoracic Society Statement: Hepatotoxicity of Antituberculosis Therapy](#)³¹ outlines possible approaches to follow-up.
- If concerns arise regarding adverse events (e.g., hepatotoxicity, hypersensitivity or thrombocytopenia), notify PHU staff (or delegate) administering DOPT.

DOPT provider (public health unit staff or delegate*)

ADMINISTER WEEKLY DOPT (WEEKS 1 TO 12)

- Use a symptom checklist at each weekly visit to assess for signs and symptoms of:
 - Active TB disease (e.g., cough, fever, night sweats)
 - Rifapentine- and/or isoniazid-associated adverse events including hepatotoxicity, hypersensitivity and thrombocytopenia.
 - Notify the prescribing health care provider as soon as possible if signs and/or symptoms of any of the above are present.
- Reinforce patient education and counselling regarding:

- The need to stop treatment and seek medical attention/contact health care provider if they develop any of the following symptoms: fever, jaundice, purpuric rash, myalgia/arthralgia, syncope, or >1 day of nausea, vomiting, anorexia, or abdominal pain.
- The need to stop treatment and contact health care provider if pregnancy is suspected.
- The need for women to add a barrier method of birth control if using oral, transdermal patch, or systemic hormonal contraceptives.
- The potential discolouration of body fluids and the need to switch from contact lenses to glasses if necessary.
- If indicated (i.e., patient misses one or more scheduled doses), identify potential barriers to treatment adherence. Problem-solve with patient and consult with prescribing health care provider if concerns persist.
- Administer the rifampine and isoniazid combination therapy regimen, along with pyridoxine (with food if possible) by providing the client with the medications and observing them being taken.

*Note: The [*Canadian tuberculosis standards*](#) state that the main function of directly observed therapy (i.e., watching the patient swallow medications to support TB treatment completion) can be achieved by public health staff, outreach workers, or volunteers.²⁹ Public health units are responsible for DOPT and should consider the optimal local strategies for providing DOPT for this LTBI regimen (e.g., LTBI providers and/or settings), ensuring adequate training and support for DOPT providers.

Table 3. Summary of health care provider and DOPT provider roles and responsibilities for evaluation, monitoring, and follow-up of individual patients on rifapentine and isoniazid combination therapy for LTBI treatment

Provider	Actions	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Health care provider	Confirm LTBI diagnosis	✓												
	Rule out active TB	✓												
	Eligibility assessment, including not pregnant	✓												
	Initial consultation with local public health unit about DOPT	✓												
	Clinical assessment	✓				✓				✓				✓
	Patient education	✓				✓				✓				✓
	Bloodwork: baseline	✓												
	Bloodwork: routine (if indicated)					✓				✓				✓
	Further consultation with PHU staff	If indicated												
DOPT provider (PHU staff or delegate)	Patient education		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Assess for adverse events		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Administer medications		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Consult with health care provider	If indicated												

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Appendix A: Guide development and expert consultation process

This document was developed by PHO medical and scientific staff in response to a May 2018 request from the Office of the Chief Medical Officer of Health at the Ontario Ministry of Health and Long-Term Care. The guide was adapted from:

Roussin B, Plourde P. Clinical practice guidelines: process for administration of rifapentine and isoniazid (INH) in adults and children for the treatment of LTBI [Internet]. Winnipeg, MB: Winnipeg Regional Health Authority; 2017 [cited 2018 Jul 17]. Available from: wrha.mb.ca/prog/tuberculosis/files/GuidelineLTBI-2018.pdf³²

PHO medical and scientific staff consulted iteratively with a small group of external clinical and public health TB experts, as well as Ontario Ministry of Health and Long-Term Care (MOHLTC) to inform updates and changes to the 2017 Winnipeg Regional Health Authority document for the Ontario context. PHO staff prepared background materials, including a focused scan of recently published systematic reviews examining the efficacy, acceptability and safety of this LTBI regimen, as well as recently published US and Canadian guidelines for the use of this regimen (see [References](#)). PHO staff drafted and iteratively revised this guide, addressing feedback received from consultation participants. The consultation process consisted of two in-person meetings, in June and July 2018, as well as the opportunity to provide electronic written feedback.

See below for the list of participants in the expert consultation process. Participants had no conflicts of interest to disclose.

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Appendix B: Monitoring adverse events and reporting rifapentine use: Ontario MOHLTC requirements for public health units

Procedure for data collection and monitoring

Given that rifapentine is not a licensed medication in Canada, some key indicators will need to be closely monitored and regularly reported.

Key indicators will include:

- a) **Number of patients started on rifapentine and isoniazid combination therapy (i.e., 3HP treatment):** total number of patients started on 3HP treatment.
- b) **Treatment completion:** proportion of persons starting 3HP treatment who complete at least 11 weekly doses within 16 weeks of treatment start; doses must be separated by >72 hours (numerator = number of persons **completing 3HP**; denominator = number of persons **starting 3HP**).
- c) **Reason for discontinuation:** proportion of persons who discontinue 3HP and are unable to complete a full course (at least 11 weekly doses within 16 weeks) with **reason for discontinuation** (numerator = number of persons **discontinuing 3HP**; denominator = number of persons **starting 3HP**).
- d) **Severe side effects must be reported to the *Office of the Chief Medical Officer of Health*** (in addition to completing an online report to Health Canada – see note below); generally this would be side effects that are considered Grade 3 (inability to perform work or normal daily activities), Grade 4 (life threatening or disabling) or Grade 5 (death) (numerator = number of persons with **severe side effects**; denominator = number of persons **starting 3HP**).

Note: Persons taking 3HP who develop severe side effects must be reported to Health Canada, as per: <https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>.

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