Public Health Ontario | Santé publique Ontario

Considerations for preventive treatment of latent tuberculosis infection (LTBI) during a rifampin supply shortage

July 24, 2019

Purpose

This document provides priority-based considerations for preventive treatment of LTBI in the context of a rifampin supply shortage in Ontario. It is intended to be a resource for Ontario health care providers (i.e., prescribers) and public health units. It does **not** address use of rifampin for treatment of active TB, or for prophylaxis of other infectious diseases (e.g., invasive meningococcal disease).

Background

Preventive treatment for LTBI should use established regimens, chosen for individual circumstances and should:

- Be initiated only after active TB has been ruled out.
- Avoid contraindications.
- Aim to minimize harms (i.e., risk of adverse events including hepatotoxicity and drug interactions), and maximize benefits (i.e., prevention of active TB disease).[1]
- Consider the likelihood of treatment adherence and completion, with attention to social determinants of health (i.e., homelessness, substance use).[2,3]

The *Canadian tuberculosis standards* (2014) identify the standard regimen for the preventive treatment of LTBI, nine months of daily isoniazid (9INH).[1] Four months of rifampin (4RMP) and 12 weeks of once weekly directly-observed isoniazid and rifapentine (3HP) are acceptable shorter alternatives to 9INH for preventive treatment of LTBI, which:

- Offer particular benefits for those at risk of drug-induced hepatotoxicity or for whom barriers to adherence and treatment completion exist.[1,2]
- Are supported by a growing body of evidence. A large randomized controlled trial published in 2018 found that 4RMP was non-inferior to 9INH in terms of preventing active TB, with better safety and treatment completion[4], and use of this regimen has increased recently in Ontario (personal communication, Drew Swanson, Senior Program and Policy Advisor, Ministry of Health).

Chapter 6 of the *Canadian tuberculosis standards* provides a summary of the recommended regimens for treatment of LTBI, as well as considerations for special populations (e.g., pregnant and breastfeeding persons, adults aged 65 years and over). Refer to the manufacturer's product monographs for details on specific drugs.

The following priority-based considerations for LTBI treatment (Table 1) are based on categories of risk for progression from LTBI to active TB disease, as per the *Canadian tuberculosis standards* (Appendix 1).

Table 1. Priority-based considerations for preventive treatment of LTBI in the context of a rifampin supply shortage in Ontario

Priority Group Description	Regimen Options[†]	Key Considerations for Providers	Notes
1. Highest priority groups			
Individuals who have already started a preventive treatment regimen for LTBI that includes rifampin (e.g., 4RMP).	4RMP	*Consult local public health unit (PHU).* The local supply of rifampin should be anticipated to be sufficient to ensure treatment completion. If preventive treatment for LTBI with rifampin is interrupted, consultation with a TB specialist is recommended.	To avoid wastage, ensure the exact number of doses is dispensed (i.e., do not give 3 full bottles [300 x 300 mg capsules] if only 120 doses [240 x 300 mg capsules] are needed). During the shortage, 150 mg capsules may need to be used (i.e., doubling the pill burden).
Contacts who have LTBI and the source case has an INH-resistant strain of TB.	4RMP	See above.	See above.
Contacts who need window prophylaxis pending definitive LTBI testing (e.g., children < 5 years of age, immuno-suppressed/people with HIV).	INH or RMP	*Consult local PHU and/or a TB specialist.* Contacts < 5 years of age who were exposed to an INH-sensitive source case should receive INH pending definitive LTBI testing. Consult a pediatric TB specialist if exceptions are being considered.	Window prophylaxis involves giving treatment for LTBI in the interval between an initial negative LTBI test result (e.g., negative tuberculin skin test) and the definitive LTBI test result at least 8 weeks after the last day of exposure, for those at highest risk of progression to active TB.[5] See chapters 9 and 12 of the *Canadian tuberculosis standards* for additional information on window prophylaxis treatment.[5]

Priority Group Description	Regimen Options†	Key Considerations for Providers	Notes
2. Second highest priority groups			
Individuals at high risk of progression to active TB (see Appendix 1). **Preventive treatment of LTBI should <u>not</u> be delayed for this group.**	9INH	Standard regimen (see Appendix 2).	For HIV-infected individuals, consider consulting local PHU/a TB specialist.
	3HP	*Consult local PHU.* Consider 3HP especially for individuals: • For whom a shorter and/or less hepatotoxic regimen may be critical for achieving treatment completion (e.g., those who are homeless/underhoused, substance users, teenagers), AND • Where there is local capacity for providing directly observed preventive treatment in close collaboration with a willing prescriber.	See Use of rifapentine and isoniazid combination therapy for the treatment of latent tuberculosis infection in Ontario. Rifapentine must be requested by the local Medical Officer of Health and approved through the provincial Office of the Chief Medical Officer of Health, Public Health. Rifapentine is incompatible with most HIV antiretrovirals. Consider consulting a TB specialist.
	4RMP	*Consult local PHU.* As an alternative shorter regimen, 4RMP can be considered, if the local supply of rifampin is anticipated to be sufficient to ensure treatment completion.	To avoid wastage, see suggestions above. 4RMP is an alternative regimen for HIV-infected individuals with INH intolerance, or for whom shorter duration of therapy is perceived as critical to achieving treatment completion, as long as it is compatible with HIV antiretroviral treatment. Consider consulting a TB specialist.

Priority Group Description	Regimen Options[†]	Key Considerations for Providers	Notes
3. Lower priority groups, in whom to consider alternatives to 4RMP or deferral of LTBI preventive treatment initiation			
Individuals at moderate risk of progression to active TB (see Appendix 1).	9INH	Standard regimen (see Appendix 2).	n/a
	3HP	*Consult local PHU.* Consider 3HP especially for individuals: • For whom a shorter and/or less hepatotoxic regimen may be critical for achieving treatment completion (e.g., those who are homeless/underhoused, substance users, teenagers), AND • Where there is local capacity for providing directly observed preventive treatment in close collaboration with a willing prescriber.	See Use of rifapentine and isoniazid combination therapy for the treatment of latent tuberculosis infection in Ontario. Rifapentine must be requested by the local Medical Officer of Health and approved through the provincial Office of the Chief Medical Officer of Health, Public Health.
	Defer	*Consider consulting the local PHU.* If 4RMP is the only acceptable option for the individual, consider deferring treatment until the rifampin shortage is over.	n/a
Individuals at slightly increased, low, or very low risk of progression to active TB (see Appendix 1).	9INH	Standard regimen (see Appendix 2).	n/a
	Defer	If 4RMP is the only acceptable option for the individual, consider deferring treatment until the rifampin shortage is over.	n/a

[†]4RMP = 4 months of daily rifampin; INH = isoniazid; RMP = rifampin; 9INH = 9 months of daily INH ; 3HP = 12 weeks of once weekly INH and rifapentine

References

1. Menzies D, Alvarez G, Khan K. Treatment of latent tuberculosis infection. In: Menzies D, editor. Canadian tuberculosis standards. 7th ed. Ottawa, ON: Her Majesty the Queen in Right of Canada; 2014. p. 1-32. Available from: canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition/edition-18.html

2. Houston S, Wong T. Tuberculosis and human immunodeficiency virus. Treatment of latent tuberculosis infection. In: Menzies D, editor. Canadian tuberculosis standards. 7th ed. Ottawa, ON: Her Majesty the Queen in Right of Canada; 2014. p. 1-29. Available from: canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition/edition-6.html

3. Greenaway C, Khan K, Schwartzman K. Tuberculosis surveillance and screening in selected high-risk populations. In: Menzies D, editor. Canadian tuberculosis standards. 7th ed. Ottawa, ON: Her Majesty the Queen in Right of Canada; 2014. p. 1-26. Available from: canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition/edition-9.html

4. Menzies D, Adjobimey M, Ruslami R, Trajman A, Sow O, Kim H, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. NEJM. 2018;379:440-453. Available from: nejm.org/doi/full/10.1056/NEJMoa1714283

5. Rea E, Rivest P. Contact follow-up and outbreak management in tuberculosis control. In: Menzies D, editor. Canadian tuberculosis standards. 7th ed. Ottawa, ON: Her Majesty the Queen in Right of Canada; 2014. p. 1-32. Available from: canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition/edition-8.html

6. Toronto Public Health. Isoniazid (INH) – latent tuberculosis infection (LTBI) treatment guidelines [Internet]. Toronto, ON: City of Toronto; 2019 [cited 2019 Jul 8]. Available from: toronto.ca/community-people/health-wellness-care/information-for-healthcare-professionals/communicable-disease-info-for-health-professionals/tuberculosis-information-for-health-professionals/tb-resources-for-your-patients/

Appendix 1: Risk groups for progression to active TB[1]

Risk group	Risk factors for progression to active TB disease

High	• Close contacts of a recent active pulmonary TB case within the last 2 years.
	• Medical risk factors including:
	  ○ HIV/AIDS
	  ○ Transplantation
	  ○ Chronic renal failure
	  ○ Silicosis
	  ○ Carcinoma of the head and neck
	  ○ Abnormal chest x-ray (fibronodular disease)

Moderate	• Medical risk factors including:
	  ○ Tumour necrosis factor alpha inhibitors
	  ○ Diabetes mellitus (all types)
	  ○ Treatment with glucucorticoids (≥ 15 mg/day)
	  ○ Young age when infected (under 5 years of age)

Slightly increased, low, very low	• Medical risk factors including:
	  ○ Heavy alcohol consumption (three or more drinks per day)
	  ○ Underweight (i.e., < 90% ideal body weight; for most people this is a body mass index of ≤ 20)
	  ○ Cigarette smoker (1 pack per day)
	  ○ Abnormal chest x-ray (granuloma)
	  ○ Person with positive tuberculin skin test (TST), no known risk factor, normal chest x-ray ('low risk reactor')
	  ○ Person with positive two-step TST (booster), no known risk factor, normal chest x-ray

Appendix 2: INH regimen for the treatment of LTBI[6]

Drug	Dose and duration	Comments
Isoniazid (INH)	**Adults:** 5 mg/kg to a maximum of 300 mg daily for 9 months **Children:** 10-15 mg/kg to a maximum of 300 mg daily for 9 months	• With ≥ 80% compliance: • INH daily for 12 months gives 93% protection and INH daily for 6 months gives 69% protection from progression to TB disease (INH for 12 months is not much more effective than 9 months). • Duration is the most important variable, not continuity (i.e., extend treatment long enough to achieve the equivalent of 9 months of 100% compliance). • Test for HIV. • INH is available in a liquid suspension.
Vitamin B6 (pyridoxine)	25 mg daily	• Use with INH in adults when there is malnutrition, alcoholism, pregnancy, diabetes, uremia, and/or other disorders that may predispose patient to neuropathy; also recommended in the postpartum period. • Not indicated in pediatric patients, except in breastfed infants or malnourished children.

Table adapted with permission from Toronto Public Health.

Citation

Ontario Agency for Health Protection and Promotion (Public Health Ontario). Considerations for preventive treatment of latent tuberculosis infection (LTBI) during a rifampin supply shortage. Toronto, ON: Queen's Printer for Ontario; 2019.

Disclaimer

This document was developed by Public Health Ontario (PHO). PHO provides scientific and technical advice to Ontario's government, public health organizations and health care providers. PHO's work is guided by the current best available evidence at the time of publication.

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 preventive treatment of latent tuberculosis infection in the context of a rifampin supply shortage. 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.

Public Health Ontario

Public Health Ontario is a Crown corporation dedicated to protecting and promoting the health of all Ontarians and reducing inequities in health. Public Health Ontario links public health practitioners, front-line health workers and researchers to the best scientific intelligence and knowledge from around the world.

Public Health Ontario provides expert scientific and technical support to government, local public health units and health care providers relating to the following:

- communicable and infectious diseases
- infection prevention and control
- environmental and occupational health
- emergency preparedness
- health promotion, chronic disease and injury prevention
- public health laboratory services

Public Health Ontario's work also includes surveillance, epidemiology, research, professional development and knowledge services. For more information about PHO, visit: publichealthontario.ca.