



Process for monitoring Rifampin administration in adults for the treatment of LTBI

AUTHORED BY: J. Gabor, MD FRCPC & C. Jacobson, RN PHN

APPROVED BY:

ITBS Oversight

Date

May 9, 2017

Date

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1.0 INTENT:

- 1.1 To provide clinical practice and operational guidance to Primary Care clinical teams to ensure consistency in the monitoring of Rifampin administration for the treatment of Latent Tuberculosis Infection (LTBI) in adults.
- 1.2 To provide the minimum recommended clinical and laboratory monitoring (including in rural and/or remote communities) needed to administer Rifampin for the treatment of LTBI (either directly observed preventative therapy [DOPT] or self-administered therapy [SAT]), as well as recommended action when Rifampin toxicity is suspected or confirmed.

2.0 DEFINITIONS:

- 2.1 **Active TB disease:** active clinical disease due to *Mycobacterium tuberculosis* (MTb) that is usually symptomatic and for which microbiologic tests are usually positive and radiologic tests usually abnormal.
- 2.2 **Latent tuberculosis infection (LTBI):** the presence of latent or dormant infection with MTb. Persons with LTBI have no evidence of clinically active TB disease, i.e. they have no symptoms, no evidence of radiologic changes that suggest active TB disease and negative microbiologic tests; they are not infectious.
- 2.3 **Rifampin:** Rifampin is an anti-tuberculosis antibiotic that is used in combination with other anti-TB medications to treat active TB disease; but can also be used alone to treat LTBI. A course of Rifampin taken once daily SAT (or 5 days per week Mon-Fri DOPT) for 3 to 4 months is used to treat LTBI.
- 2.4 **Nursing Station:** a field unit/facility staffed (primarily with nurses but may also include visiting physicians, dentist, mental health counsellor, physiotherapist, pediatrician and other specialties) in order to carry out community and primary health care programs including: out-patient



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treatment and short-term in-patient care, public health services, chronic disease management, acute and emergency care.

2.5 Primary Care Provider: a provider who is specialized in LTBI management and legally authorized to order and receive results of tests, and are able to prescribe medication, in this instance Physicians and Nurse Practitioners. They must also receive LTBI education and training through WRHA Integrated Tuberculosis Services. The Primary Care Provider is ultimately responsible to initiate baseline and follow up testing, monitoring and adjusting Rifampin lab investigations and medication doses.

2.6 Primary Care Nurses: role may include follow up with tracking of lab results, review them, and alert the prescriber to abnormal results.

2.7 Clinical Support Staff: unregulated health care workers, e.g., Primary Care Assistants, Unit Assistants, Nursing Assistants or Medical Office Assistants, or equivalent role.

2.8 Clinical Team: refers to LTBI prescribing clinicians (physicians/nurse practitioners), nursing station nurses, clinical support staff, learners (health care students, residents), laboratory and diagnostic imaging staff, specialist providers (Chest Medicine, Infectious Diseases), and individuals with LTBI and their families.

2.9 Individual: refers to Patient and/or Client

3.0 BACKGROUND

3.1 Rifampin is increasingly being utilized for the treatment of LTBI because of its relatively shorter course of treatment (3 to 4 months), its lower hepatotoxicity versus isoniazid, its higher treatment completion rates, and its equivalent effectiveness versus isoniazid. The Canadian TB Standards (7th edition) provide recommendations for the monitoring of liver enzymes during administration of 9-month isoniazid treatment courses for the management of LTBI (Chapter 6). If an alternative regimen is used, such as Rifampin, then the same monitoring schedule is suggested until the end of



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therapy. These recommendations are admittedly based on “very weak evidence” in that there is little to no published experimental or trial data to guide the monitoring of liver biochemistry in these situations. All recommendations are therefore based primarily on expert opinion upon review of the available medical literature.

- 3.2 The recommendations of the Canadian TB Standards are based on the ready availability of monthly medical evaluations and do not take into account monitoring challenges in remote communities or other unique circumstances.
- 3.3 The LTBI Committee of WRHA Integrated TB Services have created modified recommendations (informed by the CTS 7th edition) for baseline and follow up monitoring of liver enzymes and complete blood counts (CBC) during the administration of Rifampin to treat LTBI.

4.0 Cautions and Drug Interactions

- 4.1 Rifampin is considered safe in pregnancy according to the Canadian TB Standards (Chapter 6).
- 4.2 Rifampin is considered safe to administer to nursing mothers according to the Canadian TB Standards (Chapter 6).
- 4.3 Initiation of concomitant warfarin, oral contraceptives, methadone, sulfonylureas, benzodiazepines, digoxin, beta-blockers, anticonvulsants, antimicrobials, or immunosuppressants during treatment with Rifampin requires review by the local prescribing physician given the drug-drug interactions between Rifampin and the aforementioned agents, and discussion with a TB specialist if concerns persist is recommended.
- 4.4 Rifampin is contraindicated with the use of protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) for the treatment of HIV infection. Treatment decisions in HIV-positive patients therefore require consultation with an HIV specialist.



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5.0 PROCEDURE (Laboratory Investigations)

5.1 Baseline testing:

- 5.1.1 Baseline alanine aminotransferase (ALT) and complete blood count (CBC) is recommended for everyone being started on Rifampin for LTBI treatment. Nursing Station staff or Primary Care Providers should ensure that this baseline testing has been performed.
- 5.1.2 Bilirubin testing is optional and may be considered based on clinical suspicion of underlying liver disease and/or age >50 years. Some Nursing Station staff or Primary Care Providers may also order baseline bilirubin testing based on the remoteness of the community and desire for additional baseline results.

5.2 Follow up testing:

- 5.2.1 During the course of Rifampin therapy for LTBI, monthly testing of liver enzymes (minimally an ALT; bilirubin is optional) and CBC is recommended for all persons over the age of 35 years.
- 5.2.2 Monthly ALT (bilirubin optional) and CBC testing is also recommended for persons with other risk factors for acute liver injury regardless of age, including daily alcohol consumption, concomitant treatment with other potentially hepatotoxic drugs, chronic liver disease, or baseline elevation of ALT to >2X upper limit of normal (ULN).
- 5.2.3 Some Primary Care Providers may choose to order monthly ALT (and possibly bilirubin) and CBC based on the remoteness of the community and desire for additional monitoring.
- 5.2.4 Nursing Station staff and Primary Care clinic teams have a shared responsibility and should ensure that all follow up monthly ALT (and bilirubin if ordered) and CBC testing is performed, in addition to a monthly clinical assessment of each person taking Rifampin for LTBI.
- 5.2.5 Clinical team communication is expected between all key team members to ensure role clarity for each aspect of LTBI follow-up and monitoring. Ensuring tests are done and consultations have occurred is a shared responsibility among all members of



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the clinical team. Efforts to follow-up on outstanding orders should be guided by clinical urgency and the principles of patient self-management and choice as per PCOG #30 Results

Management: Outstanding Orders

<http://home.wrha.mb.ca/prog/primarycare/files/PCOG30-ResultsMgt-OO.pdf>.

- 5.2.6 Clinical Support Staff are responsible for: manual tracking of letters, daily monitoring and management of the status of tracked orders, documenting relevant information in the report, and bringing items of concern to the attention of the Primary Care Provider. Additionally, Clinical Support Staff could be requested to ensure a monthly clinic appointment for assessment of each individual taking Rifampin for LTBI. If the Primary Care Provider provides direction to Clinical Support Staff they will follow up with the individual (appointment reminders, following up to reschedule a missed appointment).
- 5.2.7 Monthly clinical assessment by Nursing Station Nurses or Primary Care Nurses consists of symptom review, with particular attention to symptoms associated with liver injury or other toxicity, with notification of the Primary Care Provider of any of the following symptoms:

Symptoms associated with Rifampin toxicity:	
Fatigue	Orthostatic symptoms
Easy bruising	Arthralgia/myalgia
Weakness	Yellow skin
Anorexia	Spontaneous bleeding
Vague abdominal pain	Facial/lip swelling
Right upper quadrant pain	Wheezing
Nausea/vomiting	Dyspnea
Itching	Fever
Skin rash	

- 5.2.8 Any symptoms listed in 5.2.7 should lead to prompt review by the Primary Care Provider of laboratory results to ensure that



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symptoms are not attributable to an adverse reaction to Rifampin, with further action/clinician notification as directed below.

6.0 PROCEDURE (Responding to suspected Rifampin toxicity)

6.1 ALT slightly elevated but less than 3X upper limit of normal (ULN):

- 6.1.1 Continue Rifampin.
- 6.1.2 Nursing Station staff or Primary Care Nurse could communicate results to the individual and Primary Care Provider to review whether the individual is at increased risk for Rifampin liver injury (such as underlying chronic liver disease, other medications including acetaminophen, or heavy alcohol use).
- 6.1.3 Nursing Station staff or the Primary Care Provider is responsible to advise the Primary Care Nurse to encourage the individual to avoid or minimize use of acetaminophen or alcohol (as appropriate).
- 6.1.4 Nursing Station staff or Primary Care Provider is responsible for ordering the test to repeat all liver enzymes and CBC in one week.

6.2 ALT elevated >3X (but less than 5X) ULN with NO symptoms of liver injury or other adverse reaction:

- 6.2.1 Continue Rifampin.
- 6.2.2 Nursing Station staff or Primary Care Nurse to communicate results to the individual and monitors closely for symptoms of Rifampin liver toxicity and/or other adverse effects (see 4.2.7), and reports any symptoms to Primary Care Provider.
- 6.2.3 Nursing Station staff or Primary Care Provider is responsible to review whether the individual is at increased risk for Rifampin liver injury such as underlying chronic liver disease, other medications including acetaminophen, or heavy alcohol use.
- 6.2.4 Nursing Station staff or Primary Care Provider and Primary Care Nurse encourages the individual to avoid or minimize use of acetaminophen or alcohol (as appropriate).
- 6.2.5 Nursing Station staff or Primary Care Provider is responsible to repeat all liver enzymes and CBC in one week.



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6.2.6 If becomes symptomatic, go to 6.3.

6.3 ALT elevated >3X (but less than 5X) ULN WITH symptoms of liver injury or other adverse reaction:

6.3.1 The Nursing Station staff or Primary Care Provider would give direction to **stop the Rifampin** and complete the following:

6.3.1.1 Repeat ALT and obtain AST, total and direct bilirubin, INR, albumin and CBC as soon as possible.

6.3.1.2 Follow liver enzymes every 5 to 7 days. If further elevation occurs to > 5X ULN, or if direct bilirubin elevated, go to 6.4.

6.3.1.3 Continue to check liver enzymes weekly until back to normal. Nursing Station staff or Primary Care Provider would give direction to arrange appointment to review adverse reaction.

6.4 ALT elevated >5X ULN (or doubling of ALT if baseline elevation of ALT, or any elevation in total or direct bilirubin, or INR > 1.4):

6.4.1 Nursing Station staff or Primary Care Provider would give direction to **stop the Rifampin** and complete the following:

6.4.1.1 If has symptoms of liver injury or other adverse effects are present, an urgent clinical evaluation is warranted. If clinically unwell with multiple symptoms or if jaundiced, notify Primary Care Provider immediately and consider hospitalization to expedite further evaluation.

6.4.1.2 If no symptoms, repeat ALT and obtain AST, alkaline phosphatase, GGT, total and direct bilirubin, CBC, INR, and albumin as soon as possible.

6.4.1.3 If no symptoms, but either bilirubin or INR is elevated, notify Primary Care Provider and consider hospitalization to expedite further evaluation including hepatic ultrasound (to exclude other causes of liver toxicity – see 6.4.1.4).

6.4.1.4 Consider other causes of liver injury including acute viral hepatitis (HAV, HBV, HCV), toxic insult (e.g.



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acetaminophen, alcohol), ischemic insult (thrombosis), or obstructive jaundice (gallstones).

- 6.4.1.5 If no symptoms, and direct bilirubin and INR are normal, follow liver enzymes every 5 to 7 days until results return to normal (which may take a few weeks).
- 6.4.2 When ALT <2 times ULN, Primary Care Provider may restart Rifampin and repeat ALT on day 3 and day 7 of re-challenge to make sure that ALT is not rising again. If ALT rises again, and more than 3 months of Rifampin is needed to complete LTBI therapy, then it may be faster (and safer if no other drug interactions) to give INH or moxifloxacin/levofloxacin as alternative treatment for LTBI.
- 6.4.3 If any liver enzymes rise further or fail to normalize, Primary Care Provider should consider consultation with a Hepatologist.

6.5 Thrombocytopenia (platelets less than 80 X10⁹/L):

- 6.5.1 Nursing Station staff or Primary Care Provider would give direction to **stop the Rifampin** and complete the following:
 - 6.5.1.1 If has any symptoms of rifampin-induced thrombocytopenia (purpura at any site, ecchymosis not attributable to trauma, mucosal bleeding from any site including but not limited to epistaxis, gum bleeding, hemoptysis, hematuria, hematemesis, or menorrhagia) an urgent clinical evaluation is warranted. Notify Primary Care Provider immediately and consider hospitalization to expedite further evaluation.
 - 6.5.1.2 If platelets between 80 and 150 X10⁹/L, repeat CBC and also obtain peripheral blood smear, total and direct bilirubin, INR, urea, creatinine, and urinalysis.
 - 6.5.1.3 Repeat CBC in 48-72 hours. If platelets decrease further or fail to return to normal, Primary Care Provider should consider an urgent consultation with a Hematologist.
 - 6.5.1.4 Continue to check CBC every 5 days until platelets are greater than 150 X10⁹/L. Do NOT re-challenge with Rifampin.



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6.5.1.5 If more than 3 months of Rifampin is needed to complete LTBI therapy, then it may be faster (and safer if no other drug interactions) to give INH or moxifloxacin/levofloxacin as alternative treatment for LTBI.

SCOPE: Applicable exclusively to WRHA Primary Care Direct Operations Clinics (Access Downtown) and can be adopted by the Community Health Agencies (Klinik), who provide Adult treatment for Latent TB Infection (either 5 days per week Mon-Fri Directly Observed Therapy or daily self-administered therapy), by Latent TB clinicians who work in collaboration with the WRHA Public Health Program TB team and First Nations and Inuit Health Branch.

Consultation Process: Integrated Tuberculosis Services: LTBI Committee, ITBS Management Committee & ITBS Oversight Committee

SOURCE/REFERENCES

1. Public Health Agency of Canada (2014) *Canadian Tuberculosis Standards 7th ed.*
2. Stagg HR, Zenner D, Harris RJ, et al. Treatment of Latent Tuberculosis Infection. *Ann Intern Med* 2014;161:419-428 doi:10.7326/M14-1019

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