



Process for administration of rifapentine and isoniazid (INH) in adults and children for the treatment of LTBI

AUTHORED BY: B. Roussin, P. Plourde, H. Chang

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PAGE

Page 1 of 15

1.0 INTENT:

- 1.1 To provide clinical practice and operational guidance to clinical care teams to ensure consistency in the administration and monitoring of rifapentine and INH for the treatment of Latent Tuberculosis Infection (LTBI) in adults and children over 2 years old.
- 1.2 To provide the minimum recommended clinical and laboratory monitoring needed to administer rifapentine and INH for the treatment of LTBI (via once weekly directly observed preventative therapy [DOPT]), as well as recommended action when rifapentine or INH toxicity is suspected or confirmed.
- 1.3 To provide the minimum dataset required for the monitoring and evaluation of rifapentine and INH use.

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 **Rifapentine:** Rifapentine is an anti-tuberculosis antibiotic that is used in combination with INH to treat LTBI. It is not licensed in Canada, but can be accessed via Health Canada's Special Access Program (<https://www.canada.ca/en/health-canada/services/drugs-health-products/special-access/drugs.html>) or acquired through the Importation of Drugs for Urgent Public Health Need (<https://www.canada.ca/en/health-canada/services/drugs-health-products/access-drugs-exceptional-circumstances/list-drugs-urgent-public-health-need.html>). A course of



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PAGE

Page 2 of 15

rifapentine and INH taken once weekly DOPT for 12 weeks is used to treat LTBI.

- 2.4 **INH:** isoniazid (INH) 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 latent tuberculosis infection (LTBI). A course of rifapentine and INH taken once weekly DOPT for 12 weeks is used to treat LTBI.
- 2.5 **Directly Observed Preventative Therapy (DOPT):** DOPT is a process whereby a health care provider or delegate watches the patient swallow each dose of LTBI medication, helping to ensure that higher treatment completion rates are achieved. DOPT also provides a valuable opportunity to address client concerns, client dignity, and access to social services.
- 2.6 **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 treatment and short-term in-patient care, public health services, chronic disease management, acute and emergency care.
- 2.7 **Primary Care Provider:** a provider who with some education and training is specialized in LTBI management and legally authorized to order and receive results of tests, and is able to prescribe medication, in this instance Physicians and Nurse Practitioners. The Primary Care Provider is ultimately responsible to initiate baseline and follow up testing, monitoring and adjusting rifapentine and INH lab investigations and medication doses.
- 2.8 **Primary Care Nurses:** role may include follow up with tracking of lab results, review them, and alert the prescriber to abnormal results.
- 2.9 **Clinical Support Staff:** unregulated health care workers, e.g., Primary Care Assistants, Unit Assistants, Nursing Assistants or Medical Office Assistants, or equivalent role.
- 2.10 **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



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PAGE

Page 3 of 15

providers (Chest Medicine, Infectious Diseases), and individuals with LTBI and their families.

2.11 **Individual:** refers to Patient and/or Client.

3.0 BACKGROUND

- 3.1 Rifapentine and INH in combination is increasingly being utilized for the treatment of LTBI, because of its shorter course of treatment (12 weeks), its ease of administration (once weekly DOPT), its lower hepatotoxicity versus daily INH, its higher treatment completion rates (>80%), and its equivalent effectiveness versus daily INH. The Canadian TB Standards (7th edition) provide a recommendation in favour of the use of once weekly rifapentine and INH for 12 weeks, as long as it is administered via DOPT with “very close monitoring” (Chapter 6). This recommendation is based on “moderate evidence” since there is reasonably good published data to support the use of rifapentine/INH combination therapy.
- 3.2 This rifapentine/INH administration guideline has been created using the “*Northern Guidelines for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection*”



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TARGET REVIEW DATE

PAGE

Page 4 of 15

developed in the Northern Regional Health Authority on July 15, 2014 (informed by the CTS 7th edition).

4.0 CRITERIA for use of rifapentine and INH

- 4.1 **Rifapentine and INH should only be used for the management of LTBI (and not for the treatment of active TB disease), and requires administration by DOPT.**
- 4.2 The following additional criteria must all be met to qualify for rifapentine and INH once weekly DOPT:
 - 4.2.1 Age over 2 years
 - 4.2.2 Positive result on a test for LTBI (tuberculin skin test or interferon gamma release assay)
 - 4.2.3 Normal chest radiography or evidence of healed pulmonary TB on chest radiography (i.e., active pulmonary TB disease is ruled out) AND no current symptoms suggestive of active TB disease
 - 4.2.4 Expectation of a high probability that treatment completion will be achieved, as foreseen from medical and social circumstances.
- 4.3 If there is any suspicion of active tuberculosis on CXR or current symptoms suggestive of possible active TB disease, three (induced) sputum for

INTERIM DRAFT



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PAGE

Page 5 of 15

mycobacterial culture should be obtained and negative results confirmed prior to using rifapentine/INH.

- 4.4 Persons diagnosed with LTBI should be offered testing for HIV serology.
- 4.5 If being treated in a remote northern community, the Nursing Station and/or Primary Care Provider must have the resources to be able to closely monitor a once weekly rifapentine/INH DOPT course of treatment.
- 4.6 Rifapentine and INH combination therapy is **NOT recommended** in the following circumstances:
 - 4.6.1 Children aged <2 years, because the safety and pharmacokinetics of rifapentine have not been established for them
 - 4.6.2 HIV-infected patients receiving antiretroviral treatment, because the drug interactions have not been studied
 - 4.6.3 Pregnant women or women expecting to become pregnant during treatment, as safety in pregnancy is unknown
 - 4.6.4 Persons with a history of previous adverse reactions to rifampin (such as hypersensitivity or thrombocytopenia)
 - 4.6.5 Persons who have LTBI with presumed INH or rifampin resistance.

5.0 MEDICATION ADMINISTRATION

- 5.1 Rifapentine and INH must be administered by DOPT once weekly for 12 weeks.
- 5.2 Weekly DOPT administration of rifapentine and INH must be accompanied by a complete assessment for adverse effects (see appendix 1 for Latent Tuberculosis Infection Directly-Observed Preventive Therapy Tracking Record).
- 5.3 Completion of rifapentine and INH will be defined as at least 11 weekly doses administered within 16 weeks of treatment start; doses must be separated by > 72 hours to count. Doses should not be routinely administered at a 72-hour interval. Any single 'catch up' dose administered



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TARGET REVIEW DATE

PAGE

Page 6 of 15

within a <6 day interval should include planning for the next dose to be no less than 7 days later.

5.4 Dosage of INH for adults and children older than 11 years is 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum.

5.4.1 Vitamin B6 (pyridoxine) 50 mg should also be administered once weekly.

5.5 Dosage of rifapentine is based on weight ranges as follows:

5.5.1 10.0-14.0 kg = 300 mg

5.5.2 14.1-25.0 kg = 450 mg

5.5.3 25.1-32.0 kg = 600 mg

5.5.4 32.1-49.9 kg = 750 mg

5.5.5 ≥ 50 kg = 900 mg (maximum).

5.6 Dosage of INH for children aged 2-11 years is 25 mg/kg; 900 mg maximum.

6.0 CAUTIONS AND DRUG INTERACTIONS

6.1 There is no data on the use of rifapentine in pregnancy or with nursing mothers; hence it should not be administered in these settings. Women of childbearing age who will be prescribed rifapentine/INH should be counseled to avoid pregnancy, with fertility control methods offered if appropriate (keeping in mind interaction between rifapentine and oral contraceptives). If pregnancy is suspected during the course of treatment with rifapentine/INH, treatment should be discontinued, a pregnancy test ordered, and the prescribing clinician should be notified.

6.2 Rifapentine reddens secretions, including urine and tears, and can stain contact lenses; to avoid this staining it may be prudent to recommend using glasses instead of contact lenses for the duration of treatment.

6.3 Initiation of concomitant warfarin, oral contraceptives, corticosteroids, methadone, sulfonyleureas, benzodiazepines, digoxin, beta-blockers, calcium channel blockers, anticonvulsants, macrolide antibiotics, quinolone antibiotics,azole antifungals, or immunosuppressants (i.e., cyclosporine) during treatment with rifapentine requires review by the prescribing



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TARGET REVIEW DATE

PAGE

Page 7 of 15

clinician given the drug-drug interactions, and discussion with a TB specialist is recommended if concerns persist.

- 6.4 Rifapentine 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.

7.0 PROCEDURE FOR MONITORING TREATMENT

- 7.1 Patients will undergo regular clinical assessment, including the following components:

- 7.1.1 Monthly inquiries about symptoms of active TB disease
- 7.1.2 Weekly inquiries about rifapentine/INH side effects
- 7.1.3 Baseline and subsequent monthly laboratory tests

- 7.2 In addition, clinical support staff (such as DOPT workers) must use a Latent Tuberculosis Infection Directly-Observed Preventive Therapy Tracking Record (see appendix 1) for weekly inquiries about adverse effects and must report problems promptly to the prescribing clinician.

- 7.3 At each weekly encounter, patients will be instructed in their preferred language to **seek medical attention immediately if they have fever, yellow eyes, dizziness, rash, an influenza-like illness, or > 1 day of nausea, vomiting, weakness, abdominal pain, or loss of appetite.**

- 7.4 **Rifapentine and INH will be withheld while the cause of suspected adverse effect symptoms is being determined.**

- 7.5 **Baseline testing:**

- 7.5.1 Baseline alanine aminotransferase (ALT), as well as complete blood count (CBC) is recommended for everyone being started on rifapentine and INH for LTBI treatment. Nursing Station staff or Primary Care Providers should ensure that this baseline testing has been performed.

- 7.5.2 All persons being considered for LTBI treatment should have HIV testing.

- 7.6 **Follow up testing:**

- 7.6.1 During the course of rifapentine and INH therapy for LTBI, monthly testing of liver enzymes (minimally an ALT; bilirubin is



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Date

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TARGET REVIEW DATE

PAGE

Page 8 of 15

optional) and CBC is recommended for all persons over the age of 35 years.

- 7.6.2 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).
- 7.6.3 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.
- 7.6.4 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 weekly clinical assessment of each person taking directly observed rifapentine and INH for LTBI.
- 7.6.5 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 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.
- 7.6.6 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 rifapentine and INH for LTBI. If the Primary Care Provider provides direction to Clinical Support Staff they



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Date

October 2021

TARGET REVIEW DATE

PAGE

Page 9 of 15

will follow up with the individual (appointment reminders, following up to reschedule a missed appointment).

- 7.6.7 Weekly clinical assessment by Nursing Station Nurses or Primary Care Nurses or by those administering DOPT 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 rifapentine/INH toxicity:
Fatigue
Weakness
Fever
Flushing, chills or sweats
Headache
Arthralgia/myalgia
Orthostatic symptoms (dizziness)
Wheezing
Dyspnea
Anorexia
Nausea/vomiting
Vague abdominal pain
Right upper quadrant pain
Itching
Hives
Swollen skin/membranes
Facial/lip swelling
Skin rash
Yellow skin or yellow eyes
Easy bruising
Spontaneous bleeding

- 7.6.8 Any symptoms listed in 7.6.7 should lead to withholding any further administration of rifapentine and INH until prompt review is completed by the Primary Care Provider, to ensure that



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Date

October 2021

TARGET REVIEW DATE

PAGE

Page 10 of 15

symptoms are not attributable to an adverse reaction to rifapentine/INH, with further action to be determined by prescribing clinician. Using clinical judgment, prescribing clinician may choose to discontinue rifapentine/INH due to side effects or to continue with once weekly rifapentine/INH if symptom(s) deemed not related to LTBI treatment.

8.0 PROCEDURE FOR RESPONDING TO SUSPECTED RIFAPENTINE/INH TOXICITY

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

- 8.1.1 Continue rifapentine/INH.
- 8.1.2 Repeat ALT and check AST, ALP and total bilirubin in 1 week. If increasing but asymptomatic, repeat weekly liver enzymes as above. If stable or decreasing, and still asymptomatic, check monthly liver enzymes.
- 8.1.3 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 liver injury (such as underlying chronic liver disease, other medications including acetaminophen, or heavy alcohol use).
- 8.1.4 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).
- 8.1.5 Nursing Station staff or Primary Care Provider is responsible for ordering the test to repeat all liver enzymes.

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

- 8.2.1 Continue rifapentine/INH.
- 8.2.2 Repeat ALT and check AST, ALP and total bilirubin in 1 week. If increasing but still asymptomatic, repeat weekly liver enzymes as



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Date

December 2017

Updated

Date

October 2021

TARGET REVIEW DATE

PAGE

Page 11 of 15

above. If stable or decreasing, and still asymptomatic, check monthly liver enzymes.

8.2.3 Nursing Station staff or Primary Care Nurse to communicate results to the individual and monitors closely for symptoms of liver toxicity and/or other adverse effects (see 7.6.7), and reports any symptoms to Primary Care Provider.

8.2.4 Nursing Station staff or Primary Care Provider is responsible to review whether the individual is at increased risk for liver injury such as underlying chronic liver disease, other medications including acetaminophen, or heavy alcohol use.

8.2.5 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).

8.2.6 Nursing Station staff or Primary Care Provider is responsible to repeat all liver enzymes.

8.2.7 If becomes symptomatic, go to 8.3.

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

8.3.1 The Nursing Station staff or Primary Care Provider would give direction to **stop rifapentine/INH** and complete the following:

8.3.1.1 Check liver enzymes, INR, albumin and CBC as soon as possible.

8.3.1.2 Follow liver enzymes every 5 to 7 days. If further elevation occurs to > 5X ULN, or if direct bilirubin elevated, go to 8.4.

8.3.1.3 Continue to check liver enzymes weekly until back to normal. Nursing Station staff or Primary Care Provider



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TARGET REVIEW DATE

PAGE

Page 12 of 15

would give direction to arrange appointment to review adverse reaction.

8.4 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):

- 8.4.1 Nursing Station staff or Primary Care Provider would give direction to **stop rifapentine/INH** and complete the following:
 - 8.4.1.1 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.
 - 8.4.1.2 If no symptoms, check liver enzymes, CBC, INR, and albumin as soon as possible.
 - 8.4.1.3 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 8.4.1.4).
 - 8.4.1.4 Consider other causes of liver injury including acute viral hepatitis (HAV, HBV, HCV), toxic insult (e.g. acetaminophen, alcohol), ischemic insult (thrombosis), or obstructive jaundice (gallstones).
 - 8.4.1.5 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).
- 8.4.2 When ALT <2 times ULN, Primary Care Provider may restart rifapentine/INH and repeat liver enzymes 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 weekly doses of rifapentine/INH is needed to complete LTBI therapy, then consideration may be



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Date

October 2021

TARGET REVIEW DATE

PAGE

Page 13 of 15

given to switching to moxifloxacin or levofloxacin as alternative treatment for LTBI.

8.4.3 If any liver enzymes rise further or fail to normalize over time, Primary Care Provider should consider consultation with a Hepatologist.

8.5 Thrombocytopenia (platelets between 80 and 150 X10⁹/L):

8.5.1 Continue rifapentine/INH.

8.5.2 Repeat CBC and also obtain peripheral blood smear, total and direct bilirubin, INR, urea, creatinine, and urinalysis.

8.5.3 Repeat CBC in 48-72 hours. If platelets decrease to below 80 X10⁹/L, go to 8.6.

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

8.6.1 Nursing Station staff or Primary Care Provider would give direction **to stop the rifapentine/INH** and complete the following:

8.6.1.1 If has any symptoms of rifapentine-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.

8.6.1.2 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.

8.6.1.3 Continue to check CBC every 5 days until platelets are greater than 150 X10⁹/L.

8.6.1.4 **DO NOT re-challenge** with rifapentine or rifampin, or any other rifamycin.

8.6.1.5 If more than 3 weekly doses of rifapentine/INH is needed to complete LTBI therapy, then consideration may be given to switching to moxifloxacin or levofloxacin as alternative treatment for LTBI.



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Updated

Date

October 2021

TARGET REVIEW DATE

PAGE

Page 14 of 15

9.0 PROCEDURE FOR DATA COLLECTION AND MONITORING

9.1 Given that rifapentine is not a licensed medication in Canada, some key indicators will need to be closely monitored and regularly reported. Any clinics prescribing rifapentine/INH will need to report quarterly to WRHA Integrated TB Services Oversight Committee the following minimum indicators.

9.2 Key indicators which need to be measured include:

9.2.1 **Treatment completion** – proportion of persons starting rifapentine/INH treatment who complete at least 11 weekly doses within 16 weeks of treatment start; doses must be separated by > 72 hours to count (numerator = number of persons **completing rifapentine/INH**; denominator = number of persons **starting rifapentine/INH**)

9.2.2 **Reason for discontinuation** – proportion of persons who discontinue rifapentine/INH 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 rifapentine/INH**; denominator = number of persons **starting rifapentine/INH**).

9.2.3 **Severe side effects** – proportion of persons taking rifapentine/INH with severe side effects (requiring reporting to Health Canada <https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>); 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 rifapentine/INH**).

9.2.4 **Severe side effects should also be reported to the WRHA regional Population and Public Health TB team by fax to 204-957-0884** (in addition to completing an online report to Health Canada – see 9.2.3).



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TARGET REVIEW DATE

PAGE

Page 15 of 15

- 9.3 A data collection form may assist with monitoring and evaluation of rifapentine/INH indicators (see appendix 2 – rifapentine treatment reporting form).
- 9.4 Data for monitoring and evaluation of rifapentine/INH will be reviewed at quarterly meetings of WRHA Integrated Tuberculosis Services Oversight Committee.

SCOPE: Applicable to select Primary Care Clinicians and Specialists who are prescribing LTBI treatments in Manitoba, in clinics that are **able to provide once weekly Directly Observed Preventative Therapy** and that are **able to perform monitoring and evaluation of rifapentine use**, in collaboration with the WRHA Public Health Program Surveillance and Epidemiology unit and/or First Nations and Inuit Health Branch.

Consultation Process: WRHA Integrated Tuberculosis Services: ITBS Oversight Committee

SOURCE/REFERENCES

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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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