Consultation or referral to a TB specialist is recommended for persons who are:

- HIV positive
- Children
- Have an abnormal CXR (other than simple granulomas)
- Contacts of multidrug-resistant TB
- Pregnant women at high risk of TB

Drug	Adverse reactions	Monitoring	Comments
Isoniazid (INH)	• Liver enzyme elevation • Hepatitis • Peripheral neuropathy • CNS • Gastrointestinal • Hematological • Hypersensitivity * Drug interactions – refer to Compendium of Pharmaceuticals and Specialties	• Baseline serum aminotransferases • Monitor monthly • Monthly ALT, AST for patients with: ▫ Pre-existing liver disease (particularly Hepatitis C) ▫ Age ≥35 ▫ History of alcohol abuse or prior drug induced hepatitis ▫ Pregnant or within 3 months postpartum • If AST level >5 times baseline level, or if symptoms of hepatotoxicity develop (i.e., anorexia, nausea, vomiting, abdominal discomfort, dark-coloured urine, jaundice or scleral icterus), then INH should be stopped and a TB specialist consulted • Repeat monitoring of liver enzymes for patients with symptoms consistent with hepatic side effects	Hepatitis risk correlated with age: Age Group / Risk < 20 — 0.1–0.2% 20–34 — 0.3% 35–49 — 0.5% 50–64 — 1.0–3.0% ≥ 65 — 2.0–5.0% • Hepatitis risk increases with daily alcohol consumption, or viral hepatitis • INH-induced hepatitis is almost always reversible • INH given alone to persons with active TB disease can lead to INH-resistant TB
Rifampin (RMP)	• CNS • Dermatologic • Hypersensitivity • Hepatitis • Gastrointestinal • Hematological • Renal * ***Many drug interactions – refer to Compendium of Pharmaceuticals and Specialties***	• Baseline bilirubin, serum creatinine, CBC, platelets, and liver enzymes • Repeat measurements if: - Baseline results are abnormal - Patient has symptoms of an adverse reaction	• Colours bodily fluids reddish-orange • May permanently discolour contact lenses • By accelerating estrogen metabolism, RMP may interfere with effectiveness of birth control pills; alternative contraceptive method should be advised • Contraindicated in severe chronic liver disease • **RMP given alone to persons with active TB disease can lead to resistance.**

Management of LTBI when treatment is refused, contraindicated or stopped before completion

Patients who cannot or will not start or complete LTBI treatment should be instructed carefully regarding the symptoms of active TB and instructed to return for medical assessment if those symptoms arise. Routine CXR or follow up is not recommended unless the risk of TB disease is high. In this situation, consider regular follow up for 2 years, as this is the period of highest risk (e.g., at 6, 12 and 24 months). For further information, contact your local health unit.

Source: CTS, 2013

Additional Information: Interferon Gamma Release Assays (IGRAs)

- Two types of IGRAs are approved by Health Canada for use: QuantiFERON-TB Gold In-Tube (QFT) and TSPOT.
- Currently, these tests are not covered by OHIP. At printing, QFT testing is currently available on a limited basis through Gamma-Dynacare Medical Laboratories. Refer to www.gamma-dynacare.com/Content/HealthcareProviders/ImportantNotices.aspx?expandable=1

Websites

www.tstin3d.com
www.phac-aspc.gc.ca
www.who.org
www.lung.ca
www.bcgatlas.org
www.cdc.gov/tb/
www.on.lung.ca

For more information or to order more copies:

Toronto Public Health
416-338-7600
toronto.ca/health

References

1. Greenaway, C., et al. Tuberculosis: Evidence review for newly arriving immigrants and refugees. CMAJ 2011; 183 (12): E852 - E857.
2. Canadian Tuberculosis Standards, 7th edition, Public Health Agency of Canada and the Canadian Lung Association/Canadian Thoracic Society, 2013, p. 125A.
3. Canadian Pharmacists Association. (2013). Compendium of Pharmaceuticals and Specialties (e-CPS). Retrieved Sept. 2013 from https://www.e-therapeutics.ca/home.faq.action
4. Canadian Tuberculosis Standards, 7th edition, Public Health Agency of Canada and the Canadian Lung Association/Canadian Thoracic Society, 2013.
5. Centers for Disease Control and Prevention. (2000). 6th edition. Core Curriculum on Tuberculosis. Treatment of Latent Tuberculosis (Chap. 5), updated 2013. Retrieved from http://www.cdc.gov/TB/education/corecurr/default.htm

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Quick reference

Assessment and Treatment Of Latent Tuberculosis Infection

Indications for tuberculin skin testing (TST)

- To diagnose tuberculosis TB infection in persons at increased risk for progression to active disease
- It is **not** reliable for diagnosis of active disease

Who should be tested

- Contacts of persons recently diagnosed with active pulmonary TB
- Foreign-born persons and visitors from TB-endemic countries, especially those <20 years old and those who have arrived in the last two years
- All refugees, between the ages of 20 and 50, from countries with a high incidence of TB, as soon as possible, after their arrival in Canada[1]
- All other adult immigrants if they have risk factors that increase the risk of active tuberculosis[1]
- People who are at increased risk of progression to active TB disease
- People with radiographic evidence of old, healed TB and no history of treatment
- Health care workers at risk for occupational exposure to TB
- Staff and residents in communal care, including correctional facilities, long-term care, and shelters/services for homeless/underhoused
- Persons from Aboriginal communities with high rates of TB
- Travelers to countries with high TB incidence[2]

Tuberculin testing is generally discouraged for those with no elevated risk of infection with TB and no known risk factors for progression to active TB disease.

Risk factors for development of active tuberculosis in those with latent TB infection (LTBI)

High risk – screen at any age

- Acquired immunodeficiency syndrome (AIDS)
- Human immunodeficiency virus infection (HIV)
- Transplantation (related to immune-suppressant therapy)
- Silicosis
- Chronic renal failure requiring hemodialysis
- Carcinoma of head/neck
- Recent TB infection (≤2 years)
- Abnormal chest x-ray (fibronodular disease)

Moderate risk/increased risk-screen ≤ 65 years

- Treatment with TNF inhibitors
- Diabetes mellitus
- Treatment with glucocorticoids equivalent to prednisone (≥15mg/day)
- Young age when infected (0–4 years)
- Heavy alcohol consumption (≥3 drinks/day)
- Underweight (≤90% ideal body weight, generally BMI ≤20)
- Cigarette smoking (1 pack/day)
- Abnormal chest x-ray (granuloma)

Low risk ≤ 50 years

- Person with positive TST, no known risk factors, normal chest x-ray ("low risk reactor")

Contraindications for tuberculin skin testing

- **Documented positive skin test** or **active tuberculosis** in the past
- Tuberculin reactions that have severely blistered in the past
- Clear past history of treatment for TB infection or disease
- Extensive burns or eczema at the usual test site. Choose another site
- Major viral infections or live-virus vaccinations in the past month, for example, measles, mumps, rubella, varicella or yellow fever

The following are <u>not</u> contraindications for TB skin testing:

- Common cold
- Immunized with any vaccine on the same day
- Recently been vaccinated with non-live virus vaccines
- Pregnant or breastfeeding
- Received BCG vaccination in the past
- History of positive tuberculin skin test that is **not** documented
- Taking low dose corticosteroids (≤15 mg Prednisone daily)

Technique for the skin test

- 0.1ml (5-TU) of purified protein derivative (PPD)
- Inject **intradermally** on volar (inner) aspect of the forearm
- Injection should raise a small wheal approximately 6-10 mm in diameter, which will disappear in 10–15 minutes

Reading

- Skin test must be read by a trained health professional. Self reading is inaccurate and should not be done.
- Read 48–72 hours after administration.
- Use a ruler or caliper to measure **induration** of the transverse diameter (i.e., at right angle to the long axis of the forearm). Record in millimetres (mm) even if no induration (0 mm).
- Do not measure erythema (redness).

Interpretation

Proper interpretation of the TST should include all of the following:

1. Size of the reaction (induration), in mm
2. Predictive value of the test (considering likelihood of true exposure, false-negative and/or false-positive reactions)
3. Risk of progression to active disease

Online TST interpreter available at the McGill University website: www.tstin3d.com

TST Result	Situation in which reaction is considered positive
0–4 mm	In general this is considered negative, and no treatment is indicated. Children under 5 years of age who are contacts of an infectious case should be treated pending results of repeat TST 8 weeks after exposure.
≥5 mm	• HIV Infection • Close contact of active contagious case within past 2 years • Abnormal chest x-ray with fibronodular disease • Treatment with immunosuppressive medications (e.g., TNF inhibitors) • End-stage Renal Disease/Dialysis
≥10 mm	All others, including diabetes, malnutrition (<90% ideal body weight), cigarette smoking, daily alcohol consumption (>3 drinks/day), silicosis, hematologic malignancies (leukemia, lymphoma) and certain carcinomas (e.g., head and neck)

Adapted from Canadian TB Standards (CTS), 2013, p. 46A, Table 2

Causes of false-negative TST

- Error in administration or reading
- Age <6 months or advanced age
- Immunization within the past 4 weeks with MMR, varicella or yellow fever
- Immune suppression
- Major viral illness in the past 4 weeks (e.g., measles, mumps, mononucleosis)
- Severe malnutrition, chronic renal failure, severe physiological stress (surgery, burns)
- **Active tuberculosis** or other severe illness

Causes of false-positive TST

- Infection with non-tuberculous mycobacteria (i.e., environmental mycobacteria)
- Prior BCG vaccination (see below for details)

BCG

May have been received by population groups including:

- Persons born in developing countries or TB-endemic countries and many European countries
- Aboriginal persons from communities with high rates of TB
- Persons born in Canada prior to 1970's, particularly health-care workers (detailed information available on PHAC website)

BCG vaccination and relationship to TST results

Received in infancy	Unlikely to cause a tuberculin reaction of 10 mm or greater after 10 years of age or older.
Received at 1 to 5 years of age	10–15% will have a positive TST up to 25 years later.
Received at 6 years or older	40% chance of having persistent positive TST later in life.

Source: CTS, 2013. p. 27A

Ignore prior history of BCG vaccination for:

- Close contacts of an active case
- Populations with a high risk of developing infection
- Immigrants from countries with a high burden of TB – BCG World Atlas available online at: www.bcgatlas.org
- Persons from Aboriginal communities with high rates of TB
- BCG vaccination in infancy and person tested is now age 10 years or older
- Immunocompromised, including HIV and renal failure
- Diabetes
- Chest x-ray consistent with old healed inactive TB

Two-step TST

- Should be performed **only** for people who will be getting serial TSTs at regular intervals (e.g., health care workers and correctional service workers)
- Distinguishes a booster effect (due to previous infection) from a conversion due to recent infection
- Consider for travelers to high-prevalence countries for prolonged visits
- If the first test is negative, do a second skin test 1 week to 4 weeks later

Management for positive TST

- All persons with a positive TST should be reported to your local public health department.
- Persons with a positive TST should be further evaluated to rule out active TB disease.

This evaluation should include the following: Clinical picture, interpretation of radiographic findings and sputum collection, if necessary.

Evaluation

1. Clinical picture (history, risk factors, and physical examination for signs and symptoms of active TB disease).
2. Chest x-ray, anteroposterior (AP) and lateral views.
3. In the presence of symptoms or chest x-ray findings consistent with pulmonary TB, collect 3 sputum specimens to send for AFB Smear and Culture. The sputum specimens (either spontaneous or induced) can be collected on the same day, at least 1 hour apart.

1. Clinical picture

- Many patients with pulmonary tuberculosis have a normal physical exam, even if symptomatic.
- The most common symptom of pulmonary TB disease is a new or worsening cough of at least 2–3 weeks duration.
- Cough is initially dry and may become productive after several weeks.
- Fever and night sweats may be absent in the very young and elderly.
- Hemoptysis, anorexia, weight loss and chest pain are generally seen in more advanced disease.

Note: TB can occur in any part of the body with site-specific symptoms. Lymph node TB is the most common extra-pulmonary site.

2. Interpretation of radiographic findings

- Chest x-rays should always be interpreted in the context of clinical and laboratory findings.
- The interpretation of chest x-rays is highly variable between readers.
- 10% of persons with HIV infection and active TB disease will have a normal chest x-ray.

Source: CTS, 2013, p. 17A

3. Sputum collection and timelines for results

Sputum collection

- Collect 3 sputum specimens (either spontaneous or induced). The specimens can be collected on the same day, at least 1 hour apart (early morning collection not essential).
- Collect 5 to 10 cc of sputum per specimen.
- If immediate delivery (<1 hour) is not possible, protect specimens from light in a paper bag and refrigerate at 4ºC pending transport to the lab. Deliver to the lab as soon as possible to avoid overgrowth of normal flora.

Note: Instructions for patient sputum collection can be obtained from your local health department.

Public health lab timelines and results

- Smear for Acid Fast Bacilli (AFB) – results are available in 1 business day from arrival at the lab.
- Amplified Mycobacterium Tuberculosis Direct (AMTD) distinguishes between TB and other non-tuberculous mycobacteria, for example, Mycobacterium Avium Complex (MAC). AMTD is performed automatically on AFB smear positive specimens from new patients – results are available in 2–3 business days from arrival at the lab.
- Culture for Mycobacterium Tuberculosis – results may be available anywhere from 4 days to 7 weeks.
- Sensitivity testing for susceptibility to first-line antituberculosis drugs (4 to 7 days after organism has grown in culture), is done automatically on all positive cultures – first-line results are available in 8–10 business days. Full panel second-line drug sensitivity testing is automatically done if resistance is detected to Rifampin or 2 or more drugs – results are available in 4–15 business days.
- Contact the public health lab in your area for any questions related to tests, timelines and results.

Contacts who are HIV+ or are <age 5 or are <age 18 with a positive TST

- Contacts who are < 5 years of age or are HIV+ should be assessed by a specialist. Window prophylaxis is strongly recommended pending the TST at 8–10 weeks post-exposure.
- Treatment for LTBI should be initiated as soon as active disease is ruled out.
- Children do not require baseline liver function tests unless they have known or suspected liver disease and are taking hepatotoxic drugs.
- Parents and older children should be educated about symptoms indicative of adverse reactions and signs of hepatotoxicity.
- Consider Directly-Observed Prophylactic Therapy (DOPT) by the local public health department, if available.

Refer to Paediatric Latent Tuberculosis Infection (LTBI) Treatment Guidelines at http://www.toronto.ca/health/professionals/communicable_diseases/tb/pdf/paediatric_treatment_ltb.pdf

Source: CTS, 2013, chpt. 9, 10, 12.

Quick reference

Treatment of latent tuberculosis infection (LTBI)

Approximately **10%** of persons infected with TB will go on to develop active TB disease: **5%** within 2 years of infection and **5%** for the remainder of life.

Treatment of LTBI reduces an individual's risk of developing active TB. Before starting treatment for LTBI, rule out active TB first!

Decision to start latent TB infection (LTBI) treatment – should be based on:

1. Interpretation of TST in context of patient's history:
   - Size of the reaction (induration), in mm
   - Predictive value of the test (considering likelihood of true exposure, false-negative, false-positive reactions)
   - Risk of progression to active disease
   - *Refer to online TST interpreter – http://www.tstin3d.com
2. Medical Contraindications (see table below). Patients under 65 years old with no comorbidities have low rates of hepatotoxicity
3. Likelihood of adherence to full length of LTBI treatment
   - Patient ability and commitment
   - Provider ability to continue monthly follow-up for adherence, side effects, etc.
4. Discussion of risks/benefits with patient
5. Active TB has been ruled out (history, risk factors, and physical examination; negative sputum cultures if patient is symptomatic, has abnormal CXR or is being treated with Rifampin).

Source: CTS, 2013, chpt. 4, 6.

Recommendations for treatment of LTBI

Medications are free when ordered through your local public health department

First-Line Regimen	Interval & duration	Oral dosage	Criteria for completion	Comments	Effectiveness
Isoniazid (INH)	Daily for 9 months	Adult: 5 mg/kg/day to a maximum of 300 mg/day	9 months is equivalent to 270 doses. Completing 270 doses within a 12 month period can be considered adequate treatment	• Recommended treatment regimen • Provides optimal protection in preventing progression toward active disease • **For children, especially those < 5 years old, consult a specialist**	Assuming good adherence to treatment: • INH, when taken for 9 months, is up to 90% effective in preventing progression to active disease and is the recommended duration of treatment.
Vitamin B6 (Pyridoxine)	Daily with INH	25 mg		Protects against neurotoxic effects of INH; Usually prescribed, particularly important for clients with diabetes, renal failure, malnutrition, substance abuse or seizure disorders, or for women who are pregnant or breastfeeding.	
2nd-Line/ Alternative Regimen	**Interval & duration**	**Oral dosage**	**Criteria for completion**	**Comments**	**Effectiveness**
Isoniazid and Rifampin (INH/RMP)	Daily for 3- 4 months	Adult: • INH – 5 mg/kg/ day to a maximum of 300 mg/day • RMP – 10 mg/kg/day to a maximum of 600 mg/day	For the preferred 4 month regimen, a minimum of 120 doses completed within 6 months can be considered adequate treatment.	**Use this regimen in consultation with a specialist.** ***Consider collecting sputum and pending for culture results prior to initiation to avoid inducing drug resistance.** Alternate regimen for persons: • Who are unlikely to be able to complete 9 months of INH (i.e., adherence concerns)	Published efficacy of 3 months of INH/RMP is 64%; 4 months is expected to have higher efficacy. Efficacy and safety is similar to 6-9 months of INH.
Rifampin (RMP)	Daily for 4 months	Adult: 10 mg/kg/day to a maximum of 600 mg/day	A minimum of 120 doses completed within 6 months can be considered adequate treatment.	**Use this regimen in consultation with a specialist.** ***Consider collecting sputum and pending for culture results prior to initiation to avoid inducing drug resistance.** Alternate regimen for persons: • Who cannot tolerate INH • Who are contacts of INH-resistant TB • Higher risk of side effects if not taken consistently Risk of side effects is higher if Rifampin is not taken consistently.	Published efficacy rates 63% equivalent to 6 months INH. Excellent safety and high completion rates.