

Let's Talk TB

A Series on Tuberculosis, A Disease That Affects Over 2 Million Indians Every Year

Management of Latent Tuberculosis Infection

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Abstract

*Most individuals who get exposed to *Mycobacterium tuberculosis* (MTB) manage to eliminate or contain the infection using host T-cell immune defenses. However, some MTB bacilli may remain viable (latent) and “reactivate” later to cause active TB disease. This state is called Latent TB Infection (LTBI). Identification and treatment (i.e. preventive therapy or prophylaxis) of LTBI can substantially reduce the risk of development of active disease (by as much as 60%). However, because 40% of Indians are latently infected, LTBI screening must be restricted to specific high risk populations in India, where the benefits of LTBI treatment outweigh any risks. These include people living with HIV, adult and child contacts of pulmonary TB cases, patients initiating anti-tumour necrosis factor (TNF- α) treatment, patients with end stage renal failure on dialysis, patients preparing for organ or haematologic transplantation, and patients with silicosis. While either tuberculin skin test (Mantoux) or interferon-gamma release assays (e.g., TB Gold) can be used for LTBI screening, it is important to make sure that these tests are not used for active TB diagnosis. For persons with symptoms or abnormal chest x-rays, physicians should order smears, cultures, and molecular tests (e.g., Xpert MTB/RIF). If LTBI is diagnosed, then physicians must rule-out TB disease with chest x-rays before starting one of the recommended drug regimens. It is important to ensure adherence, and provide adequate counseling to ensure that patients do not stop therapy prematurely.*

Key words: tuberculosis; treatment; latent TB infection, Mantoux test, IGRA

INTRODUCTION

Most individuals who get exposed to *Mycobacterium tuberculosis* (MTB) manage to eliminate or contain the infection using host T-cell immune defenses. However, some MTB bacilli may remain via-

ble (latent) and “reactivate” later to cause active TB disease. This state is called Latent TB Infection (LTBI).

Although LTBI and active TB disease are part of a dynamic spectrum,¹ people with LTBI are asymptomatic and not infectious. For example, nearly 50% of doctors and healthcare workers in India will test positive on the Mantoux tuberculin skin test, but a majority will not display any TB symptoms, or develop active TB disease.² Such individuals, presumably, have LTBI. However, some healthcare workers may go on to develop symptoms, and if found to have active TB require the standard 4-drug short course anti-TB therapy.

Identification and treatment (i.e., preventive therapy or prophylaxis) of LTBI can substantially reduce the risk of development of active disease (by as much as 60%), and is an important TB control strategy in low-TB incidence settings where reactivation disease usually accounts for the majority of non-imported TB disease.³ For example, LTBI screening and treatment is a major component of TB control programs in both USA and Canada, and large numbers of individuals are tested for LTBI and treated with isoniazid for 9 months. However, LTBI screening and treatment is rarely done in high TB burden countries such as India. This is because nearly 40% of the population is estimated to have latent TB infection.

The goal of testing for LTBI is to identify individuals who are at

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Figure 1 – Tuberculin skin test being administered, using the Mantoux method.



Figure 2 – QuantiFERON TB Gold In Tube is an ELISA-based IGRA test for TB infection. It is not recommended for active TB detection.

increased risk for the development of active TB; these individuals would benefit most from treatment of LTBI. There is no diagnostic gold standard for LTBI and all existing tests are immunological tests that provide indirect evidence of sensitization of the host to TB antigens.

There are two available tests for identification of LTBI: tuberculin skin test (TST) and interferon-gamma release assays (IGRA). TST is usually performed using the Mantoux skin test method (**Figure 1**), and purified protein derivative (PPD) is the antigen injected intradermally. Skin induration is read after a period of 48 – 72 hours. In India, a 10 mm induration is considered positive.

IGRAs are done *in vitro*, and instead of PPD, they use highly specific peptides from two main antigens – early secreted antigenic target (ESAT6) and culture filtrate protein (CFP10). Commercial IGRAs include QuantiFERON-TB Gold In Tube (Qiagen, USA) (**Figure 2**), and T-SPOT. TB (Oxford Immunotec, UK). Both TST and IGRA depend on cell-mediated immunity (memory T-cell response), and a positive result suggests that the patient has been exposed and sensitized to MTB in the past.

A detailed recent review of these tests is available elsewhere.⁴ Briefly, published data suggests that both TST and IGRA are acceptable, but somewhat imperfect tests. Both represent indirect markers of MTB exposure and measure a cellular immune response to MTB (read as mm induration with the TST, and amount of interferon-gamma released by T-cells in IGRAs). Neither test can accurately differentiate between LTBI and active TB. Neither test can resolve the various stages within the spectrum of MTB infection.

Both TST and IGRA have reduced sensitivity in immunocompromised patients (e.g., people living with

HIV/AIDS), and have low predictive value for progression to active TB. In other words, a majority of individuals with positive TST or IGRA results will not progress to active TB disease.⁵

Tuberculin skin test surveys in India show a very high annual risk of TB infection.⁶ Given the very high TB burden of active TB in India, it is not surprising that nearly 40% of Indians are estimated to be latently infected.⁷ Given the large number of latently infected individuals in the country, the Revised National TB Control Program (RNTCP) does not give priority to LTBI detection and treatment in the public sector. This is true for most high TB burden countries around the world.

For high burden countries like India, what should be the approach towards management of LTBI? In 2014, WHO published its first comprehensive guideline on management of latent TB infection.⁸ This guideline offers a clear, evidence-based algorithm (**Figure 3**).⁸

As shown in the algorithm, WHO recommends that only selected risk groups should be evaluated for LTBI.⁸ These include people living with HIV, adult and child contacts of pulmonary TB cases, patients initiating anti-tumour necrosis factor (TNF-alpha) treatment, patients with end stage renal failure on dialysis, patients preparing for organ or haematologic transplantation, and patients with silicosis. The rationale for giving priority to these subgroups is that they are at very high risk of progressing from latent infection to active disease, and this could be prevented by treating LTBI.

If an individual has any of the above risk factors, the WHO algorithm requires that they be assessed for TB symptoms. If any TB symptom is present (e.g., cough, fever, weight loss, hemoptysis, night sweats), then the focus should be on diagnosing active TB using WHO

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and RNTCP-endorsed microbiological tests such as smear microscopy, TB cultures and molecular tests such as Xpert MTB/RIF (GeneXpert, Cepheid Inc, USA), and line probe assays such as Genotype MTBDRplus (Hain LifeScience, Germany). A chest x-ray can also be used as part of the work-up for active TB. If the individual has no symptoms, then WHO recommends that either TST or an IGRA be used to test for LTBI in high-income and upper middle-income countries with estimated TB incidence less than 100 per 100000. TST is preferred and IGRA should not replace TST in low-income and other middle-income countries.⁸

If either TST or IGRA is positive, then the next step is to rule out active disease, before starting LTBI treatment. This is done by getting a chest x-ray. If the x-ray shows any abnormalities, then it is critical to investigate for active TB, using smear microscopy, TB cultures and molecular tests. If the x-ray is normal, then the likelihood of active TB is very low, and LTBI treatment can be initiated.

What are the drug regimens available for LTBI treatment? Unlike active TB where 4 drugs are required

in the intensive phase, the burden of bacteria in LTBI is quite low. So, even a single TB drug is sufficient. As shown in the WHO algorithm, treatment options recommended by WHO include 6 to 9 months of isoniazid, 3-month regimen of weekly rifapentine plus isoniazid, or 3–4 months isoniazid plus rifampicin, or 3–4 months rifampicin alone.⁸ All regimens are known to be efficacious, but adherence can be poor with longer regimens such as 9 months of isoniazid.³ Rifampicin containing regimens may be more suitable in populations with a high background level of isoniazid mono-resistance.

Regardless of the regimen used for LTBI, it is important to ensure adherence, and provide patients adequate counseling about why they are being treated for LTBI (despite not having symptoms), likely adverse events, and monthly follow-up visits. The risk of toxicity is highest with isoniazid, especially in older individuals, and those who consume alcohol.³

In India, there is concern that tests such as Mantoux and IGRAs (e.g., TB Gold, TB Platinum) are being misused for active TB diagnosis.⁹ The WHO algorithm clearly shows that when doctors suspect active TB, they

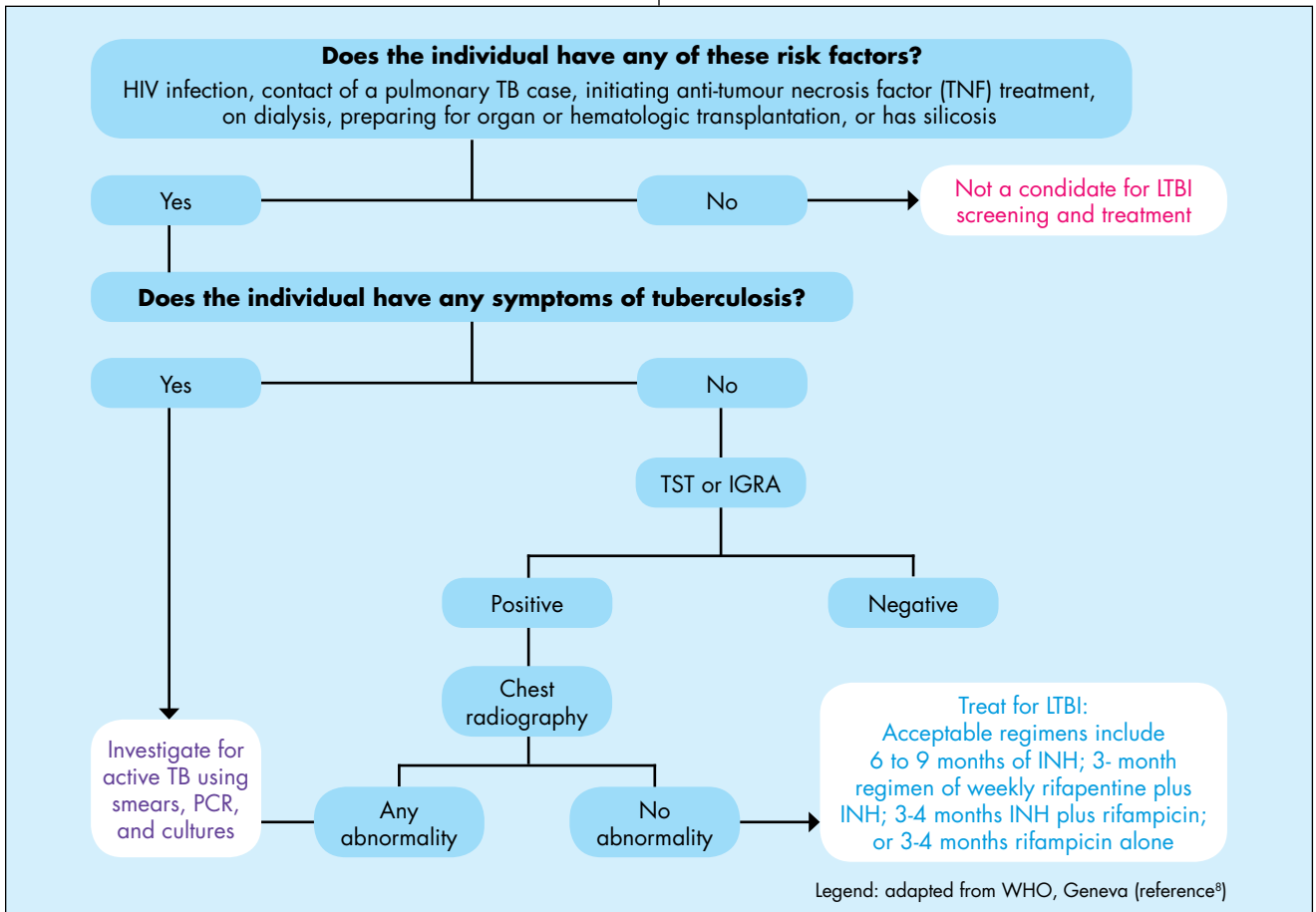


Figure 3 – WHO algorithm for latent TB infection management.

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Table 1– Recommended drug dosages for acceptable LTBI treatment regimens

Drug regimen	Dose per body weight	Maximum dose
Daily Isoniazid alone for 6 or 9 months	Adults = 5mg/kg Children = 10 mg/kg	300 mg
Daily Rifampicin alone for 3-4 months	Adults = 10 mg/kg Children = 10 mg/kg	600 mg
Daily Isoniazid plus Rifampicin for 3-4 months	Isoniazid Adults = 5 mg/kg Children = 10 mg/kg Rifampicin Adults and children = 10 mg/kg	Isoniazid = 300 mg Rifampicin = 600 mg
Weekly Rifapentine plus Isoniazid for 3 months (12 doses)	Adults and children Isoniazid: 15 mg/kg Rifapentine (by body weight): 10.0-14.0 kg = 300 mg 14.1-25.0 kg = 450 mg 25.1-32.0 kg = 600 mg 32.1-49.9 kg = 750 mg	Isoniazid = 900 mg Rifapentine = 900 mg

Legend: adapted from WHO, Geneva (reference⁸)

should be testing for active TB, not screening for LTBI. In fact, the Standards for TB Care in India (STCI) clearly states that both TST and IGRAs should not be used for the diagnosis of active TB in high endemic settings like India.¹⁰ If IGRAs are used for active TB diagnosis, this will result in significant over-diagnosis of TB, because of the high background prevalence of LTBI in India. In children, STCI suggests that the Mantoux test may have some value as a test for infection, in addition to chest x-rays, symptoms, history of contact, and other microbiological investigations (e.g., gastric juice acid fast bacilli and Xpert MTB/RIF).¹⁰

In conclusion, LTBI screening must be restricted to specific high risk populations in India, where the benefits of LTBI treatment outweigh any risks. While either TST or IGRA can be used for LTBI screening, it is important to make sure that these tests are not used for active TB diagnosis. For persons with symptoms or abnormal chest x-rays, physicians should order smears, cultures, and molecular tests (these tests are now available in the public as well as the private sector in India). If LTBI is diagnosed, then physicians must rule-out TB disease with chest x-rays before starting one of the recommended drug regimens. It is important to ensure adherence, and provide adequate counseling to ensure that patients do not stop therapy prematurely.

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CIS CME—Questions

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Questions

- 1** What is the estimated prevalence of latent TB infection in India?
 - a. 5%
 - b. 10%
 - c. 40%
 - d. 80%

- 2** Which of the following tests can be used to screen for latent TB infection?
 - a. GeneXpert (Xpert MTB/RIF)
 - b. Sputum smear examination
 - c. TB IgG, IgM antibodies
 - d. Mantoux (tuberculin skin test)

- 3** Which of these high-risk populations should be targeted for LTBI screening and treatment?
 - a. People living with HIV/AIDS
 - b. Child contacts of pulmonary TB cases
 - c. Patients initiating anti-tumour necrosis factor (TNF-alpha) treatment
 - d. Patients with end stage renal failure on dialysis
 - e. All of the above

- 4** Which of the following statements is TRUE about interferon-gamma release assays (e.g., TB Gold)?
 - a. IGRAs cannot separate latent infection from active TB, and, therefore, not recommended for active TB detection
 - b. IGRAs are skin tests for latent infection
 - c. IGRAs are useful for diagnosing active, pulmonary TB
 - d. IGRAs are banned in India

- 5** Which of the following drug regimens are NOT recommended for latent TB infection?
 - a. 6 to 9 months of isoniazid
 - b. 3-month regimen of weekly rifapentine plus isoniazid
 - c. 3–4 months isoniazid plus rifampicin
 - d. 3–4 months rifampicin alone
 - e. Isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) for 2 months, followed by isoniazid and rifampicin (HR) for 4 months

(See answers on the next page)

CIS CME—Answers

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Answers

- 1 The correct answer is (c).** An estimated 40% of the Indian population is estimated to be latently infected, using tuberculin surveys.
- 2 The correct answer is (d).** The tuberculin skin test, using Mantoux technique, is one of the two accepted tests for latent TB infection screening. The other test is interferon-gamma release assays (e.g., TB Gold)
- 3 The correct answer is (e).** Latent TB screening should be restricted to high-risk groups. These include people living with HIV and AIDS, adult and child contacts of pulmonary TB cases, patients initiating anti-tumour necrosis factor (TNF-alpha) treatment, patients with end stage renal failure on dialysis, patients preparing for organ or haematologic transplantation, and patients with silicosis.
- 4 The correct answer is (a).** IGRAs cannot separate latent infection from active TB, and, therefore, not recommended for active TB detection. This is also true for Mantoux skin test. Both IGRAs and TST should be restricted to LTBI screening, and should not be used for active TB diagnosis. In children, Mantoux test may have some value as a test for infection, in addition to chest x-rays, symptoms, history of contact, and other microbiological investigations (e.g., gastric juice acid fast bacilli and Xpert MTB/RIF).
- 5 The correct answer is (e).** The HRZE drug regimen is meant for treating active tuberculosis. For latent TB infection, treatment options recommended by WHO include 6 to 9 months of isoniazid, 3-month regimen of weekly rifapentine plus isoniazid, or 3–4 months isoniazid plus rifampicin, or 3–4 months rifampicin alone.