



Latent Tuberculosis Infection (LTBI)

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Accreditation Statement

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- 18.25 ANCC
- 18.25 Attendance
- 18.25 IPCE

Disclosures

- **Financial**
 - No relevant financial disclosures to report
- **Off label drugs**
 - Rifampin, rifabutin, quinolones not FDA approved for LTBI Rx but recommended by scientific statements & guidelines

Learning Objectives

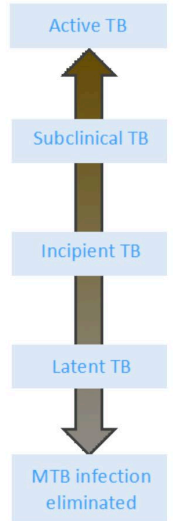
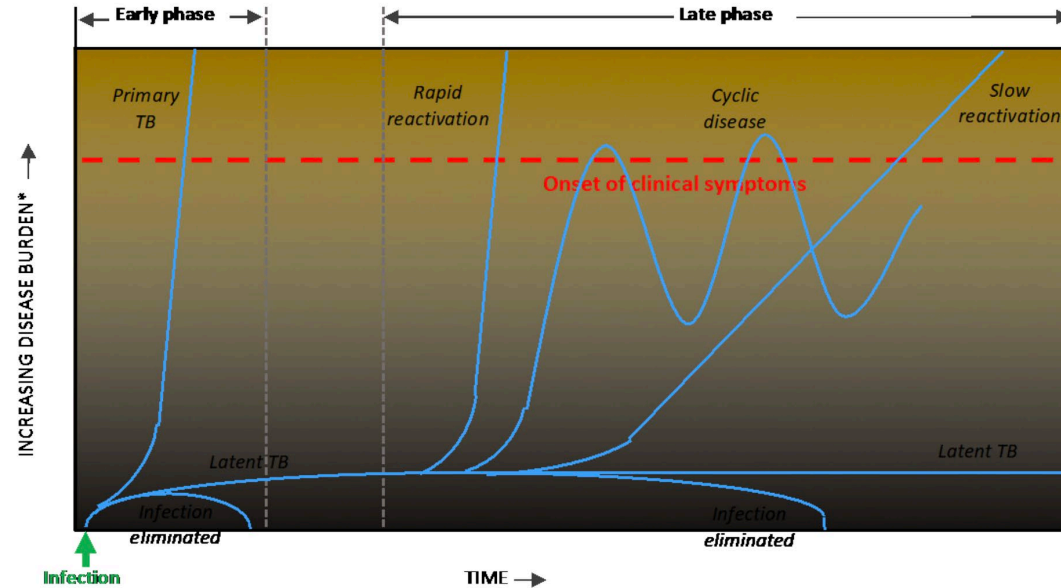
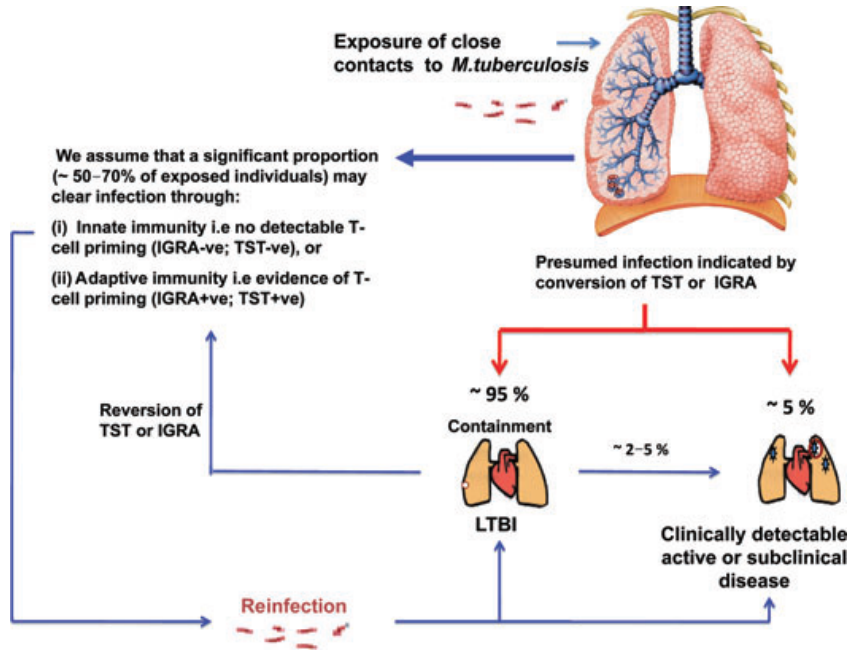
1. Definition of LTBI
2. Diagnosis of LTBI
3. Treatment of LTBI

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Definition of LTBI



Natural History of TB Infection & Disease



Approximately 25% of people clear the TB infection before T-cell priming and never develop a positive TST or IGRA.

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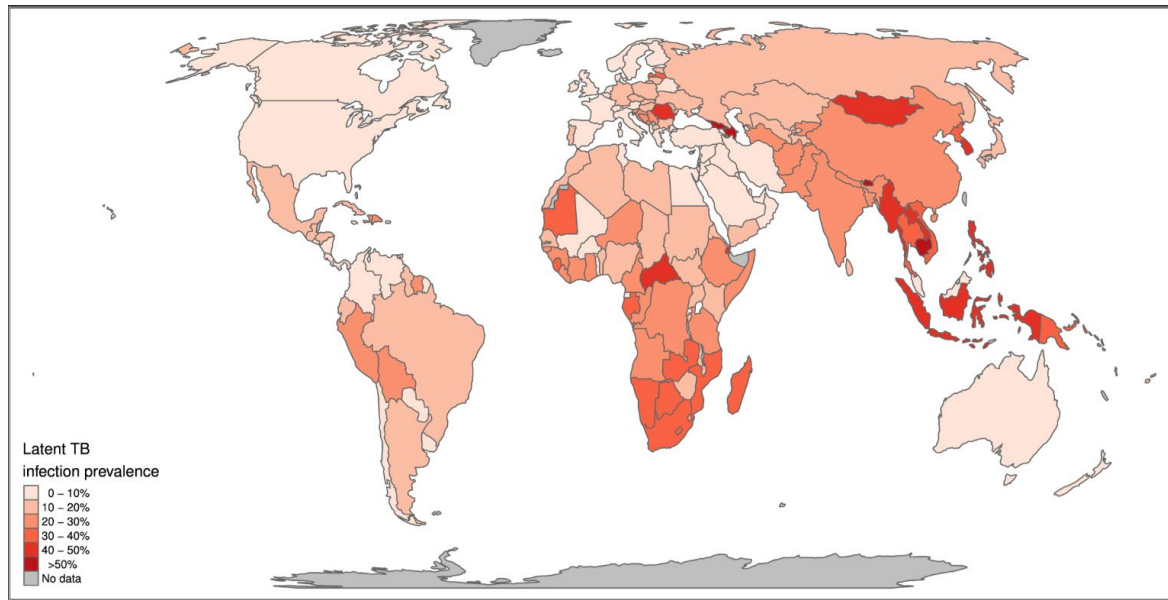
Latent TB Infection: Definition & Comparison

LTBI is the presence of *M. tuberculosis* organisms (tubercle bacilli) without signs/symptoms or radiographic/bacteriologic evidence of TB disease.



Person with LTBI	Person with TB Disease
Small amount of inactive TB bacteria	Large amount of active TB bacteria
Cannot spread TB bacteria to others	May spread TB bacteria to others
Does not feel sick	May feel sick (cough, fever, weight loss)
Usually positive TST / IGRA	Usually positive TST / IGRA
Chest radiograph typically normal	Chest radiograph may be abnormal
Sputum smears / cultures negative	Sputum smears / cultures may be positive
Treat to prevent disease; no isolation; not a TB case	Needs treatment; may need isolation; is a TB case

Global & US Burden of LTBI



Houben RMGJ, Dodd PJ (2016) PLoS Med 13(10): e1002152.
<https://www.cdc.gov/tb/statistics/ltni.htm>

23.0%

Global LTBI prevalence — approximately 1.7 billion people

5%

US LTBI prevalence — approximately 13 million people

>80%

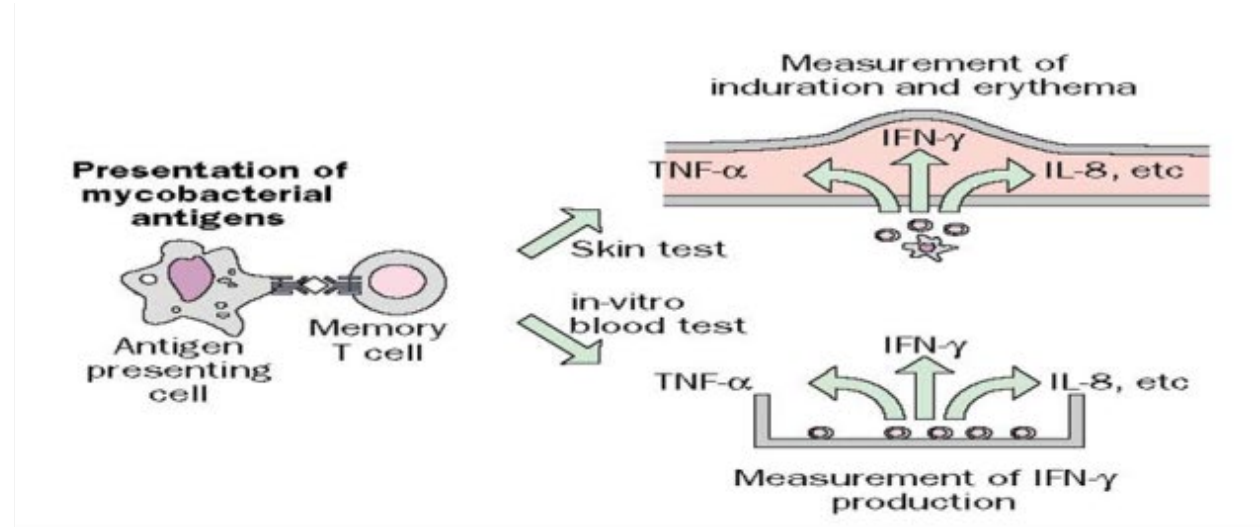
of US TB cases result from longstanding, untreated LTBI

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Diagnosis of LTBI



Diagnosis of Latent TB Infection



Tuberculin Skin Test (TST)

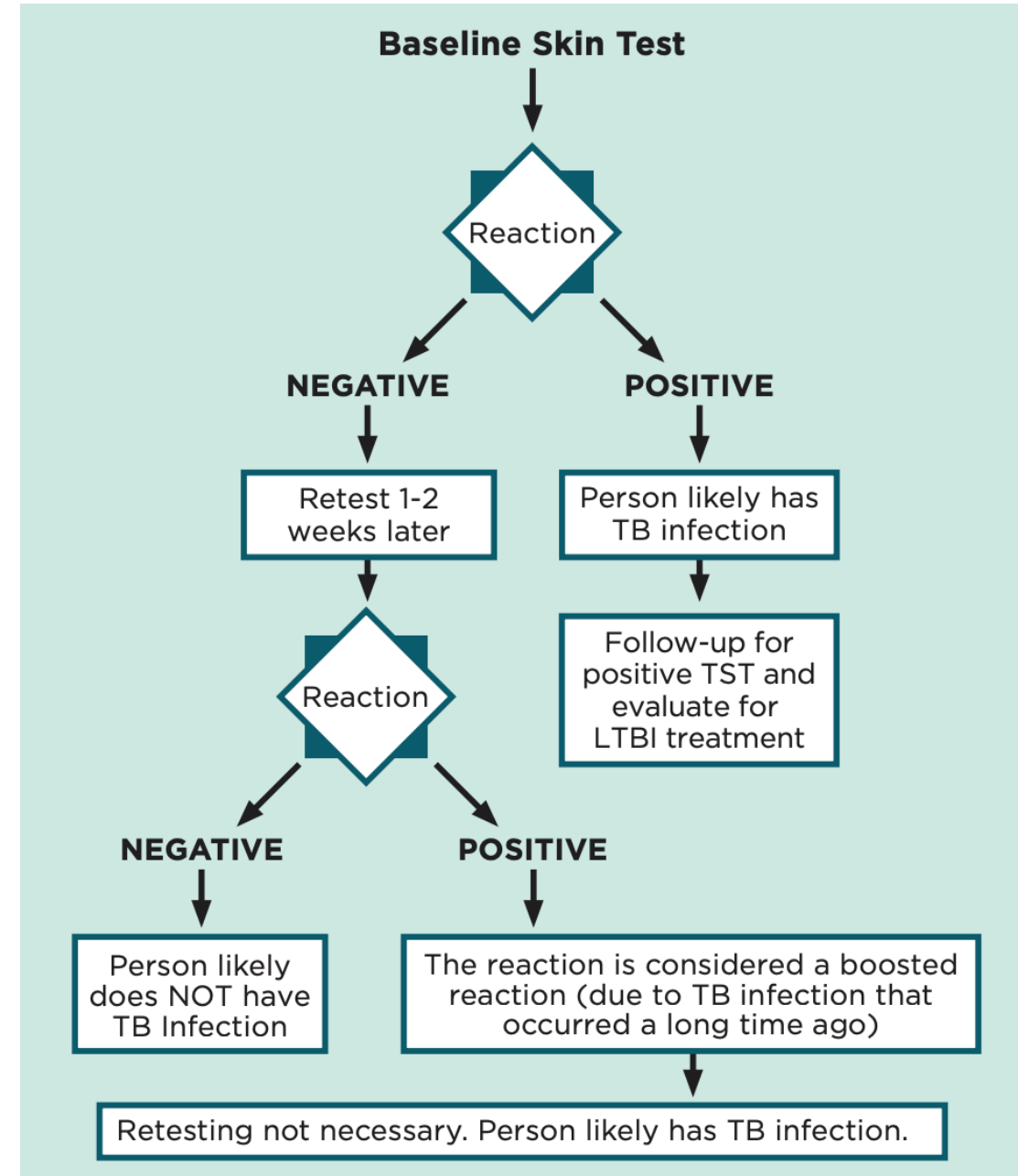
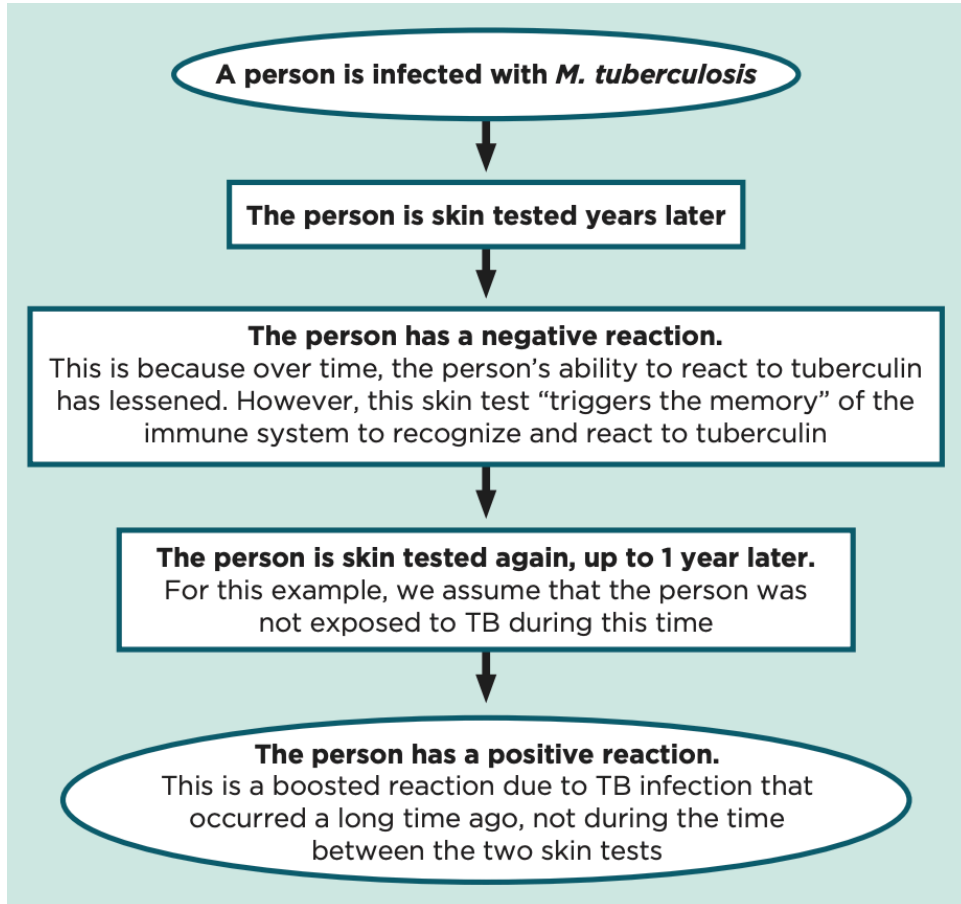
Developed in 1907 by Charles Mantoux

Contains PPD, buffered saline, polysorbate 80 (stabilizer), phenol (preservative)

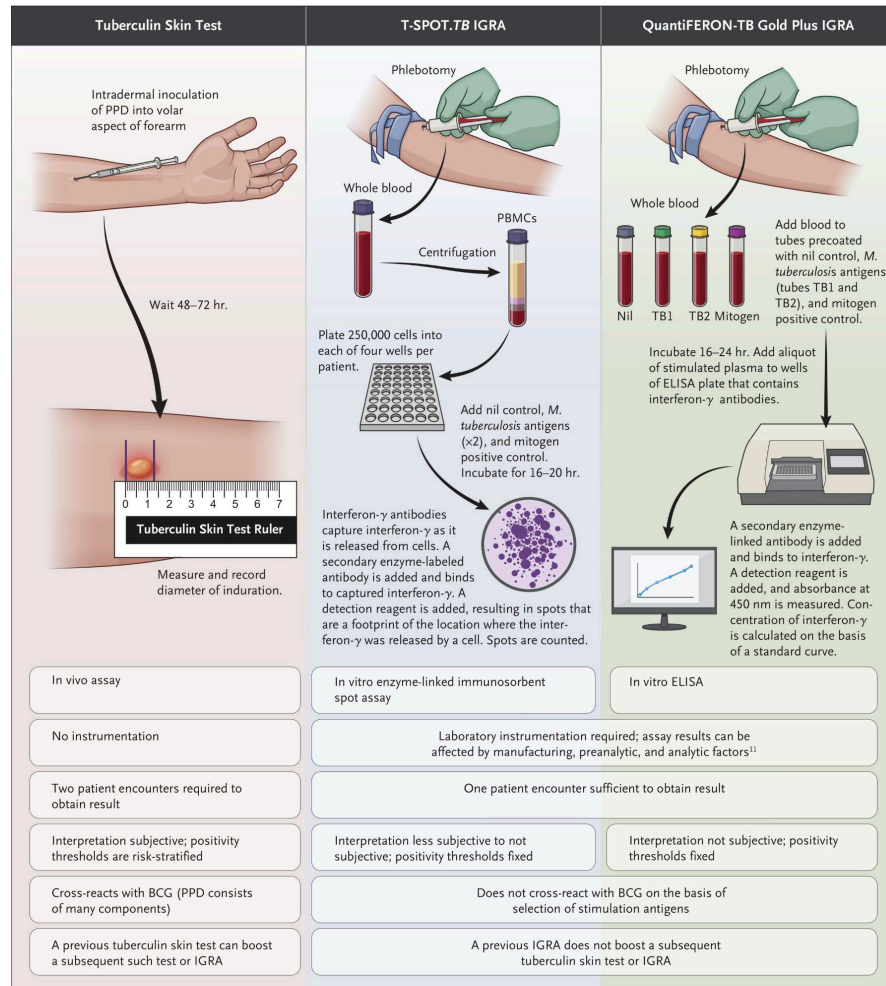
Read 48–72 hours after placement; measure induration, not erythema

Induration	Considered positive in
≥ 5 mm	HIV infection; recent close contact with infectious TB; fibrotic CXR changes; organ transplant or other immunosuppression (≥ 15 mg/day prednisone or TNF- α antagonist)
≥ 10 mm	Born in / lived in high-TB-prevalence countries; injection drug use; high-risk congregate settings or lab workers; silicosis, diabetes, renal disease, cancer; low body weight; children <5 ; recently exposed children/adolescents
≥ 15 mm	No known risk factors for TB

Booster phenomenon



TST vs IGRA: Overview & Test Performance

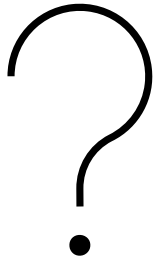


Mayo Clinic Center for Tuberculosis

Test	Sensitivity (95% CI)	Specificity (95% CI)
TST $\geq$ 5 mm	0.79 (0.69–0.89)	Varies with BCG status*
TST $\geq$ 10 mm	0.79 (0.71–0.87)	0.97 (0.96–0.99)
TST $\geq$ 15 mm	0.52 (0.35–0.68)	0.99 (0.98–0.99)
T-SPOT.TB	0.90 (0.87–0.93)	0.95 (0.92–0.98)
QFT-Gold	0.77 (0.74–0.81)	0.98 (0.90–1.0)
QFT-Gold In-Tube	0.80 (0.77–0.84)	0.97 (0.94–0.99)

*Pooled TST $\geq$ 5mm specificity ranged 0.30–0.97 across studies, driven largely by prior BCG vaccination status. Jonas DE, et al. JAMA. 2016;316(9):970-983.

Polling Question 1



In addition to *Mycobacterium marinum*, which organism can cause a false positive result for the QuantiFERON Gold Plus test?

- A. *Mycobacterium chelonae*
- B. *Mycobacterium lentiflavum*
- C. *Mycobacterium arupense*
- D. *Mycobacterium kansasii*

IGRA Tests: Mechanism & Cross-Reactivity

How IGRAs work

- Measure T-cell response to *M. tuberculosis*-specific antigens: ESAT-6, CFP-10 (plus TB7.7 for QFT-GIT only)
- These antigens are encoded in Region of Difference 1 (RD1), which is deleted from the BCG vaccine strain
- Because RD1 is absent from BCG, IGRAs avoid cross-reactivity with prior BCG vaccination
- RD1 is required for full *Mtb* virulence and encodes the ESX-1 secretion system

Cross-reactivity to know

- RD1 is present throughout the M. tuberculosis complex: M. tuberculosis, M. africanum, M. bovis, M. canettii, M. caprae, M. microti, M. pinnipedii, M. mungi, M. orygis
- Some non-tuberculous mycobacteria (NTM) closely related to Mtb also encode ESAT-6/CFP-10 and can cross-react: M. kansasii, M. marinum, M. szulgai, M. gastri, M. gordonae, M. riyadhense, M. flavescens
- Pooled IGRA positivity was ~57% (33/58) in patients infected with M. marinum, M. kansasii, or M. szulgai

IGRA Interpretation Criteria

T-SPOT.TB

Interpretation	Nil	TB response	Mitogen
Positive	≤10 spots	≥8 spots	any
Borderline	≤10 spots	5–7 spots	any
Negative	≤10 spots	≤4 spots	≥20 spots
Indeterminate	>10 or ≤10	any / <5	any / <20

An indeterminate result is essentially an invalid test and does not convey information about TB status; it may or may not resolve on retesting.

QuantiferON-TB Gold In-Tube (QFT-GIT)

Interpretation	Nil	TB response	Mitogen
Positive	≤8.0	≥0.35 & ≥25% of Nil	any
Negative	≤8.0	<0.35 or <25% of Nil	≥0.5
Indeterminate	≤8.0 / >8.0	<0.35 or <25% / any	<0.5 / any

“Low positive” results near the 0.35 IU/mL cutoff may need cautious interpretation (no “borderline” category exists for QuantiferON); SD ≈ 0.03 IU/mL for TB1 and TB2.

Diagnostic Approach for LTBI

Risk Group	Testing Strategy	Considerations
Likely infected High risk of progression (TST $\geq$ 5 mm)	Adults: IGRA or TST (consider dual testing). Children $\leq$ 5 yrs: TST preferred.	Prevalence of BCG vaccination; test availability; laboratory expertise; patient/staff preferences; programmatic concerns
Likely infected Low–intermediate risk (TST $\geq$ 10 mm)	IGRA preferred where available; TST acceptable.	Increasing risk of progression to TB if infected: clinical predisposition (diabetes, chronic renal failure, IV drug use) = intermediate risk (RR 1.3–3); children $<$ 5, HIV, immunosuppression, abnormal CXR, silicosis = high risk (RR 3–10)
Unlikely infected (TST $>$ 15 mm, no risk factors)	Testing for LTBI generally not recommended.	

Horsburgh CR, Rubin EJ. N Engl J Med. 2011;364:1441-1448. | DOI: 10.1093/cid/ciw694

Who Should Be Screened for LTBI – USPSTF 2023

- **In asymptomatic adults at increased risk:**
 - Born in or former resident of countries with high TB prevalence
 - Live or have lived in high-risk congregate settings (homeless shelters, correctional facilities)
 - Local communities at increased risk
 - Persons with immunosuppression (people living with HIV, chemotherapy or TNF-inhibitor use, organ transplant)
 - Silicosis (already standard of care)
 - Contacts of people with active TB, healthcare workers, workers in high-risk congregate settings (public health & employee health surveillance)
- **Frequency of screening:**
 - Lack of evidence — ranges from once to yearly if continued risk of exposure

doi:10.1001/jama.2023.4899

Treatment of LTBI

3HP

INH + Rifapentine, once weekly × 12 weeks

4R

Rifampin, daily × 4 months

3HR

INH + Rifampin, daily × 3 months

6H / 9H

Isoniazid, daily × 6–9 months

Treatment Regimens Overview – CDC & NTCA 2020

Priority	Regimen	Recommendation	Evidence
Preferred	3 mo isoniazid + rifapentine, once weekly (3HP)	Strong	Moderate
Preferred	4 mo rifampin, daily (4R)	Strong	Moderate (HIV-negative)
Preferred	3 mo isoniazid + rifampin, daily (3HR)	Conditional	Very low (HIV-neg) / Low (HIV+)
Alternative	6 mo isoniazid, daily (6H)	Strong	Moderate (HIV-neg) / Conditional (HIV+)
Alternative	9 mo isoniazid, daily (9H)	Conditional	Moderate

CDC/NTCA. MMWR Recomm Rep. 2020;69(RR-1):1-11. | <https://www.cdc.gov/mmwr/volumes/69/rr/rr6901a1.htm>

Landmark RCTs in LTBI Treatment

Trial	Setting	Population	Comparison
IUAT (1982)	7 European countries	27,830 adults with fibrotic lesions, TST $\geq$ 6mm	INH 12/24/52 wk vs placebo
PREVENT TB (Sterling 2011)	US, Canada, Brazil, Spain, Peru, Hong Kong	7,731 high-risk contacts/converters (children $\geq$ 2 yrs through adults, incl. HIV)	3HP (weekly) vs 9H (daily)
Menzies (2018)	9 countries (high- & low-incidence)	6,063 adults at increased risk of progression	4R vs 9H
HIV-population trials (Martinson, BRIEF-TB)	South Africa & multinational	Adults living with HIV	3HP vs INH alone

Efficacy & Safety Across Landmark Trials

Trial	Efficacy	Hepatotoxicity / Safety
IUAT	24-wk INH: RR 0.35 (0.24–0.52) vs placebo; NNT 112	INH hepatotoxicity RR 4.59 (2.03–10.39); NNH 279
PREVENT TB	3HP noninferior: cumulative TB 0.19% vs 0.43% (9H)	Hepatotoxicity 0.4% (3HP) vs 2.7% (9H)
Menzies	4R noninferior: 0.10 vs 0.11 cases/100 person-yr (9H)	Grade 3–5 hepatotoxicity 0.3% (4R) vs 1.8% (9H)
HIV-population	Comparable TB prevention; pooled mortality 30 vs 34 (3HP vs INH)	No significant difference in grade 3/4 AEs; nonsignificant ↓ hepatotoxicity with 3HP

Shorter rifamycin-based regimens (4R, 3HP) match longer isoniazid monotherapy for efficacy while producing less hepatotoxicity and higher completion rates.

Network Meta-Analysis: Efficacy & Safety Rankings

15 RCTs (1982–2018) compared LTBI regimens in a network meta-analysis

No regimen was significantly superior to another for preventing active TB

Compared with standard 6H, adverse events were significantly reduced by:

3HP: -4.53% • 4R: -4.39% • 9H: -3.77%

3HR did not differ significantly from 6H in adverse events

SUCRA ranking: 4R had both the highest efficacy and the lowest adverse-event probability

Regimen	Δ Adverse Events vs 6H	SUCRA Rank Note
4R	-4.39%	Best efficacy + best safety
3HP	-4.53%	Largest AE reduction
9H	-3.77%	Modest AE reduction
3HR	not significant	Combines toxicities of both drugs

Yoopetch P, et al. Sci Rep. 2023;13(1):16240.

Regimen-Specific Side Effects to Watch For

Isoniazid (6H / 9H)

Highest hepatotoxicity risk, increasing with duration and age; peripheral neuropathy (mitigate with pyridoxine); rash

Rifampin (4R)

Most favorable safety signal — lowest hepatotoxicity (grade 3–4 ~0.3–0.7%); leukopenia, thrombocytopenia, orange body fluids; significant drug interactions (hormonal contraceptives, methadone, antiretrovirals)

3HP (INH + Rifapentine)

Well tolerated with low hepatotoxicity; flu-like / systemic hypersensitivity reaction (rifapentine-associated) can drive discontinuation

3HR (INH + Rifampin)

Combines toxicity profiles of both drugs; Korean real-world cohort found highest rate of any AE and highest hepatotoxicity signal (6.48-fold vs control); 4R had the lowest

Evidence Base: Study Populations & Generalizability

15

RCTs pooled
(1982–2018)

96–13,955

participants
per trial

10–50 yrs

median age
across trials

17–100%

proportion
male

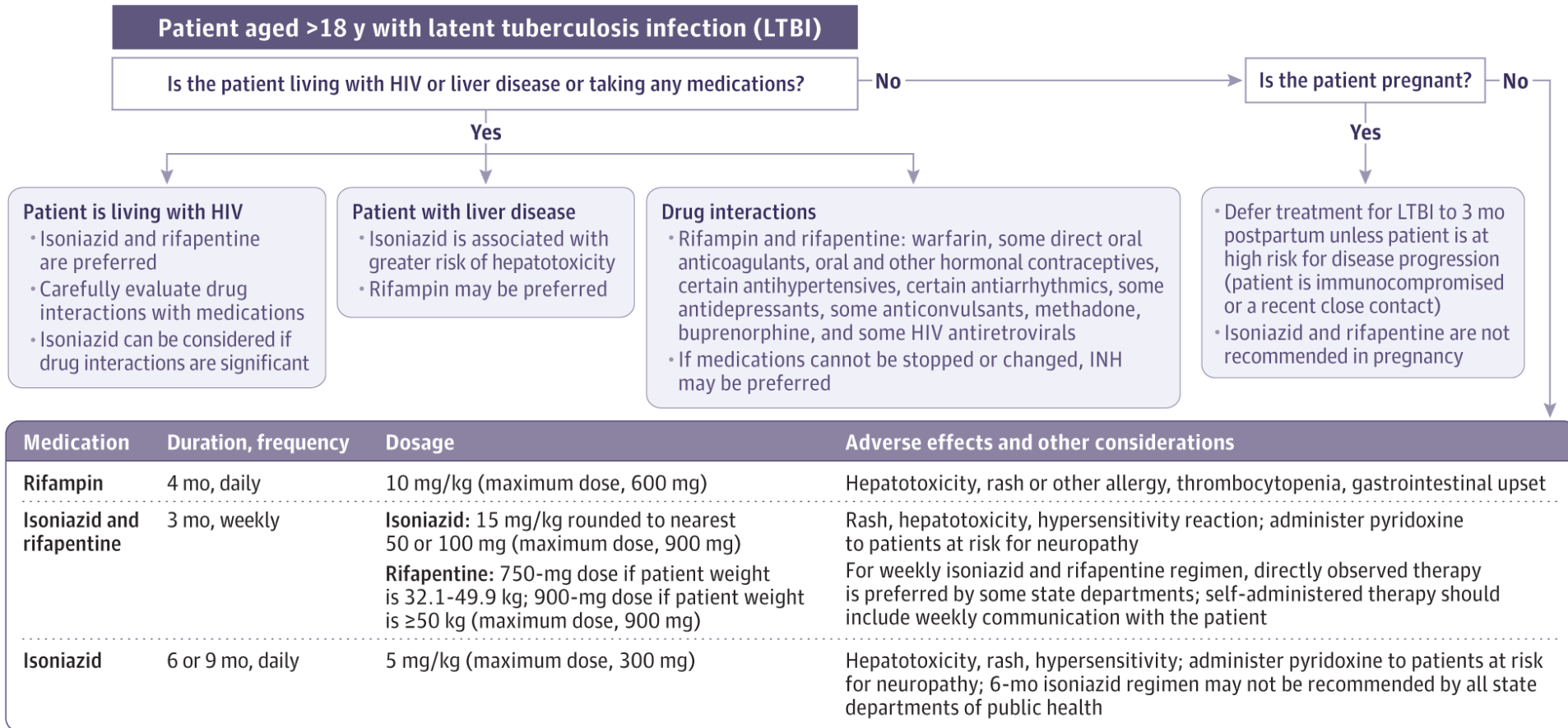
Diagnosis: TST alone (11 studies), TST + IGRA (3 studies), IGRA alone (1 study)

4 trials specifically enrolled people living with HIV; others focused on prisoners, immigrants, kidney transplant recipients, and children — supporting generalizability across key at-risk groups

Limitation: trials were not powered to detect differences in rare outcomes such as TB death or transmission, and none reported quality-of-life or transmission endpoints

From: **Management of Latent Tuberculosis Infection**

JAMA. 2023;329(5):421-422. doi:10.1001/jama.2022.24362



Choosing a Regimen: Clinical Decision Points

- Shorter rifamycin-based regimens (4R, 3HP) are preferred when feasible: comparable efficacy to 9H with less hepatotoxicity and higher completion
- 4R: best combination of efficacy and safety in network meta-analysis; watch for drug interactions
- 3HP: once-weekly, directly observed option; monitor for flu-like / hypersensitivity reactions
- 3HR: reasonable when a daily combination fits patient/programmatic needs, but carries a combined toxicity profile
- Isoniazid monotherapy (6H/9H): reserve for situations where rifamycins are contraindicated; requires longer duration and closer hepatotoxicity monitoring
- Individualize based on comorbidities, drug interactions, pregnancy status, and adherence support available
- Evidence gaps: trials not powered for rare outcomes (TB death/transmission); no quality-of-life data

Prescribing Information for LTBI Regimens

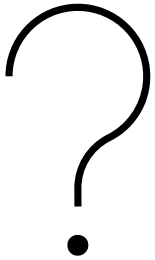
Regimen	Adult Dose	Key Adverse Reactions	Key Interactions
3HP (INH + Rifapentine, weekly)	INH 15 mg/kg (max 900mg) + Rifapentine 750–900mg by weight	Hypersensitivity 3.8%, rash 0.8%, hepatotoxic 0.4%	↓ warfarin, DOACs, hormonal contraceptives, levothyroxine, methadone, many ARVs
4R (Rifampin, daily)	10 mg/kg/day (max 600mg)	Hepatotoxic 0.3%, rash/allergy 0.2%, hematologic 0.2%	Same interaction class as rifapentine
3HR (INH + Rifampin, daily)	INH 5 mg/kg/day (max 300mg) + Rifampin 10 mg/kg/day (max 600mg)	Hepatotoxic 1–6%, rash 1–8%, GI 0–6%; peripheral neuropathy (mitigate with pyridoxine)	As above, plus isoniazid interactions
6H / 9H (Isoniazid, daily)	5 mg/kg/day (max 300mg)	Hepatotoxic 2–3% (6mo), rash 0.6%, hypersensitivity 0.5%; peripheral neuropathy	↑ carbamazepine, phenytoin, warfarin, disulfiram; ↓ itraconazole, ketoconazole

Shah M, Dorman SE. N Engl J Med. 2021;385(24):2271-2280.

LTBI in pregnancy, lactation, post partum

- Retrospective data suggest ↑ active TB in pregnancy and postpartum
- Evaluate risk of TB in pregnant women & do targeted testing
- If IGRA/TST + → signs/symptoms + CXR (w/lead shield) if high risk
- Consider treating after 1st trimester or delay for 2-3 months postpartum
- Preferred regimen is Rifampin monotherapy >> INH monotherapy
 - If Pregnant HIV+ on ART, INH was associated with increased composite pregnancy adverse outcomes in clinical trials
- With breastfeeding any regimen can be used
- Add pyridoxine with INH with pregnancy/lactation use

Polling Question 3



What regimen do you recommend for treating contacts exposed to MDR-TB?

- A. Levofloxacin or Moxifloxacin +/- 2nd agent based on source patient DST for 6-12 months
- B. Quinolone + PZA for 6-12 months
- C. Ethambutol + PZA for 6-12 months
- D. No treatment



Thank you