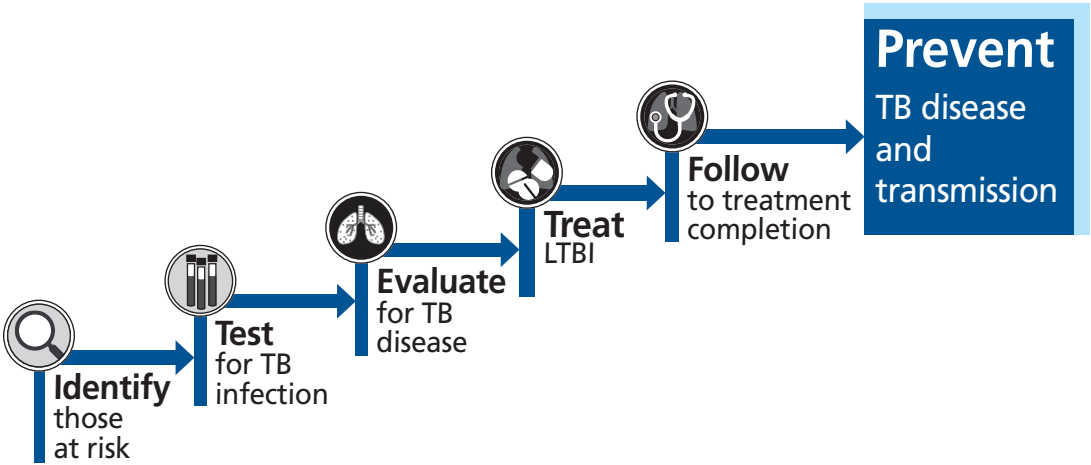
2021

Diagnosis and Treatment of Latent Tuberculosis Infection (LTBI) in Adults

Content based on national TB guidelines with consideration for practical applications



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Identify, Test, and Treat LTBI in Adults

Test individuals with risk factors for TB infection or host risk for progression to TB disease. *Testing is not recommended in those without risk factors.* LTBI diagnosis is based on tuberculin skin test (TST) or interferon-gamma release assay (IGRA) result and exclusion of TB disease. Evaluate for TB disease before initiating LTBI treatment. Expert consultation is available from state or local health departments; consultation is recommended for diagnosis of TB disease or of LTBI in complex clinical situations (e.g., those on or about to start immunosuppressive therapy).

Identify these adults and test for TB infection	Consider positive if	Evaluate for TB disease
❑ Birth, residence, or extended travel (>1 month) to a country with increased TB prevalence (countries other than the US, Canada, Australia, New Zealand, or in western or northern Europe)	IGRA (+) or TST ≥10 mm (≥5 mm if immunosuppressed)	• Clinical evaluation • Assessment for signs and symptoms • Radiography • Microbiological exams (if indicated) **Treat for LTBI if TB disease is excluded[3]**
❑ Current or planned immunosuppression (e.g., biologic response modifiers such as TNF-α antagonists, systemic corticosteroids equivalent to ≥15 mg prednisone/day, organ transplantation, or HIV infection) *See Additional Considerations*	IGRA (+) or TST ≥5 mm	
❑ Household contact or recent exposure to a person with TB disease[1]	IGRA (+) or TST ≥5 mm IGRA (–) or TST <5 mm **AND** immunosuppressed → **Window period treatment[2]**	
❑ Current or former residents of high-risk congregate settings (e.g., homeless shelters and correctional facilities); consider local epidemiology	IGRA (+) or TST ≥10 mm (≥5 mm if immunosuppressed)	

ADDITIONAL CONSIDERATIONS

- Persons living with HIV: Test for LTBI at HIV diagnosis and again after immune reconstitution; consider repeat or annual testing in those at high risk for ongoing exposure to active TB
- Persons on immunosuppressive therapy: Test for LTBI prior to treatment initiation; repeat testing is recommended for those who live, work, or travel in situations where TB exposure is likely
- Other medical conditions that increase the risk of progression to TB disease: Identifying risk, diagnosing, and treating LTBI is a priority in persons with certain medical conditions. This includes: poorly controlled diabetes, chronic renal failure, prior healed TB on CXR without a history of appropriate treatment, IV drug use, lymphoma or leukemia, etc.
- Repeat testing: Periodic testing may be warranted in those with medical conditions that increase the risk of progression or other groups (e.g., residents of high-risk congregate settings) based on history and local epidemiology (risk of exposure)
- Health care personnel: Should receive a TB risk assessment, symptom screen, and baseline testing for TB infection at hire (unless documentation of previous positive result). Serial testing is not recommended unless there is known exposure or ongoing transmission
- Reporting: TB is a reportable disease; LTBI is reportable in some areas
- Vaccines: Some vaccines, e.g., live-virus vaccines, may affect the accuracy of TB testing. For guidance on COVID-19 vaccines and TB testing, visit tbcontrollers.org/resources/tb-and-covid-19/

1. Retest contacts who have an initial negative result 8-10 weeks after last exposure (based on time needed to develop an immune response).
2. In more severely immunosuppressed adult contacts, empiric initiation of LTBI therapy (window period treatment) in consultation with the local health department may be indicated. In some situations, treatment *may* be continued to completion (with expert consultation) even if the repeat test is negative, as false negative tests are more likely in this group.
3. Patient age and length of time since infection should not be a barrier to LTBI treatment.

Select a Test

Two types of tests are available: blood-based IGRAs and the TST:
- Neither test can distinguish between LTBI and TB disease
- A negative result from either or both tests does not exclude LTBI or TB disease
- Test results may remain positive for the patient's lifetime, even after treatment for LTBI

Recommendation for type of test in adults:
- IGRAs are generally preferred though TST is acceptable; test selection may depend on availability, logistics, and resources
- IGRAs are strongly preferred in BCG-vaccinated persons and those who are unlikely to return for interpretation of TST result

IGRAs available in the United States

QuantiFERON®-*TB* Gold Plus (QFT-Plus)	T-SPOT®.*TB*
• Results reported as positive, negative, or indeterminate	• Results reported as positive, negative, invalid, or borderline
• Indeterminate results: Do not have diagnostic interpretation; may be a result of an error in performing the test or immunosuppression. Repeat IGRA or administer TST	• Invalid results: Do not have diagnostic interpretation; may be a result of testing/laboratory issues, patient health or improper specimen handling. Repeat IGRA or administer TST • Borderline results: Quantitative values are near but not reaching the threshold for positivity and result interpretation will depend on patient risk factors. In general, the test should be repeated

TSTs
- Require two patient visits
- Interpretation of result is based on size of reaction in mm, risk for TB infection, and risk for progression; *see previous panel*

Expert consultation is suggested when test results are inconsistent with the clinical picture (e.g., positive tests in a person with low risk), borderline T-SPOT®.*TB* results, or results close to the cut point with QFT-Plus.

Dual testing with both TST and IGRA is not routinely recommended, but *may* be indicated in some situations:

- **Likely to be infected AND**
- **High risk of developing disease**

(e.g., born in a country with high TB prevalence **and** starting immunosuppressive therapy) + Initial test is **NEGATIVE** → Consider dual testing to increase sensitivity → Considered infected if **EITHER** test is positive*

- **Low risk of infection[1] AND**
- **Low risk of progression**

(e.g., healthy US-born college student with no known risk factors) + Initial test is **POSITIVE** → Consider dual or repeat testing to identify false positive results → Considered infected if **BOTH** tests are positive*

***Consider expert consultation when both results are available; see resources for more information**

- An IGRA may be used for confirmation in TST-positive BCG-vaccinated persons
- Some experts recommend using both tests to increase sensitivity for those who are about to start immunosuppressive therapy, or those who are already on immunosuppressive therapy and have not been tested

1. Testing is NOT recommended in this group, but may be required by law or for credentialing. An IGRA is preferred. Either a TST or IGRA may be used for the second test. A TST result of ≥15 mm is considered positive in those without risk factors.

Treatment of LTBI in Adults[1]

Shorter rifamycin-based regimens are preferred over isoniazid monotherapy

Exclude TB disease with clinical evaluation including symptom screen, chest radiograph, and other studies as indicated before starting LTBI treatment

TREATMENT REGIMENS

PREFERRED

REGIMEN	ADULT DOSAGE	COMPLETION CRITERIA	USE IN ADULTS
3 Months of Once-Weekly Isoniazid (INH) Plus Rifapentine[2]	**Isoniazid** 15 mg/kg rounded to nearest 50 or 100 mg; 900 mg max **Rifapentine** Weight (kg) / Dose (mg) 25.1–32.0 / 600 32.1–49.9 / 750 ≥50 / 900 max	12 doses within 16 weeks	Recommended for all adults, including people living with HIV (as drug interactions allow) Not indicated for: ➢ Persons with *M.tb* infection that is presumed resistant to INH and/or rifampin ➢ Persons who had prior adverse events or hypersensitivity to INH, rifampin, or rifapentine ➢ Women who are pregnant or expecting to become pregnant
4 Months of Daily Rifampin	10 mg/kg; 600 mg max	120 doses within 6 months	Recommended for HIV-negative adults Careful consideration is recommended when using this regimen in severely immunosuppressed persons; *see considerations column*
3 Months of Daily Isoniazid Plus Rifampin[3]	**Isoniazid** 5 mg/kg; 300 mg max **Rifampin** 10 mg/kg; 600 mg max	90 doses within 4 months	Recommended for all adults, including people living with HIV (as drug interactions allow)

ALTERNATIVE

6 or 9 Months of Daily Isoniazid[4]	5 mg/kg; 300 mg max	**6 months:** 180 doses within 9 months **9 months:** 270 doses within 12 months	6 months of INH is recommended for treatment of all adults 9 months of INH is also acceptable May be used when preferred regimens are contraindicated

PATIENT EDUCATION AND ADHERENCE

- Educate patients about importance of good adherence at treatment initiation and throughout treatment
- Explain possible side effects and adverse drug reactions and provide patients with written information
- **Advise to promptly seek medical evaluation for adverse reactions and provide guidance for when to stop treatment in the case of serious adverse reactions**
- Support adherence to ensure successful completion by:
  - Identifying and addressing possible barriers to adherence (appointment conflicts, misinformation about TB, health beliefs and practices, limited financial resources, co-morbidities, side effects, language barriers, and stigma)
  - Collaborating with community agencies to obtain incentives and/or enablers, case management, or in-person or video-based directly observed therapy (DOT); DOT is preferred by many health departments for those at high risk of progression to severe forms of disease and/or if there is evidence of non-adherence
  - Providing effective patient-centered education with opportunities to bring up concerns or questions
  - Discussing pill burden with the patient; although the 12-dose isoniazid-rifapentine regimen has a higher pill burden per dose than other regimens, the total number of doses is much lower

1. Based on Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020 cdc.gov/mmwr/volumes/69/rr/pdfs/rr6901a1-H.pdf. State or local health department guidelines may differ.
2. Can be self administered or provided by DOT based on local practice, individual patient attributes and preferences, and other considerations, including risk for progression to severe forms of TB disease.
3. Included in the above referenced 2020 NTCA/CDC LTBI treatment guidelines as a conditional recommendation with limited evidence.
4. Twice-weekly dosing may be used if daily dosing cannot be provided; however, it must be delivered by DOT. See Table 4 in 2020 NTCA/CDC LTBI treatment guidelines for additional information.

Treatment of LTBI in Adults

ADVERSE DRUG REACTIONS (ADRs) AND CONSIDERATIONS FOR ALL REGIMENS

Adverse Drug Reactions

Serious adverse drug reactions are rare. The risk of hepatotoxicity is minimal in most patients and should not deter treatment. However, periodic monitoring is recommended. In case of possible severe ADRs, discontinue treatment and provide supportive medical care as indicated.

Isoniazid: Hepatic enzyme elevation, rash, peripheral neuropathy, mild CNS effects

Rifampin and rifapentine: GI intolerance, hepatitis, bleeding problems (from gums or other sites), easy bruising, flu-like symptoms

More commonly associated with 12-dose isoniazid-rifapentine regimen: Hematologic toxicity, hypersensitivity reaction (e.g., hypotension or thrombocytopenia)

Considerations for Treatment

- Rifamycin-based regimens should be used whenever possible, based on individual patient attributes and preferences including potential for drug-drug interactions, local practice, and drug susceptibility results of the presumed source case, if known
- 6 or 9 month INH regimens have lower treatment completion rates than shorter-rifamycin based regimens, but may be used when the preferred regimens are contraindicated due to intolerance, resistance, or drug interactions
- Rifamycin-associated drug interactions include, but are not limited to, hormonal contraceptives, certain HIV antiretrovirals, methadone, and anticoagulants
  - **Weekly** rifapentine has fewer drug interactions than rifabutin, which has fewer interactions than rifampin; thus the 12-dose rifapentine containing regimen can be considered when rifampin is contraindicated
  - Rifabutin has a lower drug interaction profile than rifampin; to minimize drug-drug interactions, consider use of rifabutin in place of rifampin in the 4-month rifampin regimen
  - See clinicalinfo.hiv.gov for current guidelines on treatment for LTBI in people living with HIV and information on drug-drug interactions with HIV antiretrovirals
- Hepatitis risk increases with age, alcohol use, and concurrent use of other hepatotoxic drugs
- Potential for acquired drug resistance if TB disease is not adequately excluded is an important consideration for all regimens
- In any persons with severe immunosuppression (e.g., those on biologic response modifiers such as TNF-α antagonists or those living with HIV who have low CD4 lymphocyte counts), there is an increased risk of subclinical, atypical, or asymptomatic disease. Rifampin resistance could develop if a person is inadvertently treated with rifampin monotherapy for LTBI, when they actually have TB disease
- Women who become pregnant while on LTBI treatment should consult their provider
- If interruptions in therapy occur such that patients cannot complete treatment within the recommended time frame, treatment should be restarted, after a careful evaluation for TB disease
- Patients on INH containing regimens:
  - Pyridoxine (vitamin B6) should be added for pregnant women, patients with malnutrition, alcoholism, diabetes, and those with other conditions associated with neuropathy. Give 50 mg/week with the 12-dose isoniazid-rifapentine regimen and 25–50 mg/day with other INH containing regimens
- Patients on rifamycin containing regimens:
  - Patients should be educated that temporary orange discoloration of urine, sweat, tears, and other bodily fluids is a normal and expected side effect
  - Women who use hormonal birth control should be instructed to **add, or switch to a barrier method**

MONITORING & EVALUATION FOR ALL PATIENTS

Provide education and discuss monitoring plan with patients at treatment initiation.

Clinical monitoring: Patients should be evaluated monthly for:

- Adherence to the prescribed regimen
- Signs and symptoms of TB disease
- Adverse reactions:

  Evidence of hepatotoxicity such as:
  - Nausea or vomiting
  - Abdominal pain or tenderness (especially in right upper quadrant)
  - Anorexia
  - Jaundice

  Other adverse reactions such as:
  - Fever
  - Rash
  - Persistent paresthesia
  - Fatigue ≥3 days
  - Easy bruising/bleeding
  - Arthralgia

  Systemic drug reactions and influenza-like syndrome is usually self-limiting and mild, but can rarely include severe reactions such as syncope and hypotension (more frequently associated with the 12-dose isoniazid-rifapentine regimen).

  If adverse reactions occur, a prompt clinical evaluation is necessary with treatment changes as indicated.

Laboratory Monitoring: Routine monthly monitoring of liver function tests (LFTs) is not generally indicated.

- **Baseline LFTs are indicated for those:**
  - With a history of liver disease or liver disorders
  - Living with HIV
  - Who are regular alcohol users
  - Who are pregnant or <3 months postpartum
  - Taking other potentially hepatotoxic drugs (e.g., anti-convulsants) or over-the-counter drugs (e.g., acetaminophen)
- **LFT monitoring based on clinical scenario is indicated for:**
  - Persons at risk for, or with a history of liver disease
  - Persons who have abnormal baseline LFTs
  - Those who develop symptoms consistent with hepatotoxicity
- **Medications should be withheld and patients evaluated if:**
  - Transaminase levels ≥3 times upper limit of normal in presence of symptoms
  - Transaminase levels ≥5 times upper limit of normal in asymptomatic patients

  When LFTs have returned to normal, consider an alternate regimen, with close clinical and laboratory monitoring. Consult a TB expert

Report adverse events to CDC Division of Tuberculosis Elimination by sending an email to ltbidrugevents@cdc.gov and to FDA MedWatch at accessdata.fda.gov/scripts/medwatch/index.cfm or 1-888-INFO-FDA).

Diagnosis and Treatment of LTBI in Adults

Identify those at risk

This includes those at risk for TB infection and/or those at risk for progression to TB disease:

- Birth, travel, or residence in a country with increased TB prevalence
- Immune suppression
- Close contact to person with infectious TB
- Residence in high-risk congregate settings

Consider use of a risk assessment tool

Test for TB infection

Use IGRA or TST as appropriate to test for TB infection:

- IGRAs generally preferred in adults
- IGRAs strongly preferred in BCG-vaccinated and those unlikely to return

Consider risk of infection and progression to disease when interpreting results

Positive tests do not distinguish LTBI from TB disease

Evaluate for TB disease

Exclude TB disease in those with positive testing:

- Clinical evaluation
- Symptom screen
- Chest radiograph (other studies based on history and physical)
- Microbiological testing, if indicated

LTBI diagnosis is based on IGRA or TST result and exclusion of TB disease

Treat LTBI

Select appropriate regimen based on medical history, clinical characteristics, and patient preference

Shorter rifamycin-based regimens are preferred and have higher completion rates and in general, have lower toxicity

Follow to treatment completion

Monitor patient monthly to assess for adverse reactions and adherence

Provide education and supportive services to enhance adherence

Prevent

TB disease and transmission

For additional resources

Consultation is available from your TB program:
cdc.gov/tb/php/tb-programs/index.html

Regional TB Centers of Excellence
cdc.gov/tb-programs/php/about/tb-coe.html

California TB Risk Assessment Tools
cdph.ca.gov/Programs/CID/DCDC/Pages/TB-Risk-Assessment.aspx

Educational materials and consultation are available at globaltb.njms.rutgers.edu