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

Content based on national TB guidelines with consideration for practical applications

Identify those at risk

Test for TB infection

Evaluate for TB disease

Treat LTBI

Follow to treatment completion

Prevent TB disease and transmission

225 Warren Street
Newark, NJ 07103
(973) 972-3270
globaltb.njms.rutgers.edu
**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).

<table>
<thead>
<tr>
<th>Identify these adults and test for TB infection</th>
<th>Consider positive if</th>
<th>Evaluate for TB disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth, residence, or extended travel (&gt;1 month) to a country with increased TB prevalence (countries other than the US, Canada, Australia, New Zealand, or in western or northern Europe)</td>
<td>IGRA (+) or TST (\geq 10) mm ((\geq 5) mm if immunosuppressed)</td>
<td>Clinical evaluation</td>
</tr>
<tr>
<td>Current or planned immunosuppression (e.g., biologic response modifiers such as TNF-(\alpha) antagonists, systemic corticosteroids equivalent to (\geq 15) mg prednisone/day, organ transplantation, or HIV infection) See Additional Considerations</td>
<td>IGRA (+) or TST (\geq 5) mm</td>
<td>Assessment for signs and symptoms</td>
</tr>
<tr>
<td>Household contact or recent exposure to a person with TB disease</td>
<td>IGRA (+) or TST (\geq 5) mm</td>
<td>Radiography</td>
</tr>
<tr>
<td>Current or former residents of high-risk congregate settings (e.g., homeless shelters and correctional facilities); consider local epidemiology</td>
<td>IGRA (-) or TST &lt;5 mm AND immunosuppressed</td>
<td>Microbiological exams (if indicated)</td>
</tr>
</tbody>
</table>

**Treat for LTBI if TB disease is excluded**

**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.

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

<table>
<thead>
<tr>
<th>QuantiFERON®-TB Gold Plus (QFT-Plus)</th>
<th>T-SPOT®.TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Results reported as positive, negative, or indeterminate</td>
<td>• Results reported as positive, negative, invalid, or borderline</td>
</tr>
<tr>
<td>• 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</td>
<td>• 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</td>
</tr>
<tr>
<td>• 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</td>
<td></td>
</tr>
</tbody>
</table>

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)
- **Low risk of infection**¹ AND **Low risk of progression** (e.g., healthy US-born college student with no known risk factors)

*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

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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

### 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

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Adult Dosage</th>
<th>Completion Criteria</th>
<th>Use in Adults</th>
</tr>
</thead>
</table>
| 3 Months of Once-Weekly Isoniazid (INH) Plus Rifapentine | Isoniazid 15 mg/kg rounded to nearest 50 or 100 mg; 900 mg 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.tuberculosis 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 |

### Use in Adults

- Use in adults
- 3 Months of Once-Weekly Isoniazid (INH) Plus Rifapentine
  - Isoniazid: 15 mg/kg rounded to nearest 50 or 100 mg; 900 mg max
  - Rifapentine: Weight (kg) x Dose (mg)
    - 25.1–32.0: 600
    - 32.1–49.9: 750
    - ≥50: 900 max
  - 12 doses within 16 weeks

### Alternative

6 or 9 Months of Daily Isoniazid

- 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](https://www.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

<table>
<thead>
<tr>
<th>ADVERSE DRUG REACTIONS (ADRs) AND CONSIDERATIONS FOR ALL REGIMENS</th>
<th>MONITORING &amp; EVALUATION FOR ALL PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Drug Reactions</strong></td>
<td>Provide education and discuss monitoring plan with patients at treatment initiation.</td>
</tr>
<tr>
<td>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.</td>
<td>Clinical monitoring: Patients should be evaluated monthly for:</td>
</tr>
<tr>
<td><strong>Isoniazid:</strong> Hepatic enzyme elevation, rash, peripheral neuropathy; mild CNS effects</td>
<td>- Adherence to the prescribed regimen</td>
</tr>
<tr>
<td><strong>Rifampin and rifapentine:</strong> GI intolerance, hepatitis, bleeding problems (from gums or other sites), easy bruising, flu-like symptoms</td>
<td>- Signs and symptoms of TB disease</td>
</tr>
<tr>
<td>More commonly associated with 12-dose isoniazid-rifapentine regimen: Hematologic toxicity, hypersensitivity reaction (e.g., hypotension or thrombocytopenia)</td>
<td>- Adverse reactions:</td>
</tr>
<tr>
<td><strong>Considertations for Treatment</strong></td>
<td>- Evidence of hepatotoxicity such as:</td>
</tr>
<tr>
<td>• 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</td>
<td>- Nausea or vomiting</td>
</tr>
<tr>
<td>• 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</td>
<td>- Abdominal pain or tenderness (especially in right upper quadrant)</td>
</tr>
<tr>
<td>• Rifamycin-associated drug interactions include, but are not limited to, hormonal contraceptives, certain HIV antiretrovirals, methadone, and anticoagulants</td>
<td>- Anorexia</td>
</tr>
<tr>
<td>- 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</td>
<td>- Jaundice</td>
</tr>
<tr>
<td>- 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</td>
<td>Other adverse reactions such as:</td>
</tr>
<tr>
<td>- See <a href="http://clinicalinfo.hiv.gov">clinicalinfo.hiv.gov</a> for current guidelines on treatment for LTBI in people living with HIV and information on drug-drug interactions with HIV antiretrovirals</td>
<td>- Fever</td>
</tr>
<tr>
<td>• Hepatitis risk increases with age, alcohol use, and concurrent use of other hepatotoxic drugs</td>
<td>- Rash</td>
</tr>
<tr>
<td>• Potential for acquired drug resistance if TB disease is not adequately excluded is an important consideration for all regimens</td>
<td>- Persistent paresthesia</td>
</tr>
<tr>
<td>• 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</td>
<td>- Fatigue ≥3 days</td>
</tr>
<tr>
<td>• Women who become pregnant while on LTBI treatment should consult their provider</td>
<td>- Easy bruising/bleeding</td>
</tr>
<tr>
<td>• 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</td>
<td>- Arthralgia</td>
</tr>
<tr>
<td>• Patients on INH containing regimens:</td>
<td>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).</td>
</tr>
<tr>
<td>- 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</td>
<td>If adverse reactions occur, a prompt clinical evaluation is necessary with treatment changes as indicated.</td>
</tr>
<tr>
<td>• Patients on rifamycin containing regimens:</td>
<td>Laboratory Monitoring: Routine monthly monitoring of liver function tests (LFTs) is not generally indicated.</td>
</tr>
<tr>
<td>- Patients should be educated that temporary orange discoloration of urine, sweat, tears, and other bodily fluids is a normal and expected side effect</td>
<td>- Baseline LFTs are indicated for those:</td>
</tr>
<tr>
<td>- Women who use hormonal birth control should be instructed to add, or switch to a barrier method</td>
<td>- With a history of liver disease or liver disorders</td>
</tr>
<tr>
<td>- If adverse reactions occur, a prompt clinical evaluation is necessary with treatment changes as indicated.</td>
<td>- Living with HIV</td>
</tr>
<tr>
<td>- Medications should be withheld and patients evaluated if:</td>
<td>- Who are regular alcohol users</td>
</tr>
<tr>
<td>- Transaminase levels ≥3 times upper limit of normal in presence of symptoms</td>
<td>- Who are pregnant or &lt;3 months postpartum</td>
</tr>
<tr>
<td>- Transaminase levels ≥5 times upper limit of normal in asymptomatic patients</td>
<td>- Taking other potentially hepatotoxic drugs (e.g., anti-convulsants) or over-the-counter drugs (e.g., acetaminophen)</td>
</tr>
<tr>
<td>- When LFTs have returned to normal, consider an alternate regimen, with close clinical and laboratory monitoring. Consult a TB expert</td>
<td>- LFT monitoring based on clinical scenario is indicated for:</td>
</tr>
<tr>
<td>- 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</td>
<td>- Persons at risk for, or with a history of liver disease</td>
</tr>
<tr>
<td>- Persons who develop symptoms consistent with hepatotoxicity</td>
<td>- Persons who have abnormal baseline LFTs</td>
</tr>
<tr>
<td>- Those who develop symptoms consistent with hepatotoxicity</td>
<td>- Those who develop symptoms consistent with hepatotoxicity</td>
</tr>
</tbody>
</table>

Report adverse events to CDC Division of Tuberculosis Elimination by sending an email to [ltbldrugevents@cdc.gov](mailto:ltbldrugevents@cdc.gov) and to FDA MedWatch at [accessdata.fda.gov/scripts/medwatch/index.](http://accessdata.fda.gov/scripts/medwatch/index.htm) 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:
- IGRA generally preferred in adults
- IGRA 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/links/tboffices.htm
Regional TB Centers of Excellence
cdc.gov/tb/education/tb_coe/default.htm
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