Latent Tuberculosis Infection

This is a PDF version of the following document:
Section 1: Co-Occurring Conditions
Topic 1: Latent Tuberculosis Infection

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Background

Epidemiology of Tuberculosis in the United States

Although the incidence of tuberculosis in the United States has substantially decreased since the early 1990s (Figure 1), tuberculosis continues to occur at a significant rate among certain populations, including foreign born, incarcerated, homeless, persons who use drugs, and individuals with HIV infection.[1,2] In recent years, the majority of tuberculosis cases in the United States were among the foreign born (66.4% in 2015), with a rate approximately 13 times higher than among persons born in the United States (Figure 2).[2] Cases of tuberculosis in the United States have occurred at disproportionately higher rates among non-white races (Figure 3).[1,2] In the general United States population, the prevalence of latent tuberculosis infection (LTBI) is estimated between 3.4 to 5.8%, based on the 2011-2012 National Health and Nutrition Examination Survey (NHANES).[3] The prevalence of LTBI among persons living with HIV sampled in NHANES was 7.6%.

Epidemiology of Tuberculosis in Persons with HIV Infection

In the late 1980s and early 1990s, HIV contributed to the significant increase of tuberculosis in the U.S. (48% of tuberculosis cases occurred in persons with HIV coinfection in 1993).[4] In recent years, the overall number (Figure 4) and proportion (Figure 5) of tuberculosis cases involving persons living with HIV has substantially decreased; in 2014, 6% of persons with tuberculosis were coinfected with HIV.[2] In contrast to the overall decline of new tuberculosis cases in persons with HIV infection, the incidence of tuberculosis among persons with HIV infection who are foreign born has remained stable.[5,6] Tuberculosis continues to cause significant morbidity and mortality among people living with HIV in the United States and other low tuberculosis burden areas.[5,7] Data regarding the number of incident tuberculosis cases specifically among individuals with HIV infection is not routinely collected on the national level, but 2008 data from California estimated an incidence of tuberculosis among those with HIV of 126 per 100,000 compared with 7 per 100,000 individuals not infected with HIV.[7] Similarly in New York City, people living with HIV were 16 times more likely to have tuberculosis compared to people without HIV.[5] The risk of mortality among individuals with HIV infection who develop tuberculosis is higher than those with tuberculosis alone, even in the era of readily available antiretroviral therapy,[7] highlighting the importance of tuberculosis prevention in those with HIV infection.[8]

Progression from LTBI to Active TB

Development of tuberculosis disease can occur in the setting of recent exposure to Mycobacterium tuberculosis (primary or active disease) or with reactivation of LTBI.[9] The development of tuberculosis disease is based on complex interactions between host immune status and the bacillary load (Figure 6).[9] Investigators have identified several comorbidities that contribute to the risk of developing active disease, including HIV infection, diabetes, malnutrition, low body weight, smoking,
lung disease, drug use, and recent or current use of immunosuppressant medications.\textsuperscript{[10]} The risk of progression from LTBI to active disease is markedly increased in individuals infected with HIV (3 to 16\% per year) compared with those uninfected (5 to 10\% lifetime risk).\textsuperscript{[8,11,12]} The increased risk of LTBI reactivation begins soon after HIV infection.\textsuperscript{[13]}

**Prevention of Tuberculosis in Persons with HIV Infection**

Combination antiretroviral therapy decreases the risk of developing active tuberculosis disease by approximately 67\%, with greater declines in tuberculosis occurring with more substantial increases in CD4 cell counts and longer duration of antiretroviral therapy.\textsuperscript{[14]} Nevertheless, the risk of incident tuberculosis remains significantly higher among those with HIV compared to those without HIV, even after CD4 recovery on antiretroviral therapy, or initiation of antiretroviral therapy at higher CD4 cell counts.\textsuperscript{[15]} Identifying those with LTBI who may benefit from treatment to prevent tuberculosis disease is an important part of tuberculosis prevention in people living with HIV.\textsuperscript{[8]} Individuals with HIV infection who have positive LTBI testing, either tuberculin skin test (TST) or interferon gamma release assay (IGRA), are associated with increased risk of progression to active tuberculosis.\textsuperscript{[16,17,18,19]} Among persons with HIV infection who have a positive tuberculin skin test, treating LTBI significantly decreases their risk of developing active tuberculosis and mortality (62\% and 26\% reduction, respectively).\textsuperscript{[20,21,22]} The combination of antiretroviral therapy and LTBI treatment decreases the risk of tuberculosis more than either intervention alone.\textsuperscript{[23]}
Rationale and Indications for LTBI Screening

Rationale for LTBI Screening

Multiple factors underscore the rationale for LTBI screening in persons living with HIV, including increased risk of progression from LTBI to tuberculosis, poor outcomes associated with active tuberculosis disease, availability of screening tests to identify those with LTBI, and effective treatment for LTBI to prevent progression to active tuberculosis disease. For all these reasons, individuals with HIV infection should be routinely screened and offered treatment if found to have LTBI.[8]

Indication and Timing of LTBI Screening

The Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents recommends screening for LTBI at the time of initial HIV diagnosis or entry into medical care, regardless of the presence or absence of other epidemiologic tuberculosis risk factors.[8,24] Despite this recommendation, adherence to recommendations for LTBI screening of persons with HIV infection in the United States has been variable, with reports of adherence to routine screening practices ranging from 47 to 79%.[25,26,27,28] Individuals with advanced HIV disease (CD4 count less than 200 cells/mm³) with initially negative LTBI testing should have repeat testing after they initiate antiretroviral therapy and reach a CD4 count of at least 200 cells/mm³, due to the possibility of false-negative results in the setting of advanced immunosuppression.[8] Yearly repeat testing for LTBI is recommended only in situations where individuals have likely ongoing or repeat exposure to active tuberculosis. Examples of tuberculosis risk factors include injection drug use, living in congregate settings, incarceration, or homelessness. Recent contact with a known tuberculosis case should prompt LTBI screening, evaluation for active disease, and empiric therapy for latent tuberculosis if there is no evidence of active tuberculosis.
Methods Used to Test for Latent Tuberculosis

There are two primary methods for detection of LTBI: tuberculin skin test and interferon gamma release assay (IGRA).[29, 30] Both methods are indirect measures of tuberculosis infection that for a positive test result require infection with *M. tuberculosis* and the host’s ability to mount a T-cell mediated response. The tests differ in that tuberculin skin testing is an in-vivo skin test, while IGRA is an in-vitro blood-based approach.[31] Routine dual testing with both the tuberculin skin test and IGRA is not recommended, though CDC guidelines recommend that repeat testing (with the other test) may be appropriate when the initial test was negative in patients at high risk for tuberculosis infection.[27] Importantly, a positive tuberculin skin test or IGRA does not distinguish between LTBI and active disease, nor does negative LTBI testing rule out active tuberculosis.

**Tuberculin Skin Test**

The Mantoux method of tuberculin skin testing consists of giving an intradermal injection of 5 tuberculin units of purified protein derivative (Figure 7) and then evaluating the cutaneous induration 48 to 72 hours later.[29] In patients previously infected with *M. tuberculosis* (and sensitized to the *M. tuberculosis* antigens contained in PPD), intradermal injection of the PPD will stimulate a T-lymphocyte mediated type IV delayed hypersensitivity response, leading to induration of the site of injection within 48 to 72 hours.[31] The transverse diameter of induration (not erythema) should be measured at a follow-up visit 48 to 72 hours after placement of the PPD and should be performed by an individual trained in reading a tuberculin skin test (Figure 8).[29] For individuals with HIV infection, an induration of 5 mm or greater is considered a positive test.[24] Following exposure to *M. tuberculosis*, the tuberculin skin test conversion to positive typically occurs within 8 weeks.[32] The sensitivity of tuberculin skin test for the diagnosis of LTBI varies considerably, with estimates ranging from 45 to 85%, and specificity typically around 85%.[27, 33, 34] Previous exposure to non-tuberculosis mycobacteria, as well as immunization with Bacille Calmette-Guerin (BCG), can cause a false-positive tuberculin skin test.[30] Receipt of BCG in infancy is thought to have a relatively minimal effect on tuberculin skin testing, especially if at least 10 years have elapsed after administration.[35] False negatives can occur in the setting of advanced HIV disease, malnutrition, and active tuberculosis.[30] Persons with prior treatment of LTBI or active tuberculosis (and a prior positive tuberculin skin test), typically have a persistently positive tuberculin skin test.

**Interferon Gamma Release AssayS (IGRA)**

The two most commonly used FDA approved IGRAs in the United States for the detection of LTBI are the QuantiFERON-TB Gold (QFT) assay (Qiagen) and the T-SPOT.TB (T-SPOT) assay (Oxford Diagnostic Laboratories) (Figure 9).[27] Recently, the QuantiFERON-TB Gold Plus (QFT-Plus) was approved by the United States FDA. The QFT, QFT-Plus, and T-SPOT are in vitro tests that measure the release of interferon gamma by T-cells after stimulation to two *M. tuberculosis* specific antigens: early secreted antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10).[30] The ESAT-6 and CFP-10 antigens are encoded within the region of difference 1 (RD1) locus of the *M. tuberculosis* genome.[30, 36] Since these antigens are not found in the BCG vaccine, IGRA will not produce false-positive results due to previous immunization with BCG. These tests, however, can have cross reactivity with some non-tuberculous mycobacteria, including *M. marinum*, *M. kansasii*, *M. szulgai*, and *M. flavescens*.[30] The presence of immunosuppression may also have less impact on the IGRA than the tuberculin skin test.[30] Although IGRA testing requires a blood draw, unlike tuberculin skin testing, it does not require a follow-up visit for test result reading and IGRA cut-offs are not stratified by risk-group, including HIV status. Persons with prior treatment of LTBI or active tuberculosis (and a prior positive IGRA) usually have persistently positive IGRAs.

- **QuantiFERON-TB Gold (QFT):** The QFT is an enzyme-linked immunosorbent assay (ELISA) that measures the amount of interferon gamma released from CD4 lymphocytes after whole blood is exposed to ESAT-6, CFP-10, and TB7.7 antigens.[30] Blood is drawn into 3 specialized collection tubes: Nil (negative control), MTB antigens (ESAT-6, CFP-10, and
TB7.7), and mitogen (positive control) (Figure 10). The interferon gamma response is quantified in international units (IU) per millimeter. The test is considered positive if the MTB antigen response is 0.35 IU/mL or greater after subtracting the background Nil response (Figure 11).[37] Results are considered indeterminate if there are high Nil or low TB antigen responses. Individuals with HIV infection, especially those with low CD4 counts, are more likely to have indeterminate responses.[34] Reversion from a positive to negative test result can occur,[38,39,40] but this tends to occur when the initial test is close to the cut-off threshold.[30] In order to address the reliability and reproducibility of low level IGRA QFT positive results (e.g. 0.35-0.59 IU/mL), some experts have proposed a higher cutoff or gray zone.[41,42]

- **QuantiFERON-TB Gold Plus (QFT-Plus):** A newer version of QFT, the QuantiFERON-TB Gold Plus (QFT-Plus), was approved by the United States FDA in June 2017, but will not be available in the United States until late 2017. The QFT-Plus differs from QFT by the addition of a fourth tube designed to measure interferon gamma released from CD8 cytotoxic lymphocytes (Figure 12).[43,44]

- **T-SPOT.TB (T-SPOT):** The T-SPOT is an enzyme-linked immunosorbent spot (ELISPOT) assay that quantitates the response of mononuclear T-cells to *M. tuberculosis* antigens. First, a blood sample is obtained and peripheral blood mononuclear cells are separated from whole blood and counted. The peripheral blood mononuclear cells are then placed into microtiter wells pre-coated with high affinity antibodies to interferon-gamma; four different panels are set up by coincubating with either *M. tuberculosis* ESAT-6 antigens (Panel A), *M. tuberculosis* CFP10 antigens (Panel B), positive control that contains phytohemagglutinin (Panel C), or Nil negative control (Panel D).[45] The number of T-cells producing interferon gamma (spot-forming cells) are then counted (Figure 13). The test is considered positive if the number of spot-forming cells in either of the wells containing *M. tuberculosis* antigens is 8 or greater (Figure 14). Similar to QFT, results are considered indeterminate if there are high Nil or low *M. tuberculosis* antigen responses. In the setting of TSPOT “borderline” results (spot-forming cells 5 to 7), retesting is recommended by the manufacturer. In a meta-analysis of IGRA studies in persons with HIV infection, the pooled sensitivity was 72% for T-SPOT and 61% for QFT.[46] The authors concluded that although immunosuppression appears to impact T-SPOT less than the QFT or tuberculin skin test, the overall differences between QFT, T-SPOT, and tuberculin skin test remain small with overlapping confidence intervals.
Recommendations for LTBI Testing in Persons with HIV Infection

CHOICE OF TEST METHOD FOR LTBI SCREENING

Use of either tuberculin skin test or IGRA is appropriate for LTBI screening in persons living with HIV infection.\[8,27\] The Official American Thoracic Society-Infectious Diseases Society of America-Centers for Disease Control and Prevention Clinical Practice Guidelines for Diagnosis of Tuberculosis in Adults and Children concluded there was insufficient data to recommend a preference for either of these tests.\[29\] Although correlation between positive tuberculin skin test and IGRA in persons with HIV infection is poor to moderate,\[46\] positive tuberculin skin tests and IGRAs are both associated with increased risk of developing tuberculosis disease,\[19,47,48\] with a higher risk of progression to active tuberculosis disease among recent LTBI test converters.\[48,49,50\] Some studies indicate a positive IGRA is a stronger predictor than tuberculin skin test for the risk of developing tuberculosis disease,\[51,52\] but most of the data supporting the benefits of preventive therapy among individuals with HIV infection have been based on studies of individuals with positive tuberculin skin test results.\[20\] In recent years, many clinics have begun predominantly using IGRAs because of several negative aspects of tuberculin skin testing, including the requirement for a second visit to read the test, false-positive results in people immunized with Bacillus Calmette-Guerin (BCG) vaccine, and lower sensitivity (compared with IGRA) in patients with advanced immunosuppression. From a practical standpoint, the decision regarding which test to use is often based on a combination of the availability of the test, trained staff, lab capability, and likelihood of patient follow-up for a second visit to read a TST test.

LTBI TESTING IN PERSONS WITH HIV INFECTION

The following summarizes the key recommendations in the Opportunistic Infections Guidelines regarding testing for LTBI in persons with HIV infection:

- All persons with HIV infection should undergo testing for LTBI at the time of HIV diagnosis, regardless of their epidemiological risk of TB exposure.
- Either TST or IGRA can be used as the screening method for LTBI and the decision for which one to use may be based on likelihood of patient follow up for reading a TST.
- Annual testing for LTBI is recommended for persons with HIV infection who are at high risk for repeated or ongoing exposure to persons with active TB.
- The routine use of both TST and IGRAs to screen for LTBI is not recommended in the United States.
- All persons with a positive TST or IGRA should be evaluated for the possibility of active TB disease.
Evaluation of Persons with a Positive LTBI Screening Test

Any individual with HIV infection who has a new positive LTBI screening test should undergo tuberculosis symptom screening as well as chest radiography to exclude active tuberculosis disease.\[25\] A meta-analysis of individual patient data of more than 8,000 subjects with HIV infection found that having at least one positive symptom in a 4-symptom tuberculosis screen (cough, fever, weight loss, or night sweats) has sensitivity 78.9%, specificity 49.6%, and negative predictive value of 97.7% (at a 5% prevalence) to identify those with culture-confirmed pulmonary tuberculosis.\[53\] Sputum examination, including acid fast smear microscopy and culture is indicated for those with either an abnormal chest radiograph or a positive symptom screen (even if their chest radiograph is negative).\[54\] The Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents recommend that in a low burden setting such as in the United States, routine use of sputum culture to screen for tuberculosis in asymptomatic individuals with a negative chest radiograph is not cost-effective.\[8\]
Management of LTBI in Persons with HIV Infection

Indications and Recommended Therapy for LTBI

The Opportunistic Infections Guidelines provide recommended indications for initiation therapy for LTBI, as well as preferred and alternative agents for the treatment of LTBI (Table 1).[8]

- **Indications for Treatment of LTBI:** All individuals with HIV infection who have a new positive testing for LTBI and a negative workup for active tuberculosis should be offered LTBI treatment.[8] In addition, individuals with HIV infection who have close contact with an active tuberculosis case should receive treatment for latent tuberculosis infection after active tuberculosis has been excluded, irrespective of LTBI test result. A history of BCG vaccination should not affect the decision whether to treat LTBI in persons with HIV infection.

- **Preferred Therapy:** The preferred treatment of LTBI in persons with HIV infection is 9 months of isoniazid either given 300 mg daily or 900 mg twice weekly (by directly observed therapy).[8] Isoniazid should be given with 25 mg of pyridoxine (vitamin B6) daily to reduce the risk of peripheral neuropathy. In the situation where a patient has evidence of LTBI with a history of exposure to a drug resistant case of tuberculosis, the clinician should consult with a tuberculosis expert to identify an appropriate regimen for the treatment of LTBI.

- **Alternative Therapies:** Alternative regimens to isoniazid include 4 months of rifampin 600 mg daily or rifabutin, both of which may be complicated by drug interactions and require dose adjustment of antiretrovirals.[8,55] A short-course regimen of isoniazid (15 mg/kg weekly with 900 mg maximum doses) plus rifapentine (weight based taken once weekly) for a total of 12 weeks has efficacy equal to isoniazid monotherapy, with the added benefit of likely improved adherence due to shorter duration.[55,56] The 12-week isoniazid plus rifapentine regimen should be administered with pyridoxine 50 mg each week. For persons with HIV infection, this regimen is currently recommended only for those not on antiretroviral therapy or those taking an efavirenz- or raltegravir-based antiretroviral regimen.[8,57] It is not recommended for use with other antiretroviral therapy regimens due to concerns for drug interactions.[8,57]

Medication-Related Adverse Effects

Patients on LTBI therapy should undergo clinical monitoring on a monthly basis. Isoniazid is associated with an increased risk of hepatitis, particularly in patients with older age, alcohol use, and pregnancy.[58,59] Patients should receive education on the signs and symptoms of hepatitis (jaundice, abdominal discomfort, nausea and vomiting) and be advised to promptly stop isoniazid and report their symptoms to their provider if they occur. Baseline hepatic aminotransferase levels should be obtained. Individuals at increased risk of hepatotoxicity including those with abnormal baseline tests, hepatitis B or C infection, or on antiretroviral therapy should have routine lab monitoring during treatment with isoniazid.[8] The Opportunistic Infections Guidelines recommend that isoniazid should be withheld if hepatic aminotransferase levels exceed three times the upper limit of normal if associated with symptoms or five times the upper limit of normal if the patient is asymptomatic.[8,24] The 2-month short course regimen of rifampin and pyrazinamide has been studied, but this regimen has an unacceptably high risk of causing severe liver injury and thus should never be used for treatment of latent TB.[8,60,61]

Drug Interactions

Isoniazid has few drug interactions with most antiretroviral medications and no dose adjustment is required. Rifampin has significant drug interactions with a number of antiretroviral agents. The majority of this data is from tuberculosis disease treatment and not in the context of LTBI treatment. Rifapentine for LTBI treatment does not require dose adjustment with efavirenz- or raltegravir-based regimens. The CDC has published guidelines regarding recommended dose adjustment of
antiretroviral medications in the setting of tuberculosis treatment and these guidelines should be
followed in the setting of using rifampin and rifabutin for LTBI treatment. Of note, rifampin is not
recommended for use in persons receiving antiretroviral therapy including protease inhibitors,
etravirine, rilpivirine, elvitegravir-cobicistat or tenofovir alafenamide. Rifabutin is not recommended
for persons receiving tenofovir alafenamide or elvitegravir-cobicistat.

**Management with Missed Doses or Treatment Interruption**

If interruptions were frequent or prolonged enough to preclude completion of treatment within the
recommended time frame, therapy should be extended or re-started. When treatment has been
interrupted for more than 2 months, the patient should be re-evaluated for tuberculosis disease.
Considerations in Special Populations

Pregnancy

All pregnant women with HIV infection who have not had previous screening for LTBI (or who are at high risk of exposure to individuals with active tuberculosis) should have testing for LTBI during pregnancy.\[8\] Although data remain conflicting whether pregnancy stage affects both TST and IGRA testing,\[63,64,65\] either test is considered appropriate for screening in pregnancy. The CDC recommends that pregnant women with HIV and evidence of LTBI should receive treatment for LTBI.\[24,66\] For women with HIV infection, the LTBI therapy should not be delayed due to pregnancy, even in the first trimester.\[24,66\] Women who become pregnant while on LTBI therapy should continue treatment, as long as it is tolerated. Neither isoniazid nor rifampin are considered teratogenic, but women who are pregnant or postpartum may have a higher risk for isoniazid-associated hepatotoxicity.\[67\] The preferred regimen for treatment of LTBI in pregnancy is isoniazid, given with pyridoxine, primarily due to lack of efficacy data for the use of rifampin for LTBI treatment in pregnancy. Breastfeeding is not contraindicated during LTBI treatment, but breastfed infants of mothers taking isoniazid should also receive pyridoxine.\[24\] Isoniazid-rifapentine short-course therapy is not currently recommended in pregnancy due to lack of efficacy and safety data \[57\], though clinical trials are underway to address these questions.

Liver Disease

Individuals with chronic liver disease are at increased risk of LTBI treatment-associated hepatitis. Active hepatitis and end-stage liver disease are relative contraindications for LTBI treatment. Isoniazid or rifampin have been used in this population in the setting of stable liver disease, but close clinical and laboratory monitoring is recommended.\[66\] In addition, management of LTBI in a patient with chronic liver disease should involve consultation with a tuberculosis expert.

Children

The risk of progression from \textit{M. tuberculosis} infection to active tuberculosis disease is high in children (50\% in those younger than 1 year, 20 to 30\% at age 1 to 2 years, and 10 to 20\% in those older than 10 years).\[68\] Most tuberculosis disease in young children is due to primary infection.\[69\] All children with HIV infection should be screened for LTBI.\[70\] The American Academy of Pediatrics recommends using tuberculin skin testing for screening in children younger than 5 years of age, though some expert panels have suggested that IGRA can be used in infants older than 2 years of age.\[71\] Measles vaccine can temporarily suppress the tuberculin skin test reactivity for 4 to 6 weeks. The effect of other live virus vaccines (varicella, yellow fever, live-attenuated influenza) in tuberculin skin test and IGRA testing is unknown. Therefore, tuberculin skin tests and IGRA testing should be performed the same day as these vaccines are administered, or delayed for at least 6 weeks after live vaccine administration. A 9-month course of isoniazid is the recommended treatment for treatment of LTBI in children with HIV infection ages 2 to 11.\[70\] Pyridoxine supplementation (1-2 mg/kg, maximum 50 mg/day) is recommended for all children with HIV who are taking isoniazid.\[70\] The use of sorbitol-based liquid preparations of isoniazid should be avoided if possible due to increased abdominal cramping and diarrhea. Tablets can be crushed or capsules opened and their contents placed in food if necessary. Rifampin may be used in the setting of isoniazid intolerance or known exposure to an isoniazid-resistant tuberculosis case; in these situations the recommended treatment length with rifampin is 6 months. The isoniazid-rifapentine short course is not recommended for children younger than 2 years of age or in children with HIV infection on antiretroviral therapy.\[57,70\]
Summary Points

- Despite declining incidence of tuberculosis in the United States, individuals with HIV infection remain at significant risk for tuberculosis.
- Compared to people without HIV, individuals with HIV infection are at increased risk for tuberculosis, even those on antiretroviral therapy.
- All individuals with HIV infection should undergo screening for LTBI at either the time of HIV diagnosis or entry into care.

Limitations to tuberculin skin testing include: requirement of second visit to read the test, lower specificity especially in people immunized with Bacillus Calmette-Guerin (BCG) vaccine, and potentially lower sensitivity with advanced immunosuppression.
- Severe immunosuppression can lead to false-negative tests; therefore, LTBI screening should be repeated once CD4 counts increase to at least 200 cells/mm$^3$ on antiretroviral treatment.
- All individuals with HIV infection and positive LTBI screening tests should be offered LTBI treatment, after active tuberculosis has been ruled out.
- All individuals with HIV infection and a recent exposure to a person with active tuberculosis should also be offered LTBI treatment, irrespective of tuberculin skin test and/or IGRA results.
- The preferred regimen for LTBI treatment in those with HIV is 9 months of isoniazid, given with pyridoxine to prevent peripheral neuropathy.

- Testing for LTBI should be performed with either a tuberculin skin test or IGRA.
Citations


24. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official
statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America (IDSA), September 1999, and the sections of this statement. Am J Respir Crit Care Med. 2000;161:S221-47.

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37. Qiagen. QuantiFERON®-TB Gold. Package Insert. [Qiagen] -


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[PubMed Abstract]

[CDC]

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[PubMed Abstract]

[AIDSinfo]

References


Figures

Figure 1 Tuberculosis Cases in United States, 1980-2015*

*Data as of June 9, 2016

Figure 2 Tuberculosis Cases, Percentages, and Case Rates per 100,000 Population by Origin of Birth—United States, 1993-2015*

*Data as of June 9, 2016

Figure 3 Tuberculosis Case Rates in United States—2015, by Race*

*Data as of June 9, 2016

Source: Centers for Disease Control (CDC). Reported Tuberculosis in the United States, 2015
Figure 4 Tuberculosis Cases among Persons with HIV Infection—United States, 1993-2015

*Data as of June 9, 2016

Figure 5 Percentage of Tuberculosis Cases in Persons Coinfected with HIV*

*Data as of June 9, 2016. This graphic shows the proportion of persons diagnosed with tuberculosis who were coinfected with HIV. The data shown is from tuberculosis cases in which an HIV test result was reported.

Figure 6 Interrelationship of Host Immune Control in Person with LTBI

This graphic shows the impact of HIV-related immunosuppression on the course of latent tuberculosis infection. With progressive HIV-related immune suppression, mycobacterial load increases and symptomatic tuberculosis may develop. In contrast, taking antiretroviral therapy will restore some HIV-related immune suppression and contribute to immune control of *Mycobacterium tuberculosis*.

**Figure 7 Mantoux Tuberculin Skin Test**

The standard Mantoux tuberculin skin test is performed by injecting 0.1 mL of 5 tuberculin purified protein derivative (PPS) units of liquid tuberculin between the layers of the skin (intradermally) on the volar surface of the forearm.

Source: Centers for Disease Control and Prevention (CDC)
Figure 8 Reading a Tuberculin Skin Test

The Mantoux tuberculin skin test should be read 48 to 72 hours after the intradermal administration of the purified protein derivative. The transverse diameter of cutaneous induration (not erythema) should be measured. Use a reliable method to determine the edge of the induration on one side and mark this (black dot shown here); then do the exact same thing on the opposite side. Using a millimeter ruler, measure the distance between the two dots and that is the size in mm for the test result. In the example shown the induration is 11 mm.

Source: Centers for Disease Control and Prevention (CDC)
### Figure 9 Interferon-Gamma Release Assays (IGRAs)

<table>
<thead>
<tr>
<th>Feature</th>
<th>QFT-GIT</th>
<th>T-Spot</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Format</strong></td>
<td>Process whole blood within 16 hours</td>
<td>Process peripheral blood mononuclear cells (PBMCs) within 8 hours</td>
</tr>
<tr>
<td><strong>M. tuberculosis Antigen</strong></td>
<td>Single mixture of synthetic peptides representing ESAT-6, CFP-10 &amp; TB7.7.</td>
<td>Separate mixtures of synthetic peptides representing ESAT-6 &amp; CFP-10</td>
</tr>
<tr>
<td><strong>Measurement</strong></td>
<td>IFN-gamma concentration</td>
<td>Number of IFN-gamma producing cells (spots)</td>
</tr>
<tr>
<td><strong>Possible Results</strong></td>
<td>Positive, negative, indeterminate</td>
<td>Positive, negative, indeterminate, borderline</td>
</tr>
</tbody>
</table>

Abbreviations: QFT-GIT = QuantiFERON-TB Gold In-Tube test; T-Spot = T-SPOT TB test; CFP-10 = culture filtrate protein 10; ESAT-6 = early secretory antigenic target-6
Figure 10 QuantiFERON-TB Gold Tubes

The QuantiFERON-TB Gold utilizes three tubes and 1 ml of blood is required for each tube: (1) the gray top Nil tube that serves as a negative control to adjust for background interferon-gamma; (2) the red top TB antigen tube that contains three mycobacterial proteins (ESAT-6, CFP-10, and TB 7.7) that will stimulate CD4 T-cell responses, and (3) the purple top mitogen tube that functions as a positive control to confirm baseline immune status.

Source: Qiagen
Figure 11 Interpretation Criteria for QuantiFERON-TB Gold


<table>
<thead>
<tr>
<th>Interpretation</th>
<th>Nil*</th>
<th>TB Response†</th>
<th>Mitogen Response§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive‡</td>
<td>≤8.0</td>
<td>≥0.35 IU/ml and ≥25% of Nil</td>
<td>Any</td>
</tr>
<tr>
<td>Negative**</td>
<td>≤8.0</td>
<td>&lt;0.35 IU/ml or &lt;25% of Nil</td>
<td>≥0.5</td>
</tr>
<tr>
<td>Indeterminate††</td>
<td>≤8.0</td>
<td>&lt;0.35 IU/ml or &lt;25% of Nil</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td></td>
<td>&gt;8.0</td>
<td>Any</td>
<td>Any</td>
</tr>
</tbody>
</table>

* The interferon gamma (IFN-γ) concentration in plasma from blood incubated without antigen.
† The IFN-γ concentration in plasma from blood stimulated with a single cocktail of peptides representing early secretory antigenic target-6 (ESAT-6), culture filtrate protein-10 (CFP-10), and part of TB7.7 minus Nil.
§ The IFN-γ concentration in plasma from blood stimulated with mitogen minus Nil.
‡ Interpretation indicating that *Mycobacterium tuberculosis* infection is likely.
** Interpretation indicating that *M. tuberculosis* infection is not likely.
†† Interpretation indicating an uncertain likelihood of *M. tuberculosis* infection.
The QuantiFERON-TB Gold utilizes four tubes and 1 mL of blood is required for each tube: (1) the gray top Nil tube that serves as a negative control to adjust for background; (2) the green top TB1 tube that primarily detects CD4 T cell responses to mycobacterial antigens; (3) the yellow top TB2 tube that is optimized for detection of CD4 and CD8 T-cell responses to mycobacterial antigens; and (4) the purple top mitogen tube that functions as a positive control to confirm baseline immune status.

Source: Qiagen
**Figure 13 Interpretation of T-SPOT Results**

Results are interpreted by subtracting the spot count in the negative (Nil) control from the spot count in Panels A and B. The test is considered positive if Panel A minus Nil and/or Panel B minus Nil is 8 or more spots. The test is considered negative if both Panel A minus Nil and Panel B minus Nil is less than or equal to 4 spots. The test is considered borderline (equivocal) if the highest of the Panel A or Panel B spot count is such that the (Panel minus Nil) spot count is 5, 6, or 7 spots.

Source: Oxford Immunotec. T-SPOT.TB. Prescribing Information.

<table>
<thead>
<tr>
<th></th>
<th>Negative Result</th>
<th>Positive Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nil Control</strong></td>
<td><img src="image1.png" alt="Nil Control" /></td>
<td><img src="image2.png" alt="Nil Control" /></td>
</tr>
<tr>
<td><strong>ESAT-6 Panel A</strong></td>
<td><img src="image3.png" alt="ESAT-6 Panel A" /></td>
<td><img src="image4.png" alt="ESAT-6 Panel A" /></td>
</tr>
<tr>
<td><strong>CFP10 Panel B</strong></td>
<td><img src="image5.png" alt="CFP10 Panel B" /></td>
<td><img src="image6.png" alt="CFP10 Panel B" /></td>
</tr>
<tr>
<td><strong>Positive Control</strong></td>
<td><img src="image7.png" alt="Positive Control" /></td>
<td><img src="image8.png" alt="Positive Control" /></td>
</tr>
</tbody>
</table>
**Figure 14 Interpretation Criteria for the T-SPOT.TB Test (T-Spot)**


<table>
<thead>
<tr>
<th>Interpretation</th>
<th>Nil*</th>
<th>TB Response†</th>
<th>Mitogen§ (Positive Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive‡</td>
<td>≤10 spots</td>
<td>≥8 spots</td>
<td>Any number of spots</td>
</tr>
<tr>
<td>Borderline**</td>
<td>≤10 spots</td>
<td>5, 6, or 7 spots</td>
<td>Any number of spots</td>
</tr>
<tr>
<td>Negative††</td>
<td>≤10 spots</td>
<td>≤4 spots</td>
<td>≥ 20 spots</td>
</tr>
<tr>
<td>Indeterminate**</td>
<td>&gt;10 spots</td>
<td>Any</td>
<td>Any number of spots</td>
</tr>
<tr>
<td></td>
<td>≤10 spots</td>
<td>&lt;5 spots</td>
<td>&lt; 20 spots</td>
</tr>
</tbody>
</table>

* The number of spots resulting from incubation of PBMCs in culture media without antigens.
† The greater number of spots resulting from stimulation of peripheral blood mononuclear cells (PBMCs) with two separate cocktails of peptides representing Panel A (early secretory antigenic target-6 [ESAT-6]) minus Nil or Panel B (culture filtrate protein-10 [CFP-10]) minus Nil.
§ The number of spots resulting from stimulation of PBMCs with mitogen without adjustment for the number of spots resulting from incubation of PBMCs without antigens. Represents positive control and typically ≥ 20 spots.
‡ Result positive if (Panel A-Nil) and/or (Panel B-Nil) ≥8 spots. Interpretation indicating likely *M. tuberculosis* infection.
†† Result is negative if both (Panel A-Nil) and (Panel B-Nil) ≤4 spots and mitogen ≥ 20 spots; this includes value less than 0. Interpretation indicating that *M. tuberculosis* infection is not likely.
** Result is indeterminate if highest of Panel A or Panel B spot count is such that the (Panel-Nil) spot count is 5, 6, or 7. Interpretation indicating an uncertain likelihood of *M. tuberculosis* infection and retesting recommended.
### Table 1. Guidelines for the Prevention and Treatment of Opportunistic Infections

#### Treating Latent Tuberculosis Infection in Persons with HIV Infection

**Indications:**

- (+) screening test (tuberculin skin test or IGRA) for latent tuberculosis infection, no evidence of active TB, and no prior history of treatment for active or latent TB (AI);
- Close contact with a person with infectious TB, regardless of screening test result (AII)

**Preferred Therapy (Duration of Therapy = 9 Months):**

- Isoniazid 300 mg PO daily + pyridoxine 25 mg PO daily (AII) or
- Isoniazid 900 mg PO twice weekly (by DOT) + pyridoxine 25 mg PO daily (BII)

**Alternative Therapies:**

- Rifampin 600 mg PO daily x 4 months (BIII) or
- Rifabutin (dose adjusted based on concomitant antiretroviral therapy) x 4 months (BIII)
- Rifapentine (weight-based*, 900 mg max) PO weekly + isoniazid 15 mg/kg weekly (900 mg max) + pyridoxine 50 mg weekly x 12 weeks—in patients receiving an efavirenz- or raltegravir-based ART regimen (BIII), the rifapentine dose is:
  - 32.1–49.9 kg 750 mg
  - ≥50.0 kg 900 mg
- For persons exposed to drug-resistant TB, select anti-TB drugs after consultation with experts or with public health authorities (AII)

*Weight-based rifapentine dosing: 10-14 kg = 300 mg; 14.1-25 kg = 450 mg; 25.1-32 kg = 600 mg; 32.1-50 kg = 750 mg; >50 mg = 900 mg

**Strength of Recommendation**

A: Strong recommendation for the statement
B: Moderate recommendation for the statement
C: Optional recommendation for the statement

**Quality of Evidence for the Recommendation**

I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
II: One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes
III: Expert opinion

**Source:**
