Latent Tuberculosis Infection

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Module 4: Co-Occurring Conditions
Lesson 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 persons who are foreign born, incarcerated, homeless, persons who use drugs, and individuals with HIV.[1,2] In recent years, the majority of tuberculosis cases in the United States were among the foreign born (70% in 2017), with an incidence rate approximately 15 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 nonwhite 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 and 2012 National Health and Nutrition Examination Survey (NHANES).[3,4] Another study estimated LTBI prevalence within the United States at 3.1%, which corresponds to 8.9 million persons living with latent TB; this LTBI prevalence estimate was calculated using surveillance data of active tuberculosis cases from 2011 through 2015, at the state and local level, along with assumptions on rates of LTBI reactivation.[5] These data also demonstrate the geographic variability of LTBI in the United States, with some counties at less than 1% prevalence and some with greater than 3%. The prevalence of LTBI among persons with HIV sampled in NHANES was 7.6%.[4]

Epidemiology of Tuberculosis in Persons with HIV

In the late 1980s and early 1990s, HIV contributed to the significant increase of tuberculosis in the United States (48% of tuberculosis cases occurred in persons with HIV coinfection in 1993).[6] In the last 10 years, the overall number (Figure 4) and proportion (Figure 5) of tuberculosis cases involving persons who had HIV coinfection substantially decreased.[2] For 2017, the CDC reported that HIV status was known for 86.3% of the persons diagnosed with tuberculosis and among those with known HIV status, 5.6% had HIV coinfection.[7] In contrast to the overall decline of new tuberculosis cases in persons with HIV, the incidence of tuberculosis among persons with HIV who are foreign born has remained stable.[8,9]

Tuberculosis continues to cause significant morbidity and mortality among people with HIV in the United States and other low tuberculosis burden areas.[8,10] The risk of mortality among individuals with HIV who develop tuberculosis is higher than those with tuberculosis alone, even in the era of readily available antiretroviral therapy,[10] highlighting the importance of tuberculosis prevention in those with HIV.[11]
Development of tuberculosis disease can occur in the setting of recent exposure to *Mycobacterium tuberculosis* (primary or active disease) or with reactivation of LTBI.[12, 13] The development of tuberculosis disease is based on complex interactions between host immune status and the bacillary load; in persons with HIV, this balance is impacted both by HIV-related immunosuppression and restoration of immune function by antiretroviral therapy (Figure 6).[12]

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.[14] 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).[11, 15, 16] The increased risk of LTBI reactivation begins soon after acquisition of HIV.[17]

**Prevention of Tuberculosis in Persons with HIV**

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.[18] 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.[19] Identifying those with LTBI who may benefit from treatment to prevent tuberculosis disease is an important part of tuberculosis prevention in people with HIV.[11]

Individuals with HIV 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.[20, 21, 22, 23] Among persons with HIV who have a positive tuberculin skin test, treating LTBI significantly decreases their risk of developing active tuberculosis and mortality (62% and 26% reduction, respectively).[24, 25, 26] The combination of antiretroviral therapy and LTBI treatment decreases the risk of tuberculosis more than either intervention alone.[27]
Rationale and Indications for LTBI Screening

Rationale for LTBI Screening

Multiple factors underscore the rationale for LTBI screening in persons 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 should be routinely screened and offered treatment if found to have LTBI.[11]

Indication and Timing of LTBI Screening

The Adult and Adolescent Opportunistic Infection Guidelines 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.[11,28] Despite this recommendation, adherence to recommendations for LTBI screening of persons with HIV in the United States has been variable, with reports of adherence to routine screening practices ranging from 47 to 79%.[29,30,31,32] 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.

Repeat LTBI Screening

Individuals with advanced HIV disease (CD4 count less than 200 cells/mm$^3$) with initially negative LTBI testing should have repeat testing after they initiate antiretroviral therapy and reach a CD4 count of at least 200 cells/mm$^3$, due to the possibility of false-negative results in the setting of advanced immunosuppression.[11] Yearly repeat testing for LTBI is recommended only in situations when individuals with HIV have high risk for ongoing or repeat exposure to persons with active tuberculosis.[11]
**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).\[33,34\] 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.\[35\] 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 persons at high risk for tuberculosis infection.\[31\] 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 tuberculin skin testing method consists of giving an intradermal injection of 5 tuberculin units of purified protein derivative that contains *M. tuberculosis* antigens (Figure 7) and then evaluating the cutaneous induration 48 to 72 hours later.\[33\] In persons infected with *M. tuberculosis* (past or current), 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.\[35\] 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).\[33\]

- **Criteria for Positive Tuberculin Skin Test:** For individuals with HIV, induration of 5 mm or greater is considered a positive test.\[28\] Following exposure to *M. tuberculosis*, the tuberculin skin test conversion to positive typically occurs within 8 weeks.\[36\] The sensitivity of tuberculin skin test for the diagnosis of LTBI is estimated at 45 to 85% and specificity at approximately 85%.\[31,37,38\] Persons with prior treatment of tuberculosis (latent or active) typically have a persistently positive tuberculin skin test.

- **False-Positive Tuberculin Skin Test:** Previous exposure to nontuberculous mycobacteria, as well as immunization with bacille Calmette–Guérin (BCG), can cause a false-positive tuberculin skin test.\[34\] 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.\[39\]

- **False-Negative Tuberculin Skin Test:** False-negative tests can occur in the setting of advanced HIV disease, malnutrition, and active tuberculosis.\[34\]

**Interferon Gamma Release Assay (IGRA)**

For the diagnosis of LTBI, the two most commonly used FDA approved interferon gamma release assays (IGRAs) in the United States are the QuantiFERON-TB Gold Plus (QFT-Plus) assay and the T-SPOT.TB (T-SPOT) assay (Figure 9).\[31\] The QFT-Plus and T-SPOT are in vitro tests that measure the release of interferon gamma by T-lymphocytes after stimulation to a peptide antigen cocktail that simulates two *M. tuberculosis* specific antigens: early secreted antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10).\[34,40,41\] The ESAT-6 and CFP-10 mycobacterial antigens are absent from all mycobacterial strains used in BCG vaccines and from most nontuberculous mycobacteria, except for *M. marinum*, *M. kansasii*, and *M. szulgai*.\[34\]

- **QuantiFERON-TB Gold Plus (QFT-Plus):** This test has replaced the QuantiFERON-TB Gold test and has the advantage of measuring both CD4 and CD8 T-lymphocyte responses.\[42,43,44\] To perform the test, blood is drawn into 4 specialized collection tubes: (1) Nil (negative control), (2) mitogen (positive control), (3) TB1 (primarily detects CD4 T cell response), and (4) TB2 (optimized for detection of CD4 and CD8 T cell responses) (Figure 10).\[42,45,46,47\] The interferon gamma response is quantified in international units (IU) per millimeter and test results are reported as positive, negative, or indeterminate (Figure 11).\[45\] Reversion from a positive to negative test result can occur,\[48,49,50\] but this tends to occur when the initial test is close to the cutoff threshold.\[34,42,46\]
Initial studies using the QFT-Plus assay indicate concordance with QFT results for several settings, including active tuberculosis cases, individuals with recent exposure to *M. tuberculosis*, and in healthcare workers from areas of low tuberculosis incidence.[42,46,47,51]

- **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).[52] The number of T-cells producing interferon gamma (spot-forming cells) are then counted (Figure 12). The test results are categorized as either positive, borderline, negative, or indeterminate (Figure 13).[31] In a meta-analysis of IGRA studies in persons with HIV, the pooled sensitivity was 72% for T-SPOT and 61% for QFT.[53]

**Performance of IGRA Tests**

The presence of immunosuppression decreases the sensitivity of IGRAIs, but the impact is relatively less than on the tuberculin skin test.[34] In addition, the IGRA tests have greater specificity than the tuberculin skin test and these tests are not impacted by prior receipt of BCG vaccine.[11] Although IGRA testing requires a blood draw, unlike tuberculin skin testing, it does not require a follow-up visit for test result reading. In addition, IGRA cutoffs 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 IGRAIs.
Recommended LTBI Testing in Persons with HIV

Choice of Test Method For LTBI Screening

Use of either tuberculin skin test or IGRA is appropriate for LTBI screening in persons with HIV.\cite{11,31,33} The correlation between positive tuberculin skin test and IGRA in persons with HIV is poor to moderate.\cite{23,53,54,55} In recent years, many clinics have predominantly used 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 BCG vaccine, and lower sensitivity in persons with advanced immunosuppression. Some experts acknowledge the benefit of performing a second LTBI diagnostic test (e.g. a tuberculin skin test after a negative IGRA result or vice versa) as a strategy to increase sensitivity in the setting of an individual likely to be infected and at high risk of progression to active disease. 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 tuberculin skin test.

LTBI TESTING IN PERSONS WITH HIV

The Adult and Adolescent Opportunistic Infection Guidelines recommendations regarding testing for LTBI in persons with HIV are summarized as follows:\cite{11}

- All persons with HIV should undergo testing for LTBI at the time of HIV diagnosis, regardless of their epidemiological risk of TB exposure.
- The tuberculin skin test 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 tuberculin skin test.
- Annual testing for LTBI is recommended for persons with HIV who are at high risk for repeated or ongoing exposure to persons with active TB.
- Persons with HIV and advanced immunosuppression (CD4 count less than 200 cells/mm\(^3\)) who have negative tuberculin skin test result should undergo repeat testing for latent tuberculosis infection after they start on antiretroviral therapy and have an increase in CD4 count to 200 cells/mm\(^3\) or greater.
- The routine use of both tuberculin skin test and IGRAs to screen for LTBI is not recommended in the United States.
- All persons with a positive tuberculin skin test 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 who has a new positive LTBI screening test should undergo tuberculosis symptom screening as well as chest radiography to exclude active tuberculosis disease. A meta-analysis of individual patient data of more than 8,000 subjects with HIV 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. 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). The Adult and Adolescent Opportunistic Infection Guidelines 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 considered cost-effective.
Management of LTBI in Persons with HIV

Indications for LTBI

A positive tuberculin skin test or IGRA is associated with a significantly increased risk of developing tuberculosis disease.\[23,53,54,55\] The risk of progression to active tuberculosis disease is even higher among recent LTBI test converters.\[54,58,59\] Some studies indicate a positive IGRA is a stronger predictor than tuberculin skin test for the risk of developing tuberculosis disease.\[60,61\] All individuals with HIV who have a new positive testing for LTBI and a negative workup for active tuberculosis should be offered LTBI treatment.\[11\] In addition, individuals with HIV 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.

Therapy for LTBI

The following summarizes recommendations in the Adult and Adolescent Opportunistic Infection Guidelines for initiating therapy for LTBI, as well as preferred and alternative agents for the treatment of LTBI (Table 1).\[11\] In the situation where a patient has evidence of LTBI and a history of exposure to a person with drug-resistant tuberculosis, the clinician should consult with a tuberculosis expert to determine an appropriate regimen for the treatment of LTBI.

Preferred Therapy for LTBI

- **Isoniazid for 9 Months (9H):** The preferred treatment of LTBI in persons with HIV is 9 months of isoniazid given 300 mg daily plus pyridoxine 25 to 50 mg daily.\[11\] This regimen is referred to as 9H since it consists of taking 9 months of isoniazid (IN\(_H\)). The pyridoxine (vitamin B6) is given to reduce the risk of isoniazid-induced peripheral neuropathy.\[11\]

Alternative Therapies for LTBI

There are two alternative regimens for the treatment of LTBI in persons with HIV:

- **Isoniazid plus Rifapentine for 3 Months (3HP):** This 3-month regimen consists of weekly rifapentine (weight-based dosing) plus isoniazid (15 mg/kg, maximum weekly dose of 900 mg); pyridoxine 50 mg weekly is also added to prevent peripheral neuropathy.\[62\] A total of 12 doses are given. This regimen is commonly referred to as 3HP, with this designation based on the weekly regimen duration (3 months) of each of the medications in the regimen—isoniazid (IN\(_H\)) and rifapentine (R\(_P\)T). The 3HP regimen has efficacy equal to standard isoniazid monotherapy, with the added benefit of likely improved adherence due to shorter duration.\[62,63,64,65\] The isoniazid plus rifapentine regimen is recommended only for (1) persons not taking antiretroviral therapy or (2) persons taking an antiretroviral regimen anchored by efavirenz or twice-daily raltegravir.\[11,62,66,67\] Concurrent use of tenofovir alafenamide and rifapentine is not recommended, due to lack of data.\[11,62,68,69\]

- **Rifampin for 4 Months (4R):** This 4-month regimen consists of daily rifampin 600 mg, which may be complicated by drug interactions and may require dose adjustment of antiretroviral medications.\[11,63\] This regimen is referred to as 4R, based on 4 months of rifampin (R\(_F\)). In a recent large international open label clinical trial that enrolled persons with and without HIV, investigators demonstrated 4 months of rifampin was non-inferior to 9 months of isoniazid for the treatment of LTBI.\[70\] Furthermore, the rifampin regimen cohort had higher rates of treatment completion and fewer adverse effects.\[70\] Among all study participants, only 4% had HIV. Accordingly, caution is needed when attempting to generalize the results for the treatment of LTBI in persons with HIV.
**Isoniazid plus Rifampin for 3 Months (3HR):** The CDC and the National Tuberculosis Controller’s Association have also conditionally recommended the 3-month regimen of daily isoniazid (300 mg) plus daily rifampin (600 mg) as therapy for latent tuberculosis in adults with HIV, if not contraindicated by drug interactions.[69] This recommendation was based on data from multiple studies showing a similar incidence of tuberculosis disease among those who received 3 months of daily isoniazid plus rifampin compared with those who received at least 6 months of isoniazid monotherapy, regardless of whether they were TST positive, TST negative, or anergic.[71, 72, 73] This regimen is not currently recommended in the Adult and Adolescent Opportunistic Infection Guidelines.[11]

**Potential Future Therapy for LTBI**

In the BRIEF-TB/A5279 trial, a 1-month course of daily isoniazid plus rifapentine was noninferior to 9 months of isoniazid alone in preventing tuberculosis in persons with HIV who were taking efavirenz- or nevirapine-based antiretroviral therapy, with fewer adverse events, and higher completion rates.[74] The 1-month regimen of daily isoniazid plus daily rifapentine is referred to as 1HP (1 month, INH, RPT). This regimen has not been thoroughly evaluated in areas of low TB prevalence. Consequently, the 1HP regimen is not currently recommended for LTBI treatment in the United States.[11]

**Medication-Related Adverse Effects**

Individuals 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.[75, 76] In addition, they 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.[11] The Adult and Adolescent Opportunistic Infection Guidelines recommend withholding isoniazid if the hepatic aminotransferase level exceeds three times the upper limit of normal (with associated symptoms) or five times the upper limit of normal (with or without associated symptoms).[11] 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.[11, 77, 78]

**Drug Interactions**

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 for LTBI treatment.[79] The following summarizes key interactions between commonly used medications to treat LTBI in persons with HIV (isoniazid, rifampin, and rifapentine) and antiretroviral medications.

- **Isoniazid:** Isoniazid has few drug interactions with most antiretroviral medications and no dose adjustment is required.[11, 68]

- **Rifampin:** The use of rifampin is not recommended for use in persons receiving an antiretroviral regimen that contains a protease inhibitor, doravirine, etravirine, rilpivirine, or elvitegravir-cobicistat.[11, 68] If dolutegravir is used in combination with rifampin, the dose should be increased to 50 mg twice daily. Raltegravir, when coadministered with rifampin, should be given at a higher dose (800 mg twice daily). The regimen bictegravir-tenofovir alafenamide-emtricitabine should be avoided with rifampin due to reduced plasma concentrations of bictegravir.[80]

- **Rifapentine:** The use of rifapentine with tenofovir alafenamide should be avoided.[11] Rifapentine can be used in combination with an efavirenz- or twice daily raltegravir-based regimen, as long as tenofovir alafenamide is not part of the regimen.[11, 68] The regimen
bictegravir-tenofovir alafenamide-emtricitabine should be avoided with rifapentine due to reduced plasma concentrations of bictegravir.\[80\]

**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 restarted. When treatment has been interrupted for more than 2 months, the patient should be reevaluated for tuberculosis.
Considerations in Special Populations

LTBI in Pregnancy

Screening for LTBI in Pregnancy

All pregnant persons with HIV 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.\[11\] Although data remain conflicting whether pregnancy stage affects both TST and IGRA testing,\[81, 82, 83\] either test is considered appropriate for screening in pregnancy.

Treatment of LTBI in Pregnancy

In light of recent studies demonstrating adverse pregnancy outcomes in individuals with HIV who received isoniazid for LTBI treatment during pregnancy, the Adult and Adolescent Opportunistic Infection Guidelines guidelines now recommend delaying isoniazid preventive therapy until the post-partum period, unless the pregnant woman reports significant close contact with an active TB case or the clinician believes that the risk of developing active TB outweighs the risk of adverse birth outcomes.\[11, 84\] Neither isoniazid nor rifampin are considered teratogenic, but persons who are pregnant or postpartum may have a higher risk for isoniazid-associated hepatotoxicity.\[84, 85\] If LTBI therapy is required during in pregnancy, the recommended regimen is isoniazid, given with pyridoxine.\[11\] There are inadequate data data for the use of rifampin for LTBI treatment in pregnancy. In addition, isoniazid plus rifapentine short-course therapy is not currently recommended in pregnancy due to lack of efficacy and safety data in humans, and recent animal data with rifapentine indicating malformations and fetal loss.\[11, 65, 86\]

Treatment of LTBI in Persons with 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 in this population in the setting of stable liver disease, but close clinical and laboratory monitoring is recommended.\[87\] In addition, management of LTBI in a patient with chronic liver disease should involve consultation with a tuberculosis expert.

LTBI in Children

Screening for LTBI in 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.\[88\] Most tuberculosis disease in young children is due to primary infection.\[89\] All children with HIV should be screened for LTBI.\[90\] 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.\[91\] 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 should either be performed the same day as these vaccines are administered, or delayed for at least 6 weeks after live vaccine administration.

Treatment of LTBI in Children

A 9-month course of isoniazid is the recommended treatment of LTBI in children with HIV who are 2 through 11 years of age.\[90\] Pyridoxine supplementation (1 to 2 mg/kg, maximum 50 mg/day) is recommended for all children with HIV who are taking isoniazid.\[90\] 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 the 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 plus rifapentine short course is not recommended for children younger than 2 years of age or in children with HIV on antiretroviral therapy.[65,90] The CDC and National TB Controller’s Association conditionally recommend 3 months of daily isoniazid (10 to 20 mg/kg, maximum 300 mg/day) plus rifampin (15 to 20 mg/kg, maximum 600 mg/day) as an option for the treatment of latent tuberculosis in children with HIV, as permitted by drug interactions.[69] This 3-month regimen is not recommended in the Pediatric Opportunistic Infection Guidelines.[90]
Summary Points

- Despite declining incidence of tuberculosis in the United States, individuals with HIV remain at significant risk for tuberculosis.
- Compared to people without HIV, individuals with HIV are at increased risk for tuberculosis, even when taking antiretroviral therapy.
- All individuals with HIV should undergo screening for LTBI at either the time of HIV diagnosis or entry into care.
- Testing for LTBI should be performed with either a tuberculin skin test or IGRA test. Limitations to tuberculin skin testing include requirement of a second visit to read the test, lower specificity especially in people immunized with BCG vaccine, and potentially lower sensitivity with advanced immunosuppression.
- Severe immunosuppression can lead to false-negative LTBI 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 and positive LTBI screening tests should be offered LTBI treatment, after active tuberculosis has been ruled out.
- All individuals with HIV and a recent exposure to a person with active tuberculosis should be offered LTBI treatment, irrespective of tuberculin skin test and/or IGRA results.
- The preferred regimen for LTBI treatment in persons with HIV is 9 months of isoniazid, given with pyridoxine to prevent peripheral neuropathy.
- Alternative LTBI regimens for persons with HIV as recommended in the Adult and Adolescent Opportunistic Infection Guidelines include a 3-month course of weekly isoniazid plus rifapentine or a 4-month course of daily rifampin.
Citations


28. 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. [PubMed Abstract] -


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Figures

Figure 1 Tuberculosis Cases in United States, 1980-2017

Figure 2 Tuberculosis Case Rates per 100,000 Population by Origin of Birth—United States, 1993-2017

Figure 3 Tuberculosis Case Rates in United States—2017, by Race

Figure 4 Tuberculosis Cases among Persons with HIV Infection—United States, 1993-2017

This graphic shows the number 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 5 Percentage of Tuberculosis Cases in Persons Coinfected with HIV—United States, 1993-2017

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)

Figure 10 QuantiFERON-TB Gold Plus Blood Draw Tubes

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 interferon gamma production; (2) the green top TB1 tube that primarily detects CD4 T-lymphocytes responses to mycobacterial antigens; (3) the yellow top TB2 tube that is optimized for detection of CD4 and CD8 T-lymphocyte responses to mycobacterial antigens; and (4) the purple top Mitogen tube that functions as a positive control to confirm baseline immune status; a low response may indicate inability to generate interferon gamma.

Source: Qiagen
Figure 11 Interpretation Criteria for QuantiFERON-TB Gold Plus (QFT-Plus)

Source: Qiagen
**Figure 12 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.
Figure 13 Interpretation Criteria for the T-SPOT.TB Test (T-Spot)

### Table 1. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

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

**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 25-50 mg PO daily (AI)

**Alternative Therapies:**
- 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 (AII), the rifapentine dose is:
  - 32.1-49.9 kg = 750 mg
  - ≥50.0 kg = 900 mg

  or

- Rifampin 600 mg PO daily x 4 months (BI)

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

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**Source:**