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

In 2023, there were 9,633 cases of tuberculosis reported in the United States.[1] The incidence of tuberculosis in the United States substantially declined from 1992-2020, but cases have increased in the past 3 years.[1] The highest rates of tuberculosis in the United States have occurred among Native Hawaiian/Other Pacific Islander people and in Asian people.[1] In recent years, most tuberculosis cases in the United States were among persons who were non-United States-born (76% of all cases in 2023).[1] The following graphic shows the epidemiologic feature of tuberculosis in the United States (Figure 1).[1]

Epidemiology of Tuberculosis in Persons with HIV

In the late 1980s and early 1990s, HIV contributed to the significant increase of tuberculosis cases diagnosed in the United States (48% of tuberculosis cases occurred in persons with HIV coinfection in 1993).[2] From 2011-2021, the overall number and proportion of tuberculosis cases diagnosed in the United States involving persons with HIV coinfection declined, but increased substantially in 2022 and 2023(Figure 2).[1] For the year 2023, the CDC reported 410 cases of tuberculosis in persons with HIV coinfection.[1] Among all persons diagnosed with tuberculosis in the United States in 2023 for whom HIV status was known, 4.9% had HIV coinfection.[1]

Progression from Latent to Active TB

The development of tuberculosis can occur in the setting of recent exposure to *Mycobacterium tuberculosis* (primary or active disease) or with reactivation of latent tuberculosis infection (LTBI).[3,4] 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 3).[3] 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 without HIV (5 to 10% lifetime risk).[5,6,7] The increased risk of LTBI reactivation begins soon after acquisition of HIV.[8] Several comorbidities, in addition to HIV, have been identified that contribute to the risk of developing active tuberculosis, including diabetes, malnutrition, low body weight, smoking, lung disease, injection drug use, chronic kidney disease, and recent or current use of immunosuppressant medications.[9,10]

Prevention of Tuberculosis in Persons with HIV

Combination antiretroviral therapy markedly decreases the risk of developing active tuberculosis, with

greater declines occurring with more substantial increases in CD4 cell counts and longer duration of antiretroviral therapy.[11] Nevertheless, the risk of incident tuberculosis remains 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.[12] 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.[13,14,15,16,17]

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, widespread availability of LTBI screening tests, and effective treatment for LTBI to prevent progression to active tuberculosis disease. Among persons with HIV who have LTBI, combination antiretroviral therapy plus treatment for LTBI significantly decreases their risk of developing active tuberculosis and reduces mortality.[18,19,20,21] For all these reasons, individuals with HIV should undergo LTBI screening and be offered treatment if found to have LTBI.[6,22]

Indication and Timing of LTBI Screening

The Adult and Adolescent OI Guidelines recommend 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.[6,23] Despite this recommendation, 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%.[24,25,26,27] In addition to LTBI screening at entry to care, recent contact with a person with known tuberculosis should prompt LTBI screening, as well as 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.[6] 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.[6]

Methods Used to Test for Latent Tuberculosis

There are two primary methods for detection of LTBI: tuberculin skin test (TST) and interferon gamma release assay (IGRA).[28,29] Both methods are indirect measures of tuberculosis infection that, for a positive test result, require infection with *M. tuberculosis* and a person's ability to mount a T-cell mediated response. Tuberculin skin testing is an *in vivo* skin test, whereas IGRA is an *in vitro* blood-based approach.[30] Routine dual testing with both TST 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.[26] Importantly, a positive TST or IGRA does not distinguish between LTBI and active disease, nor does negative LTBI testing rule out active tuberculosis. After infection with *M. tuberculosis*, the TST and IGRA tests may not generate a positive result for 2 to 10 weeks. Neither TST nor IGRA tests can be used to confirm LTBI treatment response as both tests typically remain positive despite treatment.

Tuberculin Skin Test

The Mantoux TST method consists of giving an intradermal injection of 5 tuberculin units of purified protein derivative (PPD) that contains *M. tuberculosis* antigens; the transverse diameter of induration (not erythema) should be measured as the amount of induration (mm) at a follow-up visit 48 to 72 hours after placement of the PPD (Figure 4).[28] In persons with *M. tuberculosis* infection(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.[30]

Criteria for Positive TST

For individuals with HIV, induration of 5 mm or greater is considered a positive test.[23] Following exposure to *M. tuberculosis*, the TST conversion to positive typically occurs within 8 weeks.[31] The sensitivity of TST for the diagnosis of LTBI is estimated at 45 to 85% and specificity at approximately 85%.[26,32,33] Persons with prior treatment of tuberculosis (latent or active) typically have a persistently positive TST.

False-Positive TST

Previous exposure to nontuberculous mycobacteria, as well as immunization with bacille Calmette–Guérin (BCG), can cause a false-positive TST.[29] Receipt of BCG in infancy is thought to have a relatively minimal effect on TST, especially if at least 10 years have elapsed after administration.[34]

False-Negative TST

False-negative TSTs can occur in the setting of advanced HIV disease, malnutrition, active tuberculosis or early in the window period after recent *M. tuberculosis* infection.[29]

Interferon Gamma Release Assay (IGRA)

For the diagnosis of LTBI, the two most commonly used FDA-approved IGRAs in the United States are the QuantiFERON-TB Gold Plus (QFT-Plus) assay and the T-SPOT.TB (T-SPOT) assay (Figure 5).[26] 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).[29,35,36] 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*.[29] Hence, the IGRAs are less likely to show cross-reactivity in persons who have received BCG vaccination and/or had prior infection with non-tuberculous mycobacteria.

- **QuantiFERON-TB Gold Plus (QFT-Plus)**: This test has replaced the previously used QuantiFERON-

TB Gold test and has the advantage of measuring both CD4 and CD8 T-lymphocyte responses (Figure 6).[37,38,39] 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).[37,40,41,42] The interferon gamma response is quantified in international units (IU) per millimeter, and test results are reported as positive, negative, or indeterminate.[40] Reversion from a positive to negative test result can occur,[43,44,45] but this tends to occur when the initial test is close to the cutoff threshold.[29,37,41]

- **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 (Figure 7).[26] 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).[46] The number of T-cells producing interferon gamma (spot-forming cells) are then counted, The test results are categorized as either positive, borderline, negative, or indeterminate.[26] In a meta-analysis of IGRA studies in persons with HIV, the pooled sensitivity was 72% for T-SPOT and 61% for QFT.[47]

Performance of IGRA Tests

The presence of immunosuppression decreases the sensitivity of IGRAs, but the impact is relatively less than on the TST.[29] In addition, the IGRA tests have greater specificity than the TST, and these tests are not impacted by prior receipt of BCG vaccine.[6] Although IGRA testing requires a blood draw, unlike TST, 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 IGRAs. Similar to TST, the IGRA tests may be negative early in the window period after recent *M*. *tuberculosis* infection.

Recommended LTBI Testing in Persons with HIV

Choice of Test Method For LTBI Screening

Use of either TST or IGRA is appropriate for LTBI screening in persons with HIV.[6,26,28] The correlation between positive TST and IGRA in persons with HIV is poor to moderate.[13,47,48,49] In recent years, many clinics have predominantly used IGRAs because of several negative aspects of TST, 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 TST after a negative IGRA result or vice versa) as a strategy to increase sensitivity in the setting of an individual likely to have LTBI 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 TST.

LTBI TESTING IN PERSONS WITH HIV

The Adult and Adolescent OI Guidelines recommendations regarding testing for LTBI in persons with HIV are summarized as follows:[6]

- All persons with HIV should undergo testing for LTBI at the time of HIV diagnosis, regardless of their epidemiological risk of TB exposure.
- The TST or IGRA can be used as the screening method for LTBI, and the decision for which one to use may be based on the likelihood of patient follow-up for reading a TST and access to laboratory testing for IGRAs.
- 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 a negative LTBI test result should undergo repeat testing for LTBI 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 TST and IGRA to screen for LTBI is not routinely recommended, though some experts recommend dual testing to increase the sensitivity in individuals who have a high likelihood of having infection with *M. tuberculosis* and a high risk of progression to active disease.
- 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 who has a new positive LTBI screening test should undergo tuberculosis symptom screening and chest radiography to exclude active tuberculosis disease.[24] A meta-analysis of individual participant data of more than 8,000 persons with HIV found that having at least one positive symptom in a 4-symptom tuberculosis screen (cough, fever, weight loss, or night sweats) has a sensitivity of 78.9%, a specificity of 49.6%, and negative predictive value of 97.7% (at a 5% prevalence) to identify those with culture-confirmed pulmonary tuberculosis.[50] A more recent systematic review and meta-analysis found this 4-symptom tuberculosis screen had a lower pooled sensitivity, but higher specificity, when comparing people with HIV on antiretroviral therapy versus those not on antiretroviral therapy.[51] Sputum examination, including acid-fast smear microscopy, nucleic acid amplification testing, and culture, is indicated for those individuals with either an abnormal chest radiograph or a positive symptom screen (even if their chest radiograph is negative).[52] 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.[6]

Management of LTBI in Persons with HIV

Indications for LTBI Treatment

A positive TST or IGRA is associated with a significantly increased risk of developing tuberculosis disease.[13,48,49] The risk of progression to active tuberculosis disease is even higher among recent LTBI test converters.[48,53,54] Some studies indicate a positive IGRA is a stronger predictor than a positive TST for the risk of developing tuberculosis disease.[55,56] Note that a history of BCG vaccination should not affect the decision about whether to treat LTBI in persons with HIV. The following summarizes the two main indications for initiating LTBI in persons with HIV.[6]

- A new positive screening test (TST or IGRA) for LTBI with no evidence of active TB disease, and no prior history of treatment for either active disease or LTBI.
- Close contact with a person who has infectious tuberculosis, irrespective of LTBI test result.

Regimens for LTBI Treatment

The following summarizes recommendations for the preferred and alternative regimens for the treatment of LTBI in adults with HIV (Table 1).[6,57] The choice for the LTBI regimen should strongly consider the individual's antiretroviral regimen.[57] Note: all regimens are taken orally, and when isoniazid is given, concomitant pyridoxine (vitamin B6) is prescribed to prevent isoniazid-induced peripheral neuropathy. Note the LTBI regimens should only be used with the antiretroviral regimens that are outlined below.

Preferred Therapies for LTBI

- **3HP: Isoniazid plus Rifapentine Weekly for 3 Months** (**AI**): This 3-month oral regimen consists of weekly isoniazid (15 mg/kg, maximum dose of 900 mg) plus rifapentine (weight-based dosing, maximum dose of 900 mg) plus pyridoxine 50 mg weekly.[6,22,57,58] A total of 12 doses are given. The 3HP designation derives from the **3** months duration using 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 and completion rates due to a shorter duration.[58,59,60,61] Self-administered 3HP therapy is equivalent to directly observed therapy (DOT).[62] The 3HP regimen should only be used in individuals who are taking an antiretroviral regimen that contains one of the following anchor drugs: efavirenz (600 mg once daily), raltegravir (400 mg twice daily), or dolutegravir (50 mg once daily).[57] The use of 3HP regimen is not recommended with twice daily dolutegravir dosing, including in patients who have confirmed or suspected integrase inhibitor resistance.[57] The 3HP regimen can be used with the nucleoside reverse transcriptase inhibitor (NRTI) backbone combinations tenofovir DF-emtricitabine, tenofovir alafenamide-emtricitabine, and abacavir-lamivudine, but rifapentine may lower the concentrations of tenofovir alafenamide and monitoring of HIV treatment efficacy is recommended in this setting.[57]
- **3HR: Isoniazid plus Rifampin Daily for 3 Months** (**AI**): This 3-month oral regimen consists of daily isoniazid (300 mg once daily) plus rifampin (600 mg once daily) plus pyridoxine (25 to 50 mg once daily to prevent isoniazid-induced peripheral neuropathy). This regimen is referred to as 3HR due to the **3-**month duration using isoniazid (IN**H**) and rifampin (**R**IF). In studies involving use of 3HR in individuals with HIV, there was no significant difference in rates of developing TB disease among those taking 3HR compared to those taking 6 months or longer of daily isoniazid.[63,64,65] The 3HR regimen can be used in persons receiving an antiretroviral regimen that includes one of the following anchor drugs: efavirenz, dolutegravir, raltegravir, maraviroc (without a strong CYP3A inhibitor), ibalizumab, and enfuvirtide.[6,57] Dose increases are needed with dolutegravir (increase to 50 mg twice daily), raltegravir (increase to 800 mg twice daily), and maraviroc (increase to 600 mg twice daily as long as not given with a strong CYP3A inhibitor).[6,57] The 3HR can be administered with any of the NRTI backbone combinations, but caution should be used if given with tenofovir alafenamide.

Alternative Therapy for LTBI

- **6H or 9H: Isoniazid for 6 or 9 Months** (**AII**): These isoniazid monotherapy regimens are considered standard-length LTBI treatment for persons with HIV and consist of isoniazid 300 mg daily plus pyridoxine 25-50 mg daily, for 6 or 9 months.[6,57] These regimens are referred to as 6H and 9H (**6** or **9** months of INH). These regimens are generally well tolerated, but isoniazid has been associated with an increased risk of hepatotoxicity. Isoniazid does not cause problematic drug interactions with antiretroviral medications. These regimens, however, are no longer rated as preferred treatment for LTBI because completion rates are lower than with shorter-course LTBI regimens.[66,67]
- **4R: Rifampin for 4 Months (BI)**: This short-course, 4-month oral regimen, which consists of rifampin 600 mg daily, is referred to as 4R, based on **4** months of rifampin (**R**IF).[6,57,68] In a recent large international open-label clinical trial that enrolled persons with and without HIV, investigators demonstrated 4 months of rifampin was noninferior to 9 months of isoniazid for the treatment of LTBI.[69] Furthermore, the rifampin regimen cohort had higher rates of treatment completion and fewer adverse effects.[69] Among all study participants, only 4% had HIV.[69] This regimen is an alternative regimen because of minimal data in persons with HIV and potential drug interactions with rifampin. The 4R regimen can be used in persons receiving an antiretroviral regimen that includes one of the following anchor drugs: efavirenz, dolutegravir, raltegravir, maraviroc (without a strong CYP3A inhibitor), ibalizumab, and enfuvirtide.[6,57] Dose increases are needed with dolutegravir (increase to 50 mg twice daily), raltegravir (increase to 800 mg twice daily), and maraviroc (increase to 600 mg twice daily as long as not given with a strong CYP3A inhibitor).[6,57] The 4R can be administered with any of the NRTI backbone combinations, but caution should be used if given with tenofovir alafenamide.
- **1HP: Isoniazid plus Rifapentine Daily for 1 month (BI)**: This short-course oral regimen, which is an alternative regimen, consists of isoniazid 300 mg daily plus daily weight-based rifapentine (maximum 600 mg), with pyridoxine 25 to 50 mg daily to prevent peripheral neuropathy.[57] The 1-month regimen of daily isoniazid plus daily rifapentine is referred to as 1HP (**1** month, IN**H**, R**P**T). In the BRIEF-TB/A5279 trial, a short-course 1-month regimen 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.[70] The 1HP regimen can be used with the anchor drug efavirenz (600 mg) or with dolutegravir—if the person has suppressed HIV RNA levels while taking once-daily dolutegravir; during the 1HP treatment course and for 2 weeks thereafter, the dolutegravir dose should be increased to 50 mg twice daily.[57] The new recommendation that dolutegravir can be used (with the dose increase) with 1HP is based on a multi-center pharmacokinetic study that evaluated the effect of 1HP on the pharmacokinetics of dolutegravir.[71] The 1HP can be used with the NRTI backbone tenofovir DF-emtricitabine, tenofovir alafenamide-emtricitabine, and abacavir-lamivudine, but rifapentine may lower the concentrations of tenofovir alafenamide and monitoring of HIV treatment efficacy is recommended in this setting.[6,57]

Exposure to Drug-Resistant Tuberculosis

- 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 and public health authorities to determine an appropriate regimen for the treatment of LTBI.[6] The World Health Organization has recently released recommendations for the use of levofloxacin in the setting of exposure to drug resistant TB, including for people with HIV.[72]

Medication-Related Adverse Effects

Individuals on LTBI therapy should undergo clinical monitoring on a monthly basis. Isoniazid is associated with an increased risk of hepatotoxicity, particularly in patients with older age, alcohol use, and pregnancy.[74] Persons taking isoniazid 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 medical provider if they occur. Baseline hepatic aminotransferase levels should be obtained. Individuals at increased risk of hepatotoxicity, including those with abnormal baseline tests, pregnant women, persons with hepatitis B or C coinfection, or those receiving antiretroviral therapy, should have routine lab monitoring during treatment with isoniazid.[6] The Adult and Adolescent OI 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).[6] A 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.[6,75,76]

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 active tuberculosis.

Considerations in Special Populations

LTBI in Pregnancy

Screening for LTBI in Pregnancy

All pregnant women 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.[6] Although data remain conflicting if the pregnancy stage affects both TST and IGRA testing,[77,78,79] either test is considered appropriate for screening in pregnancy.

Treatment of LTBI in Pregnancy

Based on a randomized controlled trial that demonstrated an increase in adverse pregnancy outcomes in women with HIV who received isoniazid for TB prevention during pregnancy, the Adult and Adolescent OI Guidelines now recommend delaying isoniazid LTBI until the postpartum 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 (for example in the setting of recent contact or LTBI test conversion) outweighs the risk of adverse birth outcomes.[6,80] Although isoniazid is not considered teratogenic, data from two randomized-controlled trials suggest that women who are pregnant or in the postpartum period may have a higher risk for isoniazid-associated hepatotoxicity.[80,81] In contrast, two recent observational studies from South Africa have demonstrated no hepatotoxicity and improved pregnancy outcomes in women with HIV on antiretroviral therapy who are given isoniazid for LTBI.[82,83] Rifampin is generally considered safe in pregnancy and some experts recommend its use in pregnancy due to a lower risk of hepatotoxicity, though drug interactions with antiretroviral therapy may limit its use. There are inadequate efficacy and safety data for the use of rifapentine in pregnancy.[84,85] Thus, if LTBI therapy is required during pregnancy, and there are problematic drug interactions with rifampin, the recommended regimen is isoniazid, given with pyridoxine.[6] If there are no problematic drug interactions with rifampin, the two options are daily rifampin for 4 months (4R) or daily isoniazid, given with pyridoxine plus rifampin, for 3 months (3HR). Regimens that use rifapentine are not recommended during pregnancy.[6]

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 this population in the setting of stable liver disease, but close clinical and laboratory monitoring is recommended.[6] In addition, management of LTBI in a patient with chronic liver disease should involve consultation with a tuberculosis expert.

Summary Points

- Despite a declining incidence of tuberculosis in the United States, individuals with HIV remain at significant 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 TST or IGRA. Limitations to TST, when compared with IGRA testing, include the requirement for a second visit to read the test, lower specificity, 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 a positive LTBI screening test should receive LTBI treatment after active tuberculosis has been ruled out.
- All individuals with HIV who have recent exposure to a person with active tuberculosis should receive LTBI treatment, irrespective of TST and/or IGRA results.
- There are two preferred regimens for LTBI treatment in persons with HIV: a 3-month course of weekly isoniazid plus rifapentine (3HP) or a 3-month course of daily isoniazid plus rifampin (3HR). Whenever isoniazid is given, pyridoxine is also given to prevent the development of isoniazid-induced peripheral neuropathy.
- There are three alternative LTBI regimens for persons with HIV: daily isoniazid for 6 or 9 months (6H or 9H), a 4-month course of daily rifampin (4R), or a 1-month course of daily isoniazid plus rifapentine (1HP).
- For pregnant women diagnosed with LTBI, delaying treatment of LTBI until after the pregnancy is typically recommended. For women requiring LTBI treatment during pregnancy, isoniazid monotherapy given daily for 6 or 9 months is the preferred regimen.
- Selection of an LTBI treatment regimen will depend on duration and frequency of the regimen, the likelihood of patient completion of the regimen, and drug interactions between the LTBI treatment medications and the antiretroviral regimen.

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Figures

Figure 1 Tuberculosis Epidemiology in the United States

Source: Centers for Disease Control (CDC). Reported Tuberculosis in the United States, 2023. National Data. Atlanta, GA: U.S. Department of Health and Human Services, CDC.

This is a dynamic visualization. Please visit our website to experience this dynamic content.

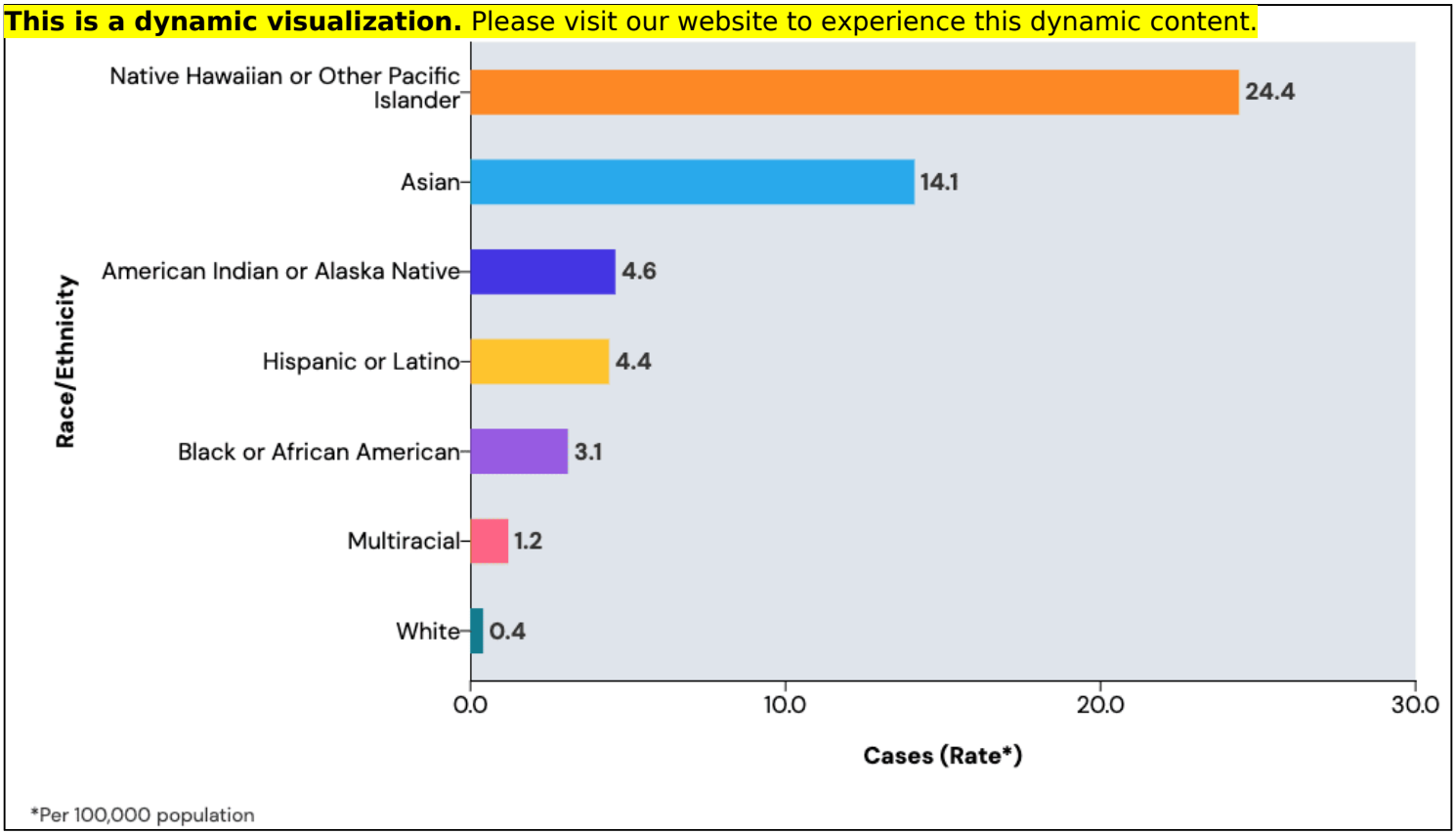

Figure 2 Tuberculosis Cases among Persons with HIV—United States, 1993-2023

This graphic shows the number of persons diagnosed with tuberculosis who had HIV coinfection. These data are from tuberculosis cases in which an HIV test result was reported.

Source: Centers for Disease Control (CDC). Reported Tuberculosis in the United States, 2023. National Data. Atlanta, GA: U.S. Department of Health and Human Services, CDC.

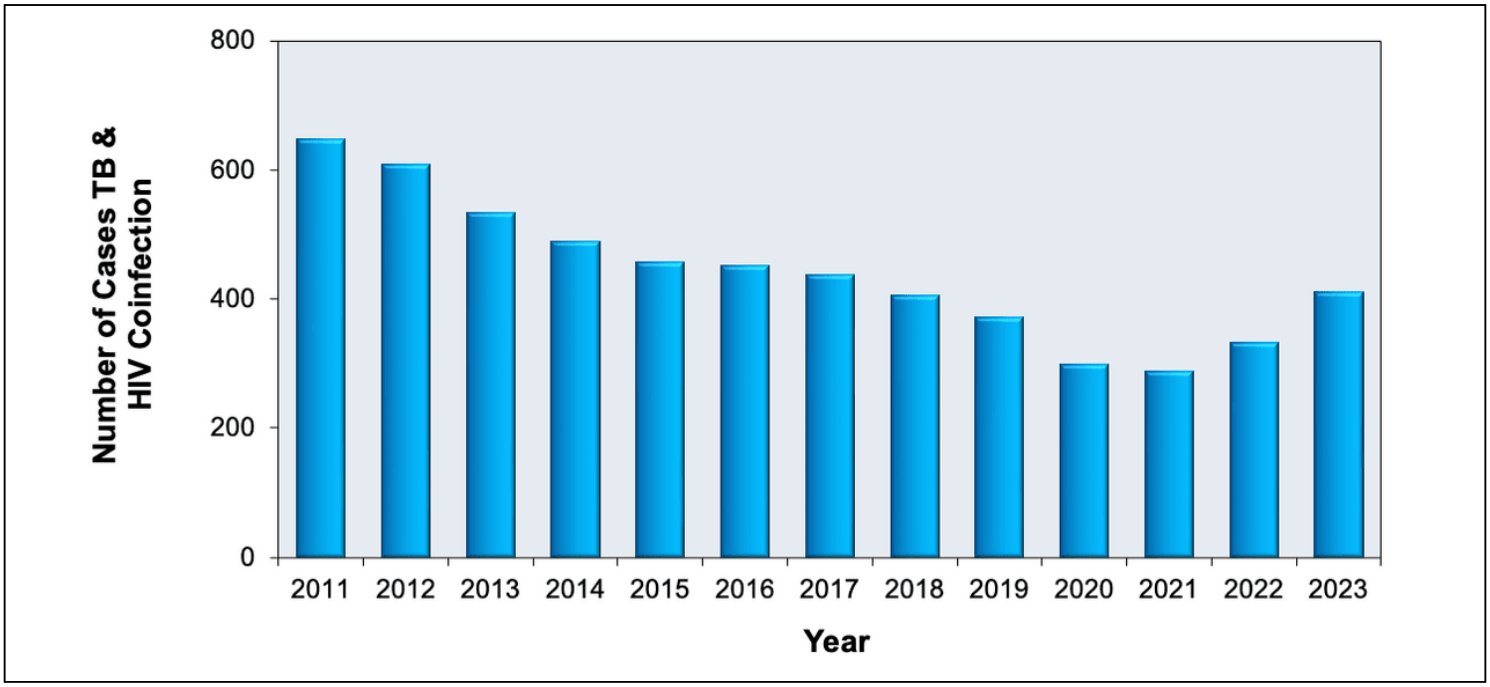

Figure 3 Interrelationship of Host Immune Control in Person with LTBI

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*.

Source: Lawn SD, Wood R, Wilkinson RJ. Changing concepts of latent tuberculosis infection in patients living with HIV infection. Clin Dev Immunol. 2011;2011. pii: 980594.

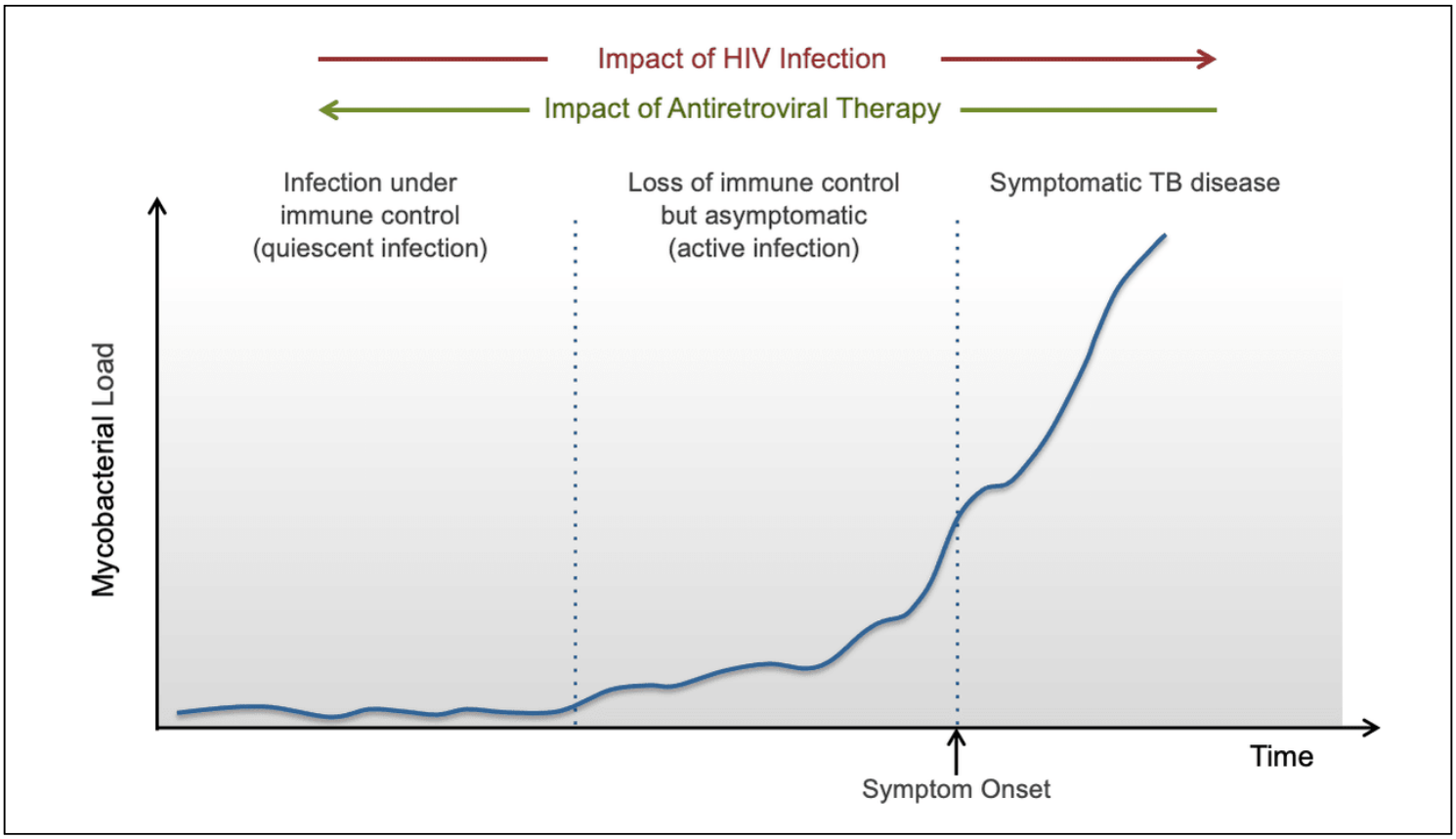

Figure 4 Mantoux Tuberculin Skin Test

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

B. The transverse diameter of cutaneous induration (not erythema) should be measured.

Source: Centers for Disease Control and Prevention (CDC)

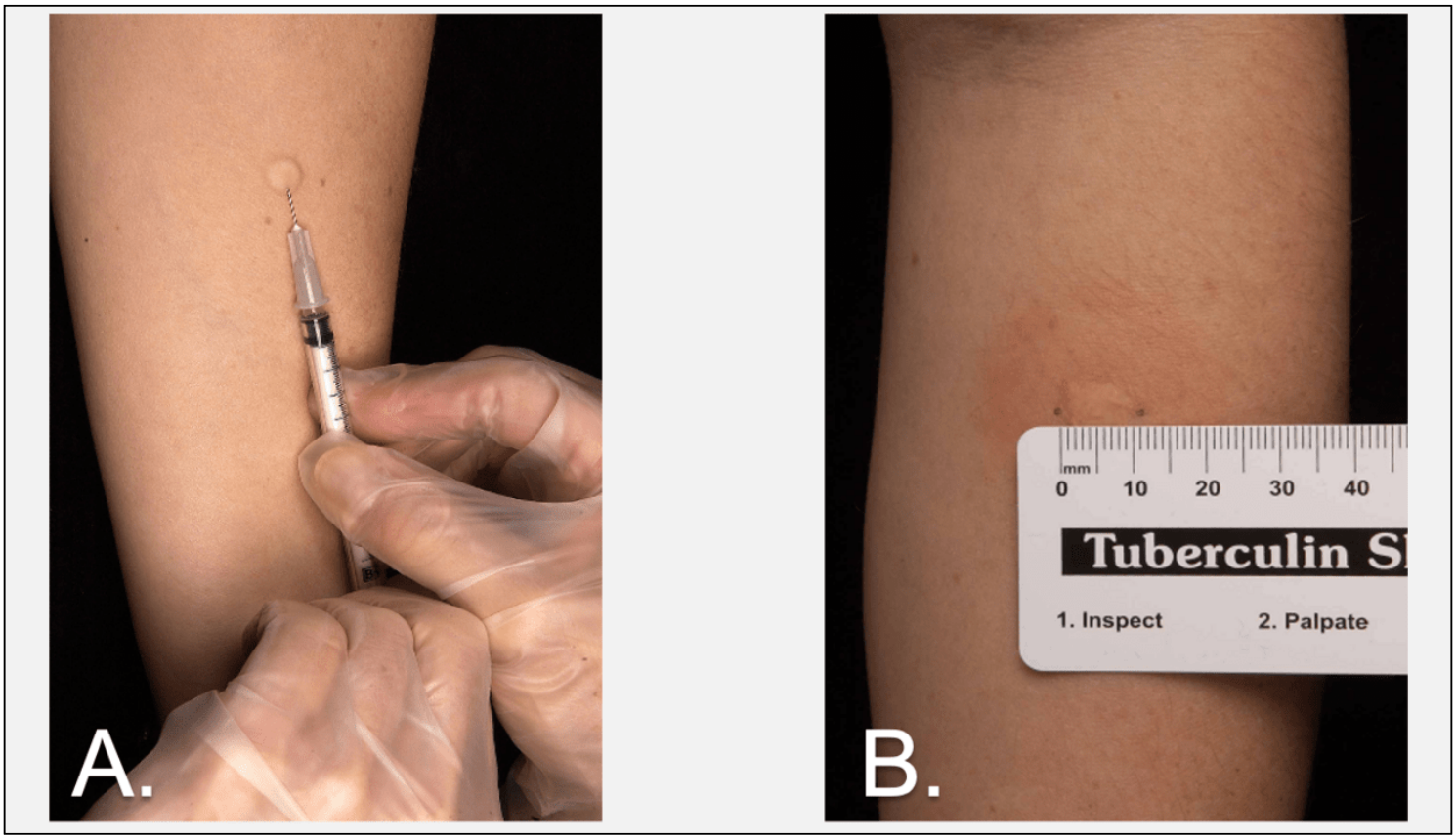

Figure 5 Interferon-Gamma Release Assays (IGRAs)

Source: Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K. Updated guidelines for using Interferon Gamma Release Assays to detect *Mycobacterium tuberculosis* infection - United States, 2010. MMWR Recomm Rep. 2010;59:1-25.

Interferon-Gamma Release Assays (IGRAs)

Feature	Quantiferon-TB Gold Plus	T-SPOT.TB
Format	Process whole blood within 16 hours	Process peripheral blood mononuclear cells (PBMCs) within 8 hours
M. tuberculosis Antigen	Single mixture of synthetic peptides representing ESAT-6 and CFP-10	Separate mixtures of synthetic peptides representing ESAT-6 and CFP-10
Measurement	IFN-gamma concentration	Number of IFN-gamma producing cells (spots)
Possible Results	Positive, negative, indeterminate	Positive, negative, indeterminate, borderline

Abbreviations: CFP-10 = culture filtrate protein 10; ESAT-6 = early secretory antigenic target-6: IFN = interferon

Figure 6 (Image Series) - QuantiFERON-TB Gold Plus (Image Series) - Figure 6 (Image Series) - QuantiFERON-TB Gold Plus
Image 6A: 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 6 (Image Series) - QuantiFERON-TB Gold Plus
Image 6B: Interpretation Criteria for QuantiFERON-TB Gold Plus (QFT-Plus)

Source: Qiagen

Interpretation Criteria for QuantiFERON-TB Gold Plus (QFT-Plus)

Result	Nil	TB Response	Interpretation
Positive	≤8.0	• TB1 and/or TB2 minus Nil ≥0.35 and ≥25% of Nil	*M. tuberculosis* infection is likely
Negative	≤8.0	• Mitogen minus Nil ≥0.5; and • TB1 and TB2 minus Nil <0.35 or ≥0.35 and <25% of Nil	*M. tuberculosis* infection is NOT likely
Indeterminate	>8.0	• Any	Likelihood of *M. tuberculosis* infection cannot be determined
	≤8.0	• TB1 and TB2 <0.35 or ≥0.35 and <25% of Nil and Mitogen minus Nil <0.5	

* All values are IU/mL interferon gamma

Figure 7 (Image Series) - T-SPOT (Image Series) - Figure 7 (Image Series) - T-SPOT
Image 7A: 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.

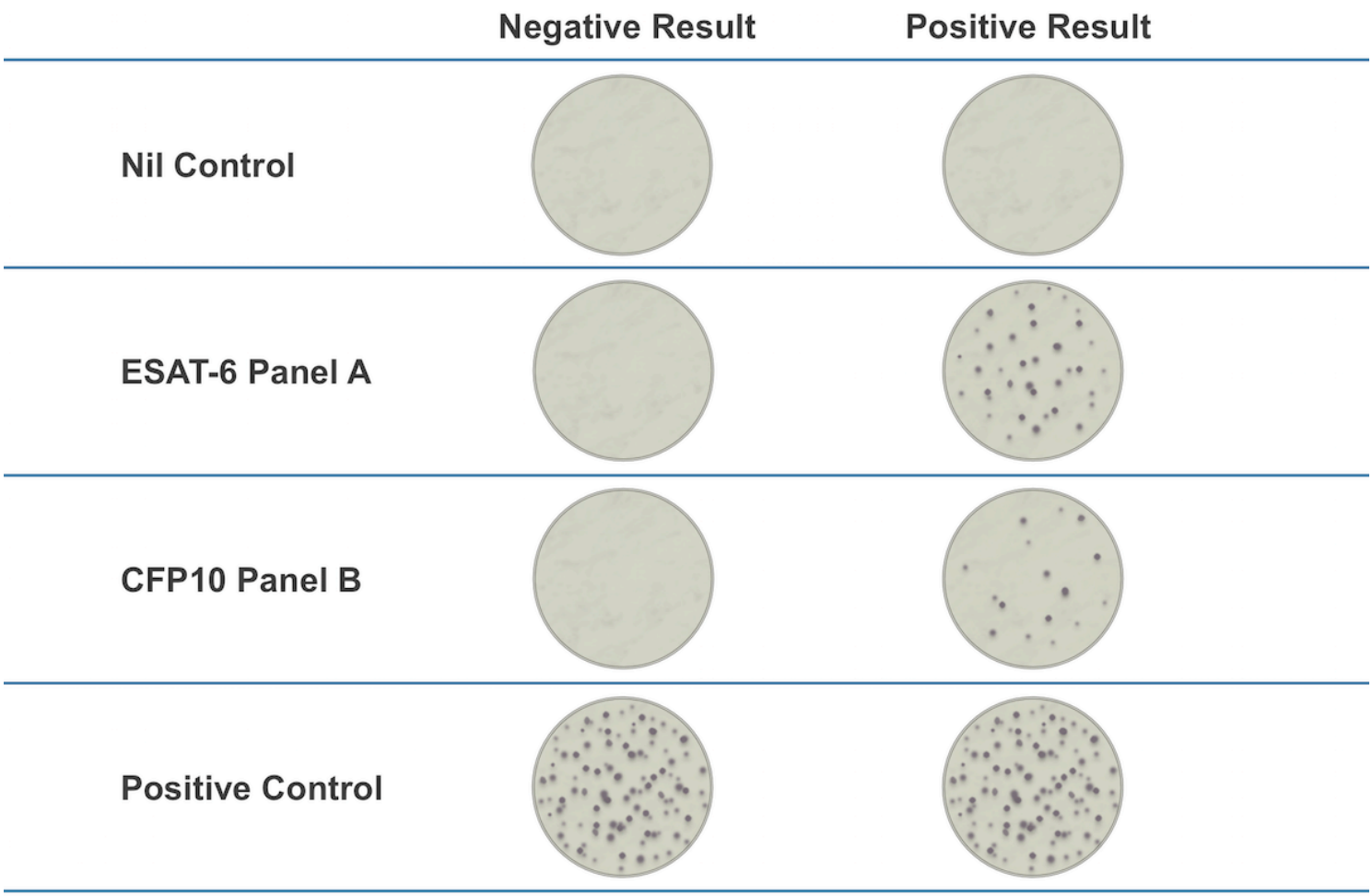

Figure 7 (Image Series) - T-SPOT
Image 7B: Interpretation Criteria for the T-SPOT.TB Test (T-Spot)

Source: Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K. Updated guidelines for using Interferon Gamma Release Assays to detect *Mycobacterium tuberculosis* infection - United States, 2010. MMWR Recomm Rep. 2010;59:1-25.

Interpretation Criteria for T-SPOT.TB Test (T-Spot)

Interpretation	Nil*	TB Response†	Mitogen§ (Positive Control)
Positive¶	≤10 spots	≥8 spots	Any number of spots
Borderline**	≤10 spots	5, 6, or 7 spots	Any number of spots
Negative††	≤10 spots	≤4 spots	≥ 20 spots
Indeterminate**	>10 spots	Any	Any number of spots
	≤10 spots	<5 spots	< 20 spots

* 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 in Adults and Adolescents with HIV**

Treating Latent Tuberculosis Infection (LTBI) in People with HIV

Indications

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

Preferred Drugs for Treatment of Latent Tuberculosis Infection

- **3HP: Weekly Isoniazid plus Rifapentine for 3 Months (AI)**
  - Isoniazid: 15 mg/kg PO once weekly (900 mg maximum dose) *plus* pyridoxine 50 mg once weekly for 12 weeks.

    plus
  - Rifapentine: weight-based PO weekly dosing for 12 weeks. Weight-based PO once weekly dose = 600 mg for weight 25.1-32.0 kg; 750 mg for weight 32.1-49.9 kg; 900 mg for weight ≥50 kg; maximum dose = 900 mg). Note: rifapentine is recommended only for virally-suppressed individuals receiving an antiretroviral regimen that has one of the following anchor drugs—efavirenz, raltegravir, or once-daily dolutegravir (AI). In addition, tenofovir alafenamide with rifapentine should be used with caution; if coadministered, monitor for HIV treatment efficacy (note: the FDA labeling recommends not to coadminister tenofovir alafenamide with rifapentine).
- **3HR: Daily Isoniazid plus Rifampin for 3 Months** (AI)
  - Isoniazid: 300 mg PO daily *plus* pyridoxine 25-50 mg PO daily for 3 months.

    plus
  - Rifampin: 600 mg PO daily for 3 months. Note: when using rifampin for LTBI treatment, either dose adjustment or substitution of key antiretroviral medications may be needed. Note: rifampin is not recommended for use with doravirine, etravirine, rilpivirine, bictegravir, cabotegravir, elvitegravir-cobicistat, or any HIV protease inhibitor. Doses of dolutegravir, raltegravir, and maraviroc need to be adjusted when used with rifampin. Tenofovir alafenamide with rifampin should be used with caution; if coadministered, monitor for HIV treatment efficacy (note: the FDA labeling recommends not to coadminister tenofovir alafenamide with rifampin).

Alternative Drugs for Treatment of Latent Tuberculosis

- **6H/9H: Daily Isoniazid for 6 to 9 Months** (AII)
  - Isoniazid: 300 mg PO daily *plus* pyridoxine 25-50 mg PO daily for 6 to 9 months. Note: this regimen is particularly useful as an alternative when drug–drug interactions between rifamycins and antiretroviral regimens limit the use of rifamycin-containing LTBI therapies.
- **4R: Daily Rifampin for 4 Months** (BI)
  - Rifampin: 600 mg PO daily for 4 months. Note: when using rifampin for LTBI treatment, either dose adjustment or substitution of key antiretroviral medications may be needed.
- **1HP: Daily Isoniazid plus Rifapentine for 1 Month** (BI)
  - Isoniazid 300 mg PO daily *plus* pyridoxine 25-50 mg PO daily for 4 weeks.

    plus
  - Rifapentine (weight-based) PO daily for 4 weeks—The 1HP regimen can be used with the anchor drug efavirenz (600 mg) or with dolutegravir—if the person has suppressed HIV RNA levels while taking once-daily dolutegravir; during the 1HP treatment course and for 2 weeks thereafter, the dolutegravir dose should be increased to 50 mg twice daily. The daily rifapentine weight-based doses are:
    - 300 mg for persons weighing <35 kg

▪ 450 mg for persons weighing 35-45 kg ▪ 600 mg for persons weighing >45 kg
Suspected Drug-Resistant TB For persons exposed to drug-resistant TB, select drugs for prevention of TB after consultation with experts and with public health authorities (AIII)
Abbreviations: TB = tuberculosis; IGRA = interferon gamma release assay; PO = orally Rating System for Prevention and Treatment Recommendations • Strength of Recommendation: A = Strong; B = Moderate; C = Weak • 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:

- Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *Mycobacterium tuberculosis* infection and disease. Last update: May 2, 2024. [HIV.gov]