Latent Tuberculosis Infection

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Module 4: Co-Occurring Conditions
Lesson 1: Latent Tuberculosis Infection

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Background

Mycobacterium tuberculosis infection is an important cause of morbidity in persons with HIV. Although combination antiretroviral therapy has significantly decreased the rates of active tuberculosis in people with HIV, the risk of developing active tuberculosis remains enhanced among those with HIV compared to those without HIV.[1,2] The development of active tuberculosis disease can occur soon after an exposure to a person with active *M. tuberculosis* disease or from reactivation of latent tuberculosis infection (LTBI).[4] Individuals with HIV who have LTBI have a substantial risk of developing active tuberculosis disease.[5,6,7,8,9] Thus, identifying a recent exposure or LTBI in a person with HIV provides an opportunity to intervene and prevent active tuberculosis disease.[2] For primary care clinicians, the main goal related to tuberculosis should be to diagnose and treat latent tuberculosis infection. In contrast, the evaluation and treatment of active tuberculosis disease in people with HIV is highly complex and typically managed by a tuberculosis expert and/or an infectious diseases specialist. Thus, the diagnosis and treatment of active tuberculosis disease is not addressed in this curriculum. For a detailed discussion and recommendations for the diagnosis and treatment of active tuberculosis disease, see the Adult and Adolescent OI Guidelines topic *Mycobacterium tuberculosis* Infection and Disease.[2]

Epidemiology of Tuberculosis in the United States

In 2023, there were 9,633 cases of tuberculosis reported in the United States.[10] The incidence of tuberculosis in the United States substantially declined from 1992 to 2020, but cases have increased in the past 3 years.[10] The highest rates of tuberculosis in the United States have occurred among Native Hawaiian/Other Pacific Islander people and in Asian people.[10] 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).[10] The following graphic shows the epidemiologic features of tuberculosis in the United States (Figure 1).[10]

Epidemiology of Tuberculosis in Persons with HIV

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).[10] For the year 2023, the CDC reported 410 cases of tuberculosis in persons with HIV coinfection.[10] Among all persons diagnosed with tuberculosis in the United States in 2023 for whom HIV status was known, 4.9% had HIV coinfection.[10]

Rationale and Indications for LTBI Screening

Rationale for LTBI Screening

Multiple factors underscore the rationale for routine LTBI screening in persons with HIV. Most notably, the risk of progression from LTBI to active disease is markedly increased in individuals with HIV: the risk is approximately 3 to 16% per year in persons with HIV compared with 5 to 10% lifetime risk in those without HIV.[2,11,12] Other factors that support routine screening and treatment of LTBI in persons with HIV include poor outcomes associated with active tuberculosis disease and the availability of multiple effective treatment options for LTBI. Among persons with LTBI who also have HIV, treatment of LTBI in conjunction with combination antiretroviral therapy markedly decreases the risk of developing active tuberculosis.[13,14,15,16]

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.[2] 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.

Repeat LTBI Screening

Individuals with advanced HIV disease (CD4 count less than 200 cells/mm^3) with an initial negative LTBI screening test 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.[2] Yearly repeat testing for LTBI is recommended only in situations when individuals with HIV have enhanced risk for ongoing or repeat exposure to persons with tuberculosis.[2]

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).[17,18] Both methods are indirect measures of T-cell-mediated immune responses to *M. tuberculosis*. Tuberculin skin testing is an *in vivo* skin test, whereas IGRA is an *in vitro* blood-based approach.[19] Routine dual testing with 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.[20] Importantly, a positive TST or IGRA does not distinguish between LTBI and active tuberculosis disease, nor does a negative LTBI test rule out active tuberculosis disease. Following initial infection with *M. tuberculosis*, the TST and IGRA tests typically have a gap of 2 to 10 weeks before they become positive. Neither TST nor IGRA tests can be used to monitor LTBI treatment responses, as both tests typically remain positive after 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 3).[17] 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.[19]

Criteria for Positive TST

For individuals with HIV, an induration of 5 mm or greater is considered a positive test.[21] Following exposure to *M. tuberculosis*, the TST conversion to positive typically occurs within 8 weeks.[22] The sensitivity of TST for the diagnosis of LTBI is estimated at 45 to 85% and specificity at approximately 85%.[20,23,24] 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.[18] 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.[25]

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.[18]

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 4).[20] 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).[18,26,27] 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*.[18] 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 5).[28,29,30] 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).[28,31,32,33] The interferon gamma response is quantified in international units (IU) per millimeter, and test results are reported as positive, negative, or indeterminate.[31] Reversion from a positive to negative test result can occur,[34,35,36] but this tends to occur when the initial test is close to the cutoff threshold.[18,28,32]

- **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 6).[20] 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).[37] 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.[20]

Performance of IGRA Tests

In a meta-analysis of IGRA studies in persons with HIV, the pooled sensitivity was 72% for T-SPOT and 61% for QFT.[38] The presence of immunosuppression decreases the sensitivity of IGRAs, but the impact is relatively less than on the TST.[18] Similar to TST, the IGRA tests may be negative early in the window period after recent *M*. *tuberculosis* infection. The IGRA tests have greater specificity than the TST, and the IGRA tests are not impacted by prior receipt of BCG vaccine.[2] 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 active tuberculosis or prior treated LTBI usually have persistently positive IGRAs.

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.[2,17,20] The correlation between positive TST and IGRA in persons with HIV is poor to moderate.[5,38,39,40] 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. 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:[2]

- 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 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 After 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.[41] 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.[42] 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.[43] 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). 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.[2]

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.[5,40] The risk of progression to active tuberculosis disease is even higher among recent LTBI test converters.[39,44,45] Some studies indicate a positive IGRA is a stronger predictor than a positive TST for the risk of developing tuberculosis disease.[46,47] 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.[2]

- A new positive screening test (TST or IGRA) for LTBI with no evidence of active tuberculosis 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 choice for the LTBI regimen should strongly consider the individual's antiretroviral regimen.[2,48] All regimens to treat LTBI are taken orally, and when isoniazid is given, concomitant pyridoxine (vitamin B6) is prescribed to prevent isoniazid-induced peripheral neuropathy.[2] The regimens for LTBI are commonly referred to as short name abbreviations:

- **3HP** = **3-**month duration with isoniazid (IN**H**) *plus* rifapentine (R**P**T)
- **3HR** = **3-**month duration with isoniazid (IN**H**) *plus* rifampin (**R**IF)
- **6H/9H** = (**6**-or **9**-month duration with IN**H**)
- **4R** = **4**-month duration with rifampin (**R**IF)
- **1HP** = **1**-month duration with isoniazid (IN**H**) *plus* rifapentine (R**P**T).

The following summarizes recommendations for the preferred and alternative regimens for the treatment of LTBI in adults with HIV (Table 1).[2,48] Note the LTBI regimens should only be used with the antiretroviral regimens that are outlined below in the table. In particular, note that the 6H and 9H regimens are the only options in persons taking bictegravir-tenofovir alafenamide-emtricitabine.[2]

Summary of Data for Regimens Used to Treat LTBI

- **3HP: Isoniazid plus Rifapentine Weekly for 3 Months**: The 3HP regimen has efficacy equal to standard isoniazid monotherapy, with the added likely benefit of improved adherence and completion rates due to a shorter duration.[49,50,51,52] Self-administered 3HP therapy is equivalent to directly observed therapy (DOT).[53]
- **3HR: Isoniazid plus Rifampin Daily for 3 Months**: 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.[54,55,56]
- **6H or 9H: Isoniazid for 6 or 9 Months**: These isoniazid monotherapy regimens are considered standard-length LTBI treatment for persons with HIV (6 or 9 months).[2,48] 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.[57,58]
- **4R: Rifampin for 4 Months (BI)**: 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.[59] Furthermore, the rifampin regimen cohort had higher rates of treatment completion and fewer adverse effects.[59] Among all study participants,

only 4% had HIV.[59] This regimen is an alternative regimen because of minimal data in persons with HIV and potential drug interactions between rifampin and other medications commonly taken by people with HIV.

- **1HP: Isoniazid plus Rifapentine Daily for 1 month (BI)**: 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.[60]

Medication-Related Adverse Effects

Individuals on LTBI therapy should undergo clinical monitoring on a monthly basis. Isoniazid can cause peripheral neuropathy, but this can be prevented with concomitant use of pyridoxine (vitamin B6). In addition, isoniazid is associated with an increased risk of hepatotoxicity, particularly in patients of older age, with alcohol use, and if used during pregnancy.[62] Persons taking isoniazid 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. 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.[2] 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).[2] 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.[2,63,64]

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.[2] Although data remain conflicting if the pregnancy stage affects both TST and IGRA testing,[65,66,67] either test is considered appropriate for screening in pregnancy.

Treatment of LTBI in Pregnancy

Ideally, pregnant women with LTBI should delay the treatment of LTBI until the postpartum period, unless the pregnant woman reports significant close contact with an active tuberculosis case or the risk of developing active tuberculosis outweighs the risk of adverse birth outcomes.[2,68] 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.[68,69] 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.[70,71] 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.[72,73] Thus, if LTBI therapy is required during pregnancy, and there are problematic drug interactions with rifampin, the recommended regimen is isoniazid (given with pyridoxine), with monitoring for hepatotoxicity.[2] 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.[2]

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.[2] 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. 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.
- 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.
- All individuals with HIV and a positive LTBI screening test should receive LTBI treatment after active tuberculosis disease has been ruled out. In addition, 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.
- 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.
- 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.

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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. Atlanta, GA: US Department of Health and Human Services, CDC; 2024.

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

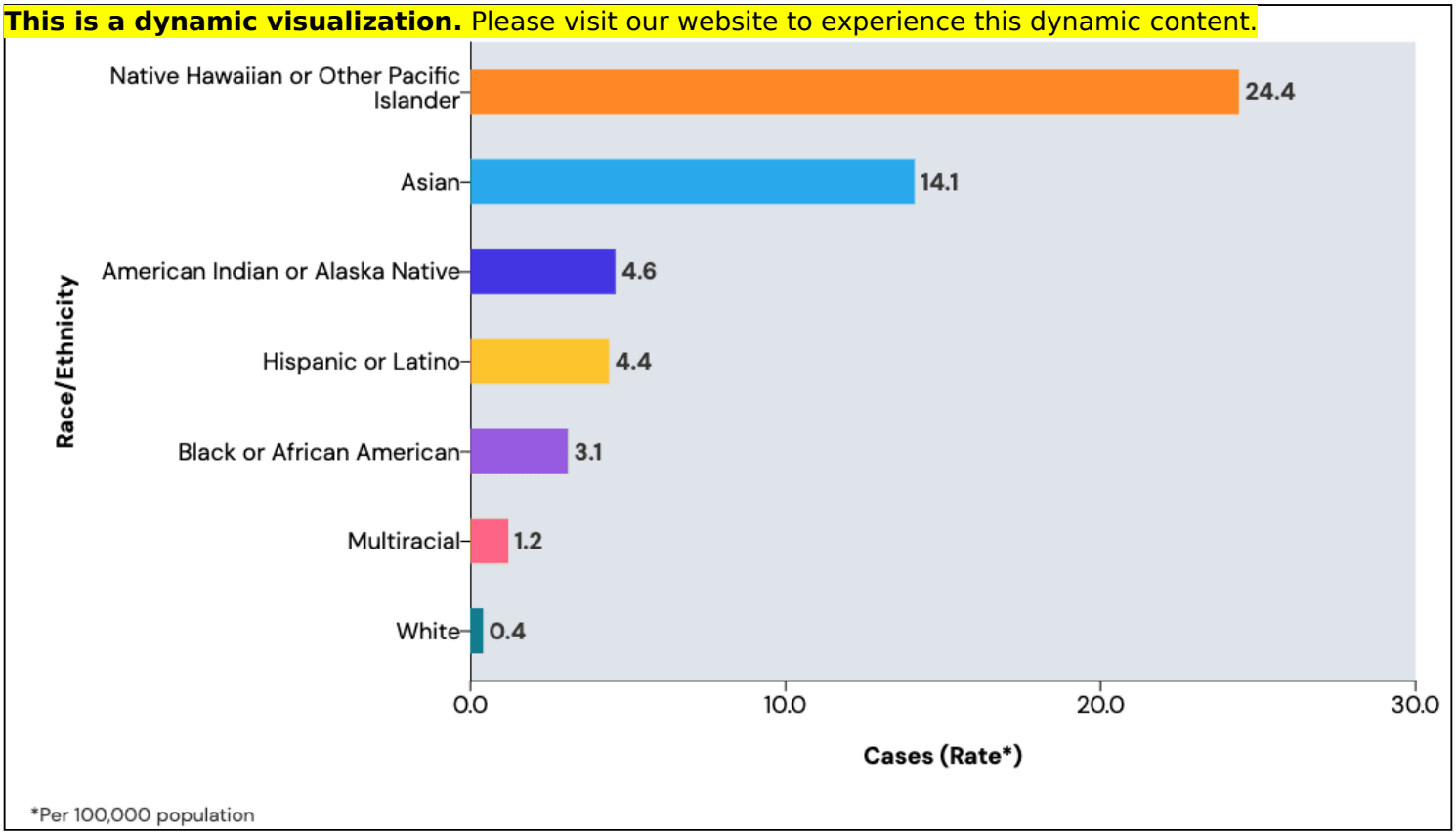

Figure 2 Tuberculosis Cases among Persons with HIV—United States, 1993-2023

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. Atlanta, GA: US Department of Health and Human Services, CDC; 2024.

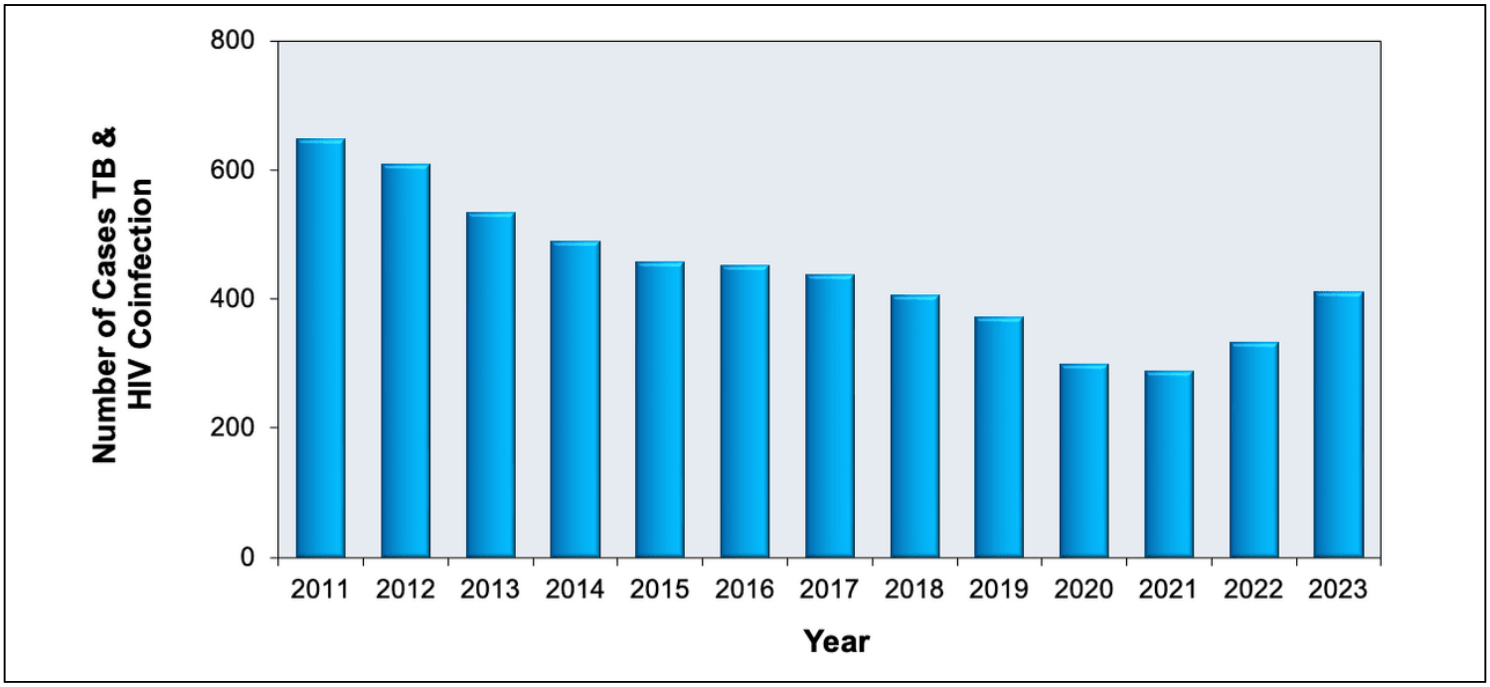

Figure 3 Mantoux Tuberculin Skin Test

A. The standard Mantoux tuberculin skin test is performed by injecting 0.1 mL of 5 tuberculin purified protein derivative (PPD) units intradermally on the volar surface of the forearm.
B. The transverse diameter of cutaneous induration (not erythema) should be measured 48 to 72 hours after placement of the PPD.

Source: Centers for Disease Control and Prevention (CDC)

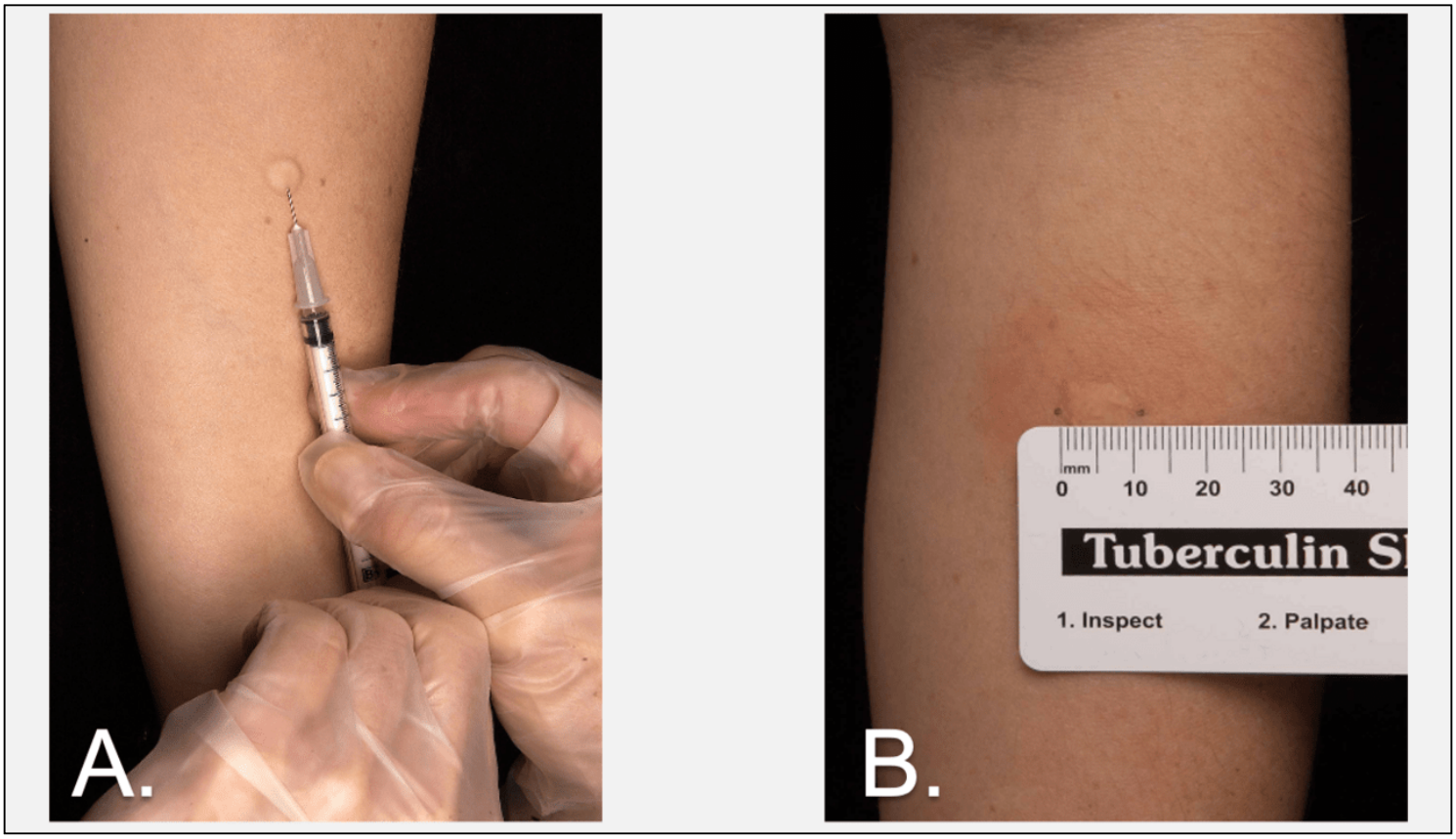

Figure 4 Interferon-Gamma Release Assays (IGRAs)

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 5 (Image Series) - QuantiFERON-TB Gold Plus (Image Series) - Figure 5 (Image Series) - QuantiFERON-TB Gold Plus
Image 5A: 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 5 (Image Series) - QuantiFERON-TB Gold Plus
Image 5B: 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 6 (Image Series) - T-SPOT (Image Series) - Figure 6 (Image Series) - T-SPOT
Image 6A: 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.

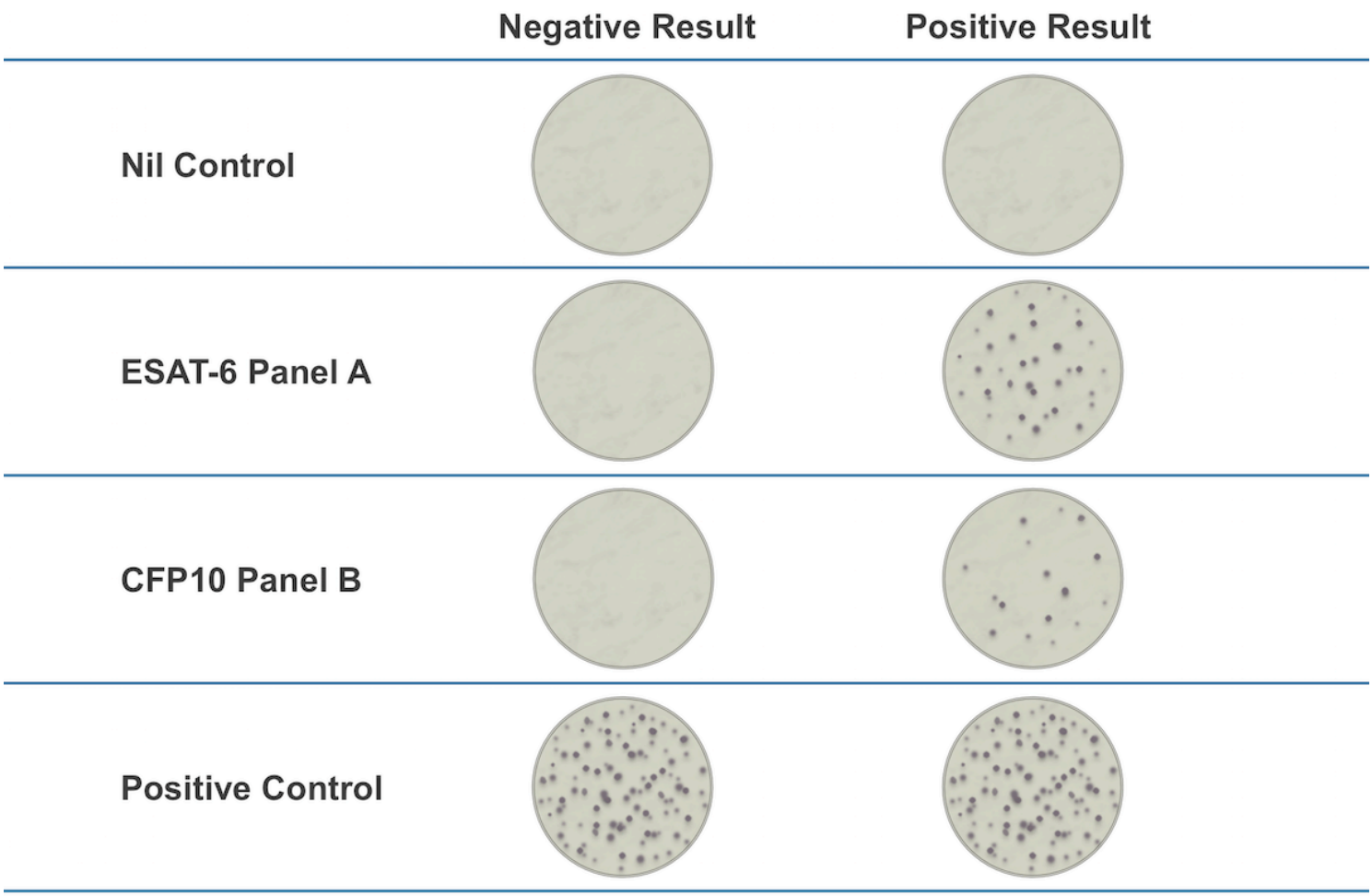

Figure 6 (Image Series) - T-SPOT
Image 6B: Interpretation Criteria for the T-SPOT.TB Test (T-Spot)

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. Treating Latent Tuberculosis Infection in Persons with HIV

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

Recommendations for Treating Latent Tuberculosis Infection in People with HIV

Indications

- Positive screening test for latent tuberculosis infection regardless of BCG status (AI): Tuberculin skin test ≥5 mm induration at 48-72 hours *or* positive interferon-gamma release assay [IGRA]), *and*
  - No evidence of active TB disease, *and*
  - No prior history of treatment for active disease or latent TB infection

- Close contact with a person with infectious tuberculosis (such as someone who has shared air space, such as in a household or close congregate setting, with a person with active pulmonary tuberculosis according to the Centers for Disease Control and Prevention Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis) regardless of screening test result and CD4 count (AII).

Preferred Drugs for Treatment of Latent Tuberculosis Infection

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

    plus
  - Rifapentine PO once weekly (weight based and maximum dose 900 mg) for 12 weeks.
    - *Weighing 25.1-32.0 kg:* 600 mg
    - *Weighing 32.1-49.9 kg:* 750 mg
    - *Weighing ≥50.0 kg:* 900 mg

Note: The 3HP regimen is recommended only for virally-suppressed individuals receiving an efavirenz-, raltegravir-, or once-daily dolutegravir-based regimen (AII). Rifapentine may lower concentrations of tenofovir alafenamide; if tenofovir alafenamide is used, monitor for virologic response.

- **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. See Drug Interaction Tables in the Opportunistic Infections Guidelines for the list of antiretroviral medications not recommended for use with rifampin (e.g., protease inhibitors, bictegravir) and those which require dosage adjustment (e.g., raltegravir [800 mg twice daily], dolutegravir [50 mg twice daily], or maraviroc [600 mg twice daily unless also taking a strong CYP3A inhibitor]).

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.
- **4R: Daily Rifampin for 4 Months** (BI)
  - Rifampin: 600 mg PO daily for 4 months.
    - Consult the Tuberculosis/HIV Coinfection section of the Adult and Adolescent Antiretroviral Guidelines for the list of antiretroviral drugs not recommended for use

with rifampin (e.g., protease inhibitors, bictegravir) and those which require dosage adjustment (e.g., raltegravir [800 mg twice daily], dolutegravir [50 mg twice daily], or maraviroc [600 mg twice daily unless also taking a strong CYP3A inhibitor]).

- **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 daily rifapentine weight-based doses are:
    - *Weighing <35 kg:* 300 mg
    - *Weighing 35–45 kg:* 450 mg
    - *Weighing >45 kg*: 600 mg

Note: The 1HP regimen is recommended only for patients receiving an efavirenz-based antiretroviral regimen (without dose adjustment of efavirenz) or a dolutegravir 50 mg once-daily regimen (the dolutegravir dose should be increased to 50 mg twice daily throughout the course of 1HP—and continued twice daily for 14 days after 1HP completion—before switching back to 50 mg once-daily dosing). Rifapentine may lower concentrations of tenofovir alafenamide; if tenofovir alafenamide is used, monitor for virologic response.

Suspected Drug-Resistant TB

For people exposed to drug-resistant tuberculosis, select drugs for prevention of tuberculosis after consultation with experts and with public health authorities (AIII)

Abbreviations: TB = tuberculosis; IGRA = interferon gamma release assay; PO = orally
Regimen Short Names: **3HP** = **3-**month duration with isoniazid (IN**H**) and rifapentine (R**P**T); **3HR** = **3-**month duration using isoniazid (IN**H**) and rifampin (**R**IF); **6H and 9H** = (**6**-or **9**-month duration with IN**H**); 4**R** = **4**-month duration with rifampin (**R**IF); **1HP** = **1**-month duration with isoniazid (IN**H**) and rifapentine (R**P**T)

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]