

Mycobacterium tuberculosis Infection and Disease

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Epidemiology

Tuberculosis (TB) is the leading cause of morbidity and mortality among people with HIV worldwide. In 2020 and 2021, progress towards reducing TB morbidity and mortality slowed amidst the widespread disruption of health services from the COVID-19 pandemic. Globally, the annual number of estimated TB deaths increased in 2020 and 2021, to 1.5 million and 1.6 million, respectively.^{1,2} Among people with HIV, there were an estimated 703,000 people who had TB, but only 52% were diagnosed and reported. A total of 187,000 deaths among people with HIV were attributed to TB in 2021, the first time there has been an increase in HIV-associated TB deaths since 2006.² People with HIV still account for a disproportionate number of TB deaths worldwide (11.8% of deaths vs. 6.7% of TB cases); however, a 47% reduction in deaths has occurred since 2010.²

In the United States, more than two-thirds (5,456; 71.4%) of people newly reported with TB in 2021 were born outside the United States, similar to 2019 and 2020 proportions.³ The incidence of HIV-related TB in the United States has declined substantially, in part because of the widespread use of antiretroviral therapy (ART).^{4,5} Among all people reported with TB with known HIV status in the United States in 2021, 293 people (4.2%) were coinfecting with HIV (6.3% among people with TB aged 25–44 years vs. 5.6% among those aged 45–64 years).⁶ Overall, the proportion of reported people with TB and HIV co-infection has been steadily declining over the past decade (7.4% in 2011).

Latent TB Infection

TB infection occurs when a person inhales droplet nuclei containing *Mycobacterium tuberculosis* organisms. Usually within 2 to 12 weeks after infection, the immune response limits the multiplication of tubercle bacilli. However, viable bacilli can persist for years, a condition referred to as latent TB infection (LTBI). People with LTBI are asymptomatic and are not infectious. TB disease (defined as clinically active disease, often with positive smears and cultures) can develop soon after exposure to *M. tuberculosis* organisms (primary disease) or after reactivation of latent infection.^{7,8} The risk of TB disease due to reactivation of LTBI for people with untreated HIV has been estimated as 3% to 16% per year, which approximates the lifetime risk of TB disease for people with LTBI who do not have HIV (approximately 5%).^{9–14} The risk of TB disease begins in the first year following HIV infection.¹⁵ TB disease can occur at any CD4 T lymphocyte (CD4) cell count, although the risk increases with progressive immunodeficiency.^{15,16} The estimated annual risk of developing TB disease among people with LTBI (diagnosed by a positive tuberculin skin test [TST] or interferon-gamma release assay [IGRA] in the absence of a TB disease diagnosis) is 3 to 12 times greater for people with untreated HIV than for those without HIV.¹⁷ Even with effective ART, the risk of TB disease among people with HIV remains greater than that among the general population.¹⁸ Since 2006, the TB incidence rate in people with HIV has been lower than in previous years, but the TB risk is still substantially higher than among people without HIV.¹⁹ In the United States, the most common predisposing factor for TB infection is birth or residence outside of the United States.²⁰

The risk of progression from LTBI to TB disease in people with HIV is reduced both by ART and by the treatment of LTBI.^{18,21-24} In combination with ART, isoniazid preventive therapy decreased the risk of TB disease by 76% among people with HIV in Brazil.²⁵ Furthermore, isoniazid preventive therapy and ART independently and additively decreased the risk of death and severe HIV-related illness.^{21,23}

Diagnosing Latent TB Infection

All people with HIV should be evaluated for LTBI at the time of HIV diagnosis, regardless of their epidemiological risk of TB exposure. In programmatic settings in the United States, TB screening has been suboptimal, with only 47% to 69% of people with HIV presenting to care completing initial screening, and 42% of those with LTBI initiating therapy.²⁶⁻³⁰ The two current diagnostics available for the detection of *M. tuberculosis* infection in the United States, IGRA and TST, help differentiate those with and without TB infection. However, the diagnostic accuracy of TST and IGRA is limited; a negative test does not exclude the diagnosis of LTBI or TB disease, and a positive test does not, by itself, mean LTBI therapy is warranted. Decisions about medical and public health management should include epidemiological risk factors, medical history, and other clinical information when interpreting IGRA or TST results.

People with advanced HIV (CD4 count <200 cells/mm³) and negative diagnostic tests for LTBI, and no indications for initiating empiric LTBI treatment (i.e., no recent exposure to a culture-confirmed TB case) should be retested for LTBI once they start ART and attain a CD4 count ≥200 cells/mm³ to ensure that the initial test result was a true negative result.³¹⁻³³ Annual testing for LTBI using TST or IGRA is recommended only for people with HIV who have a history of a negative test for infection and are at high risk for repeated or ongoing exposure to people with active TB disease (e.g., during incarceration, travel to a high-TB incidence country, homelessness, living in a congregate setting).³⁴

Traditionally, LTBI has been defined by the presence of a positive TST (≥5 mm of induration at 48–72 hours in people with HIV) in people with no clinical or radiographic evidence of TB disease. Despite the extensive experience with the TST among people with HIV, the test has several disadvantages: the requirement for two visits to place and read the test, decreased specificity (false positive results) among people who received Bacillus Calmette-Guérin (BCG) vaccination, and decreased sensitivity (false negative results) among people with advanced immunodeficiency.^{33,35} The first two limitations of the TST have led to broader use of IGRAs for the detection of LTBI.

IGRAs include the T-SPOT.TB and QFT-TB Gold Plus (QFT-Plus). Systematic reviews and meta-analyses, as well as a large study in the United States, have found that IGRAs generally have higher specificity than the TST, may correlate better with exposure to *M. tuberculosis*, and are less likely to cross-react with BCG vaccination or exposure to nontuberculous mycobacteria.^{19,36,37} A systematic review among people with HIV did not find robust evidence that IGRAs were superior to TST in diagnosing either active TB or LTBI.³³ However, in a prospective study of 1,510 people with HIV in the United States (median CD4 count of 532 cells/mm³), T.SPOT.TB was significantly more specific (99.7%) and had a significantly higher positive predictive value (PPV; 90.0%) than the older QuantiFERON Gold In-Tube (QFT-GIT) (96.5% specificity, 50.7% PPV) and TST (96.8% specificity, 45.4% PPV). QFT-GIT was significantly more sensitive (72.2%) than TST (54.2%) and T.SPOT.TB (51.9%).³⁸

As with the TST, progressive immunodeficiency is associated with decreased sensitivity of IGRAs.³⁹ In addition, the reproducibility of positive results of IGRAs may be limited. Among 46 people with HIV who had initial positive tests with the QFT-GIT assay, 33 (72%) had negative repeat tests, particularly those whose responses were at the lower range of the manufacturer's suggested range of positive results.⁴⁰ Similar to recommendations for healthcare workers, annual testing for people with HIV is no longer recommended unless high risk exists for repeated or ongoing exposure to people with active TB disease.⁴¹

Among people with HIV, the correlation between the TST and IGRA test results is poor to moderate.^{42,43} In prospective studies not limited to people with HIV, positive results with either the TST or IGRA were associated with an increased risk of developing TB disease.^{19,44-46} In some studies (again not limited to people with HIV), patients with a positive IGRA were at a higher risk of subsequently developing TB disease than those with a positive TST.^{19,47,48} Despite its limitations, a positive TST result strongly predicts that the treatment of LTBI will decrease the risk of TB progression among people with HIV.¹⁸ Studies are underway to formally evaluate if IGRAs are similarly predictive.⁴⁹

Although no definitive comparisons of the TST and IGRAs for screening people with HIV in low-burden settings have been published, both the TST and the approved IGRAs are considered appropriate for TB screening among people with HIV in the United States.^{17,38} Some experts have suggested using both the TST and an IGRA in a stepwise or sequential manner to screen for LTBI, but the predictive value of this approach is not clear, and it may be challenging to implement. The routine use of both TST and IGRAs in a single patient to screen for LTBI is not recommended in the United States.⁵⁰

As tests of immune reactivity against *M. tuberculosis*, TST and IGRAs are often positive among people with TB disease. Therefore, all people with a positive TST or IGRA should be evaluated for the possibility of active TB disease.¹⁷ Most, but not all, people with HIV and TB disease have symptoms (e.g., cough, fever, sweats, weight loss, lymphadenopathy); the absence of these symptoms had a 98% negative predictive value for culture-positive TB in low-resource settings, although this varied depending on pretest probability.⁵¹ The addition of a chest radiograph improved the sensitivity of this screening algorithm but decreased specificity.⁵² It is important to note that in a symptomatic patient with clinical suspicion of TB disease, a negative TST or IGRA does not rule out TB disease, particularly in those with CD4 count <200 cells/mm³.

Obtaining a sputum specimen for *M. tuberculosis* identification is the gold standard for diagnosing pulmonary TB disease, but it is not high yield in screening people with HIV without pulmonary symptoms, particularly in low-prevalence settings. Therefore, a negative symptom screen (including absent cough of any duration) coupled with a normal chest radiograph is usually sufficient to exclude TB disease in a patient with a positive TST or IGRA in low TB incidence settings.¹⁷ Sub-clinical TB among people with HIV is of greater concern in high TB burden settings.⁵³

Treating Latent TB Infection

Recommendations for Treating LTBI to Prevent TB Disease in People with HIV
<p>Indications</p> <ul style="list-style-type: none"> Positive screening test^a for LTBI (≥5 mm of induration at 48–72 hours in people with HIV or positive IGRA) regardless of BCG status, 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 (such as someone who has shared air space, such as in a household or close congregate setting, with a person with active pulmonary TB 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). <p>Preferred Therapy</p> <ul style="list-style-type: none"> Isoniazid 15 mg/kg PO once weekly (900 mg maximum) plus rifapentine (see weight-based dosing below) PO once weekly plus pyridoxine 50 mg PO once weekly (3HP) for 12 weeks (AI). Note: 3HP is recommended only for virally-suppressed patients receiving an efavirenz-, raltegravir-, or once-daily dolutegravir-based ARV regimen (AII). <ul style="list-style-type: none"> Rifapentine Weekly Dose (maximum 900 mg) <ul style="list-style-type: none"> Weighting 25.1–32 kg: 600 mg Weighting 32.1–49.9 kg: 750 mg Weighting ≥50.0 kg: 900 mg Isoniazid 300 mg PO daily plus rifampin 600 mg PO daily plus pyridoxine 25–50 mg PO daily (AI) for 3 months (3HR). See the Dosing Recommendations for use of ARV and Anti-TB Drugs When Treating Latent TB table for the list of ARV drugs not recommended for use with rifampin (e.g., protease inhibitors, bictegravir) and those which require dosage adjustment (i.e., raltegravir, dolutegravir, or maraviroc). <p>Alternative Therapy</p> <ul style="list-style-type: none"> Isoniazid 300 mg PO daily plus pyridoxine 25–50 mg PO daily for 6–9 months (AII) <i>or</i> Rifampin 600 mg PO daily for 4 months (BI) (4R) <ul style="list-style-type: none"> Consult the Tuberculosis/HIV Coinfection section of the Adult and Adolescent Antiretroviral Guidelines for the list of ARV drugs not recommended for use with rifampin (e.g., protease inhibitors, bictegravir) and those which require dosage adjustment (e.g., raltegravir, dolutegravir, or maraviroc). Isoniazid 300 mg PO daily plus rifapentine (see weight-based dosing below) PO daily plus pyridoxine 25–50 mg PO daily for 4 weeks (BI) (1HP) Note: 1HP is recommended only for patients receiving an efavirenz-based ARV regimen (AI). <ul style="list-style-type: none"> Rifapentine Daily Dose (maximum 600 mg) <ul style="list-style-type: none"> Weighting <35 kg: 300 mg Weighting 35–45 kg: 450 mg Weighting >45 kg: 600 mg For people exposed to drug-resistant TB, select drugs for prevention of TB after consultation with experts and with public health authorities (AIII). <p>Pregnancy Considerations</p> <ul style="list-style-type: none"> During pregnancy, 4R and 3HR are acceptable alternative regimens (BIII). For pregnant women receiving effective ART and without close household contact with infectious TB or recent test for TB infection (TST or IGRA) conversion from negative to positive, therapy for LTBI may be deferred until after delivery (BIII).

- Although rifampin generally is considered safe in pregnancy, data on the use of rifapentine are extremely limited and its use in pregnancy is not currently recommended (BIII).

Additional Considerations

- Deferring ART until after completion of treatment for LTBI is not recommended (AI).
- Given the important drug–drug interactions between rifamycins and several antiretroviral (ARV) agents, selection of an LTBI regimen will depend on a patient's current or planned ARV regimen.

^a Screening tests for LTBI include a tuberculin skin test (TST) or interferon-gamma release assay (IGRA); see text for details regarding these tests.

Key: H = Isoniazid; P = Rifapentine; R = Rifampin; ARV = antiretroviral; CDC = Centers for Disease Control and Prevention; CD4 = CD4 T lymphocyte; CNS = central nervous system; DOT = directly observed therapy; IRIS = immune reconstitution inflammatory syndrome; IPT = isoniazid preventive therapy; LTBI = latent tuberculosis infection; PI = protease inhibitor; PO = orally; TB = tuberculosis

Once active TB disease is excluded and in the absence of other medical contraindications, people with HIV with a positive TB screening test should receive LTBI treatment (**AI**), unless there is documentation of prior treatment for active TB or LTBI.⁵⁴ Additionally, people with HIV who are in close contact with anyone with infectious TB should receive LTBI treatment, regardless of their TB screening test results and CD4 count (**AII**). Selection of an LTBI regimen may depend on the potential for drug interactions, toxicity concerns, as well as medication availability and/or cost (see [Recommendations for Treating LTBI to Prevent TB Disease in People with HIV table](#) above). People with HIV who have been treated successfully for LTBI should not have repeat testing with TST or IGRA; a previously positive test result generally will not revert to negative.

People with HIV in the United States who have a negative TST or IGRA and no recent contact with a person with infectious TB likely will not benefit from the treatment of LTBI, and preventive therapy is not generally recommended (**AIII**); this is in contrast to high TB prevalence countries where isoniazid (i.e., isoniazid preventive therapy; IPT) decreased TB risk and mortality in people with HIV, regardless of TST or IGRA result.²⁴

LTBI treatment and ART act independently to decrease the risk of TB disease.^{22,23,25,55,56} Therefore, the use of both interventions is recommended for people with LTBI and HIV (**AI**). Given the important drug–drug interactions between rifamycins and several antiretroviral (ARV) agents, selection of an LTBI regimen will depend on a patient's current or planned ARV regimen. Deferring ART until after completion of treatment for LTBI is not recommended (**AI**).²³

Preferred Drugs for Treatment of Latent TB Infection

3HP

- Rifapentine (weight-based dosing) orally (PO) once weekly plus isoniazid 15 mg/kg PO once weekly (900 mg maximum) plus pyridoxine 50 mg PO once weekly for 12 weeks is one of two preferred regimens for the treatment of LTBI (**AI**).⁵⁴

In two randomized controlled trials, rifapentine plus isoniazid once weekly for 12 weeks (3HP) was as effective and well-tolerated as 6 to 9 months of daily isoniazid, including in people with HIV whose CD4 counts were generally >350 cells/mm³ and who were not yet on ART.^{57,58} 3HP treatment completion rates with self-administered therapy were inferior to those with directly observed therapy (DOT) but non-inferior among study participants enrolled in the United States—and generally high overall.⁵⁹

Although individuals taking ART were not included in the Phase 3 trial of 3HP,⁵⁷ the pharmacokinetic (PK) profile of efavirenz with daily rifapentine and isoniazid is favorable.^{60,61} Raltegravir concentrations were modestly increased when it was given with once-weekly rifapentine in healthy volunteers.⁶² In a Phase 1/2 single-arm study of people with HIV treated with dolutegravir and 3HP, rifapentine decreased dolutegravir exposure by 26%. However, trough concentrations remained above the 90% maximum inhibitory concentration for all but one participant, and all participants maintained an undetectable viral load throughout the study period.⁶³ Based on these PK data and limited outcome data, 3HP is recommended in virally suppressed people receiving efavirenz, raltegravir, or once-daily dolutegravir without dose adjustment of rifapentine, isoniazid, or ART **(AII)**.⁶⁴ A trial is currently underway examining the use of 3HP in ART-naïve participants who are initiating therapy with a dolutegravir-based regimen.⁶⁵ 3HP has not been studied in patients receiving twice-daily dolutegravir and is therefore not recommended **(AIII)**.

3HR

- Daily isoniazid 300 mg PO daily plus rifampin 600 mg PO daily plus pyridoxine 25 mg to 50 mg PO daily for 3 months is also a preferred option for the treatment of LTBI in people with HIV **(AI)**.

In studies of adults and children without HIV who had a positive TST, those who received 3HR had a similar decreased risk of TB disease, hepatotoxicity, and adverse effects requiring treatment discontinuation compared with those who received ≥ 6 months of daily isoniazid.⁶⁶⁻⁷⁰ Among people with HIV, several studies found no difference in the incidence of TB disease between those who received 3HR and those who received ≥ 6 months of daily isoniazid, regardless of TST status;⁷¹⁻⁷⁴ hepatotoxicity was less frequent among those receiving 3HR, but treatment-limiting adverse effects were more common.⁵⁴ When using rifampin for LTBI treatment, either dose adjustment or substitution of many commonly used ARVs may be needed (see [Dosing Recommendations for Use of ARV and Anti-TB Drugs When Treating Latent TB table](#)).

Alternative Drugs for Treatment of Latent TB Infection

Isoniazid

- Isoniazid 300 mg PO daily plus pyridoxine 25 mg to 50 mg PO daily for 6 to 9 months is an alternative regimen for the treatment of LTBI, particularly when drug–drug interactions between rifamycins and ARV regimens limit the use of rifamycin-containing LTBI therapies **(AII)**.

Daily isoniazid for 6 to 9 months is effective and reasonably well-tolerated; severe toxicity is infrequent.^{23,74-78} However, treatment completion rates are suboptimal, decreasing its effectiveness.⁷⁹ Longer courses of isoniazid (e.g., 12 months) are more effective at preventing TB but carry a higher risk of toxicity^{80,81} and patients are more likely to complete shorter regimens.^{57,59,79,82-85} Peripheral neuropathy, hepatitis, and rash may be caused by either isoniazid or some ARV drugs. Isoniazid, when used, should be supplemented with pyridoxine at a dose of 25 to 50 mg per day to prevent peripheral neuropathy **(AIII)**.

4R

- Rifampin 600 mg PO daily for 4 months (4R) is an alternative regimen for the treatment of LTBI in people with HIV **(BI)**.

A large trial compared 4 months of daily rifampin (4R) to 9 months of daily isoniazid (9H) in more than 6,000 participants who were predominantly HIV-seronegative.⁷⁷ Although rates of incident active TB were low in both arms, the 4R regimen was non-inferior to 9H. Treatment completion rates were significantly higher and adverse events were less common in the 4R arm than in the 9H arm (78.8% vs. 63.2%; $P < 0.001$ and 1.5% vs. 2.6%; $P = 0.003$, respectively). However, only 255 participants were people with HIV, which limits the generalizability of the findings for this population. Although the National Tuberculosis Controllers Association (NTCA)/CDC guidelines recommend 4R as a preferred treatment for LTBI in people without HIV,⁵⁴ given the lack of trial data in people with HIV, the 4R regimen is recommended only as an alternative to 3HP, 3HR, and 6 or 9 months of isoniazid in people with HIV **(BI)**. When using rifampin for LTBI treatment, either dose adjustment or substitution of key ARVs may be needed. Given the theoretical but unproven risk of selecting for drug-resistant TB with rifamycin monotherapy in undiagnosed early-stage TB disease and the relatively poor performance of symptom screens alone in people with HIV on ART,^{86,87} some clinicians would obtain a specimen for *M. tuberculosis* testing before starting 4R for LTBI. Due to limited data on 4R in people with HIV, concerns about using this regimen in people with low CD4 cell counts, and an absence of data on the use of 4 months of rifabutin either in people with or without HIV, rifabutin monotherapy is not recommended **(AIII)**.⁸⁸⁻⁹⁰

1HP

- Isoniazid 300 mg PO daily plus rifapentine (weight-based dosing to a maximum of 600 mg) PO daily plus pyridoxine 25 mg to 50 mg PO daily for 4 weeks (1HP) is an alternative therapy for the treatment of LTBI in people with HIV treated with efavirenz **(BI)**.

The BRIEF-TB study (AIDS Clinical Trials Group [ACTG] 5279) evaluated 1 month of daily rifapentine plus isoniazid (1HP) versus 9 months of daily isoniazid (9H) in people with HIV residing in mostly high TB burden settings (TB incidence >60 per 100,000 population).⁸³ The median CD4 count of study participants was 470 cells/mm³, 50% of the study population was on efavirenz or nevirapine-based ART regimens at study entry, and 21% of the study population was TST positive. 1HP was non-inferior to 9H when comparing the composite outcome of confirmed or probable TB, death due to TB, and death due to unknown cause. Treatment completion rates (by self-report) were 97% in the 1HP arm and 90% in the 9H arm. Of note, although the population of people with HIV enrolled was at increased risk for LTBI due to high endemic exposure, the number of participants with documented LTBI based on TST or IGRA testing was low (23%), and the overall event rate (i.e., the number of participants who developed active TB in either arm) was also low (0.56/100 person-years) after more than 3 years of follow-up. Based on these data, 1HP is recommended as an alternative regimen for treatment of LTBI in people with HIV **(BI)**. The NTCA/CDC guidelines do not include 1HP as a preferred or alternative regimen given that the BRIEF-TB study was performed largely in people with HIV living in high TB burden settings, most of whom did not have positive tests for LTBI.⁵⁴ In light of the strengths of the study results and the convenience and safety of the regimen, some clinicians may choose to use 1HP for treatment of LTBI as an alternative option to those recommended in the current NTCA/CDC guidelines. If ART is administered together with 1HP, an efavirenz-based regimen should be used **(AI)**.^{60,91} A study evaluating co-administration of 1HP with dolutegravir is in progress; the use of dolutegravir-based ART should await results from this trial.⁹²

Dosing Recommendations for Use of ARV and Anti-TB Drugs When Treating Latent TB Infection

TB Drug	ARV Drugs	Dose of TB Drug
Isoniazid (INH)	<ul style="list-style-type: none"> All ARVs Note: for information on coadministration of ARVs with rifampin or rifapentine, see entries below 	Use INH with pyridoxine 25–50 mg PO daily (50 mg once weekly if used with 3HP) <i>For 3HP (weekly INH + rifapentine x 12 weeks)</i> <ul style="list-style-type: none"> 15 mg/kg PO once weekly (900 mg maximum) <i>For 3HR (daily INH + rifampin x 3 months), or 1HP (daily INH + rifapentine x 4 weeks), or INH alone (daily INH x 6–9 months)</i> <ul style="list-style-type: none"> 300 mg PO daily
Rifampin ^a	<ul style="list-style-type: none"> NRTIs (TAF with caution^b) EFV 600 mg DTG, RAL (twice daily), and MVC without a strong CYP3A4 inhibitor (note: doses of these ARV drugs need to be adjusted when used with rifampin) IBA, T-20 	<i>For 3HR (daily rifampin + INH x 3 months), or 4R (daily rifampin x 4 months)</i> <ul style="list-style-type: none"> 600 mg PO daily
	• All other ARVs	Not recommended
Rifapentine ^a 3HP	<ul style="list-style-type: none"> EFV 600 mg, RAL or once daily DTG NRTIs (TAF with caution^b) IBA, T-20 	<ul style="list-style-type: none"> Weighing 32.1–49.9 kg: 750 mg PO weekly Weighing ≥50.0 kg: 900 mg PO weekly
<i>Weekly rifapentine + INH x 12 weeks</i>	• All other ARVs	Not recommended
Rifapentine ^a 1HP	<ul style="list-style-type: none"> NRTIs (TAF with caution^b) EFV 600 mg IBA, T-20 	<ul style="list-style-type: none"> Weighing <35 kg: 300 mg PO daily Weighing 35–45 kg: 450 mg PO daily Weighing >45 kg: 600 mg PO daily
<i>Daily rifapentine + INH x 4 weeks</i>	• All other ARVs	Not Recommended

^a For additional drug—drug interaction information between antiretrovirals and anti-TB drugs, see [Drug-Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines](#).

^b If TAF and rifamycins are coadministered, monitor for HIV treatment efficacy. Note that FDA labeling recommends not to coadminister. See [Drug-Drug Interactions in the Treatment of HIV-Related TB](#) below and [Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections table](#) for more information.

Key: ARV = antiretroviral; BIC = bictegravir; DTG = dolutegravir; EFV = efavirenz; IBA = ibalizumab; IM = intramuscular; INH = isoniazid; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; PO = oral; RAL = raltegravir; RTV = ritonavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TB = tuberculosis

Treatment of LTBI Following Exposure to Drug-Resistant TB

For people exposed to drug-resistant TB, a regimen for LTBI should be selected after consultation with experts or with public health authorities (AIII).⁹³ A large randomized clinical trial of 26 weeks of either isoniazid or delamanid for people at high risk for TB, including people with HIV, following household exposure to drug-resistant TB is in progress.⁹⁴

Monitoring for Adverse Events Related to Treating Latent TB Infection

Individuals receiving TB-preventive therapy should be evaluated by a clinician monthly to assess adherence and evaluate for possible drug toxicity. Although people with HIV may not have a higher risk of hepatitis from isoniazid than people without HIV, people with HIV should have serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and total bilirubin levels measured before starting LTBI treatment and repeated if abnormal.⁵⁴ People with concomitant chronic viral hepatitis and older individuals have an increased risk of isoniazid-related hepatotoxicity, and such people should be monitored closely when being treated for LTBI.^{95,96}

Following initiation of isoniazid, ALT and AST levels often increase during the first 3 months of treatment but return to normal despite continued therapy. Hepatotoxicity also can occur with rifamycins, although it is less common than with isoniazid.^{78,83} Factors that increase the risk of drug-induced clinical hepatitis include daily alcohol consumption, underlying liver disease, pregnancy and early postpartum, and concurrent treatment with other hepatotoxic drugs.⁹⁷ At each visit, patients should be asked about adherence, new medications, and alcohol use and should be screened for potential adverse effects of treatment for LTBI (e.g., unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesia of the hands and feet, persistent fatigue, weakness or fever lasting 3 or more days, abdominal tenderness, easy bruising or bleeding, arthralgia) and told to stop medications immediately and return to the clinic for an assessment should any of these occur **(AIII)**.

If the serum ALT or AST levels increase to (1) greater than five times the upper limit of normal without symptoms or (2) greater than three times the upper limit of normal AND total bilirubin greater than two times the upper limit of normal without symptoms or (3) greater than three times the upper limit of normal with symptoms (or greater than two times the baseline value for patients with baseline abnormal transaminases), LTBI treatment should be stopped **(AIII)**.

The ultimate decision regarding resumption of therapy with the same or different agents for LTBI treatment should be made after weighing the risk for additional hepatic injury against the benefit of preventing progression to TB disease,⁹⁷ and ideally in consultation with an expert in treating LTBI in people with HIV. If a local expert is not available through the public health department, clinicians and TB programs can contact the CDC (tbinfo@cdc.gov) and utilize remote TB medical consultation services available through the CDC-funded [TB Center of Excellence](#) that serves their region.

Clinical Manifestations of TB Disease

Similar to people without HIV, people with HIV and TB disease may be asymptomatic but have positive sputum cultures with or without abnormal findings on chest radiograph (subclinical TB).^{98,99} In ambulatory people with HIV, the presence of any one of the classic symptoms of TB disease (i.e., cough, fever, night sweats, weight loss) has high sensitivity but low specificity for diagnosing TB as assessed in resource-limited settings.⁵¹ Compared to treatment-naïve patients with HIV, the sensitivity of classic TB symptoms is lower in people with HIV on ART.⁸⁶

The presentation of TB disease is influenced by the degree of immunodeficiency.¹⁰⁰⁻¹⁰² In people with HIV and CD4 counts >200 cells/mm³, HIV-related TB generally resembles TB among people without HIV. Most people with or without HIV have disease limited to the lungs, and common chest radiographic manifestations are upper lobe infiltrates with or without cavitation.¹⁰³

In people with HIV and CD4 counts <200 cells/mm³, the chest radiographic findings of pulmonary TB are markedly different, with infiltrates showing no predilection for the upper lobes, and cavitation uncommon.^{100,103,104} Normal chest radiographs can be seen in some people with respiratory symptoms and positive sputum cultures. Thoracic CT scans may demonstrate mild reticulonodular infiltrates despite a normal chest radiograph.¹⁰⁵

With increasing degrees of immunodeficiency, extrapulmonary (especially lymphadenitis, pleuritis, pericarditis, and meningitis) or disseminated TB are more common. In people with HIV who are markedly immune-suppressed, TB can be a severe systemic disease with high fevers, rapid progression, and features of sepsis.¹⁰⁶ Clinical manifestations of extrapulmonary TB in people with HIV are not substantially different from those described in people without HIV. TB must be considered in disease processes involving any site in the body,¹⁰⁷ especially in those with central nervous system (CNS) disease, when early TB treatment is essential to improve outcomes.¹⁰⁸⁻¹¹¹

After initiation of ART, immune reconstitution can unmask subclinical TB disease, resulting in pronounced inflammatory reactions at the sites of infection (see [Unmasking TB-IRIS](#) below).

Diagnosis

Initial diagnostic testing for TB disease should be directed at the anatomic site of symptoms or signs (e.g., lungs, lymph nodes, urine, cerebrospinal fluid).¹⁷ Pulmonary involvement is common at all CD4 counts.^{99,112} The initial evaluation of a person suspected of having HIV-related TB should always include chest imaging, even in the absence of pulmonary symptoms or signs. However, chest radiography is an imperfect screen for pulmonary TB, particularly among individuals with advanced immunodeficiency who can have TB culture-positive sputum despite normal chest radiographs.^{113,114} Therefore, sputum acid-fast bacilli (AFB) smear, nucleic acid amplification (NAA) testing, and AFB culture should be performed in people with HIV with symptoms of TB disease who have a normal chest radiograph, as well as in those with no pulmonary symptoms but evidence of TB disease elsewhere in the body.¹⁷

Sputum culture yield is not affected by HIV or the degree of immunodeficiency. Sputum smear-negative, culture-positive TB disease is common among people with HIV, particularly those with advanced immunodeficiency and non-cavitary disease.^{115,116} NAA tests have a higher sensitivity for culture-positive disease than smear.^{17,117} Smear and culture of three sputum specimens is recommended based on a large study in people with HIV that showed a 10% incremental yield for broth culture between the second and third specimens.¹¹⁸ Additionally, up-front NAA testing for *M. tuberculosis* can expedite diagnosis.¹⁷

Lymph node involvement is common in HIV-related TB, and the combined yield of histopathology, smear, and culture from needle aspirates of enlarged lymph nodes is quite high.^{119,120} While NAA testing on specimens other than sputum is an off-label use of the test, a positive NAA test result can be useful as evidence of extrapulmonary TB and for clinical decision-making.¹²¹ Histopathologic findings also are affected by the degree of immunodeficiency. People with relatively intact immune function have typical granulomatous inflammation associated with TB disease. With progressive immunodeficiency, granulomas become poorly formed or can be completely absent.^{101,122}

Pleural fluid, pericardial fluid, ascites, and cerebrospinal fluid should be sampled if there is clinical evidence of involvement. Polymerase chain reaction (PCR) testing to aid with molecular identification of *M. tuberculosis* on formalin-fixed tissue is available through reference laboratories

and, in special situations, through the CDC. Clinical providers and pathologists should contact their state or local health department for consultation with the CDC (tbinfo@cdc.gov) and the CDC-funded [TB Center of Excellence](#) for assistance with referring specimens for evaluation. The yield of mycobacterial urine and blood cultures depends on the clinical setting; among people with HIV and advanced immunodeficiency, the yield of culture from these two readily available body fluids can be relatively high^{101,107} and may allow definitive diagnosis and be the only source of an isolate for drug-susceptibility testing (DST).¹²³

Nucleic-Acid Amplification Testing

NAA tests provide rapid diagnosis of TB, and some assays also provide rapid detection of drug resistance. NAA assays, if positive, are highly predictive of TB disease when performed on Acid-Fast Bacillus (AFB) smear-positive specimens. However, because nontuberculous mycobacterial infections (NTM) may occur in people with HIV with advanced immunodeficiency, negative NAA results in the setting of smear-positive specimens may indicate NTM infection and can be used to direct further workup and guide decisions about the need for respiratory isolation.

NAA tests are more sensitive than AFB smears, being positive in 50% to 80% of smear-negative, culture-positive sputum specimens^{124,125} and up to 90% when three NAA tests are performed. Therefore, it is recommended that for all patients with suspected pulmonary TB, an NAA test be performed on at least one sputum specimen.^{17,126} NAA tests also can be used on extrapulmonary specimens with the caveat that the sensitivity is often lower than with sputum specimens.¹⁷ Importantly, a smear-negative specimen with a negative NAA test result does not rule out active TB disease.

The Xpert MTB/RIF assay is an automated NAA test that can detect both *M. tuberculosis* and mutations in the *rpoB* gene associated with rifampin resistance. It has been implemented widely in resource-limited settings with high TB prevalence and as a frontline TB diagnostic test in people with HIV.¹²⁷ This assay combines simple processing requirements in the laboratory and rapid turnaround (results within 2 hours). In a meta-analysis, the overall sensitivity and specificity of the Xpert MTB/RIF assay were 88% (95% confidence interval [CI], 83% to 92%) and 98% (95% CI, 97% to 99%), respectively. The assay is somewhat less sensitive among people with HIV overall,¹²⁸ however, this may be, in part, attributed to a higher prevalence of smear-negative disease in people with HIV.¹²⁹ In one key study from South Africa, the sensitivity of Xpert MTB/RIF a relationship with CD4 count was demonstrated, indicating higher sensitivity among people with HIV as the CD4 count declined below 500 cells/mm³.¹³⁰ Importantly, patients in this study with the lowest CD4 count (<100 cells/mm³) actually had higher rates of smear-positivity and higher markers of severe TB disease (C-reactive protein, anemia, and WHO symptom screen).

Xpert MTB/RIF sensitivity in extrapulmonary specimens is up to 95% in smear-positive specimens and 69% in smear-negative specimens.¹³¹ Median sensitivity varied by specimen type, with higher yield from lymph nodes (96%), cerebrospinal fluid (85%), and gastric aspirates (78%) and lower yield from pleural fluid (34%) and other non-pleural serous fluids (67%). Xpert MTB/RIF also has been applied with excellent diagnostic accuracy to stool specimens in people with pulmonary TB,¹³² which may provide an alternative for people with HIV who are being evaluated for TB and unable to expectorate.

The next-generation Xpert MTB/RIF Ultra improved the sensitivity of the existing test platform, but it is not currently approved by the U.S. Food and Drug Administration (FDA) or available in the

United States. Similarly, the Xpert MTB/XDR cartridge incorporates other drug-resistance targets that may be relevant for constructing a treatment regimen for drug-resistant TB, particularly in settings without access to conventional growth-based or sequencing-based DST, but is also not currently approved by the U.S. FDA and is unavailable in the United States (see [Drug-Resistance Testing](#), below).¹³³

Lipoarabinomannan (LAM)

LAM is an *M. tuberculosis* cell wall polysaccharide that can be detected in the urine of people with TB.¹³⁴⁻¹³⁷ LAM has been shown to be more sensitive and specific as an adjunct diagnostic test in people with HIV with advanced immunosuppression. The Alere Determine TB LAM is a lateral flow strip applied to a urine sample and recommended by the WHO as an additional diagnostic test for TB among people with HIV.¹³⁸ Newer generation LAM assays have increased sensitivity and may be particularly useful in paucibacillary clinical specimens such as cerebrospinal fluid. In a study of 101 patients with suspected TB meningitis, 95 of whom were people with HIV, the SILVAMP TB LAM (Fujifilm) sensitivity from cerebrospinal fluid was 52% for definite or probable TB meningitis (with specificity of 98%), which compared favorably to the sensitivity of 55% for Xpert Ultra. LAM assays are not commercially available in the United States at this time.¹³⁹

Drug-Resistance Testing

Evaluation for TB drug resistance should be considered in all people with HIV, especially those who meet any of the following criteria:

- Known exposure to a person with drug-resistant TB,
- Residence in a setting with high rates of primary drug-resistant TB,
- Persistently positive smear or culture results at or after 4 months of treatment, *or*
- Previous TB treatment, particularly if it was not directly observed or was interrupted for any reason.

Rapid molecular DST for rifampin (and isoniazid, if available) should be performed on the initial isolates from all patients suspected of having TB, because resistance to rifampin is associated with an increased risk of treatment failure, recurrent TB, and amplification of resistance to additional TB medications.^{140,141}

The presence of multidrug-resistant TB (MDR TB; defined as resistance to at least isoniazid and rifampin) or extensively drug-resistant TB (XDR TB; defined as MDR TB with additional resistance to a fluoroquinolone and either bedaquiline or linezolid) is associated with a markedly increased risk of death.¹⁴²⁻¹⁴⁴ Therefore, early identification of drug resistance, with appropriate adjustment of the treatment regimen based on both full molecular and conventional DST results, is critical to the successful treatment of TB disease and to curbing transmission of drug-resistant *M. tuberculosis*.¹⁷

For all patients with TB disease, phenotypic DST to first-line TB drugs (isoniazid, rifampin, ethambutol, and pyrazinamide) should be performed, regardless of the source of the specimen. Given the alternative of a shorter drug-susceptible TB regimen containing moxifloxacin (see [Treating TB Disease](#)), public health laboratories in the U.S. may add routine moxifloxacin susceptibility testing as well. Molecular resistance testing should be performed, and resistance testing should be repeated if

sputum cultures remain positive for *M. tuberculosis* at or after 4 months of treatment or become positive again 1 month or longer after culture conversion to negative. Resistance testing for second-line TB medications (including bedaquiline, linezolid, clofazimine, pretomanid, cycloserine, ethionamide, and others) should be limited to specimens with resistance to first-line TB medications and should be performed in reference laboratories with substantial experience in these techniques.¹²⁶

Conventional Growth-Based Drug-Susceptibility Testing

Conventional DST is used widely and has been validated for first-line drugs. The disadvantage of this technique, however, is that the combined turnaround time of a conventional broth or agar-based culture followed by DST may be as long as 8 weeks,¹⁴⁵ due to the slow growth of *M. tuberculosis*. During this time, people with drug-resistant TB may be receiving ineffective, empiric first-line TB therapy, which could allow ongoing transmission, further clinical deterioration, acquisition of additional drug resistance, and death, particularly in individuals with HIV.¹⁴⁴ Yet, for many second-line drugs used to treat MDR and XDR TB, conventional DST remains either the gold standard or the only available technique because molecular correlates of phenotypic drug resistance are incomplete.

Molecular Tests for Drug Resistance

Genotypic testing to identify mutations that confer drug resistance allows rapid detection of resistance. The relationship between these mutations and drug resistance has been studied for a number of TB medications.^{146,147} Commercial NAA tests—such as Xpert MTB/RIF—identify resistance mutations associated with rifampin, and commercially available line probe assays (LPAs) identify genotypic resistance to other drugs.^{129,148} All probe-based assays, including Xpert MTB/RIF and LPAs, should be confirmed with sequence-based tests and growth-based DST. For initial evaluation of drug resistance or confirmation of drug resistance identified by the aforementioned assays, the CDC Division of Tuberculosis Elimination has a [Molecular Detection of Drug Resistance \(MDDR\) service](#) that offers rapid sequencing-based testing for first-and second-line TB medications at no charge for providers evaluating people for drug-resistant TB. State TB programs and state laboratories also should be consulted for resistance testing options. Several assays can be performed on cultured isolates or directly on sputum specimens. Molecular resistance testing also can be performed on extrapulmonary specimens that are NAA-positive; if unable to be performed by local or state public health laboratories, this testing can be arranged through the CDC's Division of TB Elimination Laboratory (TBLab@cdc.gov).

In low TB prevalence settings—such as the United States—the positive predictive value for NAA tests of rifampin resistance is low.¹⁴⁹ False-positive rifampin resistance on Xpert MTB/RIF is associated with lower sputum bacillary burden (i.e., high cycle thresholds on Xpert).¹⁵⁰ Therefore, isolates with an initial reading of rifampin resistance by commercial NAA test should always undergo confirmatory testing (*rpoB* gene sequencing and phenotypic DST), with results taken into consideration for treatment decisions. Clinicians who suspect drug-resistant TB in a patient with HIV should make every effort to expedite a diagnosis and consult with their state TB program and then the CDC as needed.

Treating TB Disease

Treating Active TB Disease in People with HIV
<ul style="list-style-type: none"> • After collecting a specimen for culture and molecular diagnostic tests, empiric treatment should be initiated in people with HIV with clinical and radiographic presentation suggestive of HIV-related TB (AIII). • DOT is recommended for all patients requiring treatment for HIV-related TB (AII). • Please refer to the Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB (below) for specific TB drug dosing recommendations and the Tuberculosis/HIV Coinfection section of the Adult and Adolescent Antiretroviral Guidelines for dosing recommendations of ARV drugs when used with rifampin or rifabutin. • Recommendations for monitoring during TB treatment and when to start ART in the context of TB treatment are described in the text.
For Drug-Susceptible TB
<p>Preferred Therapy</p> <p><i>Intensive Phase (8 weeks)</i></p> <ul style="list-style-type: none"> • Isoniazid plus (rifampin or rifabutin) plus pyrazinamide plus ethambutol plus pyridoxine 25–50 mg PO daily (AI) • If molecular or phenotypic drug susceptibility reports show sensitivity to isoniazid and rifampin, then ethambutol may be discontinued before the end of 8 weeks (AI). <p><i>Continuation Phase (for Drug-Susceptible TB)</i></p> <ul style="list-style-type: none"> • Isoniazid plus (rifampin or rifabutin) plus pyridoxine 25–50 mg PO daily (AII) <p><i>Total Duration of Therapy</i></p> <ul style="list-style-type: none"> • Pulmonary, drug-susceptible, uncomplicated TB: 6 months (BII) • Pulmonary TB and positive culture at 8 weeks of TB treatment, severe cavitary disease or disseminated extrapulmonary TB: 9 months (BII) • Extrapulmonary TB with TB meningitis: 9–12 months (BII) • Extrapulmonary TB in other sites: 6 months (BII) <p>Alternative Therapy (only for patients receiving an efavirenz-based ARV regimen; not recommended for extrapulmonary TB)</p> <p><i>Intensive Phase (8 weeks)</i></p> <ul style="list-style-type: none"> • Isoniazid plus rifapentine 1,200 mg plus moxifloxacin 400 mg plus pyrazinamide plus pyridoxine 25–50 mg PO daily (AI).^a <p><i>Continuation Phase (9 weeks)</i></p> <ul style="list-style-type: none"> • Isoniazid plus rifapentine 1,200 mg plus moxifloxacin 400 mg plus pyridoxine 25–50 mg PO daily (AI).
For Drug-Resistant TB
<p>Empiric Therapy for Suspected Resistance to Rifamycin With or Without Resistance to Other Drugs</p> <ul style="list-style-type: none"> • Isoniazid^b plus pyrazinamide plus ethambutol plus (moxifloxacin or levofloxacin) plus (linezolid or amikacin^c) (BII) <p>Resistant to Isoniazid</p> <ul style="list-style-type: none"> • (Moxifloxacin or levofloxacin) plus (rifampin or rifabutin) plus ethambutol plus pyrazinamide for 6 months (BII)

Resistant to Rifamycins With or Without Other Antimycobacterial Agents

Preferred Therapy

- For 14 days: pretomanid 200 mg plus linezolid 600 mg plus moxifloxacin 400 mg plus bedaquiline 400 PO daily, *followed by*
- For 24 weeks: pretomanid 200 mg plus linezolid 600 mg plus moxifloxacin 400 mg daily, *and* bedaquiline 200 mg PO three times per week
- Note: Omit moxifloxacin if resistant to fluoroquinolones (AI).

Alternative Therapy

- An individualized regimen including based on drug susceptibility test results and clinical and microbiological responses, to include ≥ 5 active drugs, and with close consultation with experienced specialists (BIII).

Duration

- 6–24 months (see [Managing Drug-Resistant TB section](#) below for discussion of treatment duration)

Treatment of TB During Pregnancy

- TB therapy should not be withheld because of pregnancy (AIII).
- Treatment of TB disease during pregnancy should be the same as for any other patient with HIV, but with attention to the following considerations (AIII):
 - Monthly monitoring of liver transaminases during pregnancy and the postpartum period is recommended (BIII).
 - If pyrazinamide is not included in the initial treatment regimen, the minimum duration of TB therapy with isoniazid, rifampin, and ethambutol should be 9 months for drug-susceptible TB (AII). The decision regarding whether to include pyrazinamide in treatment regimens during a pregnancy should be made after consultation among obstetricians, TB specialists, and the patient, while considering gestational age and likely susceptibility pattern of the TB strain.
 - Fluoroquinolones are typically not recommended during pregnancy because arthropathy has been noted in immature animals exposed to fluoroquinolones *in utero* (CIII). Fluoroquinolones can, however, be used in pregnancy for drug-resistant TB if they are required on the basis of susceptibility testing (BII).
 - Based on data derived from studies of streptomycin and kanamycin, and the theoretical risk of ototoxicity with *in utero* exposure to amikacin, aminoglycosides should be avoided during pregnancy, if possible (AIII).

TB-Associated IRIS

Preventing Paradoxical TB-IRIS

- In high-risk patients (i.e., starting ART within 30 days after TB treatment initiation and a CD4 count $\leq 100/\text{mm}^3$) who are responding well to TB therapy and who do not have rifampin resistance, Kaposi sarcoma, or active hepatitis B (BI): prednisone 40 mg/day for 2 weeks, then 20 mg/day for 2 weeks

Managing Paradoxical TB-IRIS

- Paradoxical reaction/IRIS that is not severe may be treated symptomatically (CIII).
- For moderately severe paradoxical TB-IRIS, use of prednisone is recommended (AI).
- In patients on a rifampin-based regimen: prednisone 1.5 mg/kg/day for 2 weeks, then 0.75 mg/kg/day for 2 weeks
- In patients on a rifabutin plus boosted PI-based regimen: prednisone 1.0 mg/kg/day for 2 weeks, then 0.5 mg/kg/day for 2 weeks
- Taper over 4 weeks (or longer) based on clinical symptoms; a more gradual tapering schedule over 2 to 3 months is recommended for patients whose signs and symptoms have not improved or have worsened due to tapering (BIII).

Other Considerations in TB Management

- Adjunctive corticosteroid is recommended for patients with HIV-related TB involving the CNS (AII).
- Dexamethasone has been used for CNS disease with the following dosing schedule: 0.3–0.4 mg/kg/day for 2–4 weeks, then taper by 0.1 mg/kg per week until 0.1 mg/kg, then 4 mg per day and taper by 1 mg/week; total duration of 12 weeks^d
- Despite the potential of drug–drug interactions, rifamycins remain the most potent TB drug and should remain as part of the TB regimen, unless a rifamycin-resistant isolate is detected or the patient has a severe adverse effect that is likely due to the rifamycin (please refer to the [Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB](#) below and the [Tuberculosis/HIV Coinfection section of the Adult and Adolescent Antiretroviral Guidelines](#) for dosing recommendations involving concomitant use of rifampin or rifabutin and different ARV drugs).
- Intermittent rifamycin use can result in the development of resistance in patients with HIV and is not recommended (AI).

^a This regimen was not studied and is not recommended for people who are pregnant, breastfeeding, <40kg, or who have most types of extrapulmonary TB (other than pleural TB or lymphadenitis).

^b Many patients with rifampin resistance also have resistance to isoniazid. Susceptibility should be confirmed in any patient with rifampin resistance to determine if isoniazid can be included in the treatment regimen.

^c Given the risk of ototoxicity and nephrotoxicity with aminoglycosides, use of amikacin should generally be restricted to bridging regimens, while awaiting availability of less toxic medications and/or results of drug-susceptibility testing.

^d At doses above 16 mg, dexamethasone is a CYP3A4 inducer and can decrease certain ARVs that are substrates of CYP3A4 (e.g., DOR, RPV, and protease inhibitors). Consultation with a pharmacist is recommended.

Key: ARV = antiretroviral; CNS = central nervous system; DOT = directly observed therapy; IRIS = immune reconstitution inflammatory syndrome; LTBI = latent tuberculosis infection; PI = protease inhibitor; PO = orally

TB among people with advanced immunodeficiency can be a rapidly progressive and fatal illness if treatment is delayed. Therefore, after collection of available specimens for culture and molecular diagnostic tests, empiric treatment for TB is recommended in patients with clinical and radiographic findings suggestive of HIV-related TB (**AIII**).

Treatment of TB for people with HIV is the same as for individuals without HIV¹⁵¹ although the current standard of care continues to evolve as new data emerge from clinical trials. Recommended dosing of drugs for treating active TB disease is summarized in the following table.

Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB

TB Drug	ARV Drugs	Daily Dose of TB Drug
Isoniazid	• All ARVs	5 mg/kg (usual dose 300 mg) Use INH with pyridoxine 25–50 mg PO daily
Rifampin ^{a,b}	<ul style="list-style-type: none"> • NRTIs (use TAF with caution^c) • EFV 600 mg • DTG, RAL (twice daily), MVC without a strong CYP3A4 inhibitor (note: doses of these ARVs need to be adjusted when used with rifampin) • IBA, T-20 	10 mg/kg (usual dose 600 mg)
	<ul style="list-style-type: none"> • DOR, ETR, EFV 400 mg, NVP, RPV (PO) • BIC, EVG/c, RAL (daily) • CAB/RPV (IM/PO) • HIV PIs 	Not recommended

TB Drug	ARV Drugs	Daily Dose of TB Drug
	<ul style="list-style-type: none"> • LEN (SC/PO), FTR, MVC with a strong CYP3A4 inhibitor 	
Rifabutin ^a	<ul style="list-style-type: none"> • NRTIs (use TAF with caution^c) • ETR without boosted PIs • DOR and RPV (PO) (note: doses need to be adjusted when used with rifabutin) • DTG, RAL • MVC without a strong CYP3A4 inhibitor • IBA, T-20, FTR 	5 mg/kg (usual dose 300 mg)
	<ul style="list-style-type: none"> • PIs with RTV • MVC with a strong CYP3A4 inhibitor 	150 mg daily ^e
	<ul style="list-style-type: none"> • EFV 	450–600 mg
	<ul style="list-style-type: none"> • ETR with boosted PIs • BIC, EVG/c • CAB/RPV (IM/PO) • PIs with COBI • LEN (SC/PO) 	Not recommended
Rifapentine	<ul style="list-style-type: none"> • EFV • NRTIs (use TAF with caution^c) 	1,200 mg/day for people weighing ≥40 kg
	<ul style="list-style-type: none"> • All other ARVs 	Not recommended
Pyrazinamide	<ul style="list-style-type: none"> • All ARVs 	Weight-based dosing <ul style="list-style-type: none"> • 40–55 kg: 1,000 mg • 56–75 kg: 1,500 mg • 76–90 kg: 2,000 mg • >90 kg: 2,000 mg^f
Ethambutol	<ul style="list-style-type: none"> • All ARVs 	Weight-based dosing <ul style="list-style-type: none"> • 40–55 kg: 800 mg • 56–75 kg: 1,200 mg • 76–90 kg: 1,600 mg • >90 kg: 1,600 mg^f
Moxifloxacin	<ul style="list-style-type: none"> • All ARVs 	<ul style="list-style-type: none"> • 400 mg daily for those weighing ≥40 kg

^a For more detailed guidelines on use of different ARV drugs with rifamycin, clinicians should refer to the [Drug–Drug Interactions section of the Adult and Adolescent Antiretroviral Guidelines](#).

^b Higher doses may be needed in the treatment of TB meningitis. Expert consultation is advised.

^c If TAF and rifamycins are coadministered, monitor for HIV treatment efficacy. Note that FDA labeling recommends not to coadminister. See text below and [Table 4](#) for more information.

^e Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150 mg three times per week dosing together with RTV-boosted PIs. May consider therapeutic drug monitoring (TDM) when rifabutin is used with an RTV-boosted PI and adjust dose accordingly.

^f Monitor for therapeutic response and consider TDM to assure dosage adequacy in patients weighing >90 kg.

Note: For drug-drug interaction information between antiretrovirals and anti-TB drugs for treatment of drug-resistant TB, see the [Adult and Adolescent Antiretroviral Guidelines](#).

Key: ARV = antiretroviral; BIC = bictegravir; BID = twice a day; CAB = cabotegravir; COBI = cobicistat; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FTR = fostemsavir; IBA = ibalizumab; IM = intramuscular; INH = isoniazid; LEN = lenacapavir; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PO = oral; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SC = subcutaneous; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TB = tuberculosis; TDM = Therapeutic Drug Monitoring

The preferred regimen for drug-susceptible TB includes a 2-month (8-week) intensive phase of isoniazid, rifampin, ethambutol, and pyrazinamide **(AI)**. Ethambutol can be discontinued when susceptibility to isoniazid and rifampin has been confirmed. Thereafter, isoniazid and a rifamycin are used in the continuation phase of therapy, generally recommended as an additional 4 months (18 weeks) of treatment for uncomplicated TB **(AI)**.¹⁵¹ Extension of therapy to 9 months is recommended for patients who have a positive sputum culture after 2 months of treatment or severe cavitory or disseminated extrapulmonary disease **(BII)**.

A recently completed large, randomized clinical trial that enrolled 2,516 participants at 34 clinical sites in 13 countries established that a 4-month regimen of 2 months (8 weeks) of rifapentine, moxifloxacin, isoniazid, and pyrazinamide followed by 2 months (9 weeks) of rifapentine, moxifloxacin, and isoniazid was as effective as the standard 6-month regimen of isoniazid, rifampin, ethambutol, and pyrazinamide for two months followed by isoniazid and rifampin for an additional four months.¹⁵² In this study, the four-month regimen was non-inferior to the control regimen in both the microbiologically eligible and the assessable populations, with unfavorable outcome rates of 15.5% vs. 14.6% (95% CI, -2.6 to 4.5) and 11.6% vs. 9.6% (95% CI, -1.1 to 5.1) respectively. Additionally, the four-month regimen had slightly lower rates of grade 3 or higher adverse events than the control arm. While participants with HIV were included in the trial, the only antiretroviral therapy regimen allowed during the study was efavirenz-containing.¹⁵³ This four-month regimen is now recommended as an alternative option for people with and without HIV who are 12 years of age or older **(AI)**. It is not recommended for children under 12 years of age, pregnant women, people with extrapulmonary TB, or people with HIV who are taking a non-efavirenz-based antiretroviral regimen **(AI)**.¹⁵⁴ The trial also evaluated a four-month regimen with the same high dose of rifapentine but without moxifloxacin, which was found to be inferior to the control arm.

If rapid DST results indicate resistance to rifampin, with or without resistance to other drugs, an initial MDR TB regimen, as indicated below, should be used **(BIII)** and adjusted as molecular sequencing and conventional DST results become available.

Directly Observed Therapy (DOT)

DOT monitored by trained health care workers, who can be community-based or clinic-based, is recommended for all people with HIV-related TB **(AII)**. Digital technology—such as video-DOT and pill sensors—may be useful alternatives to clinic-based or health care worker-based DOT.¹⁵⁵⁻¹⁶⁰ The likelihood of treatment success is further enhanced with comprehensive case management; assistance with housing and other social support; and, if needed, assistance to help people establish or re-engage with HIV care.¹⁵¹

Dosing and Duration of Therapy

Although intermittent dosing (administration less often than daily) facilitates DOT, regimens that included twice- or thrice-weekly dosing during the intensive or continuation phase have been

associated with an increased risk of treatment failure or relapse with acquired drug resistance to the rifamycin class, particularly in people with HIV.¹⁶¹⁻¹⁶⁹ Intermittent rifamycin use can result in the development of resistance in patients with HIV and is not recommended **(AI)**. Therefore, daily therapy is recommended during both the intensive and continuation treatment phases **(AII)**.^{151,167,168,170}

Earlier recommendations¹⁷¹ for TB treatment in people without HIV indicated that therapy should be based on the number of doses received rather than the duration of therapy. However, no data substantiate the minimum number of doses needed within a specified time interval in people with HIV.¹⁵¹ Every effort should be made to ensure that people with HIV receive daily therapy as previously described.

The optimal duration of TB treatment for people with HIV and drug-susceptible TB disease has not been fully established. In general, the outcomes of 6-month regimens given as DOT to people with HIV have been favorable.^{2,151} A 1998 randomized but underpowered trial in the United States showed excellent and comparable outcomes of TB therapy among people with HIV assigned to 6 months or 9 months of therapy.¹⁷²

Two trials in high-burden settings showed a higher risk of recurrent TB among people treated with 6 months of therapy than among those assigned to 9-month¹⁶¹ or 12-month regimens.¹⁷³ However, the applicability of these two trials to low-burden settings—such as the United States—and in the context of universal ART is uncertain. In people with HIV receiving an efavirenz-based ART regimen, the 4-month alternative regimen of rifapentine, moxifloxacin, isoniazid, and pyrazinamide previously described was not associated with a higher rate of recurrent TB compared to the standard of care arm after follow-up out to at least 18 months post-TB treatment initiation.^{152,154} Whether outcomes with this 4-month regimen will be similar to standard 6-month anti-TB therapy in people with HIV treated with non-efavirenz-based ART is not known. Additional TB treatment shortening trials using alternative strategies in participants with HIV and TB coinfection are ongoing.

Treatment of TB Meningitis

With regard to the treatment of tuberculous meningitis, data regarding optimal drugs and doses to use are sparse. Many experts suggest that TB meningitis should be treated for an extended period of 9 to 12 months, but there is no evidence to support this recommended treatment duration.¹⁷⁴ Recent clinical trials have suggested that the use of higher rifampin doses (up to 30–35 mg/kg/day) or the addition of fluoroquinolones or linezolid to initial treatment for TB meningitis may be beneficial, but the data are limited, particularly in people with HIV, and are insufficient to support a clear recommendation at this time.¹⁷⁵⁻¹⁸³ Adjunctive corticosteroid therapy is recommended for all individuals who have TB involving the CNS **(AII)** including those with HIV, as indicated below.

Adjunctive Corticosteroid Use in TB Treatment

Several clinical trials have demonstrated that adjunctive corticosteroid therapy increases survival overall for people with TB meningitis, improves treatment effectiveness, and reduces adverse event rates. These trials, however, either excluded people with HIV or were underpowered for detecting statistically significant outcome benefits in that group.^{111,184,185} A recent clinical trial compared adjunctive corticosteroids to placebo in people with HIV—the majority of whom had advanced HIV (52% of participants had a CD4 $\leq$ 50 cells/mm³)—and failed to find a statistically significant benefit (HR for death 0.85 [95% CI, 0.66–1.10]).¹⁸⁶ The trial was powered to detect a 31% improvement in

survival and it is possible that corticosteroids have a more modest effect. Importantly, the study found no evidence of harm with corticosteroids and, given the high morbidity and mortality associated with TB meningitis, adjunctive corticosteroids are still recommended in people with HIV and TB meningitis. Dexamethasone should be administered in a dose of 0.3 mg/kg/day to 0.4 mg/kg/day for 2 to 4 weeks, then tapered by 0.1 mg/kg per week until a dose of 0.1 mg/kg is reached, then 4 mg per day and tapered by 1 mg/week) for a total duration of 12 weeks **(BII)**.^{111,151}

TB involving the CNS is currently the only organ system manifestation for which corticosteroids are recommended.¹⁵¹ Adjunctive corticosteroid therapy is **not recommended** in the treatment of TB pericarditis **(AI)**. In a randomized trial that compared adjunctive prednisolone with placebo—each administered for 6 weeks in individuals with tuberculous pericarditis, with and without HIV—prednisolone was not associated with a significant reduction in the composite endpoint of death, cardiac tamponade, or constrictive pericarditis. Those receiving prednisolone also had a higher incidence of some cancers.¹⁸⁷ A Cochrane review similarly found no mortality benefit from adjunctive corticosteroids and a nonsignificant reduction in constrictive pericarditis. Notably, however, <20% of people with HIV in the trials analyzed were receiving ART.¹⁸⁸ No trials have been conducted comparing different doses and treatment durations of adjunctive corticosteroids.

Special Considerations Regarding ART Initiation

The preponderance of data from several large randomized trials in people with HIV and TB, as well as subsequent systematic reviews and meta-analyses, supports the recommendation that ART should not be withheld until completion of TB treatment **(AI)**.^{108,189-196} ART is recommended for all people with HIV and TB **(AI)**. For ART-naïve patients, ART should be started within 2 weeks after TB treatment initiation in those with CD4 count <50 cells/mm³ when TB meningitis is not suspected **(AI)**. For ART-naïve patients with higher CD4 cell counts, ART should be started within 2-8 weeks of starting anti-TB treatment when TB meningitis is not suspected **(AI)**. For ART-naïve patients with TB meningitis, ART should be started once the TB meningitis is under control—with either clinical improvement or improvement in CSF parameters—after at least 2 weeks of anti-TB treatment, to reduce the risk of immune reconstitution causing life-threatening inflammation in a closed space **(AIII)**. Rifamycin-associated drug interactions should be considered when selecting the ARV drug regimen. Preemptive prednisone therapy should be offered to patients starting ART within 30 days after TB treatment initiation, have a CD4 count ≤100/mm³, are responding well to TB therapy and who do not have rifampin resistance, Kaposi sarcoma, or active hepatitis B **(BI)** (see [TB-Associated IRIS](#) below for details).¹⁹⁷

American Thoracic Society (ATS)/CDC/Infectious Diseases Society of America (IDSA) guidelines recommend that people with TB meningitis should not start ART before 8 weeks of TB treatment is completed, regardless of CD4 count, based primarily on a randomized trial in 253 people with HIV and TB meningitis conducted in Vietnam. This trial compared immediate ART within 7 days of starting TB treatment with delayed ART started two months after starting TB treatment.^{151,193} The study showed no difference in mortality or TB outcomes, but those receiving immediate ART had a higher rate of severe adverse events. It is unclear whether the study's findings are generalizable to higher-resourced settings with access to frequent monitoring and adjustment of dosing. We recommend that for ART-naïve people with HIV and TB meningitis, ART should be started once the TB meningitis is under control, after at least 2 weeks of anti-TB treatment **(AIII)**. The greatest risk of early ART is the occurrence of intracerebral TB-IRIS after starting ART, which has been reported in up to 50% of people with HIV and TB meningitis and may increase morbidity and mortality¹⁹⁸ (although mortality was similar in both early and delayed ART arms in the only randomized trial

completed to date).¹⁹³ However, adjunctive corticosteroid therapy is recommended for all people with HIV and TB meningitis **(AII)** and precludes the need for pre-emptive use of prednisone to prevent IRIS. Whether the corticosteroid regimen recommended as adjunctive therapy for TB meningitis also further reduces the risk of TB IRIS and its consequences has not been evaluated.

In summary, early ART initiation requires close collaboration between HIV and TB care clinics, expertise in the management of ARV regimen selection, close monitoring, potential adjunctive corticosteroid therapy, and support and adherence services. The prevention and management of IRIS are discussed in detail below (see [TB-Associated IRIS](#), below).

When TB occurs in people already on ART, treatment for TB must be started immediately **(AIII)**, and ART should be modified to reduce the risk of drug interactions and to maintain virologic suppression. When TB occurs in the setting of virologic failure, ART drug-resistance testing should be performed, and intensified adherence counseling should be provided. A new ARV regimen may be required to achieve virologic suppression and minimize drug interactions with the anti-TB regimen.

Drug–Drug Interactions in the Treatment of HIV-Related TB

Dolutegravir in combination with two nucleoside(tide) reverse transcriptase inhibitors, including tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), abacavir, emtricitabine, or lamivudine, is the preferred regimen for co-treatment of HIV in most ART-naïve people with TB **(AI)**. This regimen can be managed with rifamycin-based anti-TB treatment (see [Integrase Inhibitor section](#) below for recommendations about dolutegravir dose adjustment if coadministered with rifampin). The following text summarizes the most important drug-drug interactions for antiretroviral drugs and anti-TB drugs to guide choices if other ART regimens are considered.

The rifamycin class of antibiotics is the cornerstone of effective and shorter-course first-line treatments for drug-sensitive TB. The currently available rifamycins (rifampin, rifabutin, and rifapentine) have clinically significant interactions with several ARV drugs. Most of these result from the rifamycin's potent induction of genes involved in the metabolism and transport of ARV agents, and these interactions should be taken into consideration before initiating therapy (see [Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB](#) above, and the [Tuberculosis/HIV Coinfection section of the Adult and Adolescent Antiretroviral Guidelines](#)). Every effort should be made to include a rifamycin in the TB treatment regimen. Rifamycins remain the most potent drug class for TB treatment. Older regimens that included only 2 months of rifampin were associated with increased risks of treatment failure and TB recurrence among people with HIV-related TB.^{199,200} If a rifamycin cannot be used, TB treatment duration must be extended, and treatment complexity increases substantially. Thus, individuals with rifamycin-susceptible *M. tuberculosis* isolates should be treated with a regimen that includes a rifamycin unless a serious adverse event is highly likely due to a rifamycin **(AIII)**.

No clinical trial has specifically compared rifampin- and rifabutin-containing anti-TB regimens among people with HIV and TB taking ART. Rifabutin is generally regarded as a reasonable substitute for rifampin for the treatment of active TB disease in people with HIV who concurrently receive ARVs that have adverse drug interactions with rifamycins, because rifabutin is a less potent inducer of CYP3A4 than rifampin.²⁰¹ Although clinical trial data among people with HIV are limited to one small study, observational data among people with HIV, and several trials among people without HIV have found similar outcomes between those treated with rifampin or rifabutin.²⁰²⁻²⁰⁵

Nucleoside Reverse Transcriptase Inhibitor Backbone

Nucleoside(tide) backbone drugs—including tenofovir disoproxil fumarate (TDF), abacavir, emtricitabine, and lamivudine—can be given together with rifampin-containing TB treatment without dose adjustment. Tenofovir alafenamide (TAF), a substrate of drug transporters including P-glycoprotein, may be more likely to have drug–drug interactions than TDF. A study conducted among healthy volunteers without HIV showed that concentrations of intracellular tenofovir-diphosphate (TFV-DP) were higher with TAF/emtricitabine given with rifampin than with TDF given alone, suggesting that TAF may be given together with rifampin-containing TB treatment without dose adjustment.²⁰⁶ Neither TDF nor TAF has been fully evaluated with rifabutin. In one small study, though, HIV virologic suppression was sustained during TAF-rifabutin co-administration.²⁰⁷ In one study of TAF (as part of Biktarvy™) taken with daily high-dose rifapentine and isoniazid (1HP) for the treatment of LTBI, plasma tenofovir concentration was similar when TAF was taken alone versus together with 1HP, suggesting that TAF can be taken with rifapentine for short periods of time for prevention of TB.²⁰⁸

Non-Nucleoside Reverse Transcriptase Inhibitors—Efavirenz, Nevirapine, Etravirine, Doravirine, and Rilpivirine

One alternative co-treatment regimen for HIV-related TB disease is rifampin-based TB therapy with an ARV regimen of efavirenz (600 mg daily) plus two nucleoside(tide) analogues (**AII**). Studies in people with HIV and TB (including patients with higher body weight) have not shown a significant effect of rifampin-containing TB treatment on efavirenz plasma concentrations when used at the standard 600 mg per day dose in the majority of patients.^{209–211} Given the preponderance of data and the excellent treatment outcomes of co-treatment with standard-dose efavirenz,^{212,213} the 600 mg daily dose of efavirenz is recommended (**AII**). A small study among people with HIV found similar efavirenz concentrations when the 400 mg dose was taken with isoniazid and rifampicin versus when it was taken alone,²¹⁴ suggesting that, while not recommended, rifampicin-based TB treatment could be given with efavirenz without a need for efavirenz dose adjustment. Pharmacokinetic studies also support the use of the 600mg efavirenz dose with the new 4-month rifapentine-moxifloxacin-isoniazid-pyrazinamide regimen.²¹⁵

Nevirapine is **not recommended** for HIV and TB co-treatment (**AII**).²¹⁶ The use of rifampin or rifapentine with doravirine, etravirine, or rilpivirine **is not recommended (AIII)** (see [Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB](#), above, and the [Tuberculosis/HIV Coinfection section of the Adult and Adolescent Antiretroviral Guidelines](#)).

Some experts might consider substitution of rifabutin for rifampin with an appropriate dose adjustment of rifabutin (e.g., increasing to 450–600 mg daily when given with efavirenz) or of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) (e.g., increasing doravirine dosing to 100 mg twice daily and increasing oral rilpivirine to 50 mg daily), where appropriate,^{217,218} for patients who require one of these NNRTIs,²¹⁹ however, IM rilpivirine, as used in long-acting ARV combinations, is **not recommended (AIII)**. Rifabutin has not been evaluated in combination with rilpivirine, doravirine, or etravirine in people with HIV requiring treatment for active TB disease.

Integrase Inhibitors—Bictegravir, Dolutegravir, Elvitegravir, Raltegravir, and Cabotegravir

As indicated above, dolutegravir in combination with nucleoside reverse transcriptase inhibitors is the preferred option for co-treatment of HIV in most patients with TB **(AI)**. A PK study in healthy volunteers showed that increasing the dose of dolutegravir to 50 mg twice a day with rifampin resulted in similar exposure to dolutegravir dosed 50 mg daily without rifampin, and that rifabutin 300 mg daily did not significantly reduce the area under the concentration curve of dolutegravir.²²⁰ A Phase 2 trial in people with HIV and TB (INSPIRING) demonstrated that PK targets and virologic suppression were favorable at 24 and 48 weeks when dolutegravir 50 mg twice daily was administered with rifampin-containing TB treatment.²²¹ Dolutegravir is currently recommended at a dose of 50 mg twice daily when used together with a rifampin-containing TB regimen **(AI)** (and for two weeks following the completion of TB therapy), though randomized trials evaluating standard once-daily dosing are underway.²²² Dolutegravir should be used at a standard 50 mg once-daily dose when used with rifabutin **(AII)**.

Another alternative co-treatment regimen is the combination of raltegravir-based ART, using raltegravir 800 mg twice daily, with standard rifampin dosing **(BI)**.²²³ Raltegravir concentrations are decreased significantly when co-administered with rifampin. Increasing the dose of raltegravir to 800 mg twice daily mitigates this PK interaction.²²⁴ No PK or clinical data exist regarding the use of rifampin with the once-daily, extended-release 600 mg formulation of raltegravir, and co-administration **is not recommended (AIII)**. Alternatively, raltegravir can be given with a rifabutin-containing TB regimen without a dose adjustment of either drug **(BII)**.²²⁵

At this time, bictegravir **should not be used** together with rifamycin-containing TB treatment (rifampin, rifabutin, or rifapentine) **(AII)**. A trial conducted among healthy participants without HIV evaluated bictegravir concentrations when given twice daily together with rifampin versus once daily alone.²²⁶ Bictegravir trough concentrations, with the dose adjustment, were reduced by 80%. Although studied only with rifabutin, elvitegravir/cobicistat **is not recommended** with TB treatment that contains rifamycins **(AII)**.^{227,228} When given at steady-state with oral cabotegravir, rifampin decreased cabotegravir AUC by 59% in healthy volunteers.²²⁹ The long-acting injectable formulation of cabotegravir has not been studied with rifamycins, but a pharmacokinetic model of long-acting, injectable, co-formulated cabotegravir- rilpivirine predicted that concurrent rifampin would decrease cabotegravir AUC by 41% to 46%.²³⁰ As a result, oral and long-acting injectable cabotegravir **is not recommended for use** with rifampin or rifapentine **(AII)**.²²⁹ Oral and long-acting injectable cabotegravir may be coadministered with rifabutin **(AIII)**; however, long-acting injectable cabotegravir plus rilpivirine is not recommended for use with rifabutin due to the rilpivirine component **(AIII)**.

Protease Inhibitors with Rifampin or Rifabutin

Rifampin decreases the plasma concentrations and exposure of co-administered PIs by >75%.²³¹⁻²³⁴ One trial tested adjusted doses of ritonavir-boosted darunavir (1600/200 mg once daily and 800/100 mg twice daily) with rifampin in people with HIV without TB.²³⁵ The trial was stopped early because of high rates of hepatotoxicity, and trough concentrations in the once-daily group were reduced substantially. Thus, boosted darunavir **is not recommended for use** together with rifampin, even with dose adjustment **(AI)**.

The effects of rifampin on lopinavir/ritonavir PK may be overcome by doubling the dose of lopinavir/ritonavir.^{233,236} In a study of 71 people with HIV and TB, double doses of lopinavir/ritonavir were reasonably well tolerated in those on rifampin-based TB treatment.²⁰⁵ Some experts would consider this an alternative when a PI-based ART regimen is required during TB treatment **(BI)**. Regular monitoring of transaminases and HIV RNA is recommended when double-dose lopinavir/ritonavir is used (e.g., more frequently initially, then monthly once transaminase levels are stable on full dose).

Use of rifabutin with a boosted PI is preferred to the use of rifampin with double-dose PI in settings where rifabutin is readily available. Co-administered rifabutin has little effect on ritonavir-boosted lopinavir^{205,237} or atazanavir²³⁸ and only moderately increases concentrations of ritonavir-boosted darunavir²³⁹ and fosamprenavir.²⁴⁰ However, all PIs markedly increase serum concentrations of rifabutin (and one of its principal active metabolites, 25-O-desacetyl-rifabutin). Therefore, the dose of rifabutin must be decreased from 300 mg to 150 mg daily with all ritonavir-boosted PIs to avoid dose-related toxicity, such as uveitis and neutropenia **(AI)**.^{205,241} Coadministration of cobicistat-boosted PIs with rifabutin is not recommended **(AII)**.

In studies in people with HIV, rifabutin exposures were significantly lower when rifabutin was dosed at 150 mg three times weekly (with lopinavir/ritonavir) than when dosed at 300 mg daily without a PI, but concentrations of the active desacetyl metabolite were high.^{242,243} Among people with HIV and TB, cases have been reported of acquired rifamycin resistance when doses of rifabutin of 150 mg three times weekly were co-administered with a boosted PI-based ARV regimen.^{244,245} Based on available PK data, it is generally recommended that rifabutin be dosed 150 mg daily in patients who are on a ritonavir-boosted PI-containing ARV regimen **(AI)**. However, given the potential risk of adverse events related to high levels of rifabutin's metabolite with this dosing strategy, close monitoring for toxicity (especially neutropenia and uveitis) is required.²⁰⁵ Close monitoring of adherence to ART is essential because these reduced doses of rifabutin would be inadequate if the patient stopped taking the PI, putting the patient at risk of rifamycin-resistant TB.

Monitoring the Response to Therapy

Patients with pulmonary TB should have at least monthly sputum smears and cultures performed to document culture conversion on therapy (defined as two consecutive negative cultures) **(AII)**. Sputum cultures from patients with susceptible TB typically convert to negative within 2 months of first-line TB therapy, although sputum culture conversion to negative may take longer for people with cavitary TB disease.²⁴⁶⁻²⁴⁸ Sputum cultures that do not convert to negative at or after 4 months of therapy indicate treatment failure and should prompt further evaluation, including drug-resistance testing of available specimens.

In patients with extrapulmonary TB, obtaining follow-up specimens can be challenging, making it difficult to assess a bacteriologic response to therapy. Instead, the response typically is measured by an improvement in clinical and radiographic findings, but the frequency of such evaluations will depend on the infected sites, the severity of disease, and the ease with which specimens can be obtained.

Managing Suspected Treatment Failure

The causes of treatment failure include undetected primary drug resistance, inadequate adherence to therapy, incorrect or inadequate prescribed regimen, subtherapeutic drug levels due to malabsorption

or drug interactions, reinfection or mixed infection with drug-resistant *M. tuberculosis*, and acquired drug resistance.

People with suspected treatment failure should be evaluated with a medical history, physical exam, and chest radiograph to determine whether a clinical response to therapy has occurred despite the absence of sputum culture conversion. The initial culture results and drug-resistance tests, treatment regimen, and adherence to the regimen also should be reviewed. Some experts would perform therapeutic drug monitoring to determine if serum concentrations of the TB drugs are within expected ranges and adjust dosage as necessary.^{151,249} In addition, samples from all available sites (e.g., sputum, blood, urine) should be collected for repeat culture and DST, and strong consideration should be given to performing rapid resistance testing on direct specimens or positive cultures to identify acquired drug resistance or mixed infection with a drug-resistant strain.

While awaiting results of repeat cultures and rapid resistance testing, broadening empiric TB treatment to include at least two additional second-line TB drugs should be considered in consultation with an expert in the field **(BIII)**.

Adverse Drug Reactions in TB Patients on Antiretroviral Therapy

Retrospective observational studies reported an increased risk of adverse drug reactions in patients treated with concomitant ART and anti-TB therapy. Many of these studies, however, included patients receiving older antiretrovirals which carried more frequent side effects.²⁵⁰ Three later randomized controlled trials reported similar rates of adverse events during anti-TB therapy with and without concomitant ART, suggesting no significant additive toxicity when ART is co-administered with anti-TB therapy.^{153,189,191} Nevertheless, managing suspected adverse drug reactions in this setting is complex because assigning causality to individual drugs in patients on anti-TB drugs, ART, and other agents is very difficult.

Because first-line anti-TB drugs are more effective and have fewer toxicities than alternative drugs, first-line drugs (especially isoniazid and rifampin or rifabutin) should not be stopped permanently, unless strong evidence exists that a severe drug reaction was caused by a specific anti-TB drug **(AIII)**. In such situations, decisions regarding rechallenge with first-line drugs and/or substitution of second-line drugs may be made in consultation with a specialist in treating TB disease in people with HIV.

Liver transaminases should be monitored at baseline and monthly for those with underlying risk factors for hepatotoxicity.¹⁵¹ Drug-induced liver injury (DILI) can be caused by isoniazid, rifamycins, pyrazinamide, some ARV drugs, and trimethoprim-sulfamethoxazole (TMP-SMX). Anti-TB DILI is defined as an ALT elevation ≥ 3 times the upper limit of normal (ULN) in the presence of symptoms (e.g., fever, rash, fatigue, nausea, anorexia, jaundice); ALT ≥ 3 times the ULN plus total bilirubin 2 times the ULN in the absence of symptoms; or ALT ≥ 5 times the ULN alone in the absence of symptoms. An increase in ALT concentration occurs in approximately 5% to 30% of people treated with the standard four-drug anti-TB regimen,^{97,251} but many of these have only transient, mild elevations of ALT.⁹⁷

If the criteria for anti-TB DILI are fulfilled, all potentially hepatotoxic drugs should be stopped, and the patient should be evaluated immediately **(AIII)**. Serologic testing for syphilis and hepatitis A, B, and C should be performed, and the patient should be questioned regarding symptoms suggestive of biliary tract disease and exposures to alcohol and other hepatotoxins. At least three anti-TB drugs not

associated with hepatotoxicity should be started (e.g., ethambutol, linezolid, and moxifloxacin or levofloxacin)²⁵² as a “bridging regimen” until the specific cause of hepatotoxicity can be determined and an alternative longer-term regimen constructed **(BIII)**.

After the ALT level returns to <2.5 times the ULN (or to near baseline for those with preexisting abnormalities), rechallenge with the hepatotoxic first-line anti-TB medications can be started by adding each drug individually to the bridging regimen at 7-day intervals. During the rechallenge, ALT levels should be monitored frequently.

Rechallenge was successful in almost 90% of people without HIV in one randomized controlled trial of different rechallenge regimens.²⁵² Because the rifamycins are a critical part of the TB regimen, they should be restarted first. Rechallenge with pyrazinamide is controversial because some studies have reported high rates of recurrent ALT elevations with reintroduction of the drug. Other studies, however, have demonstrated successful reintroduction of pyrazinamide,^{253,254} and some experts would therefore recommend rechallenge with pyrazinamide in people with severe forms of TB (e.g., meningitis or disseminated TB).

Bridging drugs can be stopped once three active nonbridging drugs are reinstated successfully. Depending on the outcome of the rechallenge, the anti-TB therapy regimen and duration may need to be altered, in which case, expert consultation is advised. After successful anti-TB drug rechallenge (i.e., if appropriate), relevant ARV drugs and TMP-SMX may be restarted.

Cutaneous adverse drug reactions may occur with all anti-TB drugs, notably rifampin and isoniazid²⁵⁵; some ARV drugs, notably the NNRTIs; and TMP-SMX. If the rash is minor, affects a limited area, and causes pruritus, antihistamines should be administered for symptomatic relief and all anti-TB medications should be continued. If the rash is generalized or associated with fever or DILI or involves mucous membrane or desquamation, all anti-TB medications, relevant ARVs, and TMP-SMX should be stopped. When the rash improves substantially, the TB drugs should be restarted as described in the section on DILI above. If the rash recurs, the last drug that had been added should be stopped and the TB regimen modified. Thereafter, if appropriate, relevant ARV drugs and TMP-SMX may be restarted.

Managing Drug-Resistant TB

Although drug-resistant TB represents a small fraction of the TB cases in the United States, the increasing number of people with drug-resistant TB globally plus the high proportion of TB cases in the United States in people who are from TB-endemic areas make it increasingly likely that local TB programs will be faced with this complex disease. The most active and effective TB drugs are those used in first-line TB treatment regimens. When resistance to these medications develops, alternative combinations of TB medications must be used, but clinical trial data on their optimal use are limited, and most recent studies have been conducted primarily in TB-endemic resource-constrained settings.

In the United States, approximately 7% of people with TB have baseline isoniazid mono-resistance.²⁵⁶ Growing evidence demonstrates an increased risk of treatment failure associated with isoniazid monoresistance,²⁵⁷ particularly in people with HIV and TB.²⁵⁸ For people with isoniazid monoresistance, it is recommended that a fluoroquinolone (levofloxacin or moxifloxacin) be substituted for isoniazid and given together with rifampin or rifabutin, pyrazinamide, and ethambutol for 6 months **(BII)**.^{93,259-261} Though rifampin reduces concentrations of moxifloxacin by 20% to 40%, there is no clinical evidence that a moxifloxacin dose adjustment improves outcomes.²⁶²⁻²⁶⁴

The treatment of rifampin-resistant (RR) and MDR TB (resistance to both isoniazid and rifampin) is an area of active investigation and is evolving rapidly. Historically, RR/MDR TB has been treated with individualized regimens taking into account the results of drug resistance testing and prior treatment exposure. In 2019, ATS, CDC, IDSA, and the European Respiratory Society (ERS) issued MDR TB treatment guidelines recommending a fully oral regimen consisting of at least 5 active drugs for most patients with drug-resistant TB, including people with HIV.⁹³

Since the publication of the 2019 guidelines, however, several clinical trials have examined the efficacy and safety of a 6-month, all-oral regimen comprised of bedaquiline, pretomanid, and linezolid (“BPaL”). Pretomanid is a novel oral antimycobacterial agent that was approved by the FDA in 2019 exclusively as part of the BPaL regimen. The initial study (“Nix-TB”) on which approval was based, was a single-arm study in 109 patients, of whom 51% were people with HIV.²⁶⁵ Although the study had no control arm, 90% of participants had a favorable outcome. High rates of peripheral neuropathy were seen in Nix-TB study participants, and this was attributed to the high dose of linezolid used (1200 mg daily). The follow-up ZeNix study (n=181) compared outcomes of patients receiving the BPaL regimen at different linezolid doses and showed similarly favorable outcomes with a lower dose of 600 mg daily.²⁶⁶ The TB-PRACTECAL study compared a regimen in which moxifloxacin was added to BPaL (aka “BPaLM”) to longer injectable-based regimens, which were the standard of care at the time.^{267,268} In modified intention-to-treat analyses, 121 of 138 (88%) participants in the BPaLM arm achieved treatment success compared with 81 of 137 (59%) of those receiving standard of care. Disease recurrence occurred in one participant in the BPaLM group (n=151) and four in the BPaL group (n=123); new resistance to bedaquiline was observed in the BPaL group in isolates from three of four recurrences, with no new resistance to other drugs in the regimens.²⁶⁷

The BPaL and BPaLM regimens have been used in the United States, and treatment outcomes thus far have been very successful among 152 patients with culture-positive pulmonary TB, most of whom received the 600 mg daily dose of linezolid.^{269,270} Three recurrences after treatment completion were reported among 116 who received BPaL and none among 36 patients who received BPaLM.

Based on these data, **BPaLM is recommended as the preferred therapy for people with HIV with pulmonary RR-TB and without known resistance to the component medications (AI).**²⁷¹

Patients with RR-TB with fluoroquinolone resistance should receive BPaL without moxifloxacin (**AI**). This recommendation is similar to that of WHO, which conditionally recommends both the BPaL and BPaLM regimens to patients ≥15 years of age with RR-TB who have not had previous exposure or resistance to the drugs in the regimen.²⁷² BPaLM and BPaL regimens should be given for a total of 26 weeks (6 months) (**AI**). Treatment should be extended up to a total of 39 weeks (9 months) if sputum cultures are positive between months 4 and 6 (**AI**).

For patients who have not been included in BPaL or BPaLM studies—such as those with extrapulmonary TB or those with known or suspected resistance to bedaquiline, pretomanid, or linezolid—we recommend an individualized regimen consisting of at least 5 active drugs, based on the results of resistance testing and prior treatment exposure (**AI**). Component medications should be selected using the ranking outlined in the ATS/CDC/IDSA/ERS guidelines.⁹³ When possible, an initial individualized regimen should contain bedaquiline, linezolid, a fluoroquinolone (levofloxacin or moxifloxacin), clofazimine, and a D-alanine analog (cycloserine or terizidone). All remaining drugs should be used to complete the regimen only when the recommended drugs cannot be used. Kanamycin and capreomycin are no longer recommended due to the increased risk of treatment

failure and relapse with their use.²⁷³ Such an association was not seen for amikacin, which may be used when other, less toxic drugs cannot be used. The duration of therapy with such a regimen will depend on the component drugs and the patient's response to therapy. The ATS/CDC/IDSA/ERS guidelines currently recommend a treatment duration of 15 to 24 months *after culture conversion* when using an individualized regimen, although these guidelines are currently undergoing revision.⁹³ Several clinical trials have examined different regimens with total durations as short as 9 months and show TB treatment success rates comparable to or better than longer duration therapy.²⁷⁴⁻²⁷⁸ Consultation with an expert who has experience managing drug-resistant TB is advised.

An important concern regarding BPaL(M) regimens is the growing prevalence of bedaquiline resistance and the lack of widespread availability of phenotypic second-line TB drug susceptibility testing.^{279,280} Rapid molecular testing with confirmatory sequencing for fluoroquinolones and first-line drugs should ideally be performed prior to the initiation of treatment for RR/MDR TB; phenotypic testing should also be undertaken. This testing, as well as susceptibility testing for second-line agents, is available at many local or state public health laboratories or through the CDC's [Molecular Detection of Drug Resistance \(MDDR\) service](#). To submit a sample for the MDDR service, complete the CDC's [MDDR Request Form](#).

Importantly, as with all TB drugs, there is incomplete concordance between purported bedaquiline resistance-conferring mutations and phenotypic resistance.²⁸¹ If bedaquiline is being used, then bedaquiline phenotypic testing should be pursued, if available. Treatment with BPaLM need not be delayed, however, while awaiting the results of bedaquiline susceptibility testing. Of note, pretomanid resistance testing is not currently available.

For people with HIV with RR-TB, several important drug–drug interactions occur between bedaquiline and some ARV drugs. Specifically, efavirenz decreases bedaquiline plasma concentrations.²⁸² For people with HIV with RR-TB, efavirenz **should not be used** concurrently with bedaquiline **(AI)**. Lopinavir/ritonavir increases bedaquiline plasma concentrations approximately twofold when given at steady-state,^{283,284} but this has not been associated with additional prolongation of the QT-interval or other adverse events.²⁸⁵

Given the options for regimen choice and individual drug dosing within regimens, as well as variations in local drug susceptibilities, the treatment of RR-TB should involve an expert with experience in treating drug-resistant TB.^{267,269} If a local expert is not available through the public health department, clinicians and TB programs can contact the CDC (tbinfo@cdc.gov) and one of the CDC's [TB Centers of Excellence for Training, Education, and Medical Consultation](#).

TB-Associated IRIS

TB-IRIS is a frequent, early complication of ART in people with HIV with active TB. The condition is thought to result from the recovering immune system driving inflammatory reactions directed at *M. tuberculosis* antigen present at sites of disease.²⁸⁶⁻²⁸⁸ TB-IRIS is characterized by excessive local or systemic inflammation. Two forms of TB-IRIS are recognized: paradoxical TB-IRIS and unmasking TB-IRIS. Proposed clinical case definitions for these syndromes have been published.²⁸⁹

Paradoxical TB-IRIS

Paradoxical TB-IRIS occurs in people who are diagnosed with active TB disease before starting ART. Typically, people experiencing paradoxical TB-IRIS have had clinical improvement on TB

treatment before starting ART, and within the first 1 to 4 weeks of ART (though sometimes later), they develop new or recurrent symptoms and worsening or recurrent clinical and radiologic features of TB. Common and important manifestations of paradoxical TB-IRIS include fevers, new or enlarging lymphadenopathy, and new or worsening pulmonary infiltrates. Mortality due to paradoxical TB-IRIS is uncommon,^{287,290} but life-threatening manifestations include enlarging cerebral tuberculomas, meningitis, enlargement of pericardial effusions causing cardiac tamponade, extensive pulmonary involvement with respiratory failure, nodal enlargement causing airway obstruction, and splenic rupture due to rapid enlargement.^{287,291,292} In people with disseminated TB, hepatic TB-IRIS is common, manifesting with nausea and vomiting, tender hepatic enlargement, cholestatic liver function derangement, and occasionally jaundice.^{288,293} A liver biopsy often reveals granulomatous hepatitis.²⁹⁴ Hepatic TB-IRIS may be difficult to differentiate from drug-induced liver injury.

Paradoxical TB-IRIS is relatively common among patients starting ART while on TB treatment. A meta-analysis of 40 studies reported a pooled incidence of TB-IRIS of 18% in adults with HIV-associated TB initiating ART, with death attributed to TB-IRIS in 2% of the cases.²⁹⁵ The onset of paradoxical TB-IRIS symptoms is typically between 1 to 4 weeks after ART is initiated.²⁹⁶⁻³⁰¹ The syndrome lasts for 2 to 3 months on average,^{300,302} but in some cases, symptoms may continue for several more months, and in rare cases, local manifestations may persist or recur over a year after onset.^{289,302,303} In such cases of prolonged TB-IRIS, manifestations usually include suppurative lymphadenitis and abscess formation.

The most consistently identified risk factors for paradoxical TB-IRIS are a low CD4 count at the start of ART, especially a CD4 count^{239,244} <100 cells/mm³;^{299,304} high HIV viral load before ART^{305,306}; disseminated or extrapulmonary TB^{291,298,300,304}; and a short interval between starting TB treatment and initiating ART, particularly if ART is started within the first 1 to 2 months of TB treatment.^{291,297,299} Although early ART increases the risk for TB-IRIS, ART should be started within 2 weeks of TB diagnosis in patients with CD4 counts <50 cells/mm³ and within 2 to 8 weeks of TB diagnosis in those with higher CD4 counts, as previously discussed, to reduce the risk of HIV progression and death (see [Special Considerations Regarding ART Initiation](#), above) (AI).²⁹⁵

The diagnosis of paradoxical TB-IRIS may be challenging, and no definitive confirmatory test exists. Thus, diagnosis relies upon a characteristic clinical presentation: improvement of TB symptoms with treatment before ART, deterioration with inflammatory features of TB soon after starting ART, or demonstration of a response to ART (CD4 rise and/or HIV viral load reduction). In addition, diagnosis of paradoxical TB-IRIS requires investigations to exclude alternative causes for deterioration, particularly another opportunistic infection, undetected TB drug resistance, or other cause of treatment failure (see [Managing Suspected Treatment Failure](#), above).³⁰⁷

Prevention of Paradoxical TB-IRIS

Pre-emptive treatment with prednisone may prevent or reduce the consequences of TB-IRIS. A randomized, double-blind, placebo-controlled trial of prednisone (40 mg/day for 2 weeks, then 20 mg/day for 2 weeks) versus placebo in 240 ART-naïve adults at high risk of developing IRIS at the time of ART initiation demonstrated that preemptive prednisone treatment was effective in reducing the risk of paradoxical TB-IRIS.¹⁹⁷ The incidence of TB-IRIS was 47% in the placebo arm and 33% in the prednisone arm (RR = 0.70; 95% CI, 0.51–0.96). No excess risk was observed for malignancy, severe infections, or other complications. Based on these study findings, preemptive prednisone therapy should be offered for high-risk patients as defined in this study (i.e., starting ART

within 30 days after TB treatment initiation and a CD4 count $\leq 100/\text{mm}^3$) who are responding well to TB therapy and who do not have rifampin resistance, Kaposi sarcoma, or active hepatitis B (**BI**).

Managing Paradoxical TB-IRIS

Most cases of paradoxical TB-IRIS are self-limiting. Many people require symptomatic therapy (e.g., analgesia, anti-emetics), and if symptoms are significant, anti-inflammatory therapy is appropriate. Clinicians may use non-steroidal anti-inflammatory drugs to provide symptomatic relief in patients with mild TB-IRIS (**CIII**). Needle aspiration of enlarging serous effusions, large tuberculous abscesses, or suppurative lymphadenitis may also provide symptom relief (**CIII**). Repeated aspirations may be required as abscesses and effusions often re-accumulate.²⁹¹

In people with moderately severe paradoxical TB-IRIS, treatment with prednisone is recommended (**AI**). One randomized, placebo-controlled trial among patients with moderately severe paradoxical TB-IRIS showed that treatment with prednisone (1.5 mg/kg/day for 2 weeks followed by 0.75 mg/kg/day for 2 weeks) resulted in a reduction in a combined endpoint of days hospitalized plus outpatient therapeutic procedures.³⁰⁸ In that study, however, 4 weeks of prednisone treatment was insufficient in a subset of participants. If clinical assessment indicates that signs and symptoms have not improved or have worsened as corticosteroids are tapered, a more gradual tapering of steroids over 2 to 3 months is recommended (**BIII**).³⁰⁸ Patients on prednisone experienced more rapid symptoms and radiographic improvement. No reduction in mortality was demonstrated, but immediately life-threatening cases (e.g., those with neurological involvement) were excluded from this study.^{111,292,308} Rifampin increases the clearance of prednisolone (the active metabolite of prednisone),³⁰⁹ but no such effect is expected with rifabutin; dosing of prednisone should therefore be adjusted in patients receiving rifampin or rifabutin-containing regimens (See the Treating TB-Associated IRIS section of the [Treating TB Disease table](#)). Corticosteroids should be avoided in people with Kaposi sarcoma because life-threatening exacerbations can occur. Case reports have been published of patients with steroid-refractory and prolonged IRIS or paradoxical reactions responding to TNF-blockers, IL-1 inhibitors, JAK inhibitors, or thalidomide.³¹⁰⁻³¹⁷

Unmasking TB-IRIS

Unmasking TB-IRIS may occur in people who have unrecognized TB (because TB is either symptomatic or it has eluded diagnosis) at the start of ART. These people may present with a particularly accelerated and inflammatory presentation of TB in the first weeks of ART.²⁸⁹ A common presentation is pulmonary TB with rapid symptom onset and clinical features similar to bacterial pneumonia with high fever, respiratory distress, sepsis syndrome, and consolidation on chest radiograph.^{289,308,318-320} Focal inflammatory manifestations—such as abscesses and lymphadenitis—also may develop.³²¹ In cases of unmasking TB-IRIS, the treatment should be standard TB treatment and, if the manifestations are life-threatening, adjunctive corticosteroid therapy is recommended, although steroid use in this setting has not been studied in a clinical trial (**BIII**).

Prevention of Recurrent TB

Among patients receiving the same TB treatment regimen in the same setting, the risk of recurrent TB appears to be higher among those with HIV than among those without HIV.^{322,323} In TB-endemic settings, much of the increased risk of recurrent TB appears to be due to the higher risk of re-infection with a new strain of *M. tuberculosis*, with subsequent rapid progression to TB disease.^{324,325}

In settings with low rates of TB—such as the United States—recurrent TB due to re-infection is uncommon, even among people with HIV.³²⁶

Several interventions may decrease the risk of recurrent TB among people with HIV: longer TB treatment regimens, administering therapy daily throughout the course of the intensive and continuation phases, post-treatment isoniazid therapy, and use of ART. None of these interventions has been adequately evaluated in randomized trials in settings with low TB burdens. Post-treatment isoniazid (6–9 months of daily isoniazid therapy after the completion of standard multidrug therapy) has been shown to be effective in high-burden settings in which the risk of re-exposure is high,^{327,328} suggesting that this intervention decreases the risk of re-infection. Post-treatment isoniazid **is not recommended** for patients in the United States or other low-burden settings due to a lack of evidence of effectiveness supporting a reduced risk of re-infection for these settings **(AIII)**. Given that ART reduces the risk of initially developing TB disease, it is likely that ART also decreases the risk of re-infection with TB.

Special Considerations During Pregnancy

During pregnancy, if there is no documentation of a prior negative TB screening test result or there is a high risk for repeated or ongoing exposure to people with active TB disease, then test for TB **(AIII)**. TB rates in pregnant and postpartum women are higher than in other people with HIV, after adjusting for age,³²⁹ and this is likely due to pregnancy-related immunologic shifts.^{330–334} Several studies have examined the performance of IGRAs for diagnosis of LTBI in pregnant women. In pregnant women with or without HIV, the test appears to perform well.^{335,336} Longitudinal studies conducted in high-burden countries, however, suggest that test performance may be compromised in late pregnancy versus postpartum, especially at delivery.^{337–343}

A clinical trial of isoniazid preventive therapy (IPT) among women with HIV in high TB prevalence settings (TB APPRISE) found increased adverse pregnancy outcomes in women treated with isoniazid during pregnancy compared to postpartum initiation of isoniazid.³⁴⁴ Importantly, however, none of the women were close household TB contacts, and most of the women in the trial were IGRA-negative and were receiving efavirenz-based ART. Two smaller observational studies of isoniazid given to pregnant women with HIV in South Africa did not find an increased risk of adverse pregnancy outcomes with isoniazid.^{345,346} Similarly, a study of participants in Botswana who became pregnant in a trial of 36 months of isoniazid for people with HIV also did not report increased adverse pregnancy outcomes.³⁴⁷ A subsequent systematic review of the association of adverse pregnancy outcomes and isoniazid found inconsistent associations.³⁴⁸ Among women enrolled in the BRIEF-TB study who became pregnant while taking isoniazid for TB prevention, first-trimester IPT exposure was associated with increased risk of fetal demise, though this association was attenuated when adjusted for covariates proximal to pregnancy outcome including ART use.³⁴⁹

Studies in individuals with HIV who are not receiving ART have shown a high risk of progression from LTBI to active TB disease (10% per year), and a high risk exists for maternal and infant mortality in pregnant women with HIV who have active TB disease.^{350,351} Although the risk of progression from LTBI to active TB disease in individuals on ART is decreased significantly, risk in these individuals with HIV appears higher than in pregnant and postpartum women without HIV.^{337,352} Pregnant women with HIV should be receiving ART both for their own health and for prevention of perinatal transmission **(AI)**. In the United States, isoniazid preventive therapy is recommended for pregnant women with HIV whose close household contacts include a person with

active TB disease **(AI)**. For those receiving effective ART and without recent TST or IGRA conversion or close household contacts with infectious TB, therapy for LTBI may be deferred until after delivery **(BIII)**. The risk of isoniazid-associated hepatotoxicity may be increased in pregnancy and in the first 2 to 3 months post-partum.³⁴⁴ Therefore, if isoniazid is prescribed, frequent monitoring is needed.³⁴ Pregnant women receiving isoniazid should receive daily pyridoxine supplementation **(AII)** because they are at risk of isoniazid-associated peripheral neuropathy.^{151,353} Limited data exist on alternatives to isoniazid for LTBI therapy in pregnant women with HIV. In the IMPAACT 2001 study, pregnant women with and without HIV received 3HP and no serious adverse pregnancy outcomes were observed. Drug exposures were similar to non-pregnant populations, suggesting this regimen does not require dose adjustment in pregnancy.³⁵⁴ Despite these promising data and although rifampin generally is considered safe in pregnancy, data on the use of rifapentine remain extremely limited and the use of rifapentine during pregnancy is not currently recommended **(BIII)**.³⁵⁵⁻³⁵⁷ The DOLPHIN Moms trial (NCT05122026) currently underway is examining the pharmacokinetics and safety of 3HP and 1HP in pregnant women with HIV who are virally suppressed on a dolutegravir-based regimen.

During pregnancy, the diagnostic evaluation for TB disease is the same as for other adults with HIV. It is important to recognize that standard symptom screens have lower sensitivity in pregnant women than in non-pregnant populations, and that some TB symptoms may be masked by common symptoms of pregnancy (e.g. poor appetite).³⁵⁸⁻³⁶⁰ In addition to standard sputum testing, chest radiographs with abdominal shielding are recommended and result in minimal fetal radiation exposure.³⁶¹ An increase in pregnancy complications—including preterm birth, low birthweight, and fetal growth restriction—can be seen among pregnant women with either pulmonary or extrapulmonary TB not confined to the lymph nodes, especially when TB treatment is delayed until late in pregnancy.^{34,330,333,335,336,339,344,351,362-366} Congenital TB infection has been reported, although it appears relatively uncommon; history of maternal infertility and acid-fast bacilli from placenta or endometrial biopsy may be found with this rare diagnosis.³⁶⁷⁻³⁷² While rare, congenital TB might be more common among children born to mothers with TB/HIV coinfection, especially when those children also have perinatally acquired HIV.^{373,374}

TB therapy should not be withheld because of pregnancy **(AIII)**. Treatment of TB disease during pregnancy should be the same as for any other patient with HIV, but with attention to the following considerations **(AIII)**:

- Although isoniazid is not teratogenic in animals or humans, hepatotoxicity caused by isoniazid might occur more frequently during pregnancy and the postpartum period.³⁷⁵ Monthly monitoring of liver transaminases during pregnancy and the postpartum period is recommended **(BIII)**.
- Rifampin is not teratogenic in humans.
- Ethambutol is teratogenic in rodents and rabbits at doses that are much higher than those used in humans. No evidence of teratogenicity has been observed in humans. Ocular toxicity has been reported in adults taking ethambutol but changes in visual acuity have not been detected in infants exposed to ethambutol *in utero*.
- Pyrazinamide is not teratogenic in animals. The WHO and the International Union Against Tuberculosis and Lung Diseases have made recommendations for the routine use of pyrazinamide in pregnant women.^{272,376} Pyrazinamide has been recommended for use during pregnancy in the United States, although data characterizing its safety in this setting are limited and the CDC guidance suggests that clinicians consider the use of this agent based on individual

patient considerations weighing benefit and risks.^{151,377} If pyrazinamide is not included in the initial treatment regimen, the minimum duration of TB therapy with isoniazid, rifampin, and ethambutol should be 9 months for drug-susceptible TB **(AII)**. The decision regarding whether to include pyrazinamide in treatment regimens during a pregnancy should be made after consultation among obstetricians, TB specialists, and the patient, while considering gestational age and likely susceptibility pattern of the TB strain.

Experience using the majority of the second-line drugs for TB during pregnancy is limited.³⁷⁸⁻³⁸¹ MDR TB in pregnancy should be managed in consultation with a specialist. In a small prospective study of pregnant women who received second-line MDR/RR-TB regimens that contained bedaquiline or delamanid (including linezolid, clofazimine, amikacin, capreomycin, and kanamycin) 98% had successful treatment outcomes, and at least 81% of continued pregnancies resulted in live births with 68% normal birthweight neonates.³⁷⁸ The following concerns should be considered when selecting second-line anti-TB drugs for use during pregnancy:

- **Bedaquiline:** Data on the use of bedaquiline in pregnancy are limited, but a study of 108 pregnant women from South Africa found an increased frequency of low birthweight (<2,500 g) among children exposed to bedaquiline *in utero* compared to those who were not exposed (45% vs. 26%; $P = 0.034$).³⁸² The median birthweight between the two groups, however, was not statistically significant (2690 vs. 2900 grams [$P = 0.18$]) and after 1 year, most children exposed to bedaquiline had gained weight and were doing well. Bedaquiline concentrations in breast milk may be as high or higher than concentrations in maternal plasma, which may have implications for the infant.^{383,384}
- **Cycloserine:** No data are available from animal studies or reports of cycloserine use in humans during pregnancy.
- **Ethionamide** has been associated with an increased risk for several anomalies in rats after high-dose exposure, but not in mice or rabbits.³⁸⁵⁻³⁸⁷ Case reports have documented cases of CNS defects in humans and hypothyroidism, but overall experience is limited with use during human pregnancy.³⁸⁸ Ethionamide is likely present in the breast milk, which could be associated with thyroid issues in the infant. Thus, ethionamide should be avoided, unless its use is required on the basis of susceptibility testing **(CIII)**.
- **Fluoroquinolones:** Because arthropathy has been noted in immature animals exposed to fluoroquinolones *in utero*, quinolones are typically not recommended during pregnancy or for children aged <18 years **(CIII)**. However, studies evaluating fluoroquinolone use in pregnant women did not find an increased risk of birth defects or congenital musculoskeletal abnormalities.³⁸⁹⁻³⁹³ Furthermore, fluoroquinolones were used in a larger South African case series of MDR TB treatment in pregnancy with generally good outcomes.³⁸² Thus, fluoroquinolones can be used in pregnancy for drug-resistant TB if they are required on the basis of susceptibility testing **(BII)**.³⁹⁴
- **Linezolid:** Animal studies of linezolid in pregnancy report decreased fetal body weight and increased fusion of costal cartilage.³⁹⁵ There are few studies in human pregnancy, but linezolid has been used for the treatment of DR-TB in some high-burden countries.^{378,382} In these case studies, monitoring complete blood counts for anemia and thrombocytopenia and advising iron supplementation has been recommended.^{384,396}
- **Delamanid:** Delamanid appears to be safe in animal reproductive toxicity studies. It has been used in small cohorts of pregnant women for DR-TB with favorable outcomes.^{378,397}

- **Pretomanid:** Animal studies of pretomanid do not indicate direct or indirect harmful effects with respect to embryo-fetal development. However, pretomanid has been associated with reproductive toxicity in animal models; specifically, reduced fertility in male rats.³⁹⁸ There has been very limited use in human pregnancies. Therefore, pretomanid should be avoided in pregnancy until more data is available (**AIII**).
- **Para-aminosalicylic acid** is not teratogenic in rats or rabbits.³⁷⁷ In one study, a possible increase in limb and ear anomalies was reported among 143 infants delivered by women who were exposed to para-aminosalicylic acid during the first trimester of pregnancy.³⁹⁹ No specific pattern of defects and no increase in the rate of defects have been detected in other human studies, indicating that this agent can be used with caution, if needed (**CIII**).
- **Aminoglycosides/polypeptides:** Streptomycin use has been associated with a 10% rate of vestibulocochlear nerve toxicity in infants exposed to the drug *in utero*; its use during pregnancy should be avoided, if possible (**AIII**). Hearing loss has been detected in approximately 2% of children exposed to long-term kanamycin therapy *in utero*; like streptomycin, this agent should typically be avoided, if possible (**AIII**). The fetus is at a theoretical risk for ototoxicity with *in utero* exposure to amikacin and capreomycin, but this risk has not been documented. Capreomycin is no longer recommended, but amikacin might be used as an alternative when an aminoglycoside is required for the treatment of MDR TB (**CIII**).

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