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 2019, an estimated 820,000 people with HIV had TB and 208,000 deaths among people with HIV were attributed to TB.[1] Although the overall annual number of TB patients worldwide has been relatively unchanged (1.6% global average annual rate of decline), several countries in sub-Saharan Africa have seen marked reductions by 4 percent to 8 percent per year while antiretroviral therapy (ART) coverage has expanded.[2] People with HIV still account for a disproportionate number of TB deaths worldwide (14.7% of deaths vs. 8.2% of TB cases); however, a 69 percent reduction in deaths has occurred since 2000.[1]

In the United States, TB rates are the lowest ever reported, with 8,916 people with TB reported in 2019.[3] Approximately two-thirds (6,364; 71.4%) of people newly reported with TB were born outside the United States. The incidence of HIV-related TB in the United States has declined substantially, in part because of the widespread use of ART.[4,5] Among all patients reported with TB with known HIV status in the United States in 2019, 373 persons (4.7%) were coinfected with HIV (7.6% among TB patients aged 25–44 years).[3] Four states (Florida, Georgia, Missouri, and North Dakota) and Puerto Rico have HIV coinfection rates greater than 8 percent among people with TB.

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 multiplication of tubercle bacilli. However, viable bacilli persist for years, a condition referred to as latent TB infection (LTBI). Persons 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. The annual risk of TB disease due to reactivation of LTBI for persons with untreated HIV infection has been estimated as 3 percent to 16 percent per year, which approximates the lifetime risk of TB disease for persons with LTBI who are HIV negative (approximately 5%).[6-11] The risk of TB begins in the first year following HIV infection.[12] TB infection can occur at any CD4 T lymphocyte (CD4) cell count, although the risk increases with progressive immunodeficiency.[12,13] Even with effective ART, the risk of TB disease among people with HIV remains greater than that among the general population. The estimated annual risk of developing TB disease among persons 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 untreated people with HIV than for those without HIV.[14,15] Furthermore, in two studies among adults with HIV not receiving ART, persons who developed TB disease had higher viral loads[16] and a greater risk of HIV disease progression[16] and death[17] than CD4-matched control patients without TB. In the United States, the most common predisposing factor for TB infection is birth or residence outside of the United States.[18]

The risk of progression from LTBI to TB disease in persons with HIV is reduced both by ART and by treatment of LTBI.[17,19-22] In combination with ART, isoniazid preventive therapy decreased the

risk of TB disease by 76 percent among people with HIV in Brazil.[23] Furthermore, isoniazid preventive therapy and ART independently and additively decreased the risk of death and severe HIV-related illness.[19,21]

Diagnosing Latent TB Infection

All persons with HIV should be evaluated for LTBI at the time of HIV diagnosis, regardless of their epidemiological risk of TB exposure **(AII).** The two current diagnostics available for 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. The decisions about medical and public health management should include epidemiological, historical, and other clinical information when using IGRA or TST results.

Persons with advanced HIV infection (CD4 count <200 cells/mm^3) and negative diagnostic tests for LTBI, without 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/mm^3 to ensure that the initial test result was a true negative result.[24,25] 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 persons with active TB disease (e.g., during incarceration, travel to a high-TB incidence country, homelessness, living in a congregate setting).

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 persons 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 persons who received Bacillus Calmette-Guérin (BCG) vaccination, and decreased sensitivity (false negative results) among persons with advanced immunodeficiency.[26] These limitations of the TST have led to broader use of IGRAs for detection of LTBI.

Older studies suggest 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 other nontuberculous mycobacteria.[27,28] Furthermore, in a prospective study of 1,510 people with HIV in the United States, IGRAs appeared more sensitive than the TST, although both TST and IGRA (using U.S. cutoffs of 5 mm for TST and 0.35 IU/mL for QuantiFeron-TB Gold In-Tube [QFT-GIT]) may result in more LTBI overdiagnosis than underdiagnosis in a population with 5 percent or lower LTBI prevalence.[29]

IGRAs include the T-SPOT.TB and QFT-TB Gold Plus (QFT-Plus). As with the TST, progressive immunodeficiency is associated with decreased sensitivity of IGRAs.[30] 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.[31] Similar findings among health care workers led to a revised recommendation by the Centers for Disease Control and Prevention (CDC) to no longer routinely, serially test U.S. health care personnel who do not have clear risk factors for new or ongoing TB exposure.[32] Similarly, annual testing for people with HIV is not recommended unless high risk exists for repeated or ongoing exposure to persons with active TB disease.

Among people with HIV, the correlation between the TST and IGRA test results is poor to moderate.[33,34] In prospective studies, positive results with either the TST or IGRA were associated with an increased risk of developing TB disease;[35-37] in some studies, patients with a positive IGRA were at a higher risk of subsequently developing TB disease than those with a positive TST.[38,39] Despite its limitations, a positive TST result strongly predicts that treatment of LTBI will decrease the risk of TB progression among people with HIV.[17] Studies are underway to formally evaluate if IGRAs are similarly predictive.

In programmatic settings in the United States, TB screening has been suboptimal, with only 47 percent to 69 percent of patients completing initial screening.[40-43] The use of an IGRA for TB screening may increase the proportion of patients who complete baseline and as-needed follow-up TB screening.

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.[29,44] 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 its adoption 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.[45]

As tests of immune reactivity against *M. tuberculosis*, the TST and IGRAs are often positive among persons with TB disease. Therefore, all persons with a positive TST or IGRA should be evaluated for the possibility of active TB disease.[44] Most, but not all, people with HIV with TB disease have symptoms (e.g., cough, fever, sweats, weight loss, lymphadenopathy); absence of any of these symptoms had a 97 percent negative predictive value for culture-positive TB in low-resource settings, although this varied depending on pretest probability.[46] The addition of a chest radiograph improved sensitivity of this screening algorithm but decreased specificity. It is important to note that in a symptomatic patient with clinical suspicion for TB disease, a negative TST or IGRA does not rule out TB disease.

Obtaining a sputum culture 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.[44]

Treating Latent TB Infection

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.[47] 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 **(AII).** 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 treatment of LTBI, and preventive therapy is

not generally recommended **(AIII);** this is in contrast to high TB endemic countries where isoniazid decreased TB risk and mortality in people with HIV, regardless of TST or IGRA result.[22]

LTBI treatment and ART act independently to decrease the risk of TB disease.[20,21,23,48,49] Therefore, use of both interventions is recommended for persons with LTBI **(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).**[21]

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 treatment of LTBI **(AI).**[47]

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/mm^3 and who were not yet on ART.[50,51] 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.[52]

Although individuals taking ART were not included in the Phase 3 trial of 3HP,[53] the pharmacokinetic (PK) profile of efavirenz with daily rifapentine and isoniazid is favorable.[54,55] Raltegravir concentrations were modestly increased when it was given with once-weekly rifapentine in healthy volunteers.[56] In a Phase 1/2 single-arm study of people with HIV treated with dolutegravir and 3HP, rifapentine decreased dolutegravir exposure by 26 percent; yet, trough concentrations remained above the 90 percent maximum inhibitory concentration for all but one participant, and all participants maintained an undetectable viral load throughout the study period.[57] Based on these PK data and limited outcome data, 3HP is recommended in virally suppressed persons receiving efavirenz, raltegravir, or dolutegravir (given as once daily dosing) without dose adjustment of rifapentine, isoniazid, or ART **(AII).**[58]

3HR

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

In studies of HIV-negative adults and children with 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.[59-63] 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;[64-67] hepatotoxicity was less frequent among those receiving 3HR, but treatment-limiting adverse effects were more common.[47] When using rifampin alone for LTBI treatment, either dose adjustment or substitution of key ARVs may be needed (see Dosing Recommendations for Anti-TB Drugs table [included below]).

Alternative Drugs for Treatment of Latent TB Infection

Isoniazid

- Isoniazid 300 mg PO daily plus pyridoxine 25–50 mg PO daily for 6 to 9 months is an alternative regimen for 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.[21,67-71] However, treatment completion rates are suboptimal, decreasing its effectiveness.[72] Patients are more likely to complete shorter regimens.[52,53,72-76] 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/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.[70] 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 CDC/National Tuberculosis Controllers Association (NTCA) guidelines recommend 4R as a preferred treatment for LTBI in people without HIV, given the lack of trial data in people with HIV, the 4R regimen is recommended only as an alternative to 3HP, 3HR, 6H, and 9H in people with HIV **(BI).** When using rifampin alone 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,[77,78] some clinicians would perform a sputum culture before starting 4R for LTBI. Because limited data exist on 4R in people with HIV, concerns about using this regimen in people with low CD4 cell counts, and no data on use of 4 months of rifabutin either in people with or without HIV, rifabutin monotherapy is not recommended **(AIII).** The regimen of 2 months of rifampin plus pyrazinamide is not recommended given the risk of severe and sometimes fatal hepatotoxicity **(AII).**[79,80, 81]

1HP

- Isoniazid 300 mg PO daily plus rifapentine PO daily plus pyridoxine 25–50 mg PO daily for 4 weeks is an alternative therapy for treatment of LTBI in people with HIV **(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).[74] The median CD4 count of study participants was 470 cells/mm^3, 50 percent of the study population was on ART (efavirenz or nevirapine-based regimens) at study entry, and 21 percent 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 percent in the 1HP arm and 90 percent 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 CDC/NTCA 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. 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 CDC/NTCA guidelines. If ART is administered together with 1HP, an efavirenz-based regimen should be used **(AI).** However, a study evaluating co-administration of 1HP with dolutegravir is in progress;[54,82] the use of dolutegravir-based ART should await results from this trial.

Treatment of LTBI Following Exposure to Drug-Resistant TB

For persons exposed to drug-resistant TB, a regimen for LTBI should be selected after consultation with experts or with public health authorities **(AIII).**[83]

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 persons 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.[47] Persons with concomitant chronic viral hepatitis and older individuals have an increased risk of isoniazid-related hepatotoxicity, and such patients should be monitored closely when being treated for LTBI.[84,85]

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.[71,74] Factors that increase the risk of drug-induced clinical hepatitis include daily alcohol consumption, underlying liver disease, and concurrent treatment with other hepatotoxic drugs. 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 greater than five times the upper limit of normal without symptoms or 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[86] and in consultation with an expert in treating LTBI in people with HIV.

Clinical Manifestations of TB Disease

Similar to persons without HIV infection, people with HIV with TB disease may be asymptomatic but have positive sputum cultures (subclinical TB).[87] In ambulatory people with HIV, the presence of any one of the classic symptoms of TB disease (i.e., cough, hemoptysis fever, night sweats, weight loss) has high sensitivity but low specificity for diagnosing TB as assessed in resource-limited settings.[46] The sensitivity of classic TB symptoms is lower in people with HIV on ART.[77]

The presentation of TB disease is influenced by the degree of immunodeficiency.[88,89] In patients with CD4 counts >200 cells/mm^3, HIV-related TB generally resembles TB among persons without HIV. Most patients have disease limited to the lungs, and common chest radiographic manifestations are upper lobe infiltrates with or without cavitation.[90]

In patients with CD4 counts <200 cells/mm^3, the chest radiographic findings of pulmonary TB are markedly different, with infiltrates showing no predilection for the upper lobes, and cavitation is uncommon.[88,90,91] Normal chest radiographs are not uncommon in patients with respiratory symptoms and positive sputum cultures. Thoracic CT scans may demonstrate mild reticulonodular infiltrates despite a normal chest radiograph.[92]

With increasing degrees of immunodeficiency, extrapulmonary (especially lymphadenitis, pleuritis, pericarditis, and meningitis) or disseminated TB are more common. In patients who are markedly immune-suppressed, TB can be a severe systemic disease with high fevers, rapid progression, and features of sepsis.[93] Clinical manifestations of extrapulmonary TB in people with HIV are not substantially different from those described in persons without HIV. TB must be considered in disease processes involving any site in the body,[94] especially in patients with central nervous system (CNS) disease, when early TB treatment is essential to improve outcomes.[95-97]

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).[44] Pulmonary involvement is common at all CD4 counts.[87,98] The initial evaluation of a patient 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 patients with advanced immunodeficiency who can have TB culture-positive sputum despite normal chest radiographs.[99,100] Therefore, sputum smear, nucleic acid amplification (NAA) testing, and culture should be performed in people with HIV with symptoms of TB disease who have a normal chest radiograph, as well as in persons with no pulmonary symptoms but evidence of TB disease elsewhere in the body.[44]

Sputum smear-negative, culture-positive TB disease is common among people with HIV, particularly those with advanced immunodeficiency and non-cavitary disease.[101] However, NAA tests have a higher sensitivity than smear, and the yield of sputum culture is not affected by HIV or the degree of immunodeficiency.[44,102] Smear and culture of three sputum specimens is recommended based on a

large study in patients with HIV that showed a 10 percent incremental yield for broth culture between the second and third specimens.[103]

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.[104] Histopathologic findings also are affected by the degree of immunodeficiency. Persons 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.[89]

Pleural fluid, pericardial fluid, ascites, and cerebrospinal fluid should be sampled if clinical evidence of involvement exists. The CDC Infectious Diseases Pathology Branch offers polymerase chain reaction (PCR) testing to aid with molecular identification of *M. tuberculosis* on both fresh and formalin-fixed tissue. Clinical providers and pathologists should first contact their state or local health department to refer specimens for evaluation. Health departments should then contact pathology@cdc.gov for consultation preapproval. The yield of mycobacterial urine and blood cultures depends on the clinical setting; among patients with advanced immunodeficiency, the yield of culture from these two readily available body fluids can be relatively high[89,94] and may allow definitive diagnosis and be the only source of an isolate for drug-susceptibility testing (DST).[105]

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 therapy and make decisions about the need for respiratory isolation.

NAA tests are more sensitive than AFB smear, being positive in 50 percent to 80 percent of smear-negative, culture-positive specimens[106,107] and up to 90 percent when three NAA tests are performed. Therefore, it is recommended that for all patients with suspected pulmonary TB, a NAA test be performed on at least one specimen.[44,108] NAA tests also can be used on extrapulmonary specimens with the caveat that the sensitivity is often lower than with sputum specimens.[44]

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 patients with HIV.[109] 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 percent (95% confidence interval [CI], 83% to 92%) and 98 percent (95% CI, 97% to 99%), respectively. The assay is somewhat less sensitive among people with HIV (pooled sensitivity of 80%; 95% CI, 67% to 88%) than among patients without HIV (pooled sensitivity of 89%; 95% CI, 81% to 94%);[110] however, this may be, in part, attributed to a higher prevalence of smear-negative disease in people with HIV.[111] In South Africa, the sensitivity of Xpert MTB/RIF has been related to CD4 count, with higher sensitivity among patients with more advanced immunodeficiency.[112]

Xpert MTB/RIF sensitivity in extrapulmonary specimens is up to 95 percent in smear-positive specimens and 69 percent in smear-negative specimens.[113] 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,[114] which may provide an alternative for those people with HIV who are being evaluated for TB and unable to expectorate.

The next-generation 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. Currently, the Xpert platform is being modified to incorporate other drug-resistance targets that may assist in constructing a treatment regimen for drug-resistant TB, particularly in settings without access to conventional growth-based or sequencing-based DST (see Drug-Resistance Testing, below).[115]

Lipoarabinomannan (LAM)

LAM is an *M. tuberculosis* cell wall polysaccharide that can be detected in the urine of people with TB.[116-119] LAM has been shown to be more sensitive and specific as an adjunct diagnostic test in people with HIV with advance immunosuppression, but LAM assays are not commercially available in the United States.

Drug-Resistance Testing

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 isoniazid and rifampin should be performed on the initial isolates from all patients suspected of having TB, because resistance to isoniazid or rifampin is associated with an increased risk of treatment failure, recurrent TB, and amplification of resistance to additional TB medications.[120]

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 kanamycin, amikacin, or capreomycin) is associated with a markedly increased risk of death.[121] 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*.[44]

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. Molecular resistance testing should be performed, and DSTs should be repeated if sputum cultures remain positive for *M. tuberculosis* at or after 4 months of treatment or become positive 1 month or

longer after culture conversion to negative. Resistance testing for second-line TB medications (fluoroquinolones, bedaquiline, linezolid, clofazimine, aminoglycosides, 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.[108]

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,[122] due to the slow growth of *M. tuberculosis*. During this time, patients 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.[121] 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.[123] Commercial NAA tests—such as Xpert MTB/RIF—identify resistance mutations associated with rifampin, and commercially available line probe assays (LPAs) identify genotypic resistance for rifampin and isoniazid.[111,124] Of note, 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 above 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 persons for drug-resistant TB (https://www.cdc.gov/tb/topic/laboratory/default.htm). 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 CDC's Division of TB Elimination Laboratory.

In low TB prevalence settings—such as the United States—the positive predictive value for NAA tests of rifampin resistance is low.[125] Therefore, isolates with an initial reading of rifampin resistance by commercial NAA test should undergo confirmatory testing (*rpoB* gene sequencing and phenotypic DST). 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

TB among persons 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).**

Preferred for Treatment, Including Duration of Therapy for People with HIV

Treatment of TB for people with HIV is the same as for individuals without HIV and should include an initial four-drug combination of isoniazid, rifampin, ethambutol, and pyrazinamide[126] **(AI).** The preferred regimens are indicated in the table at the end of this chapter. Recommended dosing for drugs is summarized in the following table.

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

TB Drug	ARV Drugs	Daily Dose
Isoniazid	All ARVs	5 mg/kg (usual dose 300 mg)
Rifampin[a,b] Note: DTG, RAL, and MVC doses need to be adjusted when used with rifampin.	HIV PIs, DOR, ETR, RPV, BIC, CAB, or EVG/c	Not recommended
	TAF	Use with caution[c] at dose indicated below.
	All other ARV drugs	10 mg/kg (usual dose 600 mg)
Rifabutin[a] Note: DOR and RPV[d] doses need to be adjusted when used with rifabutin.	PI with COBI, TAF, RPV (IM), BIC, CAB, EVG/c-containing regimens	Not recommended
	DTG, RAL, DOR, EFV, or RPV (PO only[d])	5 mg/kg (usual dose 300 mg)
	HIV PIs with RTV	150 mg daily[e]
	EFV	450–600 mg
Pyrazinamide	All ARVs	Weight-based dosing • *Weighing 40–55 kg*: 1,000 mg (18.2–25.0 mg/kg) • *Weighing 56–75 kg*: 1,500 mg (20.0–26.8 mg/kg) • *Weighing 76–90 kg*: 2,000 mg (22.2–26.3 mg/kg) • *Weighing >90 kg*: 2,000 mg[f]
Ethambutol	All ARVs	Weight-based dosing • *Weighing 40–55 kg*: 800 mg (14.5–20.0 mg/kg) • *Weighing 56–75 kg*: 1,200 mg (16.0–21.4 mg/kg) • *Weighing 76–90 kg*: 1,600 mg (17.8–21.1 mg/kg) • *Weighing >90 kg*: 1,600 mg[f]

[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] This combination has not been tested in patients to confirm pharmacokinetic and virologic efficacy among patients taking full-dose ARV and TB regimens.

[d] IM long-acting RPV is not recommended with rifabutin. PO RPV can be used but the dose should be increased to 50 mg daily.

[e] Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150 mg twice weekly, 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.

Key: ARV = antiretroviral; BIC = bictegravir; CAB = cabotegravir; COBI = cobicistat; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; IM = intramuscular; MVC = maraviroc; PI = protease inhibitor; PO = oral; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TB = tuberculosis

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.

DOT monitored by trained health care workers, who can be community-based or clinic-based, is recommended for all patients 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.[127-130] 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 patients establish or re-engage with HIV care.

Drug-susceptible TB should be treated with a 2-month (8-week) intensive phase regimen 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).**[126]

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.[131-139] Therefore, daily therapy given as DOT is recommended during both the intensive and continuation treatment phases **(AII).**[126,137,138,140]

Although earlier recommendations[141] for TB treatment in persons without HIV indicated that therapy should be based on the number of doses received rather than the duration of therapy, no data substantiate the minimum number of doses needed within a specified time interval in people with HIV.[126] Every effort should be made to ensure that patients receive daily therapy as previously described, allowing up to 28 weeks to complete ≥24 weeks (6 months) of treatment to accommodate brief interruptions of therapy for management of adverse drug reactions as described below.

The optimal duration of TB treatment for people with HIV and drug-susceptible TB disease is not known. In general, the outcomes of 6-month regimens given as DOT to people with HIV have been favorable.[1] A randomized but underpowered trial in the United States showed excellent and comparable outcomes of TB therapy among patients assigned to 6 months or 9 months of therapy.[142]

Two trials in high-burden settings showed higher risk of recurrent TB among patients treated with 6 months of therapy than among those assigned to 9-month[131] or 12-month regimens.[143] 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.

Treatment shortening for drug-susceptible TB remains a goal of current clinical trials. Three large international randomized trials of TB treatment shortening that used strategies involving substitution

of isoniazid, ethambutol, or both with a fluoroquinolone and/or rifapentine in 4-month regimens all found that the shorter regimens were inferior.[144-146] In each study, the 4-month regimens were associated with higher relapse rates or unfavorable outcomes than a standard 6-month regimen. However, a recently reported trial demonstrated non-inferiority for a 4-month regimen of isoniazid, rifapentine, ethambutol, and moxifloxacin compared to a standard 6-month regimen in patients with and without HIV,[147] and that 4-month regimen may emerge as an acceptable alternative. Additional TB treatment shortening trials using alternative strategies in participants with HIV and TB coinfection are ongoing.

Extension of therapy to 9 months is recommended for patients who have a positive sputum culture after 2 months of treatment or severe cavitary or disseminated extrapulmonary disease **(BII).** Most extrapulmonary TB can be treated for 6 months, but TB meningitis should be treated for 9 to 12 months **(BII).**

Recent clinical trials have suggested the use of higher rifampin doses or addition of fluoroquinolone 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 pending results of additional studies.[148-154]

Adjunctive corticosteroid therapy is recommended in individuals with HIV who have TB involving the CNS **(AII)** and should include dexamethasone (0.3–0.4 mg/kg/day for 2–4 weeks, then taper by 0.1 mg/kg per week until dose of 0.1 mg/kg, then 4 mg per day and taper by 1 mg/week) for a total duration of 12 weeks.[97,126] Adjunctive corticosteroid therapy increases survival overall for patients with TB meningitis, although studies were underpowered for detecting a statistically significant survival benefit for those with HIV.[97,155]

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.[156] A Cochrane review similarly found no mortality benefit from adjunctive corticosteroids and a nonsignificant reduction in constrictive pericarditis. Notably, however, <20 percent of people with HIV in the trials analyzed were receiving ART.[157] No trials have been conducted comparing different doses and treatment durations of adjunctive corticosteroids.

Special Considerations with Regard to Starting ART

The preponderance of data from randomized trials in people with HIV with TB disease supports the recommendation that ART should not be withheld until completion of TB treatment **(AI).**[158] Co-treatment of HIV and TB is complex due to adherence demands of multidrug therapy for two infections, drug–drug interactions between the rifamycins and many ARV drugs, overlapping side effect profiles of anti-TB and ARV drugs, and the risk of immune reconstitution inflammatory syndrome (IRIS), particularly with TB meningitis. However, concurrent treatment of HIV and TB for coinfected patients in the appropriate clinical setting improved survival[158] (particularly for persons[159] with CD4 counts <50 cells/mm^3); decreased the risk of additional opportunistic illnesses[160,161]; and, despite higher rates of IRIS in those with low CD4 counts, was not associated with higher rates of ARV or anti-TB treatment limiting toxicity.[161] Therefore, ART is recommended for all people with HIV with TB **(AI).** For ART-naive patients, ART should be started within 2 weeks after TB

treatment initiation in those with CD4 count <50 cells/mm^3 when TB meningitis is not suspected and within 8 weeks of starting anti-TB treatment in those with higher CD4 cell counts **(AI).** Rifamycin-associated drug interactions should be considered when selecting the ARV drug regimen.

The evidence supporting concurrent anti-TB therapy and ART comes primarily from four large, randomized trials. The Starting Antiretroviral Therapy at Three Points in Tuberculosis trial randomized 642 South African adults with CD4 counts <500 cells/mm^3 and AFB smear-positive TB to start ART, either after the completion of the intensive phase of TB therapy or after TB treatment completion.[158] The study was stopped early, because integrated TB and ARV treatment decreased mortality by 56 percent compared to sequential treatment. Notably, a survival benefit was observed across the range of CD4 counts among patients enrolled, including within the stratum of baseline CD4 counts from 200 to 500/mm^3.

In the Cambodian Early versus Late Introduction of Antiretrovirals trial, 661 adults in Cambodia with confirmed pulmonary TB and a median CD4 count of 25 cells/mm^3 (interquartile range [IQR], 10, 56) were randomized to receive ART at 2 or 8 weeks after starting TB treatment. The mortality rate was significantly lower in the early ART arm (8.28 per 100 person-years versus 13.77 per 100 person-years in the delayed ART arm; $P = 0.002$),[162] and >95 percent of the study participants who survived had viral suppression. The ACTG A5221 STRIDE study and the TB-HAART trial, and additional multinational trials of early versus delayed ART in 809 and 1,538 people with HIV, respectively, demonstrated similar results; although in the TB-HAART trial, differences in mortality, adverse events, and incidence of IRIS did not reach statistical significance.

The optimal approach for initiation of ART in TB meningitis remains uncertain. A randomized trial among 253 patients with HIV-related TB meningitis conducted in Vietnam compared immediate ART (within 7 days of starting TB treatment) with delayed ART initiated 2 months after starting TB treatment.[163] Mortality was similar in both arms, and early ART was associated with more frequent and severe adverse events than delayed ART (86% vs. 75% of participants, respectively). The overall mortality rate in this study was very high (58%); most participants had advanced immunosuppression (median baseline CD4 count was 41 cells/mm^3). Based upon this study, CDC/American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines recommend that patients with TB meningitis should not start ART before 8 weeks of TB treatment is completed, regardless of CD4 count,[126] but it is unclear whether the study's findings are generalizable to higher resourced settings. Many experts recommend that in people with HIV with TB meningitis, ART should be initiated within the first 2 to 8 weeks after starting anti-TB treatment, opting for the first 2 weeks in those with CD4 counts <50 cells/mm^3 in settings where close monitoring of drug-related toxicities and CNS adverse events is feasible **(AIII).**

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

When TB occurs in patients already on ART, treatment for TB must be started immediately **(AIII),** and ART should be modified to reduce the risk for 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

The rifamycin class of antibiotics is the key to effective and shorter-course treatment for drug-sensitive TB. However, the currently available rifamycins (rifampin, rifabutin, and rifapentine) have clinically significant interactions with several ARV drugs, and these interactions should be taken into consideration before initiating therapy (see Dosing Recommendations for Anti-TB Drugs table, above, and the Tuberculosis/HIV Coinfection section of the Adult and Adolescent Antiretroviral Guidelines). These drug–drug interactions are complex, but most result from the potent induction by the rifamycin of genes involved in the metabolism and transport of ARV agents. Although no clinical trials specifically compare rifampin- and rifabutin-containing anti-TB regimens among people with HIV with TB taking ART, in general, rifabutin is regarded as a reasonable substitute for rifampin for the treatment of TB in people with HIV who must concurrently receive antiretroviral drugs that have adverse drug interactions with rifamycins, because rifabutin is a less potent inducer of CYP3A4 than rifampin.[164,165]

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 when used in preferred ART regimens. The newer tenofovir formulation, tenofovir alafenamide (TAF), is a substrate of drug transporters, including P-glycoprotein, and is more likely to have drug–drug interactions than TDF. A recent study conducted among healthy volunteers without HIV infection showed that concentrations of the active form of tenofovir, namely intracellular tenofovir-diphosphate, 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.[166] Caution is urged, however, because this combination has not been tested in patients to confirm PK and virologic efficacy among patients taking full-dose ARV and TB regimens. Neither TDF nor TAF has been fully evaluated with rifabutin, and TAF has not been evaluated with rifapentine; therefore, concurrent therapy with these drugs is not recommended **(AIII).**

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

One preferred 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).** Efavirenz-based ART is associated with excellent TB and HIV treatment outcomes and has low rates of serious toxicity.[167] Recent studies in people with HIV with 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.[168-170] A disadvantage of using a higher dose of efavirenz than the recommended 600 mg daily dose when co-administered with TB treatment is that slow metabolizers of efavirenz (about 20% of people of African, Thai, or Indian ancestry) who already have high efavirenz concentrations will have a further (approximately 50%) increase in efavirenz concentrations during TB treatment due to the inhibition by isoniazid of the accessory cytochrome P450 enzyme CYP2A6.[171] Given the preponderance of data and the excellent treatment outcomes of co-treatment with standard-dose efavirenz,[167,172] the 600 mg daily dose of efavirenz is recommended **(AII).**

Although still used in some international resource-limited settings, nevirapine is used rarely in high-resource settings and **is not recommended** in these settings for HIV and TB co-treatment.[173] The use of rifampin or rifapentine with doravirine, etravirine, or rilpivirine **is not recommended (AIII)** (see the Dosing Recommendations for Anti-TB Drugs table, above, and the Tuberculosis/HIV Coinfection section of the Adult and Adolescent Antiretroviral Guidelines).

Some experts might consider substitution of rifabutin for rifampin with appropriate dose adjustment of rifabutin or of the NNRTI (e.g., increasing doravirine dosing to 100 mg twice daily and increasing oral rilpivirine to 50 mg daily), where appropriate,[174,175] for patients who require one of these NNRTIs;[176] however, IM rilpivirine is not recommended. 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

Alternatives to efavirenz-based ART for people with HIV with TB include regimens with integrase inhibitors or protease inhibitors (PIs). One alternative co-treatment regimen is the combination of raltegravir-based ART, using raltegravir 400 or 800 mg twice daily, with standard rifampin dosing **(BI).**[177] Raltegravir concentrations are decreased significantly when co-administered with rifampin. Increasing the dose of raltegravir to 800 mg twice daily mitigates this PK interaction.[178] The recommended dose of raltegravir is 800 mg twice daily if used with rifampin; this should be adjusted to standard raltegravir dosing after completion of TB treatment. 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 dose adjustment of either drug **(BII).**[179]

Dolutegravir-based ART is also an alternative integrase inhibitor option. 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.[180] A Phase 2 trial in people with HIV with 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.[181] Dolutegravir is recommended in a dose of 50 mg twice daily when used together with a rifampin-containing TB regimen **(AI)** and should be used in a standard 50 mg once-daily dose when used with rifabutin **(AII).** Bictegravir **should not be used** together with rifamycin-containing TB treatment (rifampin, rifabutin, or rifapentine) **(AI).** A recent trial conducted among healthy participants without HIV evaluated bictegravir concentrations when given twice daily together with rifampin versus once daily alone.[182] Bictegravir trough concentrations, even with the dose adjustment, were reduced by 80 percent. Although studied only with rifabutin, based on similar concerns, elvitegravir/cobicistat **should not be used** together with TB treatment that contains rifamycins **(AI).**[183] When given at steady-state with oral cabotegravir, rifampin decreased cabotegravir AUC by 59% in healthy volunteers. 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 41-46%.[184] As a result, oral and long-acting injectable cabotegravir **should not be used** with any rifamycin **(AII).**[185]

Protease Inhibitors with Rifampin or Rifabutin

Rifampin decreases the plasma concentrations and exposure of co-administered PIs by >75 percent.[186-189] The effects of rifampin on lopinavir/ritonavir may be overcome by doubling the dose of lopinavir/ritonavir.[188,190] High rates of hepatotoxicity were reported when dose-adjusted ritonavir-boosted PIs were given with rifampin to healthy volunteers.[191-193] However, in people with HIV with TB, double doses of lopinavir/ritonavir are reasonably well tolerated in those on rifampin-based TB treatment.[194] In a study in people with HIV with TB, the combination of double-dose lopinavir/ritonavir with rifampin resulted in acceptable safety, drug concentrations, and TB treatment response, although HIV suppression at 48 weeks was less than expected, unrelated to PK parameters.[194] Some experts would consider this an alternative when a PI-based ART regimen is required during TB treatment **(BI).** The strategy of increasing ritonavir dosing to 400 mg twice daily (known as "super-boosting") may lead to higher rates of hepatotoxicity.[190,195,196] Thus, a strategy of first increasing the dose of lopinavir/ritonavir by 50 percent, then increasing to a full double dose is recommended if this regimen is used **(BIII).** 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). A recent trial tested adjusted doses of ritonavir-boosted darunavir (1600/200 mg once daily and 800/100 mg twice daily) with rifampicin in people with HIV without TB.[197] 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 **should not be used** together with rifampin, even with dose adjustment **(AI).**

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[194,198] or atazanavir[199] and only moderately increases concentrations of ritonavir-boosted darunavir[200] and fosamprenavir.[201] 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 to avoid dose-related toxicity, such as uveitis and neutropenia[194,202] **(AI).**

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.[203,204] Among people with HIV with TB, cases have been reported of acquired rifamycin resistance with 150 mg three times weekly doses of rifabutin when co-administered with a boosted PI-based ARV regimen.[205,206] 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.[194] 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.

The breadth and magnitude of drug–drug interactions between the rifamycins and many ARV drugs can be daunting. Nevertheless, every effort should be made to include a rifamycin in the TB treatment regimen; the drug–drug interactions between rifamycins and ARV drugs should be managed, not avoided. Rifamycins remain the most potent drug class for TB treatment, and regimens that included only 2 months of rifampin were associated with increased risks of treatment failure and TB recurrence among patients with HIV-related TB.[146,207] If a rifamycin cannot be used, TB treatment duration must be extended, and treatment complexity increases substantially. Thus, patients

with rifamycin-susceptible *M. tuberculosis* isolates should be treated with a regimen that does not contain a rifamycin only when the patient has had a serious adverse event that is highly likely due to a rifamycin **(AIII).**

Monitoring the Response to Therapy

Patients with pulmonary TB should have 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 by 2 months of first-line TB therapy, although sputum culture conversion to negative may take longer for patients with cavitary TB disease.[208] Sputum cultures that do not convert to negative at or after 4 months of therapy indicate treatment failure and should prompt drug-resistance testing of any 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, 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.

Patients with suspected treatment failure should be evaluated with a medical history, physical exam, and chest radiograph to determine whether the patient has responded clinically to therapy, even though sputum culture conversion has not occurred. The initial culture results and drug-resistance tests, treatment regimen, and patient 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.[126,209] 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 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

Many adverse drug reactions are shared between ARVs and drugs used for anti-TB therapy. Retrospective observational studies reported an increased risk of adverse drug reactions in patients treated with concomitant ART and anti-TB therapy,[210] but two recent randomized controlled trials of ART initiated during or after anti-TB therapy 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.[158,161] However, 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 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.[126] Drug-induced liver injury (DILI) can be caused by isoniazid, rifamycins, pyrazinamide, many ARV drugs, and cotrimoxazole. 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) or ≥5 times the ULN in the absence of symptoms. An increase in ALT concentration occurs in approximately 5 percent to 30 percent of patients treated with the standard four-drug anti-TB regimen,[86,211] but many of these patients only have transient, mild elevations of ALT.[86]

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 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 should be started (e.g., ethambutol, linezolid, and moxifloxacin or levofloxacin)[212] as a "bridging regimen" until the specific cause of hepatotoxicity can be determined and an alternative longer-term regimen constructed **(BIII).**

After the patient's ALT level returns to <2.5 times the ULN (or to near baseline for those with preexisting abnormalities), a 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, the patient's ALT levels should be monitored frequently.

Rechallenge was successful in almost 90 percent of patients without HIV in one randomized controlled trial of different rechallenge regimens.[212] 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,[213,214] and some experts would therefore recommend rechallenge with pyrazinamide in patients 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 cotrimoxazole may be restarted.

Cutaneous adverse drug reactions may occur with all anti-TB drugs, notably rifampin and isoniazid[215]; many ARV drugs, notably the NNRTIs; and cotrimoxazole. 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

cotrimoxazole 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 cotrimoxazole may be recommenced.

Managing Drug-Resistant TB

Although drug-resistant TB represents a small fraction of the TB cases in the United States, the increasing number of persons with of 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 first- and second-line TB medications must be used, but clinical trial data on their optimal use are limited, and most recent studies have been conducted primarily in high TB endemic resource-constrained settings.

In the United States, approximately 7 percent of patients with TB have baseline isoniazid mono-resistance.[3] Growing evidence demonstrates that an increased risk of treatment failure associated with isoniazid monoresistance exists,[216] particularly in people with HIV with TB.[217] For patients with isoniazid monoresistance, it is recommended that a fluoroquinolone (levofloxacin or moxifloxacin) be substituted for isoniazid and given together with rifampin, pyrazinamide, and ethambutol for 6 months **(BII).**[83,218-220]

In late 2019, ATS, CDC, IDSA, and the European Respiratory Society (ERS) issued MDR TB treatment guidelines recommending a fully oral regimen for most patients with drug-resistant TB, including people with HIV.[83] Similar to the World Health Organization (WHO) drug-resistant TB guidelines,[220] the ATS/CDC/IDSA/ERS guidelines ranked the second-line drugs and recommend an initial regimen containing bedaquiline, linezolid, levofloxacin/moxifloxacin, clofazimine, and cycloserine/terizidone. All remaining drugs were placed in a lower tier to complete the regimen only when the recommended drugs cannot be used. Notably, kanamycin and capreomycin are no longer recommended because an increased risk of treatment failure and relapse is seen with their use.[221] Such an association was not seen for amikacin, which may be used when other, less toxic drugs cannot be used.

For people with HIV with MDR TB, several important drug–drug interactions occur between bedaquiline and some ARV drugs. Specifically, efavirenz decreases bedaquiline plasma concentrations.[222] For people with HIV with MDR TB, efavirenz **should not be used** concurrently with bedaquiline **(AI).** Lopinavir/ritonavir increases bedaquiline plasma concentrations approximately twofold when given at steady-state, but the clinical significance of this increase is not yet known.[223,224]

Although the ATS/CDC/IDSA/ERS guidelines are largely concordant with the WHO guidelines, they recommend using a minimum of five active drugs (versus four) and a treatment duration of 15 to 24 months *after culture conversion* (compared with 18–20 months *total duration*).[83,225] If possible, people with HIV with MDR TB should receive an all-oral regimen based on the ATS/CDC/IDSA/ERS guidelines **(AII).** Although these current guidelines recommend a total duration of 15 to 24 months following sputum culture conversion, several clinical trials examining regimens with total durations as short as 6 to 12 months have shown TB treatment success rates comparable to or better than longer duration therapy when bedaquiline was included.[225-228]

Pretomanid, a novel oral antimycobacterial agent, was approved by the FDA in 2019 as part of a 6-month all-oral "BPaL" (bedaquiline, pretomanid, and linezolid) regimen. The study on which approval was based was a single-arm study in only 109 patients,[227] of whom 51 percent were people with HIV. Although studies are underway to further evaluate this novel regimen in persons with MDR and XDR TB with and without HIV, data are insufficient to recommend the use of the BPaL regimen in individuals with or without HIV in high-resource settings like the United States, where full DST and individualized treatment options are available.

Treatment of MDR TB should involve an expert with experience in treating drug-resistant TB. If a local expert is not available through the public health department, clinicians and TB programs can contact 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's driving inflammatory reactions directed at *M. tuberculosis* antigen present at sites of disease.[229-231] 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.[232]

Paradoxical TB-IRIS

Paradoxical TB-IRIS occurs in patients who are diagnosed with active TB disease before starting ART. Typically, these patients 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,[230,233] 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.[230,234,235] In patients with disseminated TB, hepatic TB-IRIS is common, manifesting with nausea and vomiting, tender hepatic enlargement, cholestatic liver function derangement, and occasionally jaundice.[231,236] A liver biopsy often reveals a granulomatous hepatitis.[237] 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 recent meta-analysis of 40 studies reported a pooled incidence of TB-IRIS of 18 percent in adults with HIV-associated TB initiating ART, with death attributed to TB-IRIS in 2 percent of the cases.[238] The onset of paradoxical TB-IRIS symptoms is typically between 1 to 4 weeks after ART is initiated.[239-244] The syndrome lasts for 2 to 3 months on average,[243,245] 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.[232,245,246] 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/mm^3;[242,247] high HIV viral load before ART[248,249]; disseminated or extrapulmonary TB[234,241,243,247]; 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.[234,240,242] 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/mm^3, to reduce the risk of HIV progression and death **(AI).**[238]

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).[250]

Managing Paradoxical TB-IRIS

Most cases of paradoxical TB-IRIS are self-limiting. Many patients 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.[234]

In patients 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.[251] 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).**[251] Patients on prednisone experienced more rapid symptom 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. The above study,[251] observational data,[235] and clinical trials that showed reduced mortality in patients presenting with TB meningitis who were treated with corticosteroids[97] suggest that corticosteroids (either intravenous dexamethasone or oral prednisone) should be used when TB-IRIS involves the CNS (e.g., enlarging tuberculoma, new or recurrent meningeal inflammation) at the time of presentation. Rifampin increases the clearance of prednisolone (the active metabolite of prednisone),[252] but no such effect is seen with rifabutin; dosing of prednisone should therefore be adjusted in patients receiving rifampin or rifabutin-containing regimens (See the table below, Recommendations for Treating *Mycobacterium tuberculosis* Infection and Disease). Corticosteroids should be avoided in patients with Kaposi sarcoma because life-threatening exacerbations can occur. Case reports have been published of patients with steroid-refractory and prolonged IRIS responding to TNF-blockers or thalidomide.[253-255]

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-naive 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.[256] High-risk was defined as starting ART within 30 days after TB treatment initiation and a CD4 count ≤100/mm^3. Those with rifampin resistance,

neurological TB, Kaposi sarcoma, HBsAg positive, and poor clinical response to TB treatment before ART were excluded. The incidence of TB-IRIS was 47 percent in the placebo arm and 33 percent 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 ≤100/mm^3) who are responding well to TB therapy and who do not have rifampin resistance, Kaposi sarcoma, or active hepatitis B (**BI).**

Unmasking TB-IRIS

Unmasking TB-IRIS may occur in patients who have unrecognized TB (because TB is either oligo-symptomatic or it has eluded diagnosis) at the start of ART. These patients may present with a particularly accelerated and inflammatory presentation of TB in the first weeks of ART.[232] 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.[232,251,257-259] Focal inflammatory manifestations—such as abscesses and lymphadenitis— also may develop.[260] 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 no clinical trial evidence exists to support steroid use in this setting **(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.[261] 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.[262,263] In settings with low rates of TB—such as the United States—recurrent TB due to re-infection is uncommon, even among patients with HIV.[264]

Several interventions may decrease the risk of recurrent TB among patients 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,[265,266] suggesting that this intervention decreases the risk of re-infection. Post-treatment isoniazid **is not recommended** in low-burden settings—such as the United States—because of lack of evidence of effectiveness on reducing risk of re-infection for these settings **(AII).** 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

Pregnant people with HIV infection who do not have documentation of a prior negative TB screening test result or who are at high risk for repeated or ongoing exposure to individuals with active TB disease should be tested for TB during pregnancy **(AIII).** The frequency of anergy is not increased during pregnancy, and routine anergy testing in pregnant people with HIV is not recommended.[267-270]

Several studies have examined the performance of IGRAs for diagnosis of LTBI in pregnant women.[271,272] In pregnant women with or without HIV, the test appears to perform well.[273]

A recent clinical trial of isoniazid preventive therapy (IPT) among HIV-infected women in high TB prevalence settings found increased adverse pregnancy outcomes in women treated with isoniazid during pregnancy compared to deferring this treatment until after delivery.[274] 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. In the United States, IPT is recommended for pregnant women with HIV whose close household contacts include a person with active TB disease **(AI).** 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.[275,276] However, the risk of progression from LTBI to active TB disease in individuals on ART is decreased significantly.[277] Pregnant people with HIV should be receiving ART both for their own health and for prevention of perinatal transmission. For those receiving effective ART and without 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 if isoniazid is prescribed, frequent monitoring is needed.[278] Pregnant people receiving isoniazid should receive daily pyridoxine supplementation **(AII)** because they are at risk of isoniazid-associated peripheral neuropathy.[126,279] No data exist on alternatives to isoniazid for LTBI therapy in pregnant people with HIV. Although rifampin generally is considered safe in pregnancy, data on the use of rifapentine are extremely limited and its use in pregnant people is not recommended **(AIII).**[280-282]

The diagnostic evaluation for TB disease in pregnant people is the same as for nonpregnant adults. Chest radiographs with abdominal shielding are recommended and result in minimal fetal radiation exposure. 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 begins late in pregnancy.[267-278,283-287] Congenital TB infection has been reported, although it appears relatively uncommon.[288-292]

Treatment of TB disease for pregnant people should be the same as for nonpregnant people, 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.[293] 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[294,295] have made recommendations for the routine use of pyrazinamide in pregnant individuals. Pyrazinamide has been recommended for use in pregnant people in the United States, although data characterizing its safety in this setting are limited and CDC guidance suggests that clinicians consider the use of this agent based on individual patient

considerations weighing benefit and risks.[126,296] 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 for a pregnant person should be made after consultation among obstetricians, TB specialists, and the patient, while considering gestational age and likely susceptibility pattern of the TB strain.

TB therapy should not be withheld because of pregnancy **(AIII).** Considering the information above, the preferred first-line treatment for drug-susceptible TB in pregnancy is isoniazid, rifampin, and ethambutol for a duration of 9 months. Experience using the majority of the second-line drugs for TB during pregnancy is limited.[297-300] MDR TB in pregnancy should be managed in consultation with a specialist. The following concerns should be considered when selecting second-line anti-TB drugs for use in pregnant people:

- **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%; $P = 0.034$).[301] After 1 year, however, 88 percent of the children exposed to bedaquiline had gained weight and were doing well.
- **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.[302-304] Case reports have documented cases of CNS defects in humans, but overall experience is limited with use during human pregnancy.[305] 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 for pregnant people or 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.[306-308] Thus, fluoroquinolones can be used in pregnancy for drug-resistant TB if they are required on the basis of susceptibility testing **(CIII).**[309]
- **Para-aminosalicylic acid** is not teratogenic in rats or rabbits.[296] 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.[310] 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 percent 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 percent 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 treatment of MDR TB **(CIII).**

Recommendations for Treating *Mycobacterium tuberculosis* Infection and Disease

Treating LTBI to Prevent TB Disease in People with HIV

Indications

- Positive screening test[a] for LTBI, no evidence of active TB disease, and no prior history of treatment for active disease or latent TB infection (AI)
- Close contact with a person with infectious TB, regardless of screening test result (AII)

Preferred Therapy

- Rifapentine (see weight-based dosing below) PO once weekly plus isoniazid 15 mg/kg PO once weekly (900 mg maximum) plus pyridoxine 50 mg PO once weekly for 12 weeks (AI). Note: Rifapentine is recommended only for virally-suppressed patients receiving an efavirenz-, raltegravir-, or once-daily dolutegravir-based ARV regimen (AI).
  - Rifapentine Weekly Dose (maximum 900 mg)
    - *Weighing 32.1–49.9 kg*: 750 mg
    - *Weighing ≥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. See the Dosing Recommendations for Anti-TB Drugs table for the list of ARV drugs not recommended for use with rifampin and those which require dosage adjustment (i.e., raltegravir, dolutegravir, or maraviroc).

Alternative Therapies

- Isoniazid 300 mg PO daily plus pyridoxine 25–50 mg PO daily for 6–9 months (AII) *or*
- Rifampin 600 mg PO daily for 4 months (BI) See the Dosing Recommendations for Anti-TB Drugs table (above) for the list of ARV drugs not recommended for use with rifampin and those which require dosage adjustment (i.e., raltegravir, dolutegravir, or maraviroc) *or*
- Isoniazid 300 mg PO daily plus rifapentine PO daily plus pyridoxine 25–50 mg PO daily for 4 weeks (BI) Note: Rifapentine is recommended only for patients receiving an efavirenz-based ARV regimen (AI).
  - Rifapentine Daily Dose (maximum 600 mg)
    - *Weighing <35 kg*: 300 mg
    - *Weighing 35–45 kg*: 450 mg
    - *Weighing >45 kg*: 600 mg

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

Treating Active TB Disease in People with HIV

- 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 Anti-TB Drugs table (above) for 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.

For Drug-Susceptible TB

Intensive Phase (2 Months)

- Isoniazid plus (rifampin or rifabutin) plus pyrazinamide plus ethambutol (AI)
- If drug susceptibility report shows sensitivity to isoniazid and rifampin, then ethambutol may be discontinued (AI).

Continuation Phase (for Drug-Susceptible TB)

- Isoniazid plus (rifampin or rifabutin) daily (AII)

Total Duration of Therapy

- Pulmonary, drug-susceptible, uncomplicated TB: 6 months (BII)
- Pulmonary TB and positive culture at 2 months of TB treatment, severe cavitary disease or disseminated extrapulmonary TB: 9 months (BII)
- Extrapulmonary TB with CNS involvement: 9–12 months (BII)
- Extrapulmonary TB in other sites: 6 months (BII)

For Drug-Resistant TB

Empiric Therapy for Resistance to Rifamycin Plus/Minus Resistance to Other Drugs

- Isoniazid plus pyrazinamide plus ethambutol plus (moxifloxacin or levofloxacin) plus (linezolid or amikacin) (BII)
- Therapy should be modified once rifampin resistance is confirmed and based on drug susceptibility results to provide ≥5 active drugs (BII).

Resistant to Isoniazid

- (Moxifloxacin or levofloxacin) plus (rifampin or rifabutin) plus ethambutol plus pyrazinamide for 6 months (BII)

Resistant to Rifamycins Plus/Minus Other Antimycobacterial Agents

- Therapy should be individualized based on drug susceptibility test results and clinical and microbiological responses, to include ≥5 active drugs, and with close consultation with experienced specialists (AIII).

Duration

- 12–24 months (see Management of Drug-Resistant TB section above for discussion of shorter-course therapy)

Other Considerations in TB Management

- Adjunctive corticosteroid improves survival for patients with HIV-related TB involving the CNS (AI).
- 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.
- Despite the potential of drug–drug interactions, a rifamycin remains 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 Anti-TB Drugs table (above) 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 development of resistance in patients with HIV and is not recommended (AI).
- Paradoxical reaction that is not severe may be treated symptomatically (CIII).
- For moderately severe paradoxical reaction, use of corticosteroid may be considered. Taper over 4 weeks (or longer) based on clinical symptoms (BIII).

Examples of Prednisone Dosing Strategies for IRIS

- In patients on a rifampin-based regimen: prednisone 1.5 mg/kg/day for 2 weeks, then 0.75 mg/kg 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
- A more gradual tapering schedule over a few months may be necessary in some patients.
- Preemptive prednisone regimen: 40 mg/day for 2 weeks then 20 mg/day for 2 weeks

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

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