Mycobacterium tuberculosis Infection and Disease

(Last updated February 17, 2022; last reviewed February 17, 2022)

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 Table 3 [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.

Table 3. 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 Table 3, 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 [Table 3](#), 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.[267-277,283-288] Congenital TB infection has been reported, although it appears relatively uncommon.[289-293]

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.[294] 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[295,296] 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.[126,297] 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.[298-301] 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%; $P = 0.034$).[302] 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.[303-305] Case reports have documented cases of CNS defects in humans, but overall experience is limited with use during human pregnancy.[306] 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.[307-309] Thus, fluoroquinolones can be used in pregnancy for drug-resistant TB if they are required on the basis of susceptibility testing **(CIII).**[310]

- **Para-aminosalicylic acid** is not teratogenic in rats or rabbits.[297] 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.[311] 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)**.

  o 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 Table 3 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 Table 3 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)**.

  o 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 Table 3 (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 Table 3, 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

References

1. World Health Organization. Global tuberculosis report 2020. 2020. Available at: https://www.who.int/publications/i/item/9789240013131.

2. Dye C, Williams BG. Tuberculosis decline in populations affected by HIV: a retrospective study of 12 countries in the WHO African Region. *Bull World Health Organ*. 2019;97(6):405-414. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31210678.

3. Centers for Disease Control and Prevention. Reported Tuberculosis in the United States, 2019. 2019. Available at: https://www.cdc.gov/tb/statistics/reports/2019/default.htm

4. Kaplan JE, Hanson D, Dworkin MS, et al. Epidemiology of human immunodeficiency virus-associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. *Clin Infect Dis*. 2000;30 Suppl 1:S5-14. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10770911.

5. Buchacz K, Lau B, Jing Y, et al. Incidence of AIDS-defining opportunistic infections in a multicohort analysis of HIV-infected persons in the United States and Canada, 2000-2010. *J Infect Dis*. 2016;214(6):862-872. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27559122.

6. Selwyn PA, Hartel D, Lewis VA, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *N Engl J Med*. 1989;320(9):545-550. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2915665.

7. Selwyn PA, Sckell BM, Alcabes P, Friedland GH, Klein RS, Schoenbaum EE. High risk of active tuberculosis in HIV-infected drug users with cutaneous anergy. *JAMA*. 1992;268(4):504-509. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1619742.

8. Moreno S, Baraia-Etxaburu J, Bouza E, et al. Risk for developing tuberculosis among anergic patients infected with HIV. *Ann Intern Med*. 1993;119(3):194-198. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8100693.

9. Antonucci G, Girardi E, Raviglione MC, Ippolito G. Risk factors for tuberculosis in HIV-infected persons. A prospective cohort study. The Gruppo Italiano di Studio Tubercolosi e AIDS (GISTA). *JAMA*. 1995;274(2):143-148. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7596002.

10. Markowitz N, Hansen NI, Hopewell PC, et al. Incidence of tuberculosis in the United States among HIV-infected persons. The Pulmonary Complications of HIV Infection Study Group. *Ann Intern Med*. 1997;126(2):123-132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9005746.

11. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am J Epidemiol*. 1974;99(2):131-138. Available at: https://www.ncbi.nlm.nih.gov/pubmed/4810628.

12. Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S. How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort

study in South African gold miners. *J Infect Dis*. 2005;191(2):150-158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15609223.

13.   Wood R, Maartens G, Lombard CJ. Risk factors for developing tuberculosis in HIV-1-infected adults from communities with a low or very high incidence of tuberculosis. *J Acquir Immune Defic Syndr*. 2000;23(1):75-80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10708059.

14.   Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR Recomm Rep*. 2000;49(RR-6):1-51. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10881762.

15.   Horsburgh CR, Jr. Priorities for the treatment of latent tuberculosis infection in the United States. *N Engl J Med*. 2004;350(20):2060-2067. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15141044.

16.   Day JH, Grant AD, Fielding KL, et al. Does tuberculosis increase HIV load? *J Infect Dis*. 2004;190(9):1677-1684. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15478075.

17.   Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev*. 2010(1):CD000171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20091503.

18.   Miramontes R, Hill AN, Yelk Woodruff RS, et al. Tuberculosis infection in the United States: prevalence estimates from the National Health and Nutrition Examination Survey, 2011-2012. *PLoS One*. 2015;10(11):e0140881. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26536035.

19.   Badje A, Moh R, Gabillard D, et al. Effect of isoniazid preventive therapy on risk of death in west African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial. *Lancet Glob Health*. 2017;5(11):e1080-e1089. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29025631.

20.   Rangaka MX, Wilkinson RJ, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. *Lancet*. 2014;384(9944):682-690. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24835842.

21.   Temprano ANRS Study Group, Danel C, Moh R, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med*. 2015;373(9):808-822. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26193126.

22.   Ross JM, Badje A, Rangaka MX, et al. Isoniazid preventive therapy plus antiretroviral therapy for the prevention of tuberculosis: a systematic review and meta-analysis of individual participant data. *Lancet HIV*. 2021;8(1):e8-e15. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33387480.

23.   Golub JE, Saraceni V, Cavalcante SC, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. *AIDS*. 2007;21(11):1441-1448. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17589190.

24.   Fisk TL, Hon HM, Lennox JL, Fordham von Reyn C, Horsburgh CR, Jr. Detection of latent tuberculosis among HIV-infected patients after initiation of highly active antiretroviral therapy. *AIDS*. 2003;17(7):1102-1104. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12700468.

25.   Girardi E, Palmieri F, Zaccarelli M, et al. High incidence of tuberculin skin test conversion among HIV-infected individuals who have a favourable immunological response to highly active antiretroviral therapy. *AIDS*. 2002;16(14):1976-1979. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12351964.

26.   Markowitz N, Hansen NI, Wilcosky TC, et al. Tuberculin and anergy testing in HIV-seropositive and HIV-seronegative persons. Pulmonary Complications of HIV Infection Study Group. *Ann Intern Med*. 1993;119(3):185-193. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8100692.

27.   Campbell JR, Winters N, Menzies D. Absolute risk of tuberculosis among untreated populations with a positive tuberculin skin test or interferon-gamma release assay result: systematic review and meta-analysis. *BMJ*. 2020;368:m549. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32156698.

28.   Auguste P, Tsertsvadze A, Pink J, et al. Comparing interferon-gamma release assays with tuberculin skin test for identifying latent tuberculosis infection that progresses to active tuberculosis: systematic review and meta-analysis. *BMC Infect Dis*. 2017;17(1):200. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28274215.

29.   Pettit AC, Stout JE, Belknap R, et al. Optimal testing choice and diagnostic strategies for latent tuberculosis infection among U.S.-born people living with HIV. *Clin Infect Dis*. 2020:ciaa1135. Available at: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1135/5881730.

30.   Cattamanchi A, Smith R, Steingart KR, et al. Interferon-gamma release assays for the diagnosis of latent tuberculosis infection in HIV-infected individuals: a systematic review and meta-analysis. *J Acquir Immune Defic Syndr*. 2011;56(3):230-238. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21239993.

31.   Gray J, Reves R, Johnson S, Belknap R. Identification of false-positive QuantiFERON-TB Gold In-Tube assays by repeat testing in HIV-infected patients at low risk for tuberculosis. *Clin Infect Dis*. 2012;54(3):e20-23. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22057704.

32.   Sosa LE, Njie GJ, Lobato MN, et al. Tuberculosis screening, testing, and treatment of U.S. health care personnel: recommendations from the National Tuberculosis Controllers Association and CDC, 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68(19):439-443. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31099768.

33.   Luetkemeyer AF, Charlebois ED, Flores LL, et al. Comparison of an interferon-gamma release assay with tuberculin skin testing in HIV-infected individuals. *Am J Respir Crit Care Med*. 2007;175(7):737-742. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17218620.

34. Talati NJ, Seybold U, Humphrey B, et al. Poor concordance between interferon-gamma release assays and tuberculin skin tests in diagnosis of latent tuberculosis infection among HIV-infected individuals. *BMC Infect Dis*. 2009;9:15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19208218.

35. Rangaka MX, Wilkinson KA, Glynn JR, et al. Predictive value of interferon-gamma release assays for incident active tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2012;12(1):45-55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21846592.

36. Hill PC, Jackson-Sillah DJ, Fox A, et al. Incidence of tuberculosis and the predictive value of ELISPOT and Mantoux tests in Gambian case contacts. *PLoS One*. 2008;3(1):e1379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18167540.

37. Aichelburg MC, Rieger A, Breitenecker F, et al. Detection and prediction of active tuberculosis disease by a whole-blood interferon-gamma release assay in HIV-1-infected individuals. *Clin Infect Dis*. 2009;48(7):954-962. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19245343.

38. Diel R, Loddenkemper R, Meywald-Walter K, Niemann S, Nienhaus A. Predictive value of a whole blood IFN-gamma assay for the development of active tuberculosis disease after recent infection with *Mycobacterium tuberculosis*. *Am J Respir Crit Care Med*. 2008;177(10):1164-1170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18276940.

39. Leung CC, Yam WC, Yew WW, et al. T-Spot.TB outperforms tuberculin skin test in predicting tuberculosis disease. *Am J Respir Crit Care Med*. 2010;182(6):834-840. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20508217.

40. Wilson IB, Landon BE, Hirschhorn LR, et al. Quality of HIV care provided by nurse practitioners, physician assistants, and physicians. *Ann Intern Med*. 2005;143(10):729-736. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16287794.

41. Backus LI, Boothroyd DB, Phillips BR, et al. National quality forum performance measures for HIV/AIDS care: the Department of Veterans Affairs' experience. *Arch Intern Med*. 2010;170(14):1239-1246. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20660844.

42. Lee LM, Lobato MN, Buskin SE, Morse A, Costa OS. Low adherence to guidelines for preventing TB among persons with newly diagnosed HIV infection, United States. *Int J Tuberc Lung Dis*. 2006;10(2):209-214. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16499263.

43. Reaves EJ, Shah NS, France AM, et al. Latent tuberculous infection testing among HIV-infected persons in clinical care, United States, 2010-2012. *Int J Tuberc Lung Dis*. 2017;21(10):1118-1126. Available at: https://pubmed.ncbi.nlm.nih.gov/28911355/.

44. Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clin Infect Dis*. 2017;64(2):111-115. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28052967.

45.   Mazurek GH, Jereb J, Vernon A, et al. Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection - United States, 2010. *MMWR Recomm Rep*. 2010;59(RR-5):1-25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20577159.

46.   Getahun H, Kittikraisak W, Heilig CM, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. *PLoS Med*. 2011;8(1):e1000391. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21267059.

47.   Sterling TR, Njie G, Zenner D, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. *MMWR Recomm Rep*. 2020;69(1):1-11. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32053584.

48.   Golub JE, Pronyk P, Mohapi L, et al. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. *AIDS*. 2009;23(5):631-636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19525621.

49.   Samandari T, Agizew TB, Nyirenda S, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2011;377(9777):1588-1598. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21492926.

50.   Sterling TR, Scott NA, Miro JM, et al. Three months of weekly rifapentine plus isoniazid for treatment of M. tuberculosis infection in HIV co-infected persons. *AIDS*. 2016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26990624.

51.   Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med*. 2011;365(1):11-20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21732833.

52.   Belknap R, Holland D, Feng PJ, et al. Self-administered versus directly observed once-weekly isoniazid and rifapentine treatment of latent tuberculosis infection: a randomized trial. *Ann Intern Med*. 2017;167(10):689-697. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29114781.

53.   Sterling TR, Scott NA, Miro JM, et al. Three months of weekly rifapentine plus isoniazid for treatment of *Mycobacterium tuberculosis* infection in HIV co-infected persons. *AIDS*. 2016;30(10):1607-1615. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26990624.

54.   Podany AT, Bao Y, Swindells S, et al. Efavirenz pharmacokinetics and pharmacodynamics in HIV-infected persons receiving rifapentine and isoniazid for tuberculosis prevention. *Clin Infect Dis*. 2015;61(8):1322-1327. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26082504.

55.   Farenc C, Doroumian S, Cantalloube C, et al. Rifapentine once-weekly dosing effect on efavirenz emtricitabine and tenofovir PKs. Presented at: Conference on Retroviruses and Opportunistic Infections; 2014. Boston, MA. Available at:

http://www.croiconference.org/sessions/rifapentine-once-weekly-dosing-effect-efavirenz-emtricitabine-and-tenofovir-pks.

56.   Weiner M, Egelund EF, Engle M, et al. Pharmacokinetic interaction of rifapentine and raltegravir in healthy volunteers. *J Antimicrob Chemother*. 2014;69(4):1079-1085. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24343893.

57.   Dooley KE, Savic R, Gupte A, et al. Once-weekly rifapentine and isoniazid for tuberculosis prevention in patients with HIV taking dolutegravir-based antiretroviral therapy: a phase 1/2 trial. *Lancet HIV*. 2020;7(6):e401-e409. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32240629.

58.   Borisov AS, Bamrah Morris S, Njie GJ, et al. Update of recommendations for use of once-weekly isoniazid-rifapentine regimen to treat latent *Mycobacterium tuberculosis* infection. *MMWR Morb Mortal Wkly Rep*. 2018;67(25):723-726. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29953429.

59.   Hong Kong Chest Service/Tuberculosis Research Centre; Madras/British Medical Research Council. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. *Am Rev Respir Dis*. 1992;145(1):36-41. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1731596.

60.   Geijo MP, Herranz CR, Vano D, Garcia AJ, Garcia M, Dimas JF. [Short-course isoniazid and rifampin compared with isoniazid for latent tuberculosis infection: a randomized clinical trial]. *Enferm Infecc Microbiol Clin*. 2007;25(5):300-304. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17504682.

61.   Jimenez-Fuentes MA, de Souza-Galvao ML, Mila Auge C, Solsona Peiro J, Altet-Gomez MN. Rifampicin plus isoniazid for the prevention of tuberculosis in an immigrant population. *Int J Tuberc Lung Dis*. 2013;17(3):326-332. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23407221.

62.   Martinez Alfaro E, Solera J, Serna E, et al. [Compliance, tolerance and effectiveness of a short chemoprophylaxis regimen for the treatment of tuberculosis]. *Med Clin (Barc)*. 1998;111(11):401-404. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9834911.

63.   Ena J, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. *Clin Infect Dis*. 2005;40(5):670-676. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15714411.

64.   Fitzgerald DW, Severe P, Joseph P, et al. No effect of isoniazid prophylaxis for purified protein derivative-negative HIV-infected adults living in a country with endemic tuberculosis: results of a randomized trial. *J Acquir Immune Defic Syndr*. 2001;28(3):305-307. Available at: https://pubmed.ncbi.nlm.nih.gov/11694842/.

65.   Johnson JL, Okwera A, Hom DL, et al. Duration of efficacy of treatment of latent tuberculosis infection in HIV-infected adults. *AIDS*. 2001;15(16):2137-2147. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11684933.

66.   Rivero A, Lopez-Cortes L, Castillo R, et al. [Randomized clinical trial investigating three chemoprophylaxis regimens for latent tuberculosis infection in HIV-infected patients]. *Enferm Infecc Microbiol Clin*. 2007;25(5):305-310. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17504683.

67.   Whalen CC, Johnson JL, Okwera A, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda-Case Western Reserve University Research Collaboration. *N Engl J Med*. 1997;337(12):801-808. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9295239.

68.   Gordin FM, Matts JP, Miller C, et al. A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis. Terry Beirn Community Programs for Clinical Research on AIDS. *N Engl J Med*. 1997;337(5):315-320. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9233868.

69.   Hawken MP, Meme HK, Elliott LC, et al. Isoniazid preventive therapy for tuberculosis in HIV-1-infected adults: results of a randomized controlled trial. *AIDS*. 1997;11(7):875-882. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9189212.

70.   Menzies D, Adjobimey M, Ruslami R, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. *N Engl J Med*. 2018;379(5):440-453. Available at: http://www.ncbi.nlm.nih.gov/pubmed/30067931.

71.   Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*. 2011;365(23):2155-2166. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22150035.

72.   Horsburgh CR, Jr., Goldberg S, Bethel J, et al. Latent TB infection treatment acceptance and completion in the United States and Canada. *Chest*. 2010;137(2):401-409. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19793865.

73.   Gordin F, Chaisson RE, Matts JP, et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. Terry Beirn Community Programs for Clinical Research on AIDS, the Adult AIDS Clinical Trials Group, the Pan American Health Organization, and the Centers for Disease Control and Prevention Study Group. *JAMA*. 2000;283(11):1445-1450. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10732934.

74.   Swindells S, Ramchandani R, Gupta A, et al. One Month of rifapentine plus isoniazid to prevent HIV-related tuberculosis. *N Engl J Med*. 2019;380(11):1001-1011. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30865794.

75.   Menzies D, Long R, Trajman A, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. *Ann Intern Med*. 2008;149(10):689-697. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19017587.

76.   Li J, Munsiff SS, Tarantino T, Dorsinville M. Adherence to treatment of latent tuberculosis infection in a clinical population in New York City. *Int J Infect Dis*. 2010;14(4):e292-297. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19656705.

77.   Rangaka MX, Wilkinson RJ, Glynn JR, et al. Effect of antiretroviral therapy on the diagnostic accuracy of symptom screening for intensified tuberculosis case finding in a South African HIV clinic. *Clin Infect Dis*. 2012;55(12):1698-1706. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22955441.

78.   den Boon S, Matteelli A, Getahun H. Rifampicin resistance after treatment for latent tuberculous infection: a systematic review and meta-analysis. *Int J Tuberc Lung Dis*. 2016;20(8):1065-1071. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27393541.

79.   Lee AM, Mennone JZ, Jones RC, Paul WS. Risk factors for hepatotoxicity associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection: experience from three public health tuberculosis clinics. *Int J Tuberc Lung Dis*. 2002;6(11):995-1000. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12475146.

80.   McNeill L, Allen M, Estrada C, Cook P. Pyrazinamide and rifampin vs isoniazid for the treatment of latent tuberculosis: improved completion rates but more hepatotoxicity. *Chest*. 2003;123(1):102-106. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12527609.

81.   Centers for Disease Control and Prevention. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC Recommendations--United States, 2001. *MMWR*. 2001. Available at: https://www.cdc.gov/mmwr/PDF/wk/mm5034.pdf.

82.   Podany AT, Leon-Cruz J, Hakim J, et al. Nevirapine pharmacokinetics in HIV-infected persons receiving rifapentine and isoniazid for TB prevention. *J Antimicrob Chemother*. 2021;76(3):718-721. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33241266.

83.   Nahid P, Mase SR, Migliori GB, et al. Treatment of drug-resistant tuberculosis. an official ATS/CDC/ERS/IDSA clinical practice guideline. *Am J Respir Crit Care Med*. 2019;200(10). Available at: https://www.atsjournals.org/doi/ref/10.1164/rccm.201909-1874ST.

84.   Bliven-Sizemore EE, Sterling TR, Shang N, et al. Three months of weekly rifapentine plus isoniazid is less hepatotoxic than nine months of daily isoniazid for LTBI. *Int J Tuberc Lung Dis*. 2015;19(9):1039-1044. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26260821.

85.   Ngongondo M, Miyahara S, Hughes MD, et al. Hepatotoxicity during isoniazid preventive therapy and antiretroviral therapy in people living with HIV with severe immunosuppression: a secondary analysis of a multi-country open-label randomized controlled clinical trial. *J Acquir Immune Defic Syndr*. 2018;78(1):54-61. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29406428.

86.   Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med*. 2006;174(8):935-952. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17021358.

87.   Cain KP, McCarthy KD, Heilig CM, et al. An algorithm for tuberculosis screening and diagnosis in people with HIV. *N Engl J Med*. 2010;362(8):707-716. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20181972.

88. Batungwanayo J, Taelman H, Dhote R, Bogaerts J, Allen S, Van de Perre P. Pulmonary tuberculosis in Kigali, Rwanda. Impact of human immunodeficiency virus infection on clinical and radiographic presentation. *Am Rev Respir Dis*. 1992;146(1):53-56. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1626814.

89. Jones BE, Young SM, Antoniskis D, Davidson PT, Kramer F, Barnes PF. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. *Am Rev Respir Dis*. 1993;148(5):1292-1297. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7902049.

90. Perlman DC, el-Sadr WM, Nelson ET, et al. Variation of chest radiographic patterns in pulmonary tuberculosis by degree of human immunodeficiency virus-related immunosuppression. The Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). The AIDS Clinical Trials Group (ACTG). *Clin Infect Dis*. 1997;25(2):242-246. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9332519.

91. Post F, Wood R, Pillay G. Pulmonary tuberculosis in HIV infection: radiographic appearance is related to CD4+ T-lymphocyte count. *Tuber Lung Dis*. 1995;76:518-21. Available at.

92. Pepper T, Joseph P, Mwenya C, et al. Normal chest radiography in pulmonary tuberculosis: implications for obtaining respiratory specimen cultures. *Int J Tuberc Lung Dis*. 2008;12(4):397-403. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18371265.

93. Ahuja SS, Ahuja SK, Phelps KR, Thelmo W, Hill AR. Hemodynamic confirmation of septic shock in disseminated tuberculosis. *Crit Care Med*. 1992;20(6):901-903. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1597048.

94. Shafer RW, Kim DS, Weiss JP, Quale JM. Extrapulmonary tuberculosis in patients with human immunodeficiency virus infection. *Medicine*. 1991;70(6):384-397. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1956280.

95. Whalen C, Horsburgh CR, Jr., Hom D, Lahart C, Simberkoff M, Ellner J. Site of disease and opportunistic infection predict survival in HIV-associated tuberculosis. *AIDS*. 1997;11(4):455-460. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9084792.

96. Kourbatova EV, Leonard MK, Jr., Romero J, Kraft C, del Rio C, Blumberg HM. Risk factors for mortality among patients with extrapulmonary tuberculosis at an academic inner-city hospital in the US. *Eur J Epidemiol*. 2006;21(9):715-721. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17072539.

97. Thwaites GE, Nguyen DB, Nguyen HD, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med*. 2004;351(17):1741-1751. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15496623.

98. Lewis JJ, Charalambous S, Day JH, et al. HIV infection does not affect active case finding of tuberculosis in South African gold miners. *Am J Respir Crit Care Med*. 2009;180(12):1271-1278. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19745207.

99. Cavanaugh JS, Modi S, Musau S, et al. Comparative yield of different diagnostic tests for tuberculosis among people living with HIV in western Kenya. *PLoS One*. 2016;11(3):e0152364. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27023213.

100. Henostroza G, Harris JB, Chitambi R, et al. High prevalence of tuberculosis in newly enrolled HIV patients in Zambia: need for enhanced screening approach. *Int J Tuberc Lung Dis*. 2016;20(8):1033-1039. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27393536.

101. Elliott AM, Halwiindi B, Hayes RJ, et al. The impact of human immunodeficiency virus on presentation and diagnosis of tuberculosis in a cohort study in Zambia. *J Trop Med Hyg*. 1993;96(1):1-11. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8429569.

102. Reid MJ, Shah NS. Approaches to tuberculosis screening and diagnosis in people with HIV in resource-limited settings. *Lancet Infect Dis*. 2009;9(3):173-184. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19246021.

103. Monkongdee P, McCarthy KD, Cain KP, et al. Yield of acid-fast smear and mycobacterial culture for tuberculosis diagnosis in people with human immunodeficiency virus. *Am J Respir Crit Care Med*. 2009;180(9):903-908. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19628775.

104. Shriner KA, Mathisen GE, Goetz MB. Comparison of mycobacterial lymphadenitis among persons infected with human immunodeficiency virus and seronegative controls. *Clin Infect Dis*. 1992;15(4):601-605. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1420673.

105. Heysell SK, Moll AP, Gandhi NR, et al. Extensively drug-resistant Mycobacterium tuberculosis from aspirates, Rural South Africa. *Emerg Infect Dis*. 2010;16(3):557-560. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20202446.

106. Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med*. 2010;363(11):1005-1015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20825313.

107. Dinnes J, Deeks J, Kunst H, et al. A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. *Health Technol Assess*. 2007;11(3):1-196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17266837.

108. Forbes BA, Hall GS, Miller MB, et al. Practice guidelines for clinical microbiology laboratories: mycobacteria. *Clin Microbiol Rev*. 2018. Available at: https://cmr.asm.org/content/cmr/31/2/e00038-17.full.pdf.

109. World Health Organization. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system. Policy statement. 2011. Available at: http://whqlibdoc.who.int/publications/2011/9789241501545_eng.pdf.

110. Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N. Xpert(R) MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev*. 2014;1:CD009593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24448973.

111. Luetkemeyer AF, Kendall MA, Wu X, et al. Evaluation of two line probe assays for rapid detection of *Mycobacterium tuberculosis*, tuberculosis (TB) drug resistance, and non-TB mycobacteria in HIV-infected individuals with suspected TB. *J Clin Microbiol*. 2014;52(4):1052-1059. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24430455.

112. Lawn SD, Kerkhoff AD, Vogt M, Wood R. HIV-associated tuberculosis: relationship between disease severity and the sensitivity of new sputum-based and urine-based diagnostic assays. *BMC Med*. 2013;11:231. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24168211.

113. Maynard-Smith L, Larke N, Peters JA, Lawn SD. Diagnostic accuracy of the Xpert MTB/RIF assay for extrapulmonary and pulmonary tuberculosis when testing non-respiratory samples: a systematic review. *BMC Infect Dis*. 2014;14:709. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25599808.

114. Rahman SMM, Maliha UT, Ahmed S, et al. Evaluation of Xpert MTB/RIF assay for detection of Mycobacterium tuberculosis in stool samples of adults with pulmonary tuberculosis. *PLoS One*. 2018;13(9):e0203063. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30212505.

115. Xie YL, Chakravorty S, Armstrong DT, et al. Evaluation of a Rapid Molecular Drug-Susceptibility Test for Tuberculosis. *N Engl J Med*. 2017;377(11):1043-1054. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28902596.

116. Drain PK, Losina E, Coleman SM, et al. Diagnostic accuracy of a point-of-care urine test for tuberculosis screening among newly-diagnosed HIV-infected adults: a prospective, clinic-based study. *BMC Infect Dis*. 2014;14:110. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24571362.

117. Drain PK, Losina E, Coleman SM, et al. Value of urine lipoarabinomannan grade and second test for optimizing clinic-based screening for HIV-associated pulmonary tuberculosis. *J Acquir Immune Defic Syndr*. 2015;68(3):274-280. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25415288.

118. Lawn SD, Dheda K, Kerkhoff AD, et al. Determine TB-LAM lateral flow urine antigen assay for HIV-associated tuberculosis: recommendations on the design and reporting of clinical studies. *BMC Infect Dis*. 2013;13:407. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24004840.

119. Broger T, Moyoyeta M, Kerkhoff AD, Denkinger CM, Moreau E. Tuberculosis test results using fresh versus biobanked urine samples with FujiLAM. *The Lancet: Infectious Diseases*. 2020;20(1):22-23. Available at: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(19)30684-X/fulltext.

120. Lew W, Pai M, Oxlade O, Martin D, Menzies D. Initial drug resistance and tuberculosis treatment outcomes: systematic review and meta-analysis. *Ann Intern Med*. 2008;149(2):123-134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18626051.

121.   Gandhi NR, Shah NS, Andrews JR, et al. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. *Am J Respir Crit Care Med*. 2010;181(1):80-86. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19833824.

122.   Moore DA, Evans CA, Gilman RH, et al. Microscopic-observation drug-susceptibility assay for the diagnosis of TB. *N Engl J Med*. 2006;355(15):1539-1550. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17035648.

123.   Heysell SK, Houpt ER. The future of molecular diagnostics for drug-resistant tuberculosis. *Expert Rev Mol Diagn*. 2012;12(4):395-405. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22616704.

124.   Barnard M, Warren R, Gey Van Pittius N, et al. Genotype MTBDRsl line probe assay shortens time to diagnosis of extensively drug-resistant tuberculosis in a high-throughput diagnostic laboratory. *Am J Respir Crit Care Med*. 2012;186(12):1298-1305. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23087027.

125.   Rice JP, Seifert M, Moser KS, Rodwell TC. Performance of the Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis and rifampin resistance in a low-incidence, high-resource setting. *PLoS One*. 2017;12(10):e0186139. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29016684.

126.   Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis*. 2016;63(7):e147-e195. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27516382.

127.   Alipanah N, Jarlsberg L, Miller C, et al. Adherence interventions and outcomes of tuberculosis treatment: A systematic review and meta-analysis of trials and observational studies. *PLoS Med*. 2018;15(7):e1002595. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29969463.

128.   Story A, Aldridge RW, Smith C, Garber E, Hall J, Ferenando G. Smartphone-enabled video-observed versus directly observed treatment for tuberculosis: a multicenter, analyst-blinded randomized, controlled superiority trial. *Lancet*. 2019;393(10177):1216-1224. Available at: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)32993-3/fulltext.

129.   Browne SH, Umlauf A, Tucker AJ, et al. Wirelessly observed therapy compared to directly observed therapy to confirm and support tuberculosis treatment adherence: A randomized controlled trial. *PLoS Med*. 2019;16(10):e1002891. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31584944.

130.   Centers for Disease Control and Prevention. Implementing an Electronic Directly Observed Therapy (eDOT) Program: A Toolkit for Tuberculosis (TB) Programs. 2017. Available at: https://www.cdc.gov/tb/publications/guidestoolkits/tbedottoolkit.htm

131.   Swaminathan S, Narendran G, Venkatesan P, et al. Efficacy of a 6-month versus 9-month intermittent treatment regimen in HIV-infected patients with tuberculosis: a randomized clinical trial. *Am J Respir Crit Care Med*. 2010;181(7):743-751. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19965813.

132.   Nettles RE, Mazo D, Alwood K, et al. Risk factors for relapse and acquired rifamycin resistance after directly observed tuberculosis treatment: a comparison by HIV serostatus and rifamycin use. *Clin Infect Dis*. 2004;38(5):731-736. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14986259.

133.   Li J, Munsiff SS, Driver CR, Sackoff J. Relapse and acquired rifampin resistance in HIV-infected patients with tuberculosis treated with rifampin- or rifabutin-based regimens in New York City, 1997-2000. *Clin Infect Dis*. 2005;41(1):83-91. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15937767.

134.   Khan FA, Minion J, Pai M, et al. Treatment of active tuberculosis in HIV-coinfected patients: a systematic review and meta-analysis. *Clin Infect Dis*. 2010;50(9):1288-1299. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20353364.

135.   Vashishtha R, Mohan K, Singh B, et al. Efficacy and safety of thrice weekly DOTS in tuberculosis patients with and without HIV co-infection: an observational study. *BMC Infect Dis*. 2013;13:468. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24099345.

136.   Narendran G, Menon PA, Venkatesan P, et al. Acquired rifampicin resistance in thrice-weekly antituberculosis therapy: impact of HIV and antiretroviral therapy. *Clin Infect Dis*. 2014;59(12):1798-1804. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25156114.

137.   Vernon A, Burman W, Benator D, Khan A, Bozeman L. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. Tuberculosis Trials Consortium. *Lancet*. 1999;353(9167):1843-1847. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10359410.

138.   Burman W, Benator D, Vernon A, et al. Acquired rifamycin resistance with twice-weekly treatment of HIV-related tuberculosis. *Am J Respir Crit Care Med*. 2006;173(3):350-356. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16109981.

139.   Gopalan N, Santhanakrishnan RK, Palaniappan AN, et al. Daily vs intermittent antituberculosis therapy for pulmonary tuberculosis in patients with HIV: a randomized clinical trial. *JAMA Intern Med*. 2018;178(4):485-493. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29507938.

140.   Imperial MZ, Nahid P, Phillips PPJ, et al. A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis. *Nat Med*. 2018;24(11):1708-1715. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30397355.

141.   Centers for Disease Control and Prevention. Treatment of Tuberculosis. *MMWR Recomm Rep*. 2003;52(RR11):1-77. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm.

142.   el-Sadr WM, Perlman DC, Matts JP, et al. Evaluation of an intensive intermittent-induction regimen and duration of short-course treatment for human immunodeficiency virus-related pulmonary tuberculosis. Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) and the AIDS Clinical Trials Group (ACTG). *Clin Infect Dis*. 1998;26(5):1148-1158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9597244.

143. Perriens JH, St Louis ME, Mukadi YB, et al. Pulmonary tuberculosis in HIV-infected patients in Zaire: a controlled trial of treatment for either 6 or 12 months. *N Engl J Med*. 1995;332(12):779-784. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7862181.

144. Merle CS, Fielding K, Sow OB, Gninafon M. A four-month gatifloxacin-containing regimen for treating tuberculosis. *N Engl J Med 2014*. 2014;371:1588-1598. Available at: https://www.nejm.org/doi/full/10.1056/nejmoa1315817.

145. Gillespie SH, Crook AM, McHugh TD, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *N Engl J Med*. 2014;371(17):1577-1587. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25196020.

146. Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. *Lancet*. 2004;364(9441):1244-1251. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15464185.

147. Dorman SE, Nahid P, Kurbatova EV, et al. Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis. *N Engl J Med*. 2021;384(18):1705-1718. Available at: https://pubmed.ncbi.nlm.nih.gov/33951360/.

148. Dian S, Yunivita V, Ganiem AR, et al. Double-blind, randomized, placebo-controlled phase II dose-finding study to evaluate high-dose rifampin for tuberculous meningitis. *Antimicrob Agents Chemother*. 2018;62(12). Available at: https://www.ncbi.nlm.nih.gov/pubmed/30224533.

149. Heemskerk AD, Bang ND, Mai NT, et al. Intensified antituberculosis therapy in adults with tuberculous meningitis. *N Engl J Med*. 2016;374(2):124-134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26760084.

150. Te Brake L, Dian S, Ganiem AR, et al. Pharmacokinetic/pharmacodynamic analysis of an intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis. *Int J Antimicrob Agents*. 2015;45(5):496-503. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25703312.

151. Yunivita V, Dian S, Ganiem AR, et al. Pharmacokinetics and safety/tolerability of higher oral and intravenous doses of rifampicin in adult tuberculous meningitis patients. *Int J Antimicrob Agents*. 2016;48(4):415-421. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27526979.

152. Boeree MJ, Heinrich N, Aarnoutse R, et al. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. *Lancet Infect Dis*. 2017;17(1):39-49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28100438.

153. Ruslami R, Ganiem AR, Aarnoutse RE, van Crevel R. Rifampicin and moxifloxacin for tuberculous meningitis--authors' reply. *Lancet Infect Dis*. 2013;13(7):570. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23809224.

154. Velasquez GE, Brooks MB, Coit JM, et al. Efficacy and safety of high-dose rifampin in pulmonary tuberculosis. a randomized controlled trial. *Am J Respir Crit Care Med*. 2018;198(5):657-666. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29954183.

155. Prasad K, Singh MB, Ryan H. Corticosteroids for managing tuberculous meningitis. *Cochrane Database Syst Rev*. 2016;4:CD002244. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27121755.

156. Mayosi BM, Ntsekhe M, Bosch J, et al. Prednisolone and *Mycobacterium indicus pranii* in tuberculous pericarditis. *N Engl J Med*. 2014;371(12):1121-1130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25178809.

157. Wiysonge CS, Ntsekhe M, Thabane L, et al. Interventions for treating tuberculous pericarditis. *Cochrane Database Syst Rev*. 2017;9:CD000526. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28902412.

158. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med*. 2010;362(8):697-706. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20181971.

159. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med*. 2011;365(16):1482-1491. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22010914.

160. Nahid P, Gonzalez LC, Rudoy I, et al. Treatment outcomes of patients with HIV and tuberculosis. *Am J Respir Crit Care Med*. 2007;175(11):1199-1206. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17290042.

161. Mfinanga SG, Kirenga BJ, Chanda DM, et al. Early versus delayed initiation of highly active antiretroviral therapy for HIV-positive adults with newly diagnosed pulmonary tuberculosis (TB-HAART): a prospective, international, randomised, placebo-controlled trial. *Lancet Infect Dis*. 2014;14(7):563-571. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24810491.

162. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med*. 2011;365(16):1471-1481. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22010913.

163. Torok ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)--associated tuberculous meningitis. *Clin Infect Dis*. 2011;52(11):1374-1383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21596680.

164. Davies G, Cerri S, Richeldi L. Rifabutin for treating pulmonary tuberculosis. *Cochrane Database Syst Rev*. 2007(4):CD005159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17943842.

165. Singh R, Marshall N, Smith CJ, et al. No impact of rifamycin selection on tuberculosis treatment outcome in HIV coinfected patients. *AIDS*. 2013;27(3):481-484. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23014518.

166. Cerrone M, Alfarisi O, Neary M, et al. Rifampicin effect on intracellular and plasma pharmacokinetics of tenofovir alafenamide. *J Antimicrob Chemother*. 2019;74(6):1670-1678. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30815689.

167.   Boulle A, Van Cutsem G, Cohen K, et al. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. *JAMA*. 2008;300(5):530-539. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18677025.

168.   Cohen K, Grant A, Dandara C, et al. Effect of rifampicin-based antitubercular therapy and the cytochrome P450 2B6 516G>T polymorphism on efavirenz concentrations in adults in South Africa. *Antivir Ther*. 2009;14(5):687-695. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19704172.

169.   Ramachandran G, Hemanth Kumar AK, Rajasekaran S, et al. CYP2B6 G516T polymorphism but not rifampin coadministration influences steady-state pharmacokinetics of efavirenz in human immunodeficiency virus-infected patients in South India. *Antimicrob Agents Chemother*. 2009;53(3):863-868. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19124658.

170.   Luetkemeyer AF, Rosenkranz SL, Lu D, et al. Relationship between weight, efavirenz exposure, and virologic suppression in HIV-infected patients on rifampin-based tuberculosis treatment in the AIDS Clinical Trials Group A5221 STRIDE Study. *Clin Infect Dis*. 2013;57(4):586-593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23592830.

171.   McIlleron HM, Schomaker M, Ren Y, et al. Effects of rifampin-based antituberculosis therapy on plasma efavirenz concentrations in children vary by CYP2B6 genotype. *AIDS*. 2013;27(12):1933-1940. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24180002.

172.   Manosuthi W, Kiertiburanakul S, Sungkanuparph S, et al. Efavirenz 600 mg/day versus efavirenz 800 mg/day in HIV-infected patients with tuberculosis receiving rifampicin: 48 weeks results. *AIDS*. 2006;20(1):131-132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16327334.

173.   Yee KL, Khalilieh SG, Sanchez RI, et al. The Effect of Single and Multiple Doses of Rifampin on the Pharmacokinetics of Doravirine in Healthy Subjects. *Clin Drug Investig*. 2017;37(7):659-667. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28353169.

174.   Khalilieh SG, Yee KL, Sanchez RI, et al. Multiple Doses of Rifabutin Reduce Exposure of Doravirine in Healthy Subjects. *J Clin Pharmacol*. 2018;58(8):1044-1052. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29723418.

175.   Janssen Therapeutics. Edurant [package insert]. 2021. Available at: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/EDURANT-pi.pdf.

176.   Kakuda TN, Woodfall B, De Marez T, et al. Pharmacokinetic evaluation of the interaction between etravirine and rifabutin or clarithromycin in HIV-negative, healthy volunteers: results from two Phase 1 studies. *J Antimicrob Chemother*. 2014;69(3):728-734. Available at: https://pubmed.ncbi.nlm.nih.gov/24155058/.

177.   Grinsztejn B, De Castro N, Arnold V, et al. Raltegravir for the treatment of patients co-infected with HIV and tuberculosis (ANRS 12 180 Reflate TB): a multicentre, phase 2, non-comparative, open-label, randomised trial. *Lancet Infect Dis*. 2014;14(6):459-467. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24726095.

178. Wenning LA, Hanley WD, Brainard DM, et al. Effect of rifampin, a potent inducer of drug-metabolizing enzymes, on the pharmacokinetics of raltegravir. *Antimicrob Agents Chemother*. 2009;53(7):2852-2856. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19433563.

179. Brainard DM, Wenning LA, Stone JA, Wagner JA, Iwamoto M. Clinical pharmacology profile of raltegravir, an HIV-1 integrase strand transfer inhibitor. *J Clin Pharmacol*. 2011;51(10):1376-1402. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21209233.

180. Dooley KE, Sayre P, Borland J, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. *J Acquir Immune Defic Syndr*. 2013;62(1):21-27. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23075918.

181. Dooley KE, Kaplan R, Mwelase N, et al. Dolutegravir-based Antiretroviral Therapy for Patients Coinfected With Tuberculosis and Human Immunodeficiency Virus: A Multicenter, Noncomparative, Open-label, Randomized Trial. *Clin Infect Dis*. 2020;70(4):549-556. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30918967.

182. Custodio JM, West SK, Collins S, et al. Pharmacokinetics of bictegravir administered twice daily in combination with rifampin. Presented at: Conference on Retroviruses and Opportunistic Infections; 2018. Boston, MA. Available at: http://www.croiconference.org/sessions/pharmacokinetics-bictegravir-administered-twice-daily-combination-rifampin.

183. Ramanathan S, Mathias AA, German P, Kearney BP. Clinical pharmacokinetic and pharmacodynamic profile of the HIV integrase inhibitor elvitegravir. *Clin Pharmacokinet*. 2011;50(4):229-244. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21348537.

184. Rajoli RKR, Curley P, Chiong J, et al. Predicting drug-drug interactions between rifampicin and long-acting cabotegravir and rilpivirine using physiologically based pharmacokinetic modeling. *J Infect Dis*. 2019;219(11):1735-1742. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30566691.

185. Ford SL, Sutton K, Lou Y, et al. Effect of rifampin on the single-dose pharmacokinetics of oral cabotegravir in healthy subjects. *Antimicrob Agents Chemother*. 2017;61(10). Available at: https://www.ncbi.nlm.nih.gov/pubmed/28739783.

186. Burger DM, Agarwala S, Child M, Been-Tiktak A, Wang Y, Bertz R. Effect of rifampin on steady-state pharmacokinetics of atazanavir with ritonavir in healthy volunteers. *Antimicrob Agents Chemother*. 2006;50(10):3336-3342. Available at: https://pubmed.ncbi.nlm.nih.gov/17005814/.

187. Justesen US, Andersen AB, Klitgaard NA, Brøsen K, Gerstoft J, Pedersen C. Pharmacokinetic interaction between rifampin and the combination of indinavir and low-dose ritonavir in HIV-infected patients. *Clin Infect Dis*. 2004;38(3):426-429. Available at: https://pubmed.ncbi.nlm.nih.gov/14727216/.

188.   la Porte CJ, Colbers EP, Bertz R, et al. Pharmacokinetics of adjusted-dose lopinavir-ritonavir combined with rifampin in healthy volunteers. *Antimicrob Agents Chemother*. 2004;48(5):1553-1560. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15105105.

189.   Regazzi M, Carvalho AC, Villani P, Matteelli A. Treatment optimization in patients co-infected with HIV and Mycobacterium tuberculosis infections: focus on drug-drug interactions with rifamycins. *Clin Pharmacokinet*. 2014;53(6):489-507. Available at: https://pubmed.ncbi.nlm.nih.gov/24777631/.

190.   Decloedt EH, McIlleron H, Smith P, Merry C, Orrell C, Maartens G. Pharmacokinetics of lopinavir in HIV-infected adults receiving rifampin with adjusted doses of lopinavir-ritonavir tablets. *Antimicrob Agents Chemother*. 2011;55(7):3195-3200. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21537021.

191.   Nijland HM, L'Homme R F, Rongen GA, et al. High incidence of adverse events in healthy volunteers receiving rifampicin and adjusted doses of lopinavir/ritonavir tablets. *AIDS*. 2008;22(8):931-935. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18453852.

192.   Haas DW, Koletar SL, Laughlin L, et al. Hepatotoxicity and gastrointestinal intolerance when healthy volunteers taking rifampin add twice-daily atazanavir and ritonavir. *J Acquir Immune Defic Syndr*. 2009;50(3):290-293. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19194314.

193.   Schmitt C, Riek M, Winters K, Schutz M, Grange S. Unexpected hepatotoxicity of rifampin and saquinavir/ritonavir in healthy male volunteers. *Arch Drug Inf*. 2009;2(1):8-16. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19381336.

194.   Kendall MA, Lalloo U, Fletcher CV, et al. Safety and pharmacokinetics of double-dose lopinavir/ritonavir + rifampin versus lopinavir/ritonavir + daily rifabutin for treatment of human immunodeficiency virus-tuberculosis coinfection. *Clin Infect Dis*. 2021;73(4):706-715. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34398956.

195.   Decloedt EH, Maartens G, Smith P, Merry C, Bango F, McIlleron H. The safety, effectiveness and concentrations of adjusted lopinavir/ritonavir in HIV-infected adults on rifampicin-based antitubercular therapy. *PLoS One*. 2012;7(3):e32173. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22412856.

196.   Sunpath H, Winternheimer P, Cohen S, et al. Double-dose lopinavir-ritonavir in combination with rifampicin-based anti-tuberculosis treatment in South Africa. *Int J Tuberc Lung Dis*. 2014;18(6):689-693. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24903940.

197.   Ebrahim I, Maartens G, Wiesner L, Orrell C, Smythe W, McIlleron H. Pharmacokinetic profile and safety of adjusted doses of darunavir/ritonavir with rifampicin in people living with HIV. *J Antimicrob Chemother*. 2020;75(4):1019-1025. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31942627.

198.   Food and Drug Adminstration. Kaletra [package insert]. 2020. Available at: https://www.rxabbvie.com/pdf/kaletratabpi.pdf.

199.   Bristol-Myers Squibb. Atazanavir [package insert]. 2018. Available at: https://packageinserts.bms.com/pi/pi_reyataz.pdf.

200.   Sekar V, Lavreys L, Van de Casteele T, et al. Pharmacokinetics of darunavir/ritonavir and rifabutin coadministered in HIV-negative healthy volunteers. *Antimicrob Agents Chemother*. 2010;54(10):4440-4445. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20660678.

201.   Ford SL, Chen YC, Lou Y, et al. Pharmacokinetic interaction between fosamprenavir-ritonavir and rifabutin in healthy subjects. *Antimicrob Agents Chemother*. 2008;52(2):534-538. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18056271.

202.   Lin HC, Lu PL, Chang CH. Uveitis associated with concurrent administration of rifabutin and lopinavir/ritonavir (Kaletra). *Eye (Lond)*. 2007;21(12):1540-1541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17962822.

203.   Lan NT, Thu NT, Barrail-Tran A, et al. Randomised pharmacokinetic trial of rifabutin with lopinavir/ritonavir-antiretroviral therapy in patients with HIV-associated tuberculosis in Vietnam. *PLoS One*. 2014;9(1):e84866. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24465443.

204.   Naiker S, Connolly C, Wiesner L, et al. Randomized pharmacokinetic evaluation of different rifabutin doses in African HIV- infected tuberculosis patients on lopinavir/ritonavir-based antiretroviral therapy. *BMC Pharmacol Toxicol*. 2014;15:61. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25406657.

205.   Jenny-Avital ER, Joseph K. Rifamycin-resistant *Mycobacterium tuberculosis* in the highly active antiretroviral therapy era: a report of 3 relapses with acquired rifampin resistance following alternate-day rifabutin and boosted protease inhibitor therapy. *Clin Infect Dis*. 2009;48(10):1471-1474. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19368504.

206.   Boulanger C, Hollender E, Farrell K, et al. Pharmacokinetic evaluation of rifabutin in combination with lopinavir-ritonavir in patients with HIV infection and active tuberculosis. *Clin Infect Dis*. 2009;49(9):1305-1311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19807276.

207.   Johnson JL, Okwera A, Nsubuga P, et al. Efficacy of an unsupervised 8-month rifampicin-containing regimen for the treatment of pulmonary tuberculosis in HIV-infected adults. Uganda-Case Western Reserve University Research Collaboration. *Int J Tuberc Lung Dis*. 2000;4(11):1032-1040. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11092715.

208.   Benator D, Bhattacharya M, Bozeman L, et al. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. *Lancet*. 2002;360(9332):528-534. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12241657.

209.   Alsultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: an update. *Drugs*. 2014;74(8):839-854. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24846578.

210.   McIlleron H, Meintjes G, Burman WJ, Maartens G. Complications of antiretroviral therapy in patients with tuberculosis: drug interactions, toxicity, and immune reconstitution inflammatory syndrome. *J Infect Dis*. 2007;196 Suppl 1:S63-75. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17624828.

211.   Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. *Chest*. 1991;99(2):465-471. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1824929.

212.   Sharma SK, Singla R, Sarda P, et al. Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity. *Clin Infect Dis*. 2010;50(6):833-839. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20156055.

213.   Tahaoglu K, Atac G, Sevim T, et al. The management of anti-tuberculosis drug-induced hepatotoxicity. *Int J Tuberc Lung Dis*. 2001;5(1):65-69. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11263519.

214.   Abbara A, Chitty S, Roe JK, et al. Drug-induced liver injury from antituberculous treatment: a retrospective study from a large TB centre in the UK. *BMC Infect Dis*. 2017;17(1):231. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28340562.

215.   Lehloenya RJ, Todd G, Badri M, Dheda K. Outcomes of reintroducing anti-tuberculosis drugs following cutaneous adverse drug reactions. *Int J Tuberc Lung Dis*. 2011;15(12):1649-1657. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22118173.

216.   Gegia M, Winters N, Benedetti A, van Soolingen D, Menzies D. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. *Lancet Infect Dis*. 2017;17(2):223-234. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27865891.

217.   van der Heijden YF, Karim F, Mufamadi G, et al. Isoniazid-monoresistant tuberculosis is associated with poor treatment outcomes in Durban, South Africa. *Int J Tuberc Lung Dis*. 2017;21(6):670-676. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28482962.

218.   Fregonese F, Ahuja SD, Akkerman OW, et al. Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis. *Lancet Respir Med*. 2018;6(4):265-275. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29595509.

219.   World Health Organization. WHO treatment guidelines for isoniazid-resistant tuberculosis: supplement to the WHO treatment guidelines for drug-resistant tuberculosis. 2018. Available at: http://apps.who.int/iris/bitstream/handle/10665/260494/9789241550079-eng.pdf.

220.   World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. 2019. Available at: https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/.

221.   Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet*. 2018;392(10150):821-834. Available at: http://www.ncbi.nlm.nih.gov/pubmed/30215381.

222. Svensson EM, Aweeka F, Park JG, Marzan F, Dooley KE, Karlsson MO. Model-based estimates of the effects of efavirenz on bedaquiline pharmacokinetics and suggested dose adjustments for patients coinfected with HIV and tuberculosis. *Antimicrob Agents Chemother*. 2013;57(6):2780-2787. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23571542.

223. Svensson EM, Dooley KE, Karlsson MO. Impact of lopinavir-ritonavir or nevirapine on bedaquiline exposures and potential implications for patients with tuberculosis-HIV coinfection. *Antimicrob Agents Chemother*. 2014;58(11):6406-6412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25114140.

224. Pandie M, Wiesner L, McIlleron H, et al. Drug-drug interactions between bedaquiline and the antiretrovirals lopinavir/ritonavir and nevirapine in HIV-infected patients with drug-resistant TB. *J Antimicrob Chemother*. 2016;71(4):1037-1040. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26747099.

225. World Health Organization. WHO consolidated guidelines on tuberculosis: module 4: treatment - drug-resistant tuberculosis treatment. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32603040.

226. Nunn AJ, Phillips PPJ, Meredith SK, et al. A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis. *N Engl J Med*. 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30865791.

227. Conradie F, Diacon AH, Ngubane N, et al. Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. *N Engl J Med*. 2020;382(10):893-902. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32130813.

228. Conradie F, Everitt D, Olugbosi M, et al. High rate of successful outcomes treating highly resistant TB in the ZeNix study of pretomanid, bedaquiline and alternative doses and durations of linezolid Type Presented at 11th IAS Conference on HIV Science; July 21, 2021, Year; Berline, Germany. Available at: https://theprogramme.ias2021.org/PAGMaterial/PPT/3261_4845/ZeNix_July_2021_IAS_Final.pdf.

229. French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. *AIDS*. 2004;18(12):1615-1627. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15280772.

230. Lawn SD, Bekker LG, Miller RF. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. *Lancet Infect Dis*. 2005;5(6):361-373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15919622.

231. Meintjes G, Rabie H, Wilkinson RJ, Cotton MF. Tuberculosis-associated immune reconstitution inflammatory syndrome and unmasking of tuberculosis by antiretroviral therapy. *Clin Chest Med*. 2009;30(4):797-810, x. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19925968.

232. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis*. 2008;8(8):516-523. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18652998.

233. Muller M, Wandel S, Colebunders R, et al. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010;10(4):251-261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20334848.

234. Burman W, Weis S, Vernon A, et al. Frequency, severity and duration of immune reconstitution events in HIV-related tuberculosis. *Int J Tuberc Lung Dis*. 2007;11(12):1282-1289. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18229435.

235. Pepper DJ, Marais S, Maartens G, et al. Neurologic manifestations of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome: a case series. *Clin Infect Dis*. 2009;48(11):e96-107. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19405867.

236. Lawn SD, Wood R. Hepatic involvement with tuberculosis-associated immune reconstitution disease. *AIDS*. 2007;21(17):2362-2363. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18090294.

237. Sonderup MW, Wainwright H, Hall P, Hairwadzi H, Spearman CW. A clinicopathological cohort study of liver pathology in 301 patients with human immunodeficiency virus/acquired immune deficiency syndrome. *Hepatology*. 2015;61(5):1721-1729. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25644940.

238. Namale PE, Abdullahi LH, Fine S, Kamkuemah M, Wilkinson RJ, Meintjes G. Paradoxical TB-IRIS in HIV-infected adults: a systematic review and meta-analysis. *Future Microbiol*. 2015;10(6):1077-1099. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26059627.

239. Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am J Respir Crit Care Med*. 1998;158(1):157-161. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9655723.

240. Breen RA, Smith CJ, Bettinson H, et al. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. *Thorax*. 2004;59(8):704-707. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15282393.

241. Breton G, Duval X, Estellat C, et al. Determinants of immune reconstitution inflammatory syndrome in HIV type 1-infected patients with tuberculosis after initiation of antiretroviral therapy. *Clin Infect Dis*. 2004;39(11):1709-1712. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15578375.

242. Lawn SD, Myer L, Bekker LG, Wood R. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS*. 2007;21(3):335-341. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17255740.

243. Manosuthi W, Kiertiburanakul S, Phoorisri T, Sungkanuparph S. Immune reconstitution inflammatory syndrome of tuberculosis among HIV-infected patients receiving antituberculous and antiretroviral therapy. *J Infect*. 2006;53(6):357-363. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16487593.

244. Serra FC, Hadad D, Orofino RL, et al. Immune reconstitution syndrome in patients treated for HIV and tuberculosis in Rio de Janeiro. *Braz J Infect Dis*. 2007;11(5):462-465. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17962870.

245. Olalla J, Pulido F, Rubio R, et al. Paradoxical responses in a cohort of HIV-1-infected patients with mycobacterial disease. *Int J Tuberc Lung Dis*. 2002;6(1):71-75. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11931404.

246. Huyst V, Lynen L, Bottieau E, Zolfo M, Kestens L, Colebunders R. Immune reconstitution inflammatory syndrome in an HIV/TB co-infected patient four years after starting antiretroviral therapy. *Acta Clin Belg*. 2007;62(2):126-129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17547295.

247. Michailidis C, Pozniak AL, Mandalia S, Basnayake S, Nelson MR, Gazzard BG. Clinical characteristics of IRIS syndrome in patients with HIV and tuberculosis. *Antivir Ther*. 2005;10(3):417-422. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15918332.

248. Luetkemeyer AF, Kendall MA, Nyirenda M, et al. Tuberculosis immune reconstitution inflammatory syndrome in A5221 STRIDE: timing, severity, and implications for HIV-TB programs. *J Acquir Immune Defic Syndr*. 2014;65(4):423-428. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24226057.

249. Narendran G, Andrade BB, Porter BO, et al. Paradoxical tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS) in HIV patients with culture confirmed pulmonary tuberculosis in India and the potential role of IL-6 in prediction. *PLoS One*. 2013;8(5):e63541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23691062.

250. Meintjes G, Rangaka MX, Maartens G, et al. Novel relationship between tuberculosis immune reconstitution inflammatory syndrome and antitubercular drug resistance. *Clin Infect Dis*. 2009;48(5):667-676. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19191655.

251. Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS*. 2010;24(15):2381-2390. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20808204.

252. McAllister WA, Thompson PJ, Al-Habet SM, Rogers HJ. Rifampicin reduces effectiveness and bioavailability of prednisolone. *Br Med J (Clin Res Ed)*. 1983;286(6369):923-925. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6403136.

253. Brunel AS, Reynes J, Tuaillon E, et al. Thalidomide for steroid-dependent immune reconstitution inflammatory syndromes during AIDS. *AIDS*. 2012;26(16):2110-2112. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22874513.

254. Hsu DC, Faldetta KF, Pei L, et al. A paradoxical treatment for a paradoxical condition: infliximab use in three cases of mycobacterial IRIS. *Clin Infect Dis*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26394669.

255. Fourcade C, Mauboussin JM, Lechiche C, Lavigne JP, Sotto A. Thalidomide in the treatment of immune reconstitution inflammatory syndrome in HIV patients with neurological

tuberculosis. *AIDS Patient Care STDS*. 2014;28(11):567-569. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25285462.

256.   Meintjes G, Stek C, Blumenthal L, et al. Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS. *N Engl J Med*. 2018;379(20):1915-1925. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30428290.

257.   John L, Baalwa J, Kalimugogo P, et al. Response to 'Does immune reconstitution promote active tuberculosis in patients receiving highly active antiretroviral therapy?'. *AIDS*. 2005;19(17):2049-2050. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16260919.

258.   Goldsack NR, Allen S, Lipman MC. Adult respiratory distress syndrome as a severe immune reconstitution disease following the commencement of highly active antiretroviral therapy. *Sex Transm Infect*. 2003;79(4):337-338. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12902592.

259.   Lawn SD, Wainwright H, Orrell C. Fatal unmasking tuberculosis immune reconstitution disease with bronchiolitis obliterans organizing pneumonia: the role of macrophages. *AIDS*. 2009;23(1):143-145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19050399.

260.   Chen WL, Lin YF, Tsai WC, Tsao YT. Unveiling tuberculous pyomyositis: an emerging role of immune reconstitution inflammatory syndrome. *Am J Emerg Med*. 2009;27(2):251 e251-252. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19371548.

261.   Korenromp EL, Scano F, Williams BG, Dye C, Nunn P. Effects of human immunodeficiency virus infection on recurrence of tuberculosis after rifampin-based treatment: an analytical review. *Clin Infect Dis*. 2003;37(1):101-112. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12830415.

262.   Sonnenberg P, Murray J, Glynn JR, Shearer S, Kambashi B, Godfrey-Faussett P. HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. *Lancet*. 2001;358(9294):1687-1693. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11728545.

263.   Narayanan S, Swaminathan S, Supply P, et al. Impact of HIV infection on the recurrence of tuberculosis in South India. *J Infect Dis*. 2010;201(5):691-703. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20121433.

264.   Jasmer RM, Bozeman L, Schwartzman K, et al. Recurrent tuberculosis in the United States and Canada: relapse or reinfection? *Am J Respir Crit Care Med*. 2004;170(12):1360-1366. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15477492.

265.   Fitzgerald DW, Desvarieux M, Severe P, Joseph P, Johnson WD, Jr., Pape JW. Effect of post-treatment isoniazid on prevention of recurrent tuberculosis in HIV-1-infected individuals: a randomised trial. *Lancet*. 2000;356(9240):1470-1474. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11081529.

266.   Haller L, Sossouhounto R, Coulibaly IM, Dosso M, al e. Isoniazid plus sulphadoxine-pyrimethamine can reduce morbidity of HIV-positive patients treated for tuberculosis in

Africa: a controlled clinical trial. *Chemotherapy*. 1999;45(6):452-465. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10567776.

267. Mofenson LM, Rodriguez EM, Hershow R, et al. *Mycobacterium tuberculosis* infection in pregnant and nonpregnant women infected with HIV in the Women and Infants Transmission Study. *Arch Intern Med*. 1995;155(10):1066-1072. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7748050.

268. Eriksen NL, Helfgott AW. Cutaneous anergy in pregnant and nonpregnant women with human immunodeficiency virus. *Infect Dis Obstet Gynecol*. 1998;6(1):13-17. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9678142.

269. Jana N, Vasishta K, Jindal SK, Khunnu B, Ghosh K. Perinatal outcome in pregnancies complicated by pulmonary tuberculosis. *Int J Gynaecol Obstet*. 1994;44(2):119-124. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7911094.

270. Jana N, Vasishta K, Saha SC, Ghosh K. Obstetrical outcomes among women with extrapulmonary tuberculosis. *N Engl J Med*. 1999;341(9):645-649. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10460815.

271. Jonnalagadda S, Lohman Payne B, Brown E, et al. Latent tuberculosis detection by interferon gamma release assay during pregnancy predicts active tuberculosis and mortality in human immunodeficiency virus type 1-infected women and their children. *J Infect Dis*. 2010;202(12):1826-1835. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21067370.

272. Jonnalagadda SR, Brown E, Lohman-Payne B, et al. Consistency of *Mycobacterium tuberculosis*-specific interferon-gamma responses in HIV-1-infected women during pregnancy and postpartum. *Infect Dis Obstet Gynecol*. 2012;2012:950650. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22496602.

273. Lighter-Fisher J, Surette AM. Performance of an interferon-gamma release assay to diagnose latent tuberculosis infection during pregnancy. *Obstet Gynecol*. 2012;119(6):1088-1095. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22569120.

274. Gupta A, Montepiedra G, Aaron L, Theron G. Isoniazid Preventive Therapy in HIV-Infected Pregnant and Postpartum Women. *N Engl J Med*. 2019;381:1333-1346. Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa1813060.

275. Lawn SD, Wood R, De Cock KM, Kranzer K, Lewis JJ, Churchyard GJ. Antiretrovirals and isoniazid preventive therapy in the prevention of HIV-associated tuberculosis in settings with limited health-care resources. *Lancet Infect Dis*. 2010;10(7):489-498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20610331.

276. Gupta A, Nayak U, Ram M, et al. Postpartum tuberculosis incidence and mortality among HIV-infected women and their infants in Pune, India, 2002-2005. *Clin Infect Dis*. 2007;45(2):241-249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17578786.

277. Middelkoop K, Bekker LG, Myer L, et al. Antiretroviral program associated with reduction in untreated prevalent tuberculosis in a South African township. *Am J Respir Crit Care Med*. 2010;182(8):1080-1085. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20558626.

278. Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. 2020. Available at: http://www.cdc.gov/tb/publications/ltbi/treatment.htm

279. Miele K, Bamrah Morris S, Tepper NK. Tuberculosis in pregnancy. *Obstet Gynecol*. 2020;135(6):1444-1453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32459437.

280. Moro RN, Scott NA, Vernon A, et al. Exposure to latent tuberculosis treatment during pregnancy. the PREVENT TB and the iAdhere Trials. *Ann Am Thorac Soc*. 2018;15(5):570-580. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29393655.

281. Food and Drug Administration. PRIFTIN (rifapentine). 2010. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021024s009lbl.pdf.

282. Mathad JS, Savic R, Britto P, et al. Pharmacokinetics and Safety of Three Months of Weekly Rifapentine and Isoniazid for Tuberculosis Prevention in Pregnant Women. *Clin Infect Dis*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34323955.

283. Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. 2013. Available at: http://www.cdc.gov/tb/publications/ltbi/treatment.htm.

284. Mnyani CN, McIntyre JA. Tuberculosis in pregnancy. *BJOG*. 2011;118(2):226-231. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21083862.

285. Brost BC, Newman RB. The maternal and fetal effects of tuberculosis therapy. *Obstet Gynecol Clin North Am*. 1997;24(3):659-673. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9266585.

286. Bothamley G. Drug treatment for tuberculosis during pregnancy: safety considerations. *Drug Saf*. 2001;24(7):553-565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11444726.

287. Czeizel AE, Rockenbauer M, Olsen J, Sorensen HT. A population-based case-control study of the safety of oral anti-tuberculosis drug treatment during pregnancy. *Int J Tuberc Lung Dis*. 2001;5(6):564-568. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11409585.

288. Efferen LS. Tuberculosis and pregnancy. *Curr Opin Pulm Med*. 2007;13(3):205-211. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17414128.

289. Vilarinho LC. Congenital tuberculosis: a case report. *Braz J Infect Dis*. 2006;10(5):368-370. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17293929.

290. Lee LH, LeVea CM, Graman PS. Congenital tuberculosis in a neonatal intensive care unit: case report, epidemiological investigation, and management of exposures. *Clin Infect Dis*. 1998;27(3):474-477. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9770143.

291. Cantwell MF, Shehab ZM, Costello AM, et al. Brief report: congenital tuberculosis. *N Engl J Med*. 1994;330(15):1051-1054. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8127333.

292.   Rinsky JL, Farmer D, Dixon J, et al. Notes from the field: contact investigation for an infant with congenital tuberculosis infection - North Carolina, 2016. *MMWR Morb Mortal Wkly Rep*. 2018;67(23):670-671. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29902167.

293.   Chang CW, Wu PW, Yeh CH, Wong KS, Wang CJ, Chang CC. Congenital tuberculosis: case report and review of the literature. *Paediatr Int Child Health*. 2018;38(3):216-219. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28421876.

294.   Franks AL, Binkin NJ, Snider DE, Jr., Rokaw WM, Becker S. Isoniazid hepatitis among pregnant and postpartum Hispanic patients. *Public Health Rep*. 1989;104(2):151-155. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2495549.

295.   Enarson D, Rieder H, Arnodottir T, Trebucq A. Management of tuberculosis: a guide for low income countries. Vol. 4th ed. Paris, France: International Union Against Tuberculosis and Lung Disease; 1996.

296.   World Health Organization. Treatment of tuberculosis guidelines. 2010. Available at: https://apps.who.int/iris/bitstream/handle/10665/44165/9789241547833_eng.pdf.

297.   Dluzniewski A, Gastol-Lewinska L. The search for teratogenic activity of some tuberlostatic drugs. *Diss Pharm Pharmacol*. 1971;23:383-392.

298.   Shin S, Guerra D, Rich M, et al. Treatment of multidrug-resistant tuberculosis during pregnancy: a report of 7 cases. *Clin Infect Dis*. 2003;36(8):996-1003. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12684912.

299.   Lessnau KD, Qarah S. Multidrug-resistant tuberculosis in pregnancy: case report and review of the literature. *Chest*. 2003;123(3):953-956. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12628902.

300.   Drobac PC, del Castillo H, Sweetland A, et al. Treatment of multidrug-resistant tuberculosis during pregnancy: long-term follow-up of 6 children with intrauterine exposure to second-line agents. *Clin Infect Dis*. 2005;40(11):1689-1692. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15889370.

301.   Palacios E, Dallman R, Munoz M, et al. Drug-resistant tuberculosis and pregnancy: treatment outcomes of 38 cases in Lima, Peru. *Clin Infect Dis*. 2009;48(10):1413-1419. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19361302.

302.   Loveday M, Hughes J, Sunkari B, et al. Maternal and infant outcomes among pregnant women treated for multidrug/rifampicin-resistant tuberculosis in South Africa. *Clinical Infectious Diseases*. 2020;72(7):1158-1168. Available at: https://academic.oup.com/cid/article/72/7/1158/5788430.

303.   Fujimori H, et al. The effect of tuberculostatics on the fetus: an experimental production of congenital anomaly in rats by ethionamide. *Proc Congen Anom Res Assoc Jpn*. 1965;5:34-35.

304.   Takekoshi S. Effects of hydroxymethylpyrimidine on isoniazid- and ethionamide-induced teratosis. *Gunma J Med Sci*. 1965;14:233-244.

305.   Khan I, Azam A. Study of teratogenic activity of trifluoperazine, amitriptyline, ethionamide and thalidomide in pregnant rabbits and mice. *Proc Eur Soc Study Drug Toxic*. 1969;10:235-242.

306.   Potworowska M, Sianoz-Ecka E, Szufladowica R. Treatment with ethionamide in pregnancy. *Pol Med J*. 1966;5(5):1152-1158. Available at: https://www.ncbi.nlm.nih.gov/pubmed/5958801.

307.   Schaefer C, Amoura-Elefant E, Vial T, et al. Pregnancy outcome after prenatal quinolone exposure. Evaluation of a case registry of the European Network of Teratology Information Services (ENTIS). *Eur J Obstet Gynecol Reprod Biol*. 1996;69(2):83-89. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8902438.

308.   Yefet E, Schwartz N, Chazan B, Salim R, Romano S, Nachum Z. The safety of quinolones and fluoroquinolones in pregnancy: a meta-analysis. *BJOG*. 2018;125(9):1069-1076. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29319210.

309.   Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. *Antimicrob Agents Chemother*. 1998;42(6):1336-1339. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9624471.

310.   Nahum GG, Uhl K, Kennedy DL. Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks. *Obstet Gynecol*. 2006;107(5):1120-1138. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16648419.

311.   Varpela E. On the effect exerted by first-line tuberculosis medicines on the foetus. *Acta Tuberc Pneumol Scand*. 1964;45:53-69. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14209270.