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

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Mycobacterium tuberculosis Infection and Disease (Last updated September 27, 2019; last reviewed September 27, 2019)

Epidemiology

Despite being preventable and curable, tuberculosis (TB) is the leading cause of death from infectious disease globally, with 10.4 million people developing TB and 1.7 million people dying from TB in 2016.[1] TB is the leading cause of morbidity and mortality among people living with HIV worldwide, with 1 million persons with HIV reported to have TB and 374,000 deaths due to TB among PLHIV in 2016.

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% to 16% per year, which approximates the lifetime risk of TB disease for persons with LTBI who are HIV negative (approximately 5%).[2] The risk of TB begins in the first year following HIV infection.[3] TB infection can occur at any CD4 T lymphocyte (CD4) cell count, though the risk increases with progressive immunodeficiency.[3,4]

The advent of potent antiretroviral therapy (ART) resulted in a decrease in the incidence of TB disease among persons with HIV infection, and this effect has been documented in settings with low case rates of TB among PLHIV, such as the United States,[5] and in settings with very high case rates.[6-9] However, even with the beneficial effects of ART, the risk of TB disease among persons with HIV infection remains greater than that of the general population.[10]

Rates of TB in the United States are declining, with 2.8 new cases of TB disease per 100,000 population (a total of 9,105 cases) reported in 2017, a 2.3% decline in TB incidence from 2016.[11] This was the lowest number of annual cases reported on record although regional differences in incidence are noted, and TB outbreaks in U.S. communities continue to occur. The prevalence of LTBI in the general population of the United States is 4.7%,[12] which has remained unchanged since the last survey in 1999–2000. The incidence of HIV-related TB has declined more rapidly than the rate of active TB disease in the general population,[13] in part due to the widespread use of ART. Among all cases of TB reported in the United States in 2017, there were 439 persons coinfected with HIV (5.5% of TB cases that had HIV test result information).[11] Like TB disease in the general U.S. population, HIV-related TB is increasingly a disease of persons born outside of the United States.[13]

Despite these favorable epidemiological trends, TB remains an important opportunistic illness in the United States and globally. Unlike most opportunistic infections (OIs), TB is transmissible from persons to person, particularly to persons with HIV infection. Therefore, clinicians providing care for persons with HIV must remain vigilant in efforts to prevent TB, knowledgeable about the clinical presentation of HIV-related TB, and cognizant of the complexities of the co-treatment of HIV and TB.

Preventing Exposure

In the United States, the most common predisposing factor for TB infection is birth or residence outside of the United States.[12] Therefore, persons with HIV infection who live or work internationally in settings with a high prevalence of TB should be counseled about the risk of TB acquisition and the advisability of getting tested for LTBI upon returning to the United States.

Preventing Disease: Diagnosing and Treating Latent TB Infection

The estimated annual risk for active 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 persons with HIV than for those without HIV.[14,15] Furthermore, in two studies among adults with HIV, persons who developed TB had higher viral loads[16] and a greater risk of HIV disease progression[16] and death[17] than CD4-matched control patients without TB. The risk of progression from LTBI to TB disease in persons with HIV is reduced both by ART and by treatment of LTBI.[18] In combination with ART, treatment of LTBI decreases the risk of TB disease by 76% among persons with HIV infection.[19] Isoniazid preventive therapy and ART independently and additively decrease the risk of death and severe HIV-related illness.[9,18] In a study that compared isoniazid preventive therapy to placebo among persons receiving ART, isoniazid further reduced the risk of TB by 37%.[8] In a cluster randomized trial in Brazil, a country with medium TB burden, the rate of TB was lower in the isoniazid group than in the group that did not receive isoniazid at ≤7 years of follow-up, suggesting a durable effect of 6-month isoniazid in reducing the risk of TB disease in persons with HIV with a positive TST.[20] Therefore, prevention of TB disease by screening for and treating LTBI, along with ART initiation, are key components of HIV care.

Diagnosing Latent TB Infection

All persons with HIV should be tested for LTBI at the time of HIV diagnosis, regardless of their epidemiological risk of TB exposure **(AII)**. The two current methods available for detection of *M. tuberculosis* infection in the United States, IGRA and TST, help differentiate infected from uninfected people. However, diagnostic accuracy of TST and IGRA are limited; a negative test does not exclude the diagnosis of LTBI or TB disease, and a positive test does not in 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. Decisions should not be based on IGRA or TST results alone.

Among persons with HIV, some studies found that the benefit of isoniazid preventive therapy (IPT) was seen primarily in persons with a positive TST.[21,22] However, in one study in South Africa, a setting with a high TB burden, IPT decreased the TB risk among all persons with HIV regardless of TST or IGRA result.[8] Another recent study from West Africa found improved survival with IPT regardless of TST or IGRA status.[18] Persons with negative diagnostic tests for LTBI, advanced HIV infection (CD4 count <200 cells/mm^3), and without indications for initiating empiric LTBI treatment (i.e., no recent exposure to a culture-confirmed TB case) should be re-tested 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.[23,24] Annual testing for LTBI using TST is recommended for persons with HIV who are at high risk for repeated or ongoing exposure to persons with active TB disease **(AIII)**.

Traditionally, LTBI has been defined by the presence of a positive TST (≥5 mm of induration at 48 to 72 hours in persons with HIV) in persons with no clinical or radiographic evidence of TB disease. Despite the extensive experience with the TST among persons 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.[25] These limitations of the TST have led to broader use of IGRAs for detection of LTBI.

Current evidence suggests that IGRAs have higher specificity than the TST, (92% to 97% vs. 56% to 95%, respectively), better correlation with surrogate measures of exposure to *M. tuberculosis*,[26] and less cross-reactivity with BCG vaccination and nontuberculous mycobacteria.[27,28] Two IGRAs are Food and Drug Administration (FDA)-approved and available in the United States. As with the TST, progressive immunodeficiency is associated with decreased sensitivity of IGRAs.[29] In addition, the reproducibility of positive results of IGRAs has been limited among health care workers, one of the few groups that routinely undergo repeated IGRA testing in the United States.[30] Poor reproducibility might also affect those with HIV. Among 46 persons with HIV who had initial positive tests with the IGRA QuantiFERON-TB Gold In-

Tube assay, 33 (72%) had negative repeat tests, particularly those with responses at the lower range of the manufacturer's suggested range of positive results.[31]

Among persons with HIV, the correlation between the TST and IGRA test results is poor to moderate.[32,33] In prospective studies, positive results with either the TST or IGRA were associated with an increased risk of developing TB disease;[34-36] in some studies, patients with a positive IGRA were at a higher risk of subsequently developing TB disease than were those with a positive TST.[37,38] Despite its limitations, a positive TST result remains strongly predictive of decreased risk of TB progression in response to IPT among persons with HIV infection.[17] Studies are underway to formally evaluate if IGRAs are similarly predictive.

In programmatic settings in the United States, TB screening based on the TST has been suboptimal, with only 47% to 65% of patients completing screening.[39-41] The use of an IGRA for TB screening may increase the proportion of patients who complete TB screening.

There have been no published definitive comparisons of the TST and IGRAs for screening persons with HIV in low-burden settings such as the United States. Both the TST and the approved IGRAs are appropriate for TB screening among persons with HIV in the United States.[42] Some experts have suggested using both the TST and an IGRA in a stepwise 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.[42]

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. Most, but not all, persons with HIV with TB disease have symptoms (e.g., cough, fever, sweats, weight loss, lymphadenopathy); absence of any of these symptoms has a 97% negative predictive value for culture-positive TB, though this varies depending on pre-test probability.[43] The addition of a chest radiograph improved sensitivity of this screening algorithm, but decreased specificity. Obtaining a sputum culture is the gold standard for diagnosing pulmonary TB disease but is not high yield in screening asymptomatic persons with HIV, particularly in the United States where the prevalence of TB is very low. 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.

Treating Latent TB Infection

Once TB disease is excluded and in the absence of other medical contraindications, persons with HIV and a positive TB screening test should receive LTBI treatment **(AI)**, unless there is documentation of prior treatment for active TB or LTBI. Additionally, persons with HIV who are in close contact with anyone with infectious TB should receive LTBI treatment, regardless of their TB screening test results **(AI)**. Persons with HIV in the United States who have a negative TST or IGRA and no recent contact with a person with infectious TB will likely not benefit from treatment of LTBI and preventive therapy is not generally recommended **(AI)**.[21,44-46] In the international setting, two recent studies from high-burden areas of South Africa showed isoniazid decreased TB risk[8] and mortality[18] regardless of TST or IGRA result.

Preferred and Alternative Drugs for Treating Latent TB Infection, Including Duration of Therapy

Isoniazid prophylaxis for 9 months remains a preferred therapy, with proven efficacy, good tolerability, and infrequent severe toxicity **(AI)**. Although peripheral neuropathy, hepatitis, and rash may be caused by either isoniazid or various antiretroviral (ARV) drugs, the risk of hepatitis—the most important of these adverse effects—is not significantly increased when isoniazid is combined with efavirenz- or nevirapine-based regimens.[8] Isoniazid prophylaxis should be supplemented with pyridoxine at a dose of 25 to 50 mg/day to prevent peripheral neuropathy **(AIII)**. A significant disadvantage of the 9-month regimen is that the majority of patients do not complete all 9 months of therapy.[47] Patients are more likely to complete shorter regimens.[47-50] Additional regimens for chemoprophylaxis are shown in Table 1.[51] 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 LTBI treatment with isoniazid, including in persons with HIV whose CD4 counts were generally >350 cells/mm^3 and who were not yet on ART.[52,53] A recent study demonstrated that 3HP treatment completion rates with self-administered therapy were inferior to those with directly-observed therapy, but non-inferior among study participants enrolled in the United States—and generally high overall.[54] Although individuals taking ART were not included in the Phase 3 trial of once-weekly rifapentine and isoniazid, the pharmacokinetic (PK) profile of efavirenz with daily rifapentine and isoniazid is favorable.[55] In a PK study of 12 adults with HIV without TB receiving once-weekly rifapentine 900 mg with efavirenz, rifapentine had minimal effect on efavirenz exposure.[56] Raltegravir concentrations were modestly increased, not decreased, when it was given with once-weekly rifapentine.[57] Thus, despite the lack of clinical trial outcome data, once-weekly rifapentine/isoniazid without dose adjustment based on available PK data is recommended when used in persons receiving efavirenz or raltegravir[58] **(AII)**. Increased clinical monitoring is not routinely recommended, but should be based on clinical judgment.

A large trial comparing 4 months of daily rifampin (4R) to 9 months of daily isoniazid (9H) was recently published.[59] The study enrolled >6,000 participants who were predominantly HIV negative, and although rates of incident active TB were low in both arms, the 4R regimen was non-inferior to 9H for the primary efficacy outcome. Importantly, 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). Only 255 participants were HIV positive, however, which limits the generalizability of the findings to this population. Given the lack of trial data in PLWH, the 4R regimen is recommended only as an alternative to 9H and 3HP in persons with HIV who cannot receive isoniazid **(BI)**. Furthermore, given the theoretical risks of rifamycin monotherapy in undiagnosed early-stage TB disease and the relatively poor performance of symptom screens alone in patients with HIV on ART,[60] clinicians may consider performing a sputum culture or chest radiograph before starting 4R for LTBI. When using rifampin for preventive therapy, either dose adjustment or substitution of key ART drugs may be needed. Regarding rifabutin monotherapy for the treatment of LTBI there are no data demonstrating its efficacy in people with or without HIV infection. The regimen of two months rifampin plus pyrazinamide is not recommended given the risk of severe and sometimes fatal hepatotoxicity **(AII)**.[61,62]

The BRIEF-TB study (ACTG 5279) evaluated 1 month of daily rifapentine plus isoniazid (1HP) versus 9 months of daily isoniazid (9H) in PLWH residing in mostly high TB burden settings (TB incidence >60 per 100,000 population).[63] The median CD4 count of study participants was 470 cells/mm^3, 50% of the study population was on ART (efavirenz or nevirapine-based regimens) at study entry, and 21% of the study population was TST-positive. The study endpoint was the combination of confirmed or probable TB, death due to TB, and death due to unknown cause. The event rate was 0.65 per 100 person-years in the 1HP arm and 0.67 per 100 person-years in the 9H arm; non-inferiority of the 1HP arm was established. Treatment completion rates (by self-report) were 97% in the 1HP arm and 90% in the 9H arm. These results suggest that 1HP might be an alternative regimen for treatment of LTBI in certain situations, but the regimen has not been fully evaluated in low TB prevalence settings (only 10% of the study population was from the United States). Of note, only 23% of the participants had a positive test for LTBI; 10% of the participants at international sites did not have a TST due to manufacturer shortages, and IGRAs were only performed for U.S. participants. Furthermore, 13% had baseline CD4 counts <250 cells/mm^3, and 50% were not on ART at entry (although ART was started after enrollment). While the population enrolled was at high risk for LTBI in the setting of HIV and high endemic exposure, the number of persons at risk of progression to TB disease due to documented LTBI was low.

LTBI treatment and ART act independently to decrease the risk of TB disease.[8,19,64,65] Therefore, use of both interventions is recommended for persons with LTBI **(AI)**. For persons exposed to drug-resistant TB, a regimen for LTBI should be selected after consultation with experts or with public health authorities **(AII)**.

Monitoring for Adverse Events Related to Treating Latent TB Infection

Individuals receiving self-administered daily chemoprophylaxis should be seen by the prescribing clinician monthly to assess adherence and evaluate for possible drug toxicity; generally, a clinician should not prescribe >1 month's supply of drugs. Although persons with HIV may not have a higher risk of hepatitis from isoniazid than persons without HIV, it is recommended that they have serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and total bilirubin levels measured before starting LTBI treatment and repeated if abnormal.[14] Persons with concomitant chronic viral hepatitis have an increased risk of isoniazid-related hepatotoxicity, and such patients should be monitored closely when treated for LTBI.[66,67] With isoniazid, liver enzymes typically increase in the first 3 months of treatment but then, through the process of hepatic adaptation, return to normal despite continued therapy. If the serum aminotransferase level increases 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 upper limit of normal among patients with baseline abnormal transaminases), chemoprophylaxis should be stopped. Factors that increase the risk of clinical hepatitis include daily alcohol consumption, underlying liver disease, and concurrent treatment with other hepatotoxic drugs. At each visit, patients should be asked about 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, and arthralgia) and told to immediately stop medications and return to the clinic for an assessment should any of these occur.

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[68] and in consultation with an expert in treating LTBI in persons with HIV infection.

Clinical Manifestations of TB Disease

Sputum culture-positive TB disease can be subclinical and patients with HIV/TB may remain asymptomatic.[69] In ambulatory PLWH, the presence of any one of the classic symptoms of TB disease (cough, fever, night sweats, and weight loss) has high sensitivity but low specificity for diagnosing TB,[43] but, the sensitivity of classic TB symptoms is lower in PLWH on ART.[60] A clinical prediction model developed and validated in ambulatory patients with at least one classic TB symptom showed that a score consisting of ART status, CD4 count, body mass index, and presence of more than one TB symptom improved the specificity of diagnosing TB while retaining reasonable sensitivity.[70]

In patients who are markedly immune suppressed, TB can be a severe systemic disease with high fevers, rapid progression, and features of sepsis.[71] World Health Organization (WHO) algorithms for diagnosing TB distinguish between ambulatory patients and those who are seriously ill, defined by the presence of one or more danger signs (respiratory rate >30/min, heart rate >120/min, temperature >39°C, and inability to walk unaided). A study of inpatients with WHO danger signs and cough of any duration reported that the classic TB symptoms of fever, weight loss, and night sweats were not predictive of TB.[72] Rather, the following variables predicted TB: cough ≥14 days, inability to walk unaided, temperature >39°C, chest radiograph assessment, low hemoglobin, and elevated white blood cell count.

The presentation of active TB disease is influenced by the degree of immunodeficiency.[73,74] 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.[75]

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.[73,75,76] Normal chest radiographs are not uncommon in patients with respiratory symptoms and positive sputum cultures. Adjunct thoracic CT scans may demonstrate mild reticulonodular infiltrates despite a normal chest radiograph.[77]

With increasing degrees of immunodeficiency, extrapulmonary (especially lymphadenitis, pleuritis, pericarditis, and meningitis) or disseminated TB are more common. Clinical manifestations of extrapulmonary TB in persons 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,[78] especially processes related to central nervous system (CNS) or meningeal symptoms when early TB treatment is essential to improve outcomes.[79-81]

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 is directed at the anatomic site of symptoms or signs (e.g., lungs, lymph nodes, urine, cerebrospinal fluid). The initial evaluation of a patient suspected of having HIV-related TB should always include a chest radiograph or other chest imaging, even in the absence of pulmonary symptoms or signs; pulmonary involvement is common at all CD4 counts.[69,82] 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.[83,84] Therefore, sputum smear and culture should be performed in symptomatic patients being evaluated for possible 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.

Sputum smear-negative TB is common among persons with HIV, particularly those with advanced immunodeficiency and non-cavitary disease.[85] However, the yield of sputum mycobacterial culture is not affected by HIV or the degree of immunodeficiency. When a sensitive broth culture technique is used, the sensitivity of sputum culture is quite high.[86,87] Smear and culture of three sputum specimens is recommended based on a large study in patients with HIV that showed a 10% incremental yield for broth culture between the second and third specimens.[88]

Extrapulmonary and disseminated TB are more common in persons with HIV, particularly with advanced immunosuppression.[89,90] Nodal 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.[91] 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.[74]

Pleural fluid, pericardial fluid, ascites, and cerebrospinal fluid should be sampled if there is clinical evidence of involvement. The yield of acid-fast bacilli (AFB) smear, culture, and nucleic acid amplification (NAA) testing is generally lower from extrapulmonary specimens than from sputum, but nonetheless these tests can be an important diagnostic tool when *M. tuberculosis* is isolated. 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[74,78] and may allow definitive diagnosis and be a source of an isolate for drug-susceptibility testing.

Nucleic-Acid Amplification Testing: Standard mycobacterial cultures for TB may take weeks to months to grow, but rapid diagnosis is essential in patients with HIV given the risk of rapid clinical progression of TB among patients with advanced immunodeficiency. NAA tests provide rapid diagnosis of TB (some assays also provide rapid detection of drug resistance—see below). NAA tests have at least two uses among patients with suspected HIV-related TB. First, NAA assays, if positive, are highly predictive of TB disease when performed on AFB smear-positive specimens. Nontuberculous mycobacterial infections are relatively common among patients with advanced immunodeficiency, and NAA tests can be used to direct therapy and make decisions about the need for respiratory isolation of patients with a smear-positive specimen. Second, NAA tests are more sensitive than AFB smear, being positive in 50% to 80% of smear-negative, culture-

positive specimens[92,93] and up to 90% when three NAA tests are performed. Therefore, it is recommended that for all patents with suspected pulmonary TB, a NAA test be performed on at least one specimen.[94] NAA tests can also be used on extrapulmonary specimens with the caveat that the sensitivity is often lower than with sputum specimens.

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 widely implemented in resource-limited settings with high TB prevalence and as a frontline TB diagnostic test in patients with HIV.[95] Xpert MTB/RIF was licensed in the United States in 2013 for detection of *M. tuberculosis* and reporting of rifampin resistance directly from sputum samples[96] and in 2015, as an aid in decisions regarding respiratory isolation.[97] This assay combines simple processing requirements in the laboratory and rapid turnaround (results within 2 hours). In a recent meta-analysis, the overall sensitivity and specificity of the Xpert MTB/RIF assay were 88% (95% confidence interval [CI], 83% to 92%) and 98% (95% CI, 97% to 99%), respectively. The assay is somewhat less sensitive among patients 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%);[98] however, this may be in part attributed to a higher prevalence of smear negative disease in individuals with HIV.[99] In some studies, the sensitivity of Xpert MTB/RIF has been related to CD4 count, with higher sensitivity among patients with more advanced immunodeficiency.[100]

In extrapulmonary specimens, a 2014 meta-analysis reported Xpert MTB/RIF sensitivity of up to 95% in smear positive specimens and 69% in smear negative specimens.[101] Median sensitivity varied by specimen type, with higher yield from lymph nodes (96%), CSF (85%), and gastric aspirates (78%) and lower yield from pleural fluid (34%) and other non-pleural serous fluids (67%).

In 2017, a newer version of the Xpert MTB/RIF assay was developed (MTB/RIF Ultra) to improve the sensitivity of the existing test platform. With several technical modifications, the newer cartridge has a limit of detection of 16 colony forming units (cfu) (compared to 113 cfu for the original Xpert MTB/RIF) and improved detection of rifampin resistance.[102] A large, multinational study tested clinical specimens using both the old and newer cartridges in parallel, as well as solid and liquid agar culture. The study found that Xpert MTB/RIF Ultra was superior to the older version of the assay (Xpert MTB/RIF), particularly in patients with smear-negative disease (sensitivities of 63% and 46%, respectively).[103] In a separate prospective study of people with HIV with suspected TB meningitis, Xpert MTB/RIF Ultra testing of CSF was also found to have improved sensitivity of 95% versus 45% for Xpert MTB/RIF, and yield was increased with larger volumes of CSF.[104] On the basis of these findings, as well as a mathematical model, WHO has endorsed replacing the older cartridges with the new version worldwide, noting that the change will benefit most in those with smear-negative disease, such as people with HIV, children, and individuals with extrapulmonary TB such as TB meningitis.[105] The Xpert MTB/RIF Ultra is currently not FDA approved or available in the United States.

Lipoarabinomannan (LAM): LAM is an *M. tuberculosis* cell wall polysaccharide that can be detected in the urine of patients with TB. LAM can be detected using an enzyme-linked immunosorbent assay (ELISA) or a lateral flow point of care test. The diagnostic utility of LAM is limited by a low sensitivity, but it has the advantage of being available as a true point of care test that can be performed on urine. LAM has demonstrated the best performance in patients with HIV with low CD4 counts (<100 cells/mm^3) with a sensitivity of 37% to 56% and specificity of up to 95%.[106-108] In addition, LAM has higher sensitivity in patients with worse prognoses.[109] Combining LAM with other diagnostic strategies, such as Xpert MTB/RIF testing of sputum or urine, may improve the diagnostic utility of LAM and identify those at greatest risk of TB-related mortality.[110-112]

Immune-Based Tests: Immunological tests for TB infection, the TST and IGRA, may be helpful in unusual circumstances in which it is difficult to obtain definitive culture evidence for active TB disease; evidence of prior TB infection increases the likelihood that a clinical illness may be TB disease. However, these tests are not diagnostic of active TB disease, and a negative TST or IGRA should never be interpreted as ruling out TB disease because TB may cause anergy and these tests may be negative in 11% to 30% of patients with active TB.[42]

Drug Resistance Testing: The presence of drug resistance should be considered in any patient with:

- Known exposure to a person with drug-resistant TB
- Residence in a setting with high rates of primary drug-resistant TB (e.g., a country or area with high rates of drug resistance in patients with newly diagnosed TB)
- Persistently positive smear or culture results at or after 4 months of treatment
- Previous TB treatment, particularly if it was not directly observed or was interrupted for any reason.

These patients should be prioritized for rapid molecular testing. Conventional drug-susceptibility testing (DST) should be performed on the initial isolates from all patients suspected of having TB, as resistance to isoniazid and/or rifampin is associated with an increased risk of treatment failure, recurrent TB, and amplification of resistance to additional TB medications.[113] 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.[114] Thus, early identification of drug resistance, with appropriate adjustment of the treatment regimen based on conventional DST results, is critical to the successful treatment of TB disease and to curbing transmission of drug-resistant *M. tuberculosis*.

For all patients with TB disease, drug-susceptibility testing to first-line TB drugs (isoniazid, rifampin, ethambutol, and pyrazinamide) should be performed, regardless of the source of the specimen. 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, aminoglycosides, capreomycin, ethionamide, and others) should be performed only in reference laboratories with substantial experience in these techniques and should be limited to specimens with resistance to first-line TB medications.

Conventional Growth-Based Drug-Susceptibility Testing: Conventional DST is widely used and has been validated for first-line drugs. The disadvantage of this technique, however, is that the combined turn-around time of conventional broth or agar-based culture followed by DST may be as long as 6 weeks,[115] 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 for ongoing transmission, further clinical deterioration, and death, particularly in individuals with HIV.[114] 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, as molecular correlates of phenotypic drug-resistance are poor. In 2018, WHO produced a technical report based on a systematic review of available minimum inhibitory concentration (MIC) data for phenotypically wild-type and non-wild type strains and associated sequencing of related resistance-determining genes. The report provided new recommendations for phenotypic DST of the second-line medications and modifications to breakpoints which also account for PK variability observed in clinical care.[116]

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.[117] 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.[99,118] Of note, probe-based assays including Xpert MTB/RIF and LPAs should always be confirmed with sequence based tests as well as growth-based DST. For initial evaluation of drug resistance, or confirmation of drug resistance identified by the above assays, the Centers for Disease Control and Prevention (CDC), Division of Tuberculosis Elimination, has a Molecular Detection of Drug Resistance (MDDR) service that offers rapid molecular testing for first-and second-line TB medications at no charge for persons suspected of having drug-resistant TB (See the Report of Expert Consultations on Rapid Molecular Testing to Detect Drug-Resistant Tuberculosis in the United States). State TB programs and state labs should also be consulted for resistance testing options. Several assays can be

performed on cultured isolates or directly on sputum specimens.

The largest clinical experience with rapid molecular tests for rifampin resistance is with the Xpert MTB/RIF (pre-Ultra) assay. In a 2014 meta-analysis, the sensitivity of the assay for detection of rifampin resistance was 95% (95% CI, 90% to 97%) and the specificity was 98% (95% CI, 97% to 99%).[98] False-positive results for rifampin resistance with the Xpert MTB/RIF assay can occur, and sequence-based testing should be done to confirm results.[119] However, the comparator for most studies—phenotypic DST—is not an absolute gold standard.[120,121] Some isolates with rifampin resistance by the Xpert MTB/RIF assay have mutations in the *rpoB* gene, but are susceptible in phenotypic assays. Two recent analyses showed that treatment failure was more common among patients whose isolates had phenotypic susceptibility but mutations in the resistance-determining region of the *rpoB* gene than among patients whose isolates had wild type *rpoB* gene sequences.[122,123]

In low MDR TB prevalence settings such as the United States, the positive predictive value of any test for rifampin resistance is limited. Therefore, isolates with an initial reading of rifampin resistance with the Xpert MTB/RIF should undergo confirmatory testing (*rpoB* gene sequencing or phenotypic drug susceptibility testing), and in such cases, additional specimens should be obtained from the patient. Consultation with an expert in the diagnosis and treatment of MDR TB is recommended.

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 CDC as needed.

Treating Disease

Preferred and Alternative Drugs for Treatment, Including Duration of Therapy

TB among persons with advanced immunodeficiency can be a rapidly progressing and fatal illness if treatment is delayed. Furthermore, such patients often have smear-negative sputum specimens.[86] Therefore, after collection of available specimens for culture and molecular diagnostic tests, empiric treatment for TB is warranted in patients with clinical and radiographic presentation suggestive of HIV-related TB **(AIII)**.

Treatment of suspected TB for individuals with HIV is the same as for individuals without HIV and should include an initial four-drug combination of isoniazid, rifampin, ethambutol, and pyrazinamide **(AI)**. If rapid DST results indicate resistance to rifampin, with or without resistance to other drugs, an initial MDR TB regimen—including a fluoroquinolone (levofloxacin or moxifloxacin) and either an aminoglycoside or capreomycin—should be used **(BIII)** and can be adjusted as sequencing and conventional DST results become available. Directly observed therapy (DOT) is recommended for all patients with suspected HIV-related TB **(AII)**. 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 (e.g., enhanced DOT).

Drug-susceptible TB should be treated with a 2-month intensive phase of the four drugs listed above (isoniazid, rifampin, ethambutol, and pyrazinamide). 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 of treatment for uncomplicated TB **(AI)**.

Although intermittent dosing (administration less often than daily) of anti-TB treatment 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 persons with HIV.[124-132] Therefore, daily therapy given as DOT is recommended during both the intensive and continuation treatment phase **(AII)**.[130,131,133] Observational studies and meta-analyses focused primarily on the intensive phase of treatment, and thrice-weekly therapy during the continuation phase was not systematically evaluated in the context of the risk of adverse TB outcomes (treatment failure, recurrence, or acquired drug resistance).[127] Although earlier recommendations 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, there are no data substantiating the minimum number of doses needed within a specified time interval in individuals with HIV. Every effort should be made to assure 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 patients with HIV and drug-susceptible TB disease is not known. In general, the outcomes of 6-month regimens (2 months of isoniazid, rifampin, ethambutol, and pyrazinamide, followed by 4 months of isoniazid and rifampin) given as DOT to patients with HIV have been good.[134,135] A randomized trial in the United States showed excellent and comparable outcomes of TB therapy among patients assigned to 6 months or 9 months of therapy, but the trial was underpowered.[136] Two trials in high-burden settings showed higher risks of recurrent TB among patients treated with 6 months of therapy than among those assigned to 9-[124] or 12-month regimens.[137] However, the applicability of these two trials to low-burden settings in which ART is used, such as the United States, is uncertain. 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)**. TB meningitis should be treated for 9 to 12 months **(BII)**.

The use of a higher rifampin dose and/or addition of a fluoroquinolone to treatment for CNS TB may be beneficial, but there are limited data to support its use. A recent randomized trial that compared 9 months of standard TB therapy that included rifampin at a dose of 10 mg/kg with an intensified regimen in which levofloxacin was added and rifampicin was given at a higher dose of 15 mg/kg showed similar rates of survival, adverse events, and secondary outcomes in individuals both with and without HIV who had TB meningitis.[138] Importantly, however, rifampin doses in the two arms were highly overlapping, and standard or even modestly-increased rifampin doses do not produce rifampin concentrations in the CSF that are above rifampin's MIC against *M. tuberculosis* in many patients.[139,140] It is unclear whether even higher doses of rifampin may be more effective, but small prospective studies have found that doses as high as 35 mg/kg were well tolerated in adults, and additional studies are underway.[141,142] A PK study of 60 participants in Indonesia suggested that rifampin administered in doses equivalent to 13 mg/kg or higher given intravenously (similar to 26 mg/kg delivered orally) reduced mortality,[143] but this finding requires confirmation in a larger trial. Addition of a fluoroquinolone may improve outcomes in patients with isoniazid-monoresistant tuberculous meningitis.[138]

Adjunctive corticosteroid therapy is recommended in individuals with HIV who have TB involving the CNS **(AI)**.[81] The regimen used in trials of adjunctive corticosteroids for CNS disease were: dexamethasone (0.3–0.4 mg/kg/day for 2–4 weeks, then taper 0.1 mg/kg per week until dose of 0.1 mg/kg, then 4 mg per day and taper by 1 mg/week; total duration of 12 weeks).[81] Adjunctive corticosteroid therapy increases survival overall for patients with TB with CNS involvement, although studies were underpowered for detecting a statistically significant survival benefit for those with HIV.[81,144] 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 and without HIV with tuberculous pericarditis, 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.[145] A Cochrane review similarly found no mortality benefit from adjunctive corticosteroids and a non-significant reduction in constrictive pericarditis. Notably, however, <20% of patients with HIV in the trials analyzed were receiving ART.[146] There have been no trials comparing different doses and treatment durations of adjunctive corticosteroids.

Special Considerations with Regard to Starting ART

Optimal management of HIV-related TB requires that both infections be addressed. Although data are conflicting whether sequential treatment of TB followed by initiation of ART is acceptable for persons with CD4 counts >220 to 250 cells/mm^3,[147,148] results from large, international, randomized trials of immediate versus delayed initiation of ART indicate that, at all CD4 counts, people with HIV without active TB disease

gain substantial health benefits from immediate ART.[9,149,150] When coupled with the preponderance of data from randomized trials in persons with HIV and active TB disease, these results support the recommendation that ART should not be withheld until completion of TB treatment **(AI)**. 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 improves survival[147] (particularly for persons with CD4 counts <50 cells/mm^3),[151] decreases the risk of additional opportunistic illnesses,[151,152] and, despite higher rates of IRIS at low CD4 counts, is not associated with higher rates of ARV or anti-TB drug related toxicity.[148]

The evidence supporting concurrent therapy comes from four trials.

The SAPIT trial randomized 642 South African adults with CD4 counts <500 cells/mm^3 and AFB smear-positive TB to start ART at either TB treatment initiation, after the intensive phase of TB therapy but before TB treatment completion, or after TB treatment completion.[147] The study was stopped early because mortality in the two integrated treatment arms was 56% lower than in the sequential treatment arm, demonstrating that ART should be started before TB completion. Notably, there was a survival benefit across the range of CD4 counts among patients enrolled, including within the stratum of baseline CD4 counts from 200 to 500/mm^3.

The CAMELIA, STRIDE (ACTG A5221), and TB-HAART trials shed further light on the optimal timing of ART during TB treatment. In CAMELIA, 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 decreased from 13.77 per 100 person-years in the 8-week arm to 8.28 per 100 person-years ($P = 0.002$) in the 2-week arm,[153] and >95% of the study participants who survived had viral suppression.

The ACTG A5221 STRIDE study randomized 809 participants from North America, South America, Africa, and Asia with confirmed or suspected TB and a median CD4 count of 77 cells/mm^3 (IQR, 33,146) to immediate ART (within 2 weeks of TB treatment initiation) or early ART (8–12 weeks after TB treatment initiation).[151] A new OI or death occurred among 12.9% of participants in the immediate arm and 16.1% in the early arm by week 48 ($P = 0.45$). Among participants with screening CD4 count <50 cells/mm^3, 15.5% on immediate ART versus 26.6% on early ART developed AIDS or died ($P = 0.02$). TB-associated IRIS (TB-IRIS) was more common among participants in the immediate ART arm (11%) than in the early ART arm (5%) ($P = 0.002$). Viral suppression rates were similar between the arms.

The TB-HAART trial included 1,538 participants with HIV infection in South Africa, Uganda, Zambia, and Tanzania who had culture-confirmed pulmonary TB and CD4 counts ≥220 cells/mm^3 and had tolerated 2 weeks of TB treatment. Participants were randomized to early ART (initiated after 2 weeks of TB treatment) or delayed ART (until 6 months after initiation of TB treatment).[148] The median CD4 count for all participants was 367 cells/mm^3 (IQR 289, 456). The composite primary endpoint of TB treatment failure, TB recurrence, and death within 12 months of starting TB treatment occurred in 8.5% of participants in the early ART group and 9.2% in the delayed ART group (relative risk [RR] 0.91, 95% CI, 0.64–1.30; $P = 0.9$). Mortality rates and the incidence of grade 3 and 4 adverse events, and IRIS did not differ among the treatment groups. Patients in the early ART group had higher CD4 counts at all time points than those in the delayed ART group; no data on viral suppression were available. Unlike SAPIT, STRIDE, and CAMELIA, the TB-HAART study concluded that ART can be delayed until after 6 months of TB treatment for patients with CD4 counts >220 cells/mm^3.

The optimal approach for initiation of ART in TB meningitis remains uncertain. A randomized trial conducted in Vietnam compared ART initiation immediately (within 7 days of starting TB treatment) or until 2 months after starting TB treatment among 253 patients with HIV-related TB meningitis.[154] This study did not show a survival benefit to early ART initiation. On the contrary, mortality was similar in both study arms, and

early ART was associated with more frequent and severe adverse events than deferred ART (86% vs. 75% of participants, respectively). The overall mortality rates in this study were very high (58%), likely at least in part because most participants had advanced AIDS (median baseline CD4 count was 41 cells/mm^3); it is unclear if these findings are generalizable to other settings. Many experts would recommend the initiation of ART within the first 2 to 8 weeks of starting anti-TB treatment, opting for 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 **(AI)**.

In conclusion, ART is recommended for all persons with HIV and 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 and, based on the preponderance of data, when TB meningitis is not suspected, within 8 weeks of starting anti-TB treatment in those with higher CD4 cell counts **(AI)**. Given the need to initiate five to seven new medications in a short time, patients should be offered adherence support. Rifampin-associated drug interactions should be considered when selecting the ARV drug regimen. In patients with TB meningitis and low CD4 counts, early ART may pose a risk for severe adverse effects, and an expert should be consulted, and careful monitoring provided. Early ART initiation requires close collaboration between HIV and TB care clinics, expertise in management of ART regimen selection, close monitoring, and support and adherence services for clients.

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 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 ART 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, short-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 and 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.

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. 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, was higher with TAF/emtricitabine given with rifampicin than with TDF given alone, suggesting that TAF may be given together with rifampicin-containing TB treatment without dose adjustment.[155] Caution is urged, however, as this combination has not been tested in patients to confirm PK and virologic efficacy among patients taking full dose ART and TB regimens. Neither TDF nor TAF has been tested with rifabutin or rifapentine.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)—Efavirenz, Nevirapine, Etravirine, Doravirine, and Rilpivirine: Up to now, the preferred co-treatment regimen for HIV-related TB disease has been rifampin-based TB therapy with an ARV regimen of efavirenz 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.[156] Data on the magnitude of the change in efavirenz concentrations when co-administered with rifampin are conflicting. Early studies, largely conducted among healthy individuals without HIV infection, reported a 26% reduction in efavirenz plasma concentrations with rifampin,[157] but more recent and larger studies in PLWH and TB (including patients with higher body weight) have not shown a significant effect of rifampin-containing TB treatment on efavirenz plasma concentrations in the majority of patients.[158-160] Previous recommendations to increase the dose of efavirenz, especially in patients weighing

>60 kg, are thus not supported by high-quality data and have several disadvantages (complexity of dosing, inability to take advantage of the simplicity of the co-formulation of efavirenz, tenofovir disoproxil fumarate, and emtricitabine, and the possibility of increased neuropsychiatric side effects). A further disadvantage of increasing the dose of efavirenz coadministered with TB treatment is that slow metabolizers of efavirenz (about 20% of people of African, Thai, and 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.[161] Given the preponderance of data and the excellent treatment outcomes of co-treatment with standard-dose efavirenz,[156,162] the 600 mg daily dose of efavirenz is recommended **(AII)**.

Although still used in international resource-limited settings, nevirapine is rarely used in high resourced settings, and **is not recommended** in these settings for HIV and TB co-treatment. Data from more recent studies indicate that in patients on TB therapy, co-treatment with nevirapine-based ART is associated with less satisfactory virologic outcomes and increased incidence of drug discontinuation due to adverse events than efavirenz-based ART.[163-165] Drug-drug interactions between rifampin and other NNRTIs have a more significant effect on the concentrations of the NNRTIs that limit their concomitant use. The use of rifampin or rifapentine with doravirine, etravirine or rilpivirine **is not recommended (AIII)** (see Table 3 and the Adult and Adolescent Antiretroviral Guidelines). Substitution of rifabutin for rifampin with appropriate dose adjustment of rifabutin might be considered for patients who require one of these NNRTIs, however, these combinations have not been evaluated in PLWH requiring treatment for active TB disease.

Integrase Inhibitors—Bictegravir, Dolutegravir, Elvitegravir, and Raltegravir: Alternatives to efavirenz-based ARV treatment for patients with HIV/TB include regimens with integrase inhibitors or protease inhibitors (PIs). One preferred alternative co-treatment regimen is the combination of raltegravir-based ART, using raltegravir 400 or 800 mg twice daily, with standard rifampin dosing **(BI)**.[166] Raltegravir concentrations are significantly decreased when co-administered with rifampin. Increasing the dose of raltegravir to 800 mg twice daily mitigates this PK interaction.[167] The recently presented REFLATE TB2 trial compared efavirenz 600 mg daily to raltegravir 400 mg twice daily in PLWH undergoing TB treatment; the overall viral suppression rate at week 48 did not achieve the non-inferiority margin with this dose of raltegravir, although a previous Phase 2 randomized trial suggested virologic suppression was similar in non-comparative analyses of the raltegravir 400 and 800 mg twice daily arms.[166] These data suggest that the dose of raltegravir should be 800 mg twice daily if used with rifampin. Alternatively, raltegravir can be given with a rifabutin-containing TB regimen without dose adjustment of either drug.[168]

Dolutegravir may be another reasonable treatment 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.[169] A recent Phase 2 randomized, non-comparative trial (INSPIRING) was conducted among ART-naive patients with HIV-associated TB and investigated dolutegravir at a dose of 50 mg twice daily during and for 2 weeks after completing rifampin-containing TB treatment. Among the 69 patients randomized to the dolutegravir arm, the results at 24 weeks were favorable with on-target PK assessments and rapid virologic response; there were no deaths, no discontinuations for IRIS or drug toxicity, and no emergence of resistance.[170] Final 48-week data are expected in 2019. A recent trial conducted among healthy volunteers without HIV infection evaluated bictegravir concentrations when given twice daily together with rifampin versus once-daily alone.[171] Bictegravir trough concentrations, even with the dose adjustment, were reduced 80%. Thus, bictegravir **should not be used** together with rifamycin-containing TB treatment **(AI)**. Similarly, elvitegravir/cobicistat should not be used together with TB treatment that contains rifamycins **(AI)**.

Protease Inhibitors with Rifampin or Rifabutin: Another alternative co-treatment regimen is rifabutin-based TB therapy with an ARV regimen including a ritonavir-boosted PI **(BIII)**. While there are no clinical trials specifically comparing rifampin- and rifabutin-containing anti-TB regimens among persons with HIV/

TB taking ART, in general, rifabutin is regarded as a reasonable substitute for rifampin for treatment of TB.[172,173] Although the dramatic effects of rifampin on serum concentrations of lopinavir may be overcome by doubling the dose of lopinavir/ritonavir,[174,175] the safety of this strategy has yet to be firmly established. High rates of hepatotoxicity were reported when dose-adjusted ritonavir-boosted PIs were given with rifampin to healthy volunteers.[176-178] In patients with HIV and TB, double doses of lopinavir/ritonavir are reasonably well tolerated in those on rifampin-based TB treatment, but the strategy of increasing ritonavir dosing to 400 mg twice daily leads to high rates of hepatotoxicity.[175,179,180] Thus, a strategy of first increasing the dose of lopinavir/ritonavir by 50%, then increasing to full double dose is recommended **(BIII)**. Regular monitoring of transaminases is recommended when double-dose lopinavir/ritonavir is used (e.g., more frequently initially, then monthly once transaminase levels are stable on full dose).

Use of rifabutin with a boosted PI is thus preferred to use of rifampin with double-dose PI in settings where rifabutin is readily available. Co-administered rifabutin has little effect on ritonavir-boosted lopinavir[181] or atazanavir,[182] and only moderately increases concentrations of ritonavir-boosted darunavir[183] and fosamprenavir.[184] 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 to avoid dose-related toxicity, such as uveitis and neutropenia.[185] In studies of people with HIV infection, 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.[186,187] Among individuals with HIV/TB, there have been case reports of acquired rifamycin resistance with 150 mg three times weekly doses of rifabutin when co-administered with a boosted PI-based ARV regimen.[188,189] A recent study conducted in South Africa in 16 patients with HIV infection on a lopinavir/ritonavir-based ART regimen demonstrated that rifabutin administered at a dose of 150 mg daily in combination with lopinavir/ritonavir was generally safe and associated with rifabutin plasma concentrations similar to those shown to prevent acquired rifamycin resistance (i.e., rifabutin given 300 mg daily in the absence of a boosted PI).[187] A randomized clinical trial evaluating rifabutin PK and TB and ART outcomes using rifabutin 150 mg daily with lopinavir/ritonavir-based ART has been completed and results are pending. Based on available PK data, it is recommended that rifabutin should be dosed 150 mg daily in patients who are on a ritonavir-boosted PI-containing antiretroviral regimen **(BII)**. However, given that the risk of adverse events related to high levels of rifabutin's metabolite with this dosing strategy has not been firmly established, close monitoring for toxicity (especially neutropenia and uveitis) is required until larger studies provide adequate safety data. Close monitoring of adherence to ART is essential as 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.[190,191] If a rifamycin cannot be used, TB treatment duration must be extended substantially. Thus, patients with rifamycin-susceptible *M. tuberculosis* isolates should only be treated with a regimen that does not contain a rifamycin 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). 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.[192] 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.

Managing Suspected Treatment Failure

The causes of treatment failure include undetected primary drug resistance, inadequate adherence to therapy, incorrect or inadequate regimen prescribed, subtherapeutic drug levels due to malabsorption, super-infection with drug-resistant *M. tuberculosis*, and acquired drug-resistance.

Patients with suspected treatment failure should be evaluated with a history, physical exam, and chest radiograph to determine whether the patient has clinically responded 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 should also be reviewed. Some experts will perform therapeutic drug monitoring to determine if serum concentrations of the TB drugs are within expected ranges and dose adjust as necessary.[133,193] In addition, samples from all available sites (e.g., sputum, blood, urine) should be collected for repeat culture and drug-susceptibility testing, and strong consideration should be given to performing rapid resistance testing on direct specimens or positive cultures to identify acquired drug resistance or super-infection with a drug-resistant strain.

While awaiting results of repeat cultures and rapid resistance testing, broadening empiric TB treatment with 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

During the course of anti-TB therapy, patients with HIV who are not on ART are more likely to experience adverse events thought to be drug-related than patients without HIV.[194,195] 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,[194] 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 coadministered with anti-TB therapy.[147,148] 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 there is strong evidence that a drug reaction was caused by a specific anti-TB drug. In such situations, decisions regarding rechallenge with first-line drugs and/or substitution of second-line drugs should be made in consultation with a specialist in treating TB disease in persons with HIV.

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% to 30% of patients treated with the standard four-drug anti-TB regimen,[68,196] but many of these patients only have transient, mild elevations of ALT.[68] If the criteria for anti-TB DILI are fulfilled, all potentially hepatotoxic drugs should be stopped, and the patient should be evaluated immediately. 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, an aminoglycoside, and moxifloxacin or levofloxacin)[197] 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 pre-existing 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% of patients without HIV in one randomized controlled trial of different rechallenge regimens.[197] 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. However, some experts would recommend rechallenge with pyrazinamide in patients with severe forms of TB (e.g., meningitis or disseminated TB).[198] 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 anti-TB drug rechallenge, if appropriate, relevant ARV drugs and cotrimoxazole may be restarted.

Cutaneous adverse drug reactions (CADRs) may occur with all of the first-line anti-TB drugs, notably rifampin and isoniazid;[199] many antiretroviral 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 continued. If the rash is generalized, or associated with fever or DILI, or if there is mucous membrane involvement or desquamation, all anti-TB medications, relevant ARVs, and cotrimoxazole should be stopped. When the rash is substantially improved, the TB drug 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 prevalence of drug-resistant TB globally, plus the high proportion of TB cases in the United States in people who are foreign-born, 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 (isoniazid and rifampin, in particular). 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 has not yet been published.

Growing evidence demonstrates that there is an increased risk of treatment failure associated with baseline isoniazid monoresistance,[200] particularly in patients with HIV/TB.[124] 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)**.[201,202]

Resistance to rifampin alone, or to rifampin and other drugs, substantially increases the complexity and duration of treatment. Treatment of these types of drug-resistant TB requires the use of second-line and often third-line TB medications, which are less effective, more toxic, and require 12 to 24 months of treatment.[203,204] Treatment outcomes for MDR TB are considerably worse than those for drug-susceptible TB—especially in patients with HIV/TB.[114] Consensus treatment guidelines for MDR TB are based on a review of published observational studies[205,206] and recommend use of at least five drugs with known or likely activity against the patient's isolate **(BIII)**. Until recently, such regimens included a later-generation fluoroquinolone; a second-line injectable agent (i.e., kanamycin, amikacin, or capreomycin); pyrazinamide and ethambutol (if retained susceptibility); and likely two other second-line oral medications, such as ethionamide or prothionamide, linezolid, cycloserine, or clofazimine.[203] Additional resistance to one or more of these drugs (e.g., extensively drug-resistant [XDR] TB) necessitated use of alternate or third-line agents with uncertain anti-TB activity. An intensive phase of 8 months was then followed by a continuation phase without the injectable agent for an additional 12 to 18 months.

In addition to recommendations for an all-oral MDR TB regimen, in 2016, WHO also issued guidance for programs in resource-limited settings on a standardized shorter-course regimen that includes seven anti-TB drugs and a duration of 9 to 12 months of treatment for selected patients with MDR TB.[207] The regimen composition is based on combinations evaluated as "the Bangladesh regimen,"[208] and includes kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol administered for 4 to 6 months, followed by moxifloxacin, clofazimine, pyrazinamide, and ethambutol for 5 months. Based on promising data from observational studies in predominantly persons without HIV, a randomized non-inferiority designed clinical trial (STREAM) recently compared the efficacy of an intensive, shortened, 9-month treatment regimen for MDR TB using currently available medications to the

20- to 24-month regimen. Recently published study results showed that the short-course regimen was non-inferior to the longer regimen (78.8% and 79.8% of participants with successful outcome for short- and long-term regimens, respectively). Notably, treatment outcomes in the 20- to 24-month treatment arm were considerably better than those historically reported (i.e., 54% treatment success).[209] Given the overall high success rate seen in both treatment arms, as well as the cost savings associated with the shorter regimen, WHO re-affirmed their recommendation of the short-course regimen.[210] Importantly, however, participants with HIV in the STREAM trial had more than double the risk of death compared to participants without HIV, and although this difference did not reach statistical significance, the study was not powered to detect such a difference among subgroups. This finding is particularly concerning, given that a recent observational study of patients in nine African countries receiving the short-course regimen found a statistically significantly higher mortality rate in patients with HIV than in patients without HIV.[211] Many resource-limited countries have adopted the short-course regimen in their national TB treatment programs, and variations of the shortened regimen are being evaluated in several randomized clinical trials, including in the United States. Adoption of this option may be important for patients with MDR TB who have confirmed susceptibility to fluoroquinolones and second-line injectable agents.

The field is in considerable flux as clinical trials of shorter course therapy with or without injectable agents are in progress. In late 2018, WHO issued MDR treatment guidelines recommending a fully oral regimen for most patients with rifampin-resistant TB.[212] The ranking of the second-line drugs was restructured, and bedaquiline, linezolid, and levofloxacin/moxifloxacin were placed in the highest tier (Group A), followed by clofazimine and cycloserine (Group B). All remaining drugs were placed in Group C, to complete the regimen only when drugs from Group A and B cannot be used. Notably, kanamycin and capreomycin are no longer recommended, given that the recent meta-analysis found an increased risk of treatment failure and relapse seen with their use. Such an association was not seen for amikacin, which may be used when other, less toxic drugs cannot be used, or in select patients eligible for the short-course regimen. Although the WHO updated recommendations are focused on crafting an initial standardized regimen in areas where access to rapid drug-susceptibility testing may be limited, based on these data and given the inordinate complexity of treatment for MDR- and XDR-TB, it is likely that these recommendations will be adopted in many countries while awaiting data from randomized clinical trials.

The treatment of MDR TB in the United States is evolving. Bedaquiline was approved in the United States for treatment of MDR TB in 2012. Initial randomized trials showed an increased number of late-occurring, unexplained deaths among the relatively small number of patients who received bedaquiline in randomized trials[213] suggesting that this drug should be used with caution and only in patients without other MDR TB treatment options while awaiting additional studies,[214] However, a meta-analysis of subsequent cohort studies that compared MDR TB regimens with and without bedaquiline showed improved survival in patients treated with regimens containing bedaquiline (adjusted hazard ratio 0.50, 95% CI, 0.41–0.61).[215] Although clinical experience with bedaquiline in the United States is still limited, experience outside the United States is rapidly expanding. Studies have revealed several important drug-drug interactions with common ARV agents. Specifically, efavirenz decreases bedaquiline levels and should not be used concurrently with bedaquiline.[216] Lopinavir/ritonavir, by contrast, increases bedaquiline plasma concentrations approximately two-fold when given at steady-state, but the clinical significance of this increase is not yet known.[217,218]

Delamanid, a new agent with a mechanism of action distinct from bedaquiline's, showed promise in early phase clinical trials.[219] Delamanid has been approved in Europe and Japan but currently is only available in the United States through a compassionate use program. A Phase 3 trial recently compared delamanid to placebo when given with an optimized background regimen to patients with MDR TB. Results of the trial showed no significant difference in treatment success with the addition of delamanid versus placebo (81% of participants in each arm).[220] However, participants in the placebo plus optimized background therapy arm had much higher rates of treatment success than expected. Given the favorable safety profile of delamanid and the high toxicity of other drugs in the background regimen, WHO reaffirmed their prior endorsement of delamanid with the caveat that it only be given as part of a longer (i.e., 20–24 month) treatment course and when a suitable regimen cannot be constructed without it.[221]

At present, there are insufficient data to support the use of WHO recommended shorter-course regimens in individuals with or without HIV in high-resource settings like the United States where full drug-susceptibility testing and individualized treatment options are available but this is likely to change in the near future. Whenever possible, treatment should be individualized based on a patient's specific drug-susceptibility testing results or treatment history. Surgical removal of TB lesions is a potential adjunctive measure in those with localized disease.[222] In the United States, treatment of MDR TB should involve an expert with experience in treating drug-resistant TB cases (if a local expert is not available, one option is to contact one of CDC's TB Centers of Excellence for Training, Education, and Medical Consultation).

Several medications for MDR TB carry considerable toxicity, including irreversible hearing loss, hypothyroidism, psychosis, and treatment-limiting gastrointestinal discomfort. Given the prolonged treatment course for MDR TB (20–24 months), patients and family members must be counseled ahead of time about possible side effects and the importance of treatment adherence. While on therapy, patients should be monitored closely for the appearance of side effects. Such screening should include serum chemistries, liver function tests, thyroid stimulating hormone, audiometry if treated with an injectable agent, and EKG monitoring if treated with bedaquiline. Sputum cultures should be performed monthly, even after culture conversion, so that any relapse and amplified resistance are detected early.

As with drug-susceptible TB, patients with HIV with drug-resistant TB (other than meningitis) should start ART as soon as possible. Despite the considerable pill burden and potential for overlapping drug toxicities, several retrospective studies and a recent prospective cohort study from South Africa have demonstrated high treatment success rates and favorable HIV outcomes with concurrent treatment.[223,224]

TB-Associated IRIS

TB-IRIS is a frequent early complication of ART in patients with recently diagnosed or undiagnosed active TB. The condition is thought to result from the recovering immune system driving inflammatory reactions directed at *M. tuberculosis* antigen present at sites of disease.[225-227] 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.[228]

Paradoxical TB-IRIS

Paradoxical TB-IRIS occurs in patients who are diagnosed with active TB prior to starting ART. Typically, these patients have had clinical improvement on TB treatment prior to starting ART. Within the first 1 to 4 weeks of ART (though sometimes later), they develop new or recurrent symptoms, as well as new, worsening, or recurrent clinical and radiologic features of TB. Common and important manifestations of paradoxical TB-IRIS include hectic fevers, new or enlarging lymphadenopathy, and new or worsening pulmonary infiltrates. Mortality due to paradoxical TB-IRIS is uncommon,[226,229] 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.[226,230,231] In patients with disseminated TB, hepatic TB-IRIS is common. This manifests with nausea and vomiting, tender hepatic enlargement, cholestatic liver function derangement, and occasionally jaundice.[232,233] A liver biopsy reveals a granulomatous hepatitis.[234] 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 (incidence 48% to 54%). A recent meta-analysis of 40 studies reported a pooled incidence of TB-IRIS of 18% in adults with HIV-associated TB initiating ART, with death attributed to TB-IRIS in 2% of the cases.[235] The onset of paradoxical TB-IRIS symptoms is typically between 1 to 4 weeks after ART is initiated.[236-241] The syndrome lasts for 2 to 3 months on average,[230,242] but in some cases, symptoms may continue for months, and in rare cases, local manifestations may persist or recur over a year after onset.[228,242,243] 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 start of ART, especially a CD4 count <100 cells/mm^3;[239,244] high HIV viral load prior to ART;[245,246] disseminated or extrapulmonary TB;[230,238,240,244] 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.[230,237,239] Even though 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, given that this reduces risk of AIDS progression and death.[235]

The diagnosis of paradoxical TB-IRIS may be challenging, and there is no definitive confirmatory test. Thus, diagnosis relies upon a characteristic clinical presentation: improvement of TB symptoms with treatment prior to ART, deterioration with inflammatory features of TB soon after starting ART, and demonstration of a response to ART (CD4 rise and/or HIV viral load reduction). In addition, and very importantly, diagnosis of paradoxical TB-IRIS requires investigations to exclude alternative causes for deterioration, particularly another OI or undetected TB drug resistance.[233]

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. 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.[247] 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,[247] observational data,[231] and clinical trials that showed reduced mortality in patients presenting with TB meningitis who were treated with corticosteroids[81] 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. Among all patients who developed TB-IRIS in the study described above, 4 weeks of prednisone treatment was insufficient in a subset. In such instances, a more gradual tapering of steroids over 2 to 3 months is recommended **(BIII)**.[247] Tapering of corticosteroids should be guided by repeated clinical assessment of symptoms. Corticosteroids should be avoided in patients with Kaposi sarcoma, as life-threatening exacerbations can occur. There are case reports of patients with steroid-refractory and prolonged IRIS responding to TNF-blockers or thalidomide.[248-250]

Pre-emptive prednisone treatment has been shown to be effective in reducing the risk of paradoxical TB-IRIS in a trial conducted in South Africa.[251] This study was a randomized double-blind placebo-controlled trial in 240 ART-naive adults at high risk of paradoxical TB-IRIS treated with prednisone (40 mg/day for 2 weeks then 20 mg/day for 2 weeks) or placebo started at the time of ART initiation. High risk was defined as starting ART within 30 days of TB treatment initiation and a CD4 count ≤100/mm^3. Exclusion criteria included rifampin resistance, neurological TB, Kaposi's sarcoma, hepatitis BsAg positive, and poor clinical response to TB treatment prior to ART. The incidence of TB-IRIS was 47% in the placebo arm and 33% in the prednisone arm (RR = 0.70, 95% CI, 0.51–0.96). The intervention was not associated with harm; there was no excess risk of malignancy or severe infections. Based on these study findings, pre-emptive prednisone therapy should be offered for high-risk patients, as defined in this study, with a CD4 count ≤100/mm^3 who are starting ART in the context of recently initiated anti-TB therapy, are responding well to TB therapy, and who do not have rifampin resistance, Kaposi's sarcoma, or active hepatitis B **(BI)**.

Some clinicians 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.[230]

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.[228] 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.[228,247,252-254] Focal inflammatory manifestations such as abscesses and lymphadenitis may also develop.[255] 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 there is no clinical trial evidence 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.[256] 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.[257,258] 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.[259]

Several interventions have been suggested to decrease the risk of recurrent TB among patients with HIV: longer TB treatment regimens, administering therapy daily throughout the course of induction 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,[260,261] suggesting that this intervention decreases the risk of re-infection. However, post-treatment isoniazid is not recommended in low-burden settings such as the United States. 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 women 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 women with HIV is not recommended.[262-265] There are several studies examining the performance of the IGRAs for diagnosis of LTBI in pregnant women. In a study in pregnant women with HIV in Kenya, a positive IGRA result was associated with a 4.5-fold increased risk of developing active TB disease; in women with CD4 cell counts <250 cells/mm^3, a positive IGRA result was associated with a five-fold increased risk of maternal mortality or active TB disease and a three-fold increased risk of either active TB disease or mortality in infants.[266] Antenatal IGRA positivity has also been demonstrated to correlate with postpartum IGRA test positivity (i.e., TB infection) in women with HIV.[267] In women without HIV, the test appears to perform well but cost issues for routine screening are an area of debate.[268] If LTBI is diagnosed during pregnancy and active TB disease has been ruled out, treatment with isoniazid should be delayed until after delivery **(BI)**, given a recent clinical trial showing increased adverse pregnancy outcomes in women in high TB prevalence settings treated with isoniazid during pregnancy as compared to deferring to after delivery.[269] IPT is still recommended, however, for pregnant women whose close household contacts include a person with TB disease. Studies in individuals with HIV who are not receiving ART have been found to have a high risk of progression from LTBI to active TB disease (10% per year), and there is a high risk of maternal and infant mortality in pregnant women with HIV who have active TB disease.[270,271] However, the risk of progression from LTBI to active TB disease in individuals on ART is significantly decreased.[272] Pregnant women with HIV should be receiving ART both for their own health and for prevention of perinatal transmission. The risk of isoniazid-associated hepatotoxicity may be increased in

pregnancy. While treatment with isoniazid should be delayed until after delivery, if the risk of progression to active TB disease is considered to outweigh the risk of adverse birth outcomes with isoniazid and isoniazid is prescribed, frequent monitoring is needed.[273] Pregnant women receiving isoniazid should receive daily pyridoxine supplementation as they are at risk of isoniazid-associated peripheral neuropathy.[274]

The diagnostic evaluation for TB disease in pregnant women is the same as for non-pregnant adults. Chest radiographs with abdominal shielding are recommended and result in minimal fetal radiation exposure. An increase in pregnancy complications and undesirable outcomes including preterm birth, low birthweight, and fetal growth restriction might be observed among pregnant women with either pulmonary or extrapulmonary TB not confined to the lymph nodes, especially when TB treatment is not begun until late in pregnancy.[262-265,275-278] Congenital TB infection has been reported, although it appears relatively uncommon.[279-283] However, in one study of 107 women with active TB disease during pregnancy in South Africa, *M. tuberculosis* was detected in 16% of neonates (n = 16) tested within the first 3 weeks of life (12 by culture and 4 by smear microscopy).[284]

Treatment of TB disease for pregnant women should be the same as for non-pregnant women, but with attention to the following considerations **(BIII)**:

- Although isoniazid is not teratogenic in animals or humans, hepatotoxicity caused by isoniazid might occur more frequently during pregnancy and the postpartum period.[285] Monthly monitoring of liver transaminases during pregnancy and the postpartum period is recommended **(CIII)**.
- 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. Experience with its use in human pregnancy is limited. Although WHO and the International Union Against Tuberculosis and Lung Diseases[286,287] have made recommendations for the routine use of pyrazinamide in pregnant women, pyrazinamide has not been recommended for general use during pregnancy in the United States because data characterizing its effects in this setting are limited.[288] If pyrazinamide is not included in the initial treatment regimen, the minimum duration of TB therapy should be 9 months **(AII)**. The decision regarding whether to include pyrazinamide in treatment regimens for pregnant woman should be made after consultation among obstetricians, TB specialists, and patients, considering gestational age and likely susceptibility pattern of the woman's TB strain.

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.[204] Experience using the majority of the second-line drugs for TB during pregnancy is limited.[289-292] MDR TB in pregnancy should be managed in consultation with a specialist. TB therapy should not be withheld because of pregnancy **(AIII)**. The following concerns should be considered when selecting second-line anti-TB drugs for use in pregnant women:

- Streptomycin use has been associated with a 10% rate of vestibulocochlear nerve toxicity in infants exposed to the drug *in utero*; its use during pregnancy should be avoided if possible **(AIII)**.
- Hearing loss has been detected in approximately 2% of children exposed to long-term kanamycin therapy *in utero*; like streptomycin, this agent should typically be avoided, if possible **(AIII)**. The fetus is at a theoretical risk for ototoxicity with *in utero* exposure to amikacin and capreomycin, but this risk has not been documented, and these drugs might be alternatives when an aminoglycoside is required for treatment of MDR TB **(CIII)**.

- Because arthropathy has been noted in immature animals exposed to quinolones *in utero*, quinolones are typically not recommended for pregnant women or children aged <18 years **(CIII)**. However, studies evaluating quinolone use in pregnant women did not find an increased risk of birth defects or congenital musculoskeletal abnormalities.[293,294] Thus, fluoroquinolones can be used in pregnancy for drug-resistant TB if they are required on the basis of susceptibility testing **(CIII)**.[295]
- Para-aminosalicylic acid is not teratogenic in rats or rabbits.[288] 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.[296] No specific pattern of defects and no increase in rate of defects have been detected in other human studies, indicating that this agent can be used with caution, if needed **(CIII)**.
- Ethionamide has been associated with an increased risk for several anomalies in rats after high-dose exposure but not in mice and rabbits.[297-299] Case reports have documented cases of CNS defects in humans but overall experience is limited with use during human pregnancy.[300] Thus, ethionamide should be avoided unless its use is required on the basis of susceptibility testing **(CIII)**.
- No data are available from animal studies or reports of cycloserine use in humans during pregnancy.

Recommendations for Treating *Mycobacterium Tuberculosis* Infection and Disease (page 1 of 3)

Treating LTBI to Prevent TB Disease

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:

- Isoniazid 300 mg PO daily plus pyridoxine 25–50 mg PO daily **(AI)**

Duration of Therapy:

- 9 months

Alternative Therapies:

- 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 **(AII)**. **Note:** Rifapentine is only recommended for patients receiving an efavirenz- or raltegravir-based ART regimen.
  - Rifapentine Weekly Dose (maximum 900 mg)
    - *Weighing 32.1–49.9 kg:* 750 mg
    - *Weighing ≥50.0 kg:* 900 mg, *or*
      - Rifampin 600 mg PO daily for 4 months **(BI)** *or*
      - For persons exposed to drug-resistant TB, select anti-TB drugs after consultation with experts or with public health authorities **(AII)**.

Treating Active TB Disease

- After collecting specimen for culture and molecular diagnostic tests, empiric treatment should be initiated in persons 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 (below) for TB drug dosing recommendations and to the Adult and Adolescent Antiretroviral Guidelines for dosing recommendations of ARV drugs when used with rifampin or rifabutin.

For Drug-Sensitive 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.

Continuation Phase (for Drug-Susceptible TB):

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

Total Duration of Therapy:

- Pulmonary, drug-susceptible 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 w/CNS involvement: 9 to 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 (an aminoglycoside or capreomycin)
- Therapy should be modified once rifampin resistance is confirmed and based on drug susceptibility results to provide ≥5 active drugs.

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, clinical and microbiological responses, to include ≥5 active drugs, and with close consultation with experienced specialists **(AIII)**.

Duration:

- 12 to 24 months (see the 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 0.1 mg/kg per week until 0.1 mg/kg, then 4 mg per day and taper by 1 mg/week; total duration of 12 weeks.
- Despite the potential of drug-drug interactions, a rifamycin remains the most potent TB drug and should remain as part of the TB regimen unless a rifamycin-resistant isolate is detected, or the patient has a severe adverse effect that is likely due to the rifamycin (please refer to the table below and to the Adult and Adolescent Antiretroviral Guidelines for dosing recommendations involving concomitant use of rifampin or rifabutin and different ARV drugs).
- If NVP is to be added to the ARV regimen of a patient who is receiving RIF, the lead-in dose for NVP should be omitted.
- Intermittent rifamycins 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.
- Pre-emptive prednisone regimen: 40 mg/day for 2 weeks then 20 mg/day for 2 weeks

[a] Screening tests for LTBI include TST or IGRA; see text for details regarding these tests.

Key: ART = antiretroviral therapy; ARV = antiretroviral; CNS = central nervous system; DOT = directly observed therapy; EFV = efavirenz; IGRA = interferon-gamma release assay; LTBI = latent tuberculosis infection; NVP = nevirapine; PI = protease inhibitor; PO = orally; RAL = raltegravir; TB = tuberculosis; TST = tuberculin skin test

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	With HIV PIs, DOR, ETR, RPV, BIC, or EVG/c	**Not recommended**
	With TAF	Use with caution[c] at dose indicated below
	With other ARV drugs	10 mg/kg (usual dose 600 mg)
Rifabutin[a] **Note:** DOR and RPV doses need to be adjusted when used with rifabutin	With PI with COBI, TAF, BIC, or EVG/c - containing regimens	**Not recommended**
	With DTG, RAL, EFV, DOR, RPV	5 mg/kg (usual dose 300 mg)
	With HIV PIs with RTV	150 mg[d]
	With 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[e]
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[e]

[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 PK and virologic efficacy among patients taking full dose ART and TB regimens.

[d] 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 TDM when rifabutin is used with an RTV-boosted PI and adjust dose accordingly.

[e] Monitor for therapeutic response and consider TDM to assure dosage adequacy in patients weighing >90 kg.

Key: ARV = antiretroviral; ART = antiretroviral therapy; BIC = bictegravir; COBI = cobicistat; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; MVC = maraviroc; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TB = tuberculosis; TDM = therapeutic drug monitoring

References

1. World Health Organization. Global tuberculosis report. 2017. Available at: http://www.who.int/tb/publications/global_report/gtbr2017_main_text.pdf.
2. 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.
3. 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.
4. 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.
5. Jones JL, Hanson DL, Dworkin MS, DeCock KM. HIV-associated tuberculosis in the era of highly active antiretroviral therapy. The Adult/Adolescent Spectrum of HIV Disease Group. *Int J Tuberc Lung Dis*. 2000;4(11):1026-1031. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11092714.
6. Severe P, Juste MA, Ambroise A, et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. *N Engl J Med*. 2010;363(3):257-265. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20647201.
7. Badri M, Wilson D, Wood R. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. *Lancet*. 2002;359(9323):2059-2064. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12086758.
8. 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.
9. 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.
10. Seyler C, Toure S, Messou E, Bonard D, Gabillard D, Anglaret X. Risk factors for active tuberculosis after antiretroviral treatment initiation in Abidjan. *Am J Respir Crit Care Med*. 2005;172(1):123-127. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15805184.
11. Centers for Disease Control and Prevention. Reported tuberculosis in the United States, 2017. Available at: https://www.cdc.gov/tb/statistics/reports/2017/2017_Surveillance_FullReport.pdf.
12. 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.
13. Albalak R, O'Brien RJ, Kammerer JS, et al. Trends in tuberculosis/human immunodeficiency virus comorbidity, United States, 1993-2004. *Arch Intern Med*. 2007;167(22):2443-2452. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18071166.
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. 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.
19. 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.
20. Golub JE, Cohn S, Saraceni V, et al. Long-term protection from isoniazid preventive therapy for tuberculosis in HIV-infected patients in a medium-burden tuberculosis setting: the TB/HIV in Rio (THRio) study. *Clin Infect Dis*.

2015;60(4):639-645. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25365974.

21. 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.
22. 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: http://www.ncbi.nlm.nih.gov/pubmed/21492926.
23. 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.
24. 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.
25. 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.
26. Ewer K, Deeks J, Alvarez L, et al. Comparison of T-cell-based assay with tuberculin skin test for diagnosis of Mycobacterium tuberculosis infection in a school tuberculosis outbreak. *Lancet*. 2003;361(9364):1168-1173. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12686038.
27. Nahid P, Pai M, Hopewell PC. Advances in the diagnosis and treatment of tuberculosis. *Proc Am Thorac Soc*. 2006;3(1):103-110. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16493157.
28. Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. *Ann Intern Med*. 2007;146(5):340-354. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17339619.
29. 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.
30. Dorman SE, Belknap R, Graviss EA, et al. Interferon-gamma release assays and tuberculin skin testing for diagnosis of latent tuberculosis infection in healthcare workers in the United States. *Am J Respir Crit Care Med*. 2014;189(1):77-87. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24299555.
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. 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.
33. 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.
34. 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.
35. 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.
36. 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.
37. 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.
38. 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.

39. 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.
40. 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.
41. 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.
42. 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.
43. 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.
44. 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.
45. Mwinga A, Hosp M, Godfrey-Faussett P, et al. Twice weekly tuberculosis preventive therapy in HIV infection in Zambia. *AIDS*. 1998;12(18):2447-2457. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9875583.
46. Mohammed A, Myer L, Ehrlich R, Wood R, Cilliers F, Maartens G. Randomised controlled trial of isoniazid preventive therapy in South African adults with advanced HIV disease. *Int J Tuberc Lung Dis.* 2007;11(10):1114-1120. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17945069.
47. 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.
48. 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.
49. 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.
50. 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.
51. World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. 2018. Available at: http://apps.who.int/iris/bitstream/handle/10665/260233/9789241550239-eng.pdf?sequence=1. Accessed: September 13, 2019.
52. 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.
53. 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.
54. 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.
55. 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.
56. 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.

57. 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.
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. 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.
60. 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.
61. 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.
62. 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.
63. 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.
64. 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.
65. Samandari T, Mosimaneotsile B, et al. Randomized placebo-controlled trial of 8 vs. 36 months of isoniazid TB preventative therapy for HIV-infected adults in Botswana. Presented at: Conference on Retroviruses and Opportunistic Infections. 2010. San Fransisco, CA.
66. 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.
67. 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.
68. 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.
69. 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.
70. Hanifa Y, Fielding KL, Chihota VN, et al. A clinical scoring system to prioritise investigation for tuberculosis among adults attending HIV clinics in South Africa. *PLoS One*. 2017;12(8):e0181519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28771504.
71. 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.
72. Griesel R, Stewart A, van der Plas H, et al. Optimizing tuberculosis diagnosis in human immunodeficiency virus-infected inpatients meeting the criteria of seriously ill in the World Health Organization algorithm. *Clin Infect Dis*. 2018;66(9):1419-1426. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29126226.
73. 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.
74. 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.

75. 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.

76. Post FA, Wood R, Pillay GP. Pulmonary tuberculosis in HIV infection: radiographic appearance is related to CD4+ T-lymphocyte count. *Tuber Lung Dis*. 1995;76:518-21. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8593372.

77. 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.

78. 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.

79. 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.

80. 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.

81. 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.

82. 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.

83. 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.

84. 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.

85. 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.

86. 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.

87. 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.

88. 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.

89. Leeds IL, Magee MJ, Kurbatova EV, et al. Site of extrapulmonary tuberculosis is associated with HIV infection. *Clin Infect Dis*. 2012;55(1):75-81. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22423123.

90. Naing C, Mak JW, Maung M, Wong SF, Kassim AI. Meta-analysis: the association between HIV infection and extrapulmonary tuberculosis. *Lung.* 2013;191(1):27-34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23180033.

91. 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.

92. 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.

93. 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.

94. Centers for Disease Control and Prevention. Updated guidelines for the use of nucleic acid amplification tests in the diagnosis of tuberculosis. *MMWR Morb Mortal Wkly Rep*. 2009;58(1):7-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19145221.

95. 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. http://whqlibdoc.who.int/publications/2011/9789241501545_eng.pdf. Accessed: September 13, 2019.

96. Food and Drug Adminstration. FDA permits marketing of first U.S. test labeled for simultaneous detection of tuberculosis bacteria and resistance to the antibiotic rifampin. 2013.

97. Food and Drug Adminstration. New data shows test can help physicians remove patients with suspected TB from isolation earlier.2015.

98. 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.

99. 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.

100. 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.

101. 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.

102. Chakravorty S, Simmons AM, Rowneki M, et al. The new Xpert MTB/RIF Ultra: improving detection of Mycobacterium tuberculosis and resistance to rifampin in an assay suitable for point-of-care testing. *MBio*. 2017;8(4). Available at: http://www.ncbi.nlm.nih.gov/pubmed/28851844.

103. Dorman SE, Schumacher SG, Alland D, et al. Xpert MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study. *Lancet Infect Dis*. 2018;18(1):76-84. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29198911.

104. Bahr NC, Nuwagira E, Evans EE, et al. Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study. *Lancet Infect Dis*. 2018;18(1):68-75. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28919338.

105. World Health Organization. WHO meeting report of a technical expert consultation: non-inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/RIF. 2017. Available at: http://apps.who.int/iris/bitstream/handle/10665/254792/WHO-HTM-TB-2017.04-eng.pdf. Accessed: September 13, 2019.

106. 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.

107. 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.

108. 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.

109. Lawn SD, Kerkhoff AD, Burton R, et al. Diagnostic accuracy, incremental yield and prognostic value of Determine TB-LAM for routine diagnostic testing for tuberculosis in HIV-infected patients requiring acute hospital admission in South Africa: a prospective cohort. *BMC Med*. 2017;15(1):67. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28320384.

110. Peter JG, Theron G, van Zyl-Smit R, et al. Diagnostic accuracy of a urine lipoarabinomannan strip-test for TB detection in HIV-infected hospitalised patients. *Eur Respir J*. 2012;40(5):1211-1220. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22362849.

111. Shah M, Ssengooba W, Armstrong D, et al. Comparative performance of urinary lipoarabinomannan assays and Xpert MTB/RIF in HIV-infected individuals. *AIDS*. 2014;28(9):1307-1314. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24637544.

112. Kerkhoff AD, Barr DA, Schutz C, et al. Disseminated tuberculosis among hospitalised HIV patients in South Africa: a common condition that can be rapidly diagnosed using urine-based assays. *Sci Rep.* 2017;7(1):10931. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28883510.

113. 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.

114. 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: http://www.ncbi.nlm.nih.gov/pubmed/19833824.

115. 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.

116. World Health Organization. Technical report on critical concentrations for drug susceptibility testing of medicines used in the treatment of drug-resistant tuberculosis. 2018. Available at: http://apps.who.int/iris/handle/10665/260470. Accessed: September 13, 2019.

117. 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.

118. 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.

119. Osman M, Simpson JA, Caldwell J, Bosman M, Nicol MP. GeneXpert MTB/RIF version G4 for identification of rifampin-resistant tuberculosis in a programmatic setting. *J Clin Microbiol*. 2014;52(2):635-637. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24478501.

120. Van Deun A, Aung KJ, Bola V, et al. Rifampin drug resistance tests for tuberculosis: challenging the gold standard. *J Clin Microbiol*. 2013;51(8):2633-2640. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23761144.

121. Rigouts L, Gumusboga M, de Rijk WB, et al. Rifampin resistance missed in automated liquid culture system for Mycobacterium tuberculosis isolates with specific rpoB mutations. *J Clin Microbiol*. 2013;51(8):2641-2645. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23761146.

122. Williamson DA, Roberts SA, Bower JE, et al. Clinical failures associated with rpoB mutations in phenotypically occult multidrug-resistant Mycobacterium tuberculosis. *Int J Tuberc Lung Dis.* 2012;16(2):216-220. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22137551.

123. Ho J, Jelfs P, Sintchencko V. Phenotypically occult multidrug-resistant Mycobacterium tuberculosis: dilemmas in diagnosis and treatment. *J Antimicrob Chemother*. 2013;68(12):2915-2920. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23838950.

124. 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.

125. 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.

126. 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.

127. 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.

128. 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.

129. 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.

130. 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.

131. 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.
132. 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.
133. 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.
134. Centers for Disease Control and Prevention. Reported tuberculosis in the United States, 2013. 2014.
135. World Health Organization. Global Tuberculosis Report, 2015. 2015. Available at: http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf. Accessed: September 13, 2019.
136. 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.
137. 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.
138. 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.
139. 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.
140. 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.
141. Dian S, Yunivita V, Ganiem AR, et al. High dose rifampicin for the treatment of TB meningitis: a dose finding study. Presented at: International Workshop on Pharmacology of Tuberculosis Drugs. 2017.
142. 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.
143. Ruslami R, Ganiem AR, Aarnoutse RE, van Crevel R, study t. 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.
144. 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.
145. 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.
146. 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.
147. 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.
148. 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.
149. INSIGHT START Study Group, Lundgren JD, Babiker AG, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med*. 2015;373(9):795-807. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26192873.

150. Grinsztejn B, Hosseinipour MC, Ribaudo HJ, et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. *Lancet Infect Dis*. 2014;14(4):281-290. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24602844.

151. 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.

152. 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.

153. 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.

154. 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.

155. Cerrone M, Alfarisi O, Neary M, et al. Rifampin effect on tenofovir alafenamide once daily plasma and intracellular pharmacokinetics. Paper presented at: Conference on Retroviruses and Opportunistic Infections. 2018. Boston, MA.

156. 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.

157. Lopez-Cortes LF, Ruiz-Valderas R, Viciana P, et al. Pharmacokinetic interactions between efavirenz and rifampicin in HIV-infected patients with tuberculosis. *Clin Pharmacokinet*. 2002;41(9):681-690. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12126459.

158. 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.

159. 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.

160. 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.

161. 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.

162. 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.

163. Swaminathan S, Padmapriyadarsini C, Venkatesan P, et al. Efficacy and safety of once-daily nevirapine- or efavirenz-based antiretroviral therapy in HIV-associated tuberculosis: a randomized clinical trial. *Clin Infect Dis*. 2011;53(7):716-724. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21890776.

164. Bhatt NB, Baudin E, Meggi B, et al. Nevirapine or efavirenz for tuberculosis and HIV coinfected patients: exposure and virological failure relationship. *J Antimicrob Chemother*. 2015;70(1):225-232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25239466.

165. Jiang HY, Zhang MN, Chen HJ, Yang Y, Deng M, Ruan B. Nevirapine versus efavirenz for patients co-infected with HIV and tuberculosis: a systematic review and meta-analysis. *Int J Infect Dis*. 2014;25:130-135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24911886.

166. 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.

167. 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.

168. 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.

169. 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.
170. Dooley K, Kaplan R, Mwelase N, et al. Safety and efficacy of dolutegravir-based ART in TB/HIV coinfected adults at week 24. Presented at: Conference on Retroviruses and Opportunistic Infections. 2018. Boston, MA. Available at: http://www.croiconference.org/sessions/safety-and-efficacy-dolutegravir-based-art-tbhiv-coinfected-adults-week-24.
171. 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.
172. 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.
173. 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.
174. 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.
175. 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.
176. 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.
177. 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.
178. 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.
179. 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.
180. 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.
181. Abbott. Kaletra (lopinavir/ritonavir) [package insert]. 2019. Available at: https://www.rxabbvie.com/pdf/kaletratabpi.pdf.
182. Bristol-Myers Squibb. Atazanavir [package insert]. 2018. Available at: https://packageinserts.bms.com/pi/pi_reyataz.pdf.
183. 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.
184. 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.
185. 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.
186. 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.

187. 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.

188. 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.

189. 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.

190. 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.

191. 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.

192. 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.

193. 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.

194. 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.

195. Bliven-Sizemore EE, Johnson JL, Goldberg S, et al. Effect of HIV infection on tolerability and bacteriologic outcomes of tuberculosis treatment. *Int J Tuberc Lung Dis.* 2012;16(4):473-479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22325844.

196. 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.

197. 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.

198. 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.

199. 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.

200. Menzies D, Benedetti A, Paydar A, et al. Standardized treatment of active tuberculosis in patients with previous treatment and/or with mono-resistance to isoniazid: a systematic review and meta-analysis. *PLoS Med*. 2009;6(9):e1000150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20101802.

201. 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.

202. 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. Accessed: September 13, 2019.

203. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. 2011. Available at: http://apps.who.int/iris/bitstream/10665/44597/1/9789241501583_eng.pdf. Accessed: September 13, 2019.

204. American Thoracic Society, Centers for Disease Control and Prevention, Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR.* 2003;52(RR-11). Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm.

205. Ahuja SD, Ashkin D, Avendano M, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. *PLoS Med*. 2012;9(8):e1001300. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22952439.

206. 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.

207. World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis–2016 update. 2016.

208. Aung KJ, Van Deun A, Declercq E, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. *Int J Tuberc Lung Dis*. 2014;18(10):1180-1187. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25216831.

209. 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.

210. Results from the STREAM stage 1 randomised controlled trial for treatment of MDR-TB using a standardised shorter regimen: Response by the World Health Organization [press release]. October 13, 2017.

211. Trebucq A, Schwoebel V, Kashongwe Z, et al. Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. *Int J Tuberc Lung Dis*. 2018;22(1):17-25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29149917.

212. World Health Organization. Rapid communication: key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). 2018. Available at: http://www.who.int/tb/publications/2018/WHO_RapidCommunicationMDRTB.pdf. Accessed: September 13, 2019.

213. Janssen Therapeutics. Sirturo [package insert]. 2019. Edition:Description. Available at: http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SIRTURO-pi.pdf.

214. Centers for Disease Control and Prevention. Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis. *MMWR Recomm Rep*. 2013;62(RR-09):1-12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24157696.

215. World Health Organization. Report of the Guideline Development Group Meeting on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis: a review of available evidence (2016). 2017. Available at: http://apps.who.int/iris/bitstream/handle/10665/254712/WHO-HTM-TB-2017.01-eng.pdf. Accessed: September 13, 2019.

216. 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.

217. 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.

218. 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.

219. Gler MT, Skripconoka V, Sanchez-Garavito E, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. *N Engl J Med*. 2012;366(23):2151-2160. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22670901.

220. Geiter LJ. Delamanid global clinical database and Phase 3 trial results. Presented at: Union World Conference on Lung Health. 2017. Guadalajara, Mexico.

221. World Health Organization. WHO position statement on the use of delamanid for multidrug-resistant tuberculosis. 2018. Available at: http://www.who.int/tb/publications/2018/WHOPositionStatementDelamanidUse.pdf. Accessed: September 13, 2019.

222. Kempker RR, Vashakidze S, Solomonia N, Dzidzikashvili N, Blumberg HM. Surgical treatment of drug-resistant tuberculosis. *Lancet Infect Dis*. 2012;12(2):157-166. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22281142.

223. Brust JCM, Shah NS, Mlisana K, et al. Improved survival and cure rates with concurrent treatment for multidrug-resistant tuberculosis-human immunodeficiency virus coinfection in South Africa. *Clin Infect Dis*. 2018;66(8):1246-1253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29293906.

224. Shin SS, Modongo C, Boyd R, et al. High treatment success rates among HIV-infected multidrug-resistant

tuberculosis patients after expansion of antiretroviral therapy in Botswana, 2006-2013. *J Acquir Immune Defic Syndr*. 2017;74(1):65-71. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27552155.

225. 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.
226. 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.
227. 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.
228. 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.
229. 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.
230. 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.
231. 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.
232. 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.
233. 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.
234. 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.
235. 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.
236. 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.
237. 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.
238. 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.
239. 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.
240. 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.
241. 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.
242. 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.

243. 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.

244. 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.

245. 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.

246. 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.

247. 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.

248. 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.

249. 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.

250. 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.

251. 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.

252. John L, Baalwa J, Kalimugogo P, et al. Response to 'Does immune reconstitution promote active tuberculosis in patients receiving highly active antiretroviral therapy?' AIDS, 22 July 2005. *AIDS*. 2005;19(17):2049-2050. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16260919.

253. 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.

254. 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.

255. 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.

256. 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.

257. 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.

258. 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.

259. 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.

260. 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.

261. Haller L, Sossouhounto R, Coulibaly IM, Dosso M, et al. 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.

262. 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.

263. 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.

264. 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.

265. 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.

266. 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.

267. 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.

268. 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.

269. Gupta A, Montepiedra G, Aaron L, et al. Randomized trial of safety of isoniazid preventive therapy during or after pregnancy. Presented at: Conference on Retroviruses and Opportunistic Infections. 2018. Boston, MA. Available at: http://www.croiconference.org/sessions/randomized-trial-safety-isoniazid-preventive-therapy-during-or-after-pregnancy.

270. 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.

271. 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.

272. 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.

273. 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. Accessed: September 13, 2019.

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

275. 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.

276. 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.

277. 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.

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

279. 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.

280. 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.

281. 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.

282. 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.

283. 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.

284. Pillay T, Sturm AW, Khan M, et al. Vertical transmission of Mycobacterium tuberculosis in KwaZulu Natal: impact of HIV-1 co-infection. *Int J Tuberc Lung Dis.* 2004;8(1):59-69. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14974747.

285. 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.

286. World Health Organizations. Treatment of tuberculosis: guidelines for national programs. 2003. Available at: https://apps.who.int/iris/bitstream/handle/10665/67890/WHO_CDS_TB_2003.313_eng.pdf.

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

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

289. 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.

290. 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.

291. 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.

292. 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.

293. 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.

294. 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.

295. 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.

296. 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.

297. 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.

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

299. 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.

300. 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.