Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

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**Mycobacterium tuberculosis Infection and Disease** (Last updated September 22, 2017; last reviewed June 26, 2019)

**NOTE: Update in Progress**

**Epidemiology**

Despite being preventable and curable, tuberculosis (TB) is the leading cause of death from infectious disease globally, with nearly 10 million people developing TB and 1.5 million people dying from TB in 2014.\(^1\) TB is the leading cause of morbidity and mortality among people living with HIV worldwide, with 1.2 million new HIV-infected persons reported with TB and 390,000 deaths in 2014.

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.

It is estimated that the annual risk of reactivation with TB disease among persons with untreated HIV infection is 3 to 16% per year, which approximates the lifetime risk among HIV-negative persons with LTBI (~5%).\(^2\) TB incidence doubles in the first year following HIV infection\(^3\) and can occur at any CD4 cell count, though the risk increases with progressive immunodeficiency.\(^3,4\)

Antiretroviral therapy (ART) results in a prompt and marked decrease in the incidence of TB disease, and this effect has been documented in settings with low case rates, such as the United States,\(^5\) and in settings with very high case rates.\(^6,7\) 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.\(^8\)

Rates of TB in the United States are declining, with 3.0 new cases of TB disease per 100,000 population (a total of 9,412 cases) reported in 2014, a decline of 2.2% from 2013.\(^9\) The prevalence of LTBI in the general population of the United States is 4.7%,\(^10\) 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 in the general population,\(^11\) in part due to the widespread use of ART. In 2014, there were 506 reported cases of HIV/TB co-infection in the United States (6.3% of individuals with TB who were tested for HIV).\(^12\) Like TB disease in the general population of the United States, HIV-related TB is increasingly a disease of persons born outside of the United States.\(^11\) Notably, TB disease has not decreased significantly in recent years among foreign-born persons with HIV disease in the United States.\(^11,13\)

Despite these favorable epidemiological trends, TB remains an important opportunistic illness in the United States. Unlike most opportunistic infections, TB is transmissible, particularly to other 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.\(^10\) Therefore, patients with HIV infection who travel 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 return. While there are risks for TB exposure in some healthcare and correctional settings in the United States, there is no need for precautions for persons with HIV infection beyond those taken for all persons in those settings.
Preventing Disease—Diagnosis and Treatment of Latent TB Infection

The estimated annual risk for active TB among HIV-infected persons with LTBI is 3 to 12 times the risk in the general population. Furthermore, development of HIV-related TB increases viral load, and the risk of HIV disease progression and death, compared to CD4-matched HIV-seropositive controls without TB. Risk of progression from LTBI to TB disease in HIV-infected persons is reduced both by antiretroviral treatment and by treatment of LTBI. Treatment of LTBI (as defined by a positive tuberculin skin test [TST]) decreases the risk of TB disease by 62% and the risk of death by 26% among persons with HIV infection. Isoniazid preventive therapy and ART independently decrease the risk of death by 37% when compared to placebo. In Brazil, a country with medium TB burden, the protective effect of isoniazid against TB in HIV-infected persons with a positive TST lasted throughout 7 years of follow-up. Therefore, prevention of TB disease by screening and appropriate treatment for LTBI are key components of HIV care.

Diagnosis of LTBI

All persons should be tested for LTBI at the time of HIV diagnosis, regardless of their epidemiological risk of TB exposure (AII). Among HIV-infected persons, the benefit of isoniazid preventive therapy has been seen primarily in persons with evidence of LTBI (e.g., a positive TST). However, in one study in South Africa, a setting with a high TB burden, isoniazid decreased the TB risk among all persons receiving ART regardless of TST or interferon gamma release assay result. Persons with negative diagnostic tests for LTBI, advanced HIV infection (CD4 cell count <200 cells/µL), 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/µL to ensure the initial test was a true negative result. Annual testing for LTBI using TST is recommended for HIV-infected persons who are at high risk for repeated or ongoing exposure to persons with active TB (AIII).

Traditionally, LTBI has been defined by the presence of a positive TST (≥5 mm of induration at 48 to 72 hours in HIV-infected persons) in persons with no clinical or radiographic evidence of TB disease. Despite the extensive experience with the TST among persons with HIV infection, 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. These limitations of the TST have led to interest in interferon-gamma release assays (IGRA) for detection of LTBI.

Current evidence suggests that, compared to the TST, IGRAs have higher specificity (92%–97% vs. 56%–95%), better correlation with surrogate measures of exposure to M. tuberculosis, and less cross-reactivity with BCG vaccination and nontuberculous mycobacteria. Three IGRAs are FDA-approved and available in the United States. Progressive immunodeficiency is associated with decreased sensitivity of IGRAs, though the effect of immunodeficiency on the sensitivity of IGRAs may be less than its effect on the sensitivity of the TST. Like the TST, the reproducibility of positive results of IGRAs is limited. Among 46 HIV-infected patients having 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.

Among persons with HIV infection, the correlation between the TST and IGRAs is poor to moderate. In prospective studies, positive results with either the TST or IGRA were associated with an increased risk of developing TB disease; 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. For all of its limitations, a positive TST result remains strongly predictive of decreased risk of TB progression in response to isoniazid preventive therapy among persons with HIV infection. Whether the same is true of the IGRAs remains to be demonstrated.
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.41-43 The use of an IGRA for TB screening may increase the proportion of patients who complete TB screening.

There have been no definitive comparisons of the TST and IGRA for screening persons with HIV infection in low-burden settings like the United States. Both the TST and the approved IGRA are appropriate for TB screening among HIV-infected persons in the United States.44 Some experts have suggested using both the TST and an IGRA to screen for LTBI, but the predictive value of this approach is not clear, and its adoption would be more expensive and more difficult to implement. The routine use of both TST and IGRA to screen for LTBI is not recommended in the United States.44

As tests of immune reactivity against *M. tuberculosis*, the TST and IGRA 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, HIV-infected persons with TB disease have symptoms (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.45 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 this is not cost-effective in screening asymptomatic HIV-infected persons, particularly in the United States where the prevalence of TB is very low. Therefore, symptom screening (asking for cough of any duration) coupled with chest radiography is recommended to exclude TB disease in a patient with a positive screening test.

**Treatment of LTBI**

Once it is established that there is no evidence of TB disease, HIV-infected persons with a positive screening test should receive prophylaxis (AI). Additionally, HIV-infected close contacts of an infectious case of TB should receive prophylaxis, regardless of screening tests for LTBI. HIV-infected persons who have a negative TST and are not recent contacts of a case of infectious TB may not benefit from treatment of LTBI (AI),24,46-48 though at least one study from a high-burden setting in South Africa showed isoniazid decreased TB risk regardless of TST or IGRA result.22

**Preferred and Alternative Drugs for LTBI Treatment, Including Duration of Therapy**

Isoniazid prophylaxis for 9 months remains the preferred therapy, with proven efficacy, good tolerability, and infrequent severe toxicity (AII). Although peripheral neuropathy, hepatitis, and rash may be caused by either isoniazid or various antiretroviral 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 (BII).22 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.49 Shorter regimens are more likely to be completed.49-52 Alternative regimens for chemoprophylaxis are shown in Table 1. Rifapentine plus isoniazid given by directly observed therapy (DOT) once weekly for 12 weeks is as effective and well-tolerated as 6 to 9 months of daily LTBI treatment with isoniazid, including in persons with HIV infection whose CD4 lymphocyte counts are generally >350 cells/mm³ and who are not yet on ART.53-55 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 is favorable.56 In a PK study of 12 HIV-infected adults without TB receiving once-weekly 900 mg rifapentine with efavirenz, there was minimal effect on efavirenz exposure.57 Raltegravir concentrations were modestly increased, not decreased, when it was given with once-weekly rifapentine.58 Thus, despite the lack of clinical trial outcome data, once-weekly rifapentine/isoniazid can be used with efavirenz or raltegravir without dose adjustment based on available PK data. Increased clinical monitoring is not recommended, but should be based on clinical judgment. When using rifampin-containing regimens, either dose adjustment or substitution of key ART drugs may be needed. The regimen of two months rifampin plus pyrazinamide is not recommended due to the risk of severe and sometimes fatal hepatotoxicity (AII).
LTBI treatment and ART act independently to decrease the risk of TB disease. Therefore, use of both interventions is recommended for those persons with LTBI and an indication for ART (AI).

**Monitoring of Response to Treatment of LTBI**

Individuals receiving self-administered daily chemoprophylaxis should be seen by the prescribing clinician on a monthly basis to assess adherence and evaluate for possible drug toxicity; generally, a clinician should not prescribe more than one month’s supply of a drug. Although HIV-infected persons may not have a higher risk of hepatitis from isoniazid prophylaxis than HIV-uninfected persons, it is recommended that baseline serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and total bilirubin be measured and repeated if abnormal at baseline. 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. With isoniazid, liver enzymes typically increase in the first 3 months but then, through the process of hepatic adaptation, liver enzymes return to normal despite continued therapy. If the serum aminotransferase level increases 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. Patients should be reminded at each visit about potential adverse effects (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 isoniazid and return to the clinic for an assessment should any of these occur.

The ultimate decision regarding resumption of therapy with the same or a different agent for LTBI treatment should be made after weighing the risk for additional hepatic injury against the benefit of preventing progression to TB disease and in consultation with an expert in treating LTBI in persons with HIV infection.

**Clinical Manifestations of TB Disease**

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. The sensitivity of classic TB symptoms is lower in people on ART. Culture-positive TB disease can be subclinical or oligo-symptomatic. The duration of symptoms is shorter in HIV-infected patients, and in patients who are markedly immune suppressed TB can be a severe systemic disease with high fevers, rapid progression, and sepsis syndrome. After initiation of ART, immune reconstitution can unmask subclinical active TB, resulting in pronounced inflammatory reactions at the sites of infection (see section below on “Unmasking TB-IRIS”).

The presentation of active TB disease is influenced by the degree of immunodeficiency. In HIV-infected patients with CD4 counts >200 cells/µL, HIV-related TB generally resembles TB among HIV-uninfected persons. The majority of patients have disease limited to the lungs, and common chest radiographic manifestations are upper lobe infiltrates with or without cavitation.

In patients with CD4 counts <200 cells/µL, the chest radiographic findings of pulmonary TB are markedly different with infiltrates showing no predilection for the upper lobes, and cavitation is uncommon. Normal chest radiographs are not uncommon in patients with respiratory symptoms and positive sputum cultures.

With increasing degrees of immunodeficiency, extrapulmonary or disseminated TB (e.g., lymphadenitis, genitourinary TB, osteal TB, pleuritis, pericarditis, and meningitis), with or without pulmonary involvement, are more common. Clinical manifestations of extrapulmonary TB are not substantially different from those described in HIV-uninfected persons. TB must be considered in disease processes involving any site in the body, but especially those related to central nervous system (CNS) or meningeal symptoms in which early TB treatment is essential to improve outcomes.
**Diagnosis**

Initial diagnostic testing 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, even in the absence of pulmonary symptoms or signs; pulmonary involvement is common at all CD4 counts. 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. Therefore, sputum smear and culture should be considered 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.

Sputum smear-negative TB is common among persons with HIV infection, particularly those with advanced immunodeficiency and non-cavitary disease. However, the yield of sputum mycobacterial culture is not affected by HIV or the degree of immunodeficiency. If a sensitive broth culture technique is used, the sensitivity of sputum culture is quite high. Smear and culture of three sputum specimens is recommended in that there was a 10% incremental yield for broth culture between the second and third specimens in a recent large study of patients with HIV.

Extrapulmonary and disseminated TB are more common in persons with HIV infection, particularly with advanced immunosuppression. 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. 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.

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 compared to sputum but nonetheless 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 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 needed in patients with HIV infection 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, these assays are highly predictive of TB among specimens that are AFB smear-positive. Non-tuberculous 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 among 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 and up to 90% when three NAA tests are performed. Therefore, use of an NAA test is recommended on at least one specimen from all patients with suspected pulmonary TB. NAA tests can also be used on extrapulmonary specimens with the caveat that the sensitivity is often lower than in sputum specimens.

The Xpert MTB/RIF assay is an automated NAA test that can detect both *M. tuberculosis* and mutations 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 HIV-infected patients. 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 and as an aid in decisions regarding respiratory isolation in 2015. 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 83%–92%) and 98% (95% confidence interval 97%–99%), respectively. The assay is somewhat less sensitive among HIV-infected patients (pooled sensitivity of 80%, 95% confidence interval 67%–88%) than among HIV-uninfected patients (pooled sensitivity of 89%, 95% confidence interval 81%–94%); however, this may be in part attributed to a higher prevalence of smear negative disease in HIV-infected individuals. In some studies, the sensitivity of Xpert MTB/RIF has been related to CD4 cell count, with higher sensitivity among patients with more advanced immunodeficiency.

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. 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%).

**Lipoarabinomannan (LAM):** LAM is an *M. tuberculosis* cell wall polysaccharide that can be detected in the urine of TB patients. LAM can be detected using an ELISA or a lateral flow point of care test. The diagnostic utility of LAM is limited by a low sensitivity but has the advantages of being available as a true point of care test that can be performed on urine. LAM has demonstrated the best performance in HIV-infected patients with low CD4 cell counts (<100 cells/mm³) with a sensitivity of 37 to 56% and specificity of up to 95%. In addition, LAM has higher sensitivity in patients with worse prognoses, who are therefore a high priority to identify. Combining LAM with other diagnostic strategies such as Xpert MTB/RIF testing or smear may improve the diagnostic utility.

**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; 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, 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 up to 11 to 30% of patients with active TB.

**Drug susceptibility testing:** Drug-susceptibility testing should be performed on the initial isolates for 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. 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. Thus, early identification of drug resistance, with appropriate adjustment of the treatment regimen based on 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. Drug-susceptibility tests (DST) 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. DST 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.

**Phenotypic 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 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 HIV-infected individuals.

**NAA testing 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. Commercial NAA tests such as Xpert MTB/RIF identify resistance mutations associated with rifampin and commercially available line probe assays identify genotypic resistance for rifampin and isoniazid. Next generation commercial line probe assays such as GenoType MTBDRsl identify genotypic resistance to other TB medications, but results should be confirmed with standard culture-based DST. 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 assay. In a 2014 meta-analysis, the sensitivity for detection of rifampin resistance was 95% (95% confidence interval 90%–97%) and specificity was 98% (95% confidence interval 97%–99%). False-positive results for rifampin resistance with the Xpert MTB/RIF assay can occur, although this appears to be less common with the current version of the assay. However, the comparator for most studies—phenotypic drug-susceptibility testing—should not be considered an absolute gold standard. Some isolates with rifampin resistance by the Xpert MTB/RIF assay have mutations in the \textit{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 \textit{rpoB} gene compared to patients whose isolates had normal \textit{rpoB} gene sequences.

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 (\textit{rpoB} gene sequencing, phenotypic drug susceptibility testing), and additional specimens should be obtained from such patients. Consultation with an expert in the diagnosis and treatment of MDR TB should be strongly considered.

Clinicians who suspect drug-resistant TB in an HIV-infected patient should make every effort to expedite their diagnosis. In the United States, the Centers for Disease Control and Prevention (CDC), Division of TB Elimination, has a Molecular Detection of Drug Resistance (MDDR) service to make rapid molecular testing for first-and second-line TB medications available for persons suspected of having drug-resistant TB.

Drug resistance should be considered in any patient with:
- known exposure to a drug-resistant TB case
- residence in a setting with high rates of primary drug-resistant TB (e.g., a country or area with high rates of drug-resistant TB in new patients)
- 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

Treatment of Disease

**Preferred and Alternative Drugs for Treatment, Including Duration of Therapy**

TB among persons with advanced immunodeficiency can be a rapidly progressive and fatal illness if treatment is delayed. Furthermore, such patients often have smear-negative sputum specimens. 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.

Treatment of suspected TB for HIV-infected individuals is the same as for HIV-uninfected persons, and should include an initial four-drug combination of isoniazid, rifampin, ethambutol, and pyrazinamide. 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 and can be adjusted once complete DST results are available. DOT is recommended for all patients with suspected HIV-related TB. The likelihood of treatment success is further enhanced with comprehensive case management, assistance with housing and other social support,
Drug-susceptible TB should be treated with a 2-month intensive phase of the four drugs listed above. 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 (A1).

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 phase have been associated with an increased risk of treatment failure or relapse with acquired drug resistance to the rifamycin class, particularly in HIV co-infected persons. Therefore, daily therapy (5–7 days per week) given as DOT is recommended during the intensive treatment phase (AII). Regimens that included once- or twice-weekly dosing during the continuation phase of therapy were also associated with increased risks of treatment failure or relapse with acquired rifamycin resistance. Therefore, daily (5–7 days per week) dosing is also recommended during the continuation phase of therapy (AII). Although drug-drug interaction studies suggest that thrice-weekly and daily rifampin dosing is associated with similar levels of cytochrome P450 enzyme induction when dosed with raltegravir, whether there is a difference between daily and thrice-weekly dosing during the continuation phase of therapy has not been adequately studied in randomized trials. 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). Although earlier recommendations for TB treatment in HIV-uninfected persons 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 HIV-infected individuals. Every effort should be made to assure that patients receive daily therapy as previously described, allowing up to 28 weeks to complete at least 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 infection 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 co-infection have been good. 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. Two trials in high-burden settings showed higher risks of recurrent TB among patients treated with 6 months of therapy, compared to those assigned to 9-12 or 12-month regimens. However, the applicability of these two trials is uncertain in low-burden settings in which ART is used, such as the United States.

Three randomized clinical trials have evaluated strategies to reduce the duration of anti-TB treatment from 6 to 4 months in persons with drug-susceptible TB by substituting moxifloxacin or gatifloxacin for either ethambutol or isoniazid in the intensive phase of treatment and adding one of these to a 2-month continuation phase. A fourth study evaluated the substitution of moxifloxacin for ethambutol and the substitution of rifapentine for rifampin in a 4-month regimen. In each of these trials, despite evidence of more rapid sputum culture conversion, overall 2-month culture conversion rates were not significantly different than with the standard 6-month control regimen, and rates of unfavorable outcomes (as defined by treatment failure or relapse after 18 months of follow-up) were higher. The number of HIV-infected participants in these studies was small, but when analyzed by HIV status the results were similar. These findings reinforce the current recommendation to treat drug-susceptible TB in HIV-infected individuals for at least 6 months (BII). Extension of therapy to 9 months is recommended for those with a positive 2-month sputum culture (BII).

Intensified therapy for CNS TB may be beneficial, but there are limited data to support this. A recent randomized trial that compared 9 months of standard therapy that included rifampicin 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 both HIV-uninfected
and HIV co-infected individuals with tuberculous meningitis. A PK study of 60 participants in Indonesia suggested that rifampicin administered in doses equivalent to 13 mg/kg or higher given intravenously (similar to 26 mg/kg delivered orally) reduced mortality, but this finding requires confirmation in a larger trial. Addition of a fluoroquinolone may improve outcomes in patients with isoniazid-monoresistant tuberculous meningitis.

Adjunctive corticosteroid therapy should be considered in HIV-infected individuals with TB involving the CNS or pericardium (AI). Adjunctive corticosteroid therapy increases survival overall for patients with TB and CNS involvement, although studies were underpowered for detecting a statistically significant survival benefit for those with HIV infection. Adjunctive corticosteroid therapy reduces the incidence of constrictive pericarditis, although in a randomized trial of adjunctive prednisolone compared with placebo administered for 6 weeks in HIV-uninfected and co-infected individuals 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. 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 with regard to whether sequential treatment of TB followed by initiation of ART is acceptable for those with CD4 cell counts >220 to 250 cells/mm³, recently published results from large, international, randomized trials of immediate versus delayed initiation of ART indicate that substantial personal health benefits accrue at all CD4 cell counts in persons without active TB. When coupled with the preponderance of data from randomized trials in persons with HIV and active TB, 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 because of the adherence demands of multidrug therapy for two infections, drug-drug interactions between the rifamycins and many antiretroviral drugs, overlapping side effect profiles of anti-TB and antiretroviral drugs, and the development of immune reconstitution inflammatory syndrome (IRIS), although the rates of IRIS are higher primarily in those with lower CD4 cell counts. Despite these substantial clinical challenges, co-treatment of HIV-related TB improves survival (particularly for persons with CD4 cell counts <50 cells/µL), decreases the risk of additional opportunistic illnesses, can achieve high rates of viral suppression, and, despite higher rates of IRIS at low CD4 cell counts, is not associated with higher rates of other treatment-related adverse events.

The SAPIT trial randomized 642 South African adults with CD4 cell counts <500 cells/mm³ and AFB smear + TB to start ART at TB treatment initiation, after the intensive phase of TB therapy but before TB treatment completion, or after TB treatment completion. The study was stopped early when the mortality of the two integrated treatment arms was 56% lower than the sequential treatment arm, demonstrating that ART should be started before TB completion. Notably, there was a survival benefit across the range of CD4 cell counts among patients enrolled, including within the stratum of baseline CD4 cell counts from 200 to 500/mm³.

The CAMELIA, STRIDE (ACTG A5221), and TB-HAART trials shed further light on the optimal timing of ART during the course of TB treatment. In CAMELIA, 661 adults in Cambodia with confirmed pulmonary TB and a median CD4 cell count of 25 cells/mm³ (IQR, 10, 56) were randomized to receive ART at 2 or 8 weeks after starting TB treatment. The mortality rate was decreased from 13.77 per 100 person-years in the 2-week arm to 8.28 per 100 person-years in the 8-week arm, and viral suppression rates were very high among those who survived (>95%).

The ACTG A5221 STRIDE study randomized 809 patients from North America, South America, Africa, and Asia with confirmed or suspected TB and a median CD4 cell count of 77 cells/mm³ (IQR, 33,146)
to immediate ART (within 2 weeks) or early ART (8–12 weeks). A new OI or death occurred among 12.9\% of patients in the immediate arm and 16.1\% in the early arm by week 48 (\(P = 0.45\)). In patients with screening CD4 lymphocytes <50 cells/mm\(^3\), 15.5\% of patients on the immediate arm versus 26.6\% on early ART experienced AIDS or death, \(P = 0.02\). Tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) was more common in the immediate ART arm (11\%) compared to the early arm (5\%), \(P = 0.002\). Viral suppression rates were similar between the arms.

The TB-HAART trial included 1,538 HIV-infected patients in South Africa, Uganda, Zambia, and Tanzania who had culture-confirmed pulmonary TB and CD4 cell counts \(\geq 220\) cells/mm\(^3\) and who had tolerated 2 weeks of TB treatment. Subjects were randomized to early (after 2 weeks of TB treatment initiation) versus delayed (until 6 months after initiation of TB treatment) ART. The median CD4 cell count overall was 367 cells/mm\(^3\) (IQR 289, 456). The composite primary endpoint of TB treatment failure, recurrence and death within 12 months of starting TB treatment occurred in 8.5\% of patients in the early ART group and 9.2\% in the delayed group (RR 0.91, 95\% CI 0.64-1.30; \(P = 0.9\)). Mortality, grade 3 and 4 adverse events and IRIS did not differ among the treatment groups. Patients in the early ART group had higher CD4 cell 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 cell 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 2 months after starting TB treatment among 253 patients with HIV-related TB meningitis. This study did not show a survival benefit to early ART initiation. On the contrary, early ART was associated with similar mortality and more frequent and severe adverse events (86\%) compared to the deferred ART arm (75\%). The overall mortality rates in this study were very high (58\%), likely at least in part because the majority of participants had advanced AIDS (median baseline CD4 cell count 41 cells/mm\(^3\)); it is unclear if these findings would generalize to other settings. Nonetheless, caution in the timing of ART initiation with specific monitoring for drug-related toxicities is warranted in patients with TB disease affecting the CNS.

In conclusion, ART is recommended in all HIV-infected persons with TB (AI). For ART-naive patients, ART should be started within 2 weeks after TB treatment initiation when the CD4 cell count is <50 cells/mm\(^3\) and, based on the preponderance of data, within 8 weeks of starting anti-TB treatment in those with higher CD4 cell counts (AI). Given the need for the initiation of five to seven new medications in a short time, adherence support should be offered. In patients with TB meningitis and low CD4 cell 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, 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 a number of antiretroviral drugs (Table 3 [TB Drug Dosing] and the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents). 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 antiretroviral agents.

The preferred co-treatment regimen for HIV-related TB disease is rifampin-based TB therapy with an
antiretroviral 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.\textsuperscript{140} Data on the magnitude of the change in efavirenz concentrations when co-administered with rifampin are conflicting. Early studies reported a 26\% reduction in efavirenz plasma concentrations,\textsuperscript{141} but more recent and larger studies in HIV-infected patients with 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.\textsuperscript{142-144} Previous recommendations to increase the dose of efavirenz, especially in patients weighing >60 kg, are thus not supported by good 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). Given the excellent treatment outcomes of co-treatment with standard-dose efavirenz,\textsuperscript{140,145} the 600 mg daily dose of efavirenz is recommended (BII).

Rifampin has a more significant effect on the concentration of nevirapine. Earlier studies suggested that clinical outcomes were reasonably good among patients on a co-treatment regimen of rifampin-based TB treatment with an antiretroviral regimen of nevirapine plus two nucleoside analogues when nevirapine once-daily lead-in dosing was avoided.\textsuperscript{140,146-148} However, more recent data and a meta-analysis indicate that 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 in patients on TB treatment.\textsuperscript{149-151} Nevirapine should generally be avoided unless there are no other options (AI). For patients unable to take efavirenz due to intolerance, nevirapine-based ART is a reasonable alternative, but the lead-in dose of nevirapine should be omitted for patients who are established on rifampin.\textsuperscript{140}

Alternatives to efavirenz-based antiretroviral treatment for HIV/TB co-infected patients include regimens with integrase inhibitors or protease inhibitors (PIs). One preferred alternative co-treatment regimen is the combination of raltegravir-based antiretroviral treatment, using 400 or 800 mg twice daily, with standard rifampin dosing (BI).\textsuperscript{152} Another alternative co-treatment regimen is rifabutin-based TB therapy with an antiretroviral regimen including a ronavir-boosted PI (BIII). While there are no clinical trials specifically comparing rifampin and rifabutin-containing anti-TB regimens among persons with HIV/TB co-infection taking ART, in general, rifabutin is thought to be a reasonable substitute for rifampin for treatment of TB.\textsuperscript{153,154} Although the dramatic effects of rifampin on serum concentrations of lopinavir may be overcome by doubling the dose of lopinavir/ritonavir,\textsuperscript{155,156} the safety of this strategy has yet to be firmly established. High rates of hepatotoxicity were reported when adjusted ritonavir-boosted PIs were given with rifampin to healthy volunteers.\textsuperscript{157-159} In patients with HIV and TB co-infection, double doses of lopinavir/ritonavir are reasonably well tolerated in those on rifampin-based TB treatment, but the strategy of increasing ronavir dosing to 400 mg twice daily leads to high rates of hepatotoxicity.\textsuperscript{156,160,161} Thus, a strategy of first increasing the dose 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 stable on full dose).

Use of rifabutin with boosted PI is thus preferred to use of rifampin with double-dose PI in settings where rifabutin is readily available. Rifabutin has little effect on ronavir-boosted lopinavir\textsuperscript{162} or atazanavir,\textsuperscript{163} and its co-administration results in moderate increases in darunavir\textsuperscript{164} and fosampranavir concentrations.\textsuperscript{165} However, all PIs markedly increase serum concentrations of rifabutin (and one of its principal metabolites, desacetyl-rifabutin). Therefore, the dose of rifabutin must be decreased to avoid dose-related toxicity, such as uveitis and neutropenia.\textsuperscript{166} In studies of HIV-infected people, rifabutin exposures were significantly lower when rifabutin was dosed 150 mg thrice-weekly with lopinavir/ritonavir compared with rifabutin concentrations when given 300 mg daily in the absence of a protease inhibitor, but concentrations of the active desacetyl metabolite were high.\textsuperscript{167,168} Among individuals co-infected with HIV and TB, there have been case reports of acquired rifamycin resistance with 150 mg thrice-weekly doses of rifabutin in the presence of a boosted PI-based antiretroviral regimen.\textsuperscript{169,170} A recent study conducted in South Africa in 16 HIV-infected patients on a lopinavir/ritonavir-based ART regimen demonstrated that rifabutin administered in a dose of 150 mg daily in combination with

\textit{Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV}
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). A randomized clinical trial evaluating rifabutin PK and TB and ART outcomes using this dose with lopinavir/ritonavir-based ART is in progress. Based on available PK data, it is recommended that rifabutin should be dosed 150 mg daily (at least during the first 2 months of TB treatment) 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.

Raltegravir concentrations are significantly decreased when co-administered with rifampin. Increasing the dose of raltegravir to 800 mg twice daily mitigates this PK interaction. However, it is unclear whether or not an increase in dose is needed. In a Phase 2 randomized trial in HIV-infected people with TB, virologic responses appeared to be similar in non-comparative analyses of the raltegravir 400 and 800 mg twice daily arms. Alternatively, raltegravir can be given with a rifabutin-containing TB regimen without dose adjustment of either drug. Dolutegravir may be another reasonable treatment option. A pharmacokinetic 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. Dolutegravir has not yet been studied in a significant number of HIV-infected individuals with TB. Due to the potential for significant drug interactions as detailed above, the following drugs should not be used with rifampin: rilpivirine, etravirine, and elvitegravir co-formulated with cobicistat (AIII). Their use with rifabutin has not been evaluated. Tenofovir alafenamide should not be used with any of the rifamycins.

The breadth and magnitude of drug-drug interactions between the rifamycins and many antiretroviral 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 antiretroviral drugs should be managed, not avoided. Rifamycins remain the most potent drug class for TB treatment, and regimens that included just 2 months of rifampin were associated with increased risks of treatment failure and TB recurrence among patients with HIV-related TB. If a rifamycin cannot be used, TB treatment duration must be extended substantially, as there is currently no drug substitute with the curative power of rifampin. 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 to be 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). Patients with susceptible TB typically convert sputum cultures to negative by 2 months of first-line TB therapy, although patients with advanced disease (i.e., cavitory TB disease) may take longer to convert sputum cultures to negative. Patients who have not had sputum culture conversion at or after 4 months of therapy have failed treatment and should have sputum sent for resistance testing.

**Management of 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 his/her cultures have not converted. The initial culture results and drug-resistance tests, treatment regimen, and adherence should also be reviewed. Samples from all available sites (e.g., sputum, blood, urine, etc.) should be taken...
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 superinfection with a drug-resistant strain.

While awaiting results of repeat cultures and rapid resistance testing, empiric TB treatment should be broadened using second-line TB drugs, in consultation with an expert in the field (BIII).

**Adverse Drug Reactions in TB Patients on ART**

HIV-infected patients not on ART are more likely to experience adverse events thought to be drug-related during the course of anti-TB therapy than HIV-uninfected patients. Many adverse drug reactions are shared between antiretrovirals and anti-TB therapy, including the potentially life-threatening drug-induced liver injury (DILI) and cutaneous adverse drug reactions (CADRs). Retrospective observational studies had reported an increased risk of adverse drug reactions in patients treated with concomitant ART and anti-TB therapy, but two recent randomized controlled trials of ART commencement during or after anti-TB therapy reported similar rates of adverse events during anti-TB therapy with and without ART. Therefore, there does not seem to be significant additive toxicity when ART is given together with anti-TB therapy. 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 cotrimoxazole is very difficult.

Because alternative drugs are less efficacious and have more toxicities than first-line anti-TB drugs, the first-line drugs (especially isoniazid and rifampin or rifabutin) should not be stopped permanently without strong evidence that the specific anti-TB drug was the cause of the reaction. In such situations, decisions regarding re-challenge 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 infection.

DILI can be caused by isoniazid, rifamycins, pyrazinamide, many antiretroviral drugs, and cotrimoxazole. Anti-TB DILI is defined as an ALT elevation to ≥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, but many of these patients only have transient, mild elevations of ALT. If these criteria 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 (ethambutol, an aminoglycoside, and moxifloxacin or levofloxacin) as a “bridging regimen” until the specific cause of hepatotoxicity can be determined and an alternative longer-term regimen constructed (BIII). A re-challenge with the hepatotoxic first-line anti-TB medications can be started by adding them one at a time at intervals of 7 days to the “bridging regimen” after the ALT level returns to <2.5 times the ULN (or to near baseline for patients with pre-existing abnormalities) with frequent monitoring of ALT. Re-challenge was successful in almost 90% of HIV-uninfected patients in one randomized controlled trial of different re-challenge regimens. Because the rifamycins are a critical part of the TB regimen, they should be restarted first. Re-challenge with pyrazinamide is controversial, because some studies have reported high rates of recurrent ALT elevations, but this may be considered in severe forms of TB (e.g., meningitis or disseminated TB). Depending on the outcome of the re-challenge, the anti-TB therapy regimen and duration may need to be altered—expert consultation is advised. After anti-TB drug re-challenge, if appropriate, relevant antiretroviral drugs and cotrimoxazole may be restarted.

CADRs may occur with all of the first-line anti-TB drugs, notably rifampin and isoniazid, many antiretroviral drugs, notably the non-nucleoside reverse transcriptase inhibitors, and cotrimoxazole. If 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 antiretrovirals, 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 antiretroviral drugs and
cotrimoxazole may be recommenced.

Management of Drug-Resistant TB

Although drug-resistant TB represents a small fraction of TB cases seen 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. There is a need for clinical trials to determine the optimal management of patients
with drug-resistant TB. The most active and effective TB drugs are those used in first-line TB treatment
regimens (isoniazid and rifampin, in particular). When resistance develops to these medications, alternative
combinations of first- and second-line TB medications must be used, but their optimal use has not been
tested using rigorous clinical trials.

Growing evidence demonstrates that there is an increased risk of treatment failure associated with
baseline isoniazid monoresistance, particularly in patients with HIV co-infection. Substitution of a
fluoroquinolone (levofloxacin or moxifloxacin) for isoniazid is suggested for at least the first 2 months of
therapy (BIII) and considered during the continuation phase with rifampin and ethambutol as well (CIII), for
a total duration of treatment of 9 months (BII).

Resistance to rifampin alone, or to rifampin and other drugs, substantially increases the complexity and
duration of treatment. Treatment of these drug-resistant TB cases 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
(ATS/CDC/IDSA 2003). Treatment outcomes for MDR TB are considerably worse than those for drug-
susceptible TB—especially in patients with HIV co-infection. Consensus treatment guidelines for
MDR TB are based on a review of published observational studies and recommend use of at least
five drugs with known or likely activity against the patient’s isolate (BIII). In general, such regimens will
include a later-generation fluoroquinolone, a second-line injectable agent (i.e., kanamycin, amikacin, or
capreomycin), ethionamide, pyrazinamide and at least one other second-line drug, such as cycloserine or
para-aminosalicylic acid (BIII). Additional resistance to one or more of these drugs (e.g., extensively drug-
resistant [XDR] TB), however, may necessitate use of alternate or third-line agents with uncertain anti-TB
activity. Whenever possible, treatment should be individualized to the patient’s specific drug-susceptibility
testing results or based upon his or her treatment history. An intensive phase of 8 months is then followed by
a continuation phase without the injectable agent for an additional 12 to 18 months. Surgery (removal of the
TB lesion) should be considered as an adjunctive measure in those with localized disease.

The World Health Organization (WHO) recently 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. The regimen composition is based on combinations
evaluated as the Bangladesh regimen, 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. This approach has not been evaluated
in randomized clinical trials among HIV-infected persons on ART or in higher resourced settings with
consistent access to DST such as the United States. Based on promising observational data, an additional
clinical trial is examining the efficacy of an intensive, shortened, 9-month treatment regimen for MDR TB
(NCT02409290) using currently available medications, but at present there are insufficient data to support
this approach in HIV-infected individuals.

Current 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 educated regarding the importance of treatment adherence. While on therapy,
Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome

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. 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.

**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 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, 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. 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. A liver biopsy reveals a granulomatous hepatitis. 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%–54%). A recent meta-analysis provided a pooled incidence of 18%, with death attributable to TB-IRIS occurring in 2% of TB-IRIS cases. The onset of paradoxical TB-IRIS symptoms is typically between 1 to 4 weeks after ART is initiated. The syndrome lasts for 2 to 3 months on average, but some cases may have symptoms for months and rarely local manifestations may persist or recur over a year after onset. Such prolonged TB-IRIS cases usually manifest with suppurative lymphadenitis and abscess formation.

The most consistently identified risk factors for paradoxical TB-IRIS are a low CD4 cell count at start of ART, especially those patients with a CD4 cell count <100 cells/mm³, high HIV viral load prior to
ART, disseminated or extrapulmonary TB, and a short interval between starting TB treatment and ART, particularly if ART is started within the first 1 to 2 months of TB treatment. Even though early ART increases the risk for TB-IRIS, ART should be started within 2 weeks of TB diagnosis in those with CD4 cell counts <50 cells/µL, given that this reduces risk of AIDS progression and death.

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 prior to ART, deterioration with inflammatory features of TB soon after starting ART, demonstration of a response to ART (CD4 rise and/or HIV viral load reduction) and, very importantly, investigations to exclude alternative causes for deterioration, particularly undetected TB drug resistance.

**Management of Paradoxical TB-IRIS**

Most cases of paradoxical TB-IRIS are self-limiting. Many patients require symptomatic therapy (analgesia, anti-emetics), and if symptoms are significant, anti-inflammatory therapy should be considered. 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. Those 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 observational data, and clinical trials of patients treated with corticosteroids at the time of TB meningitis presentation where corticosteroids reduced mortality 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). Among all patients developing TB-IRIS, 4 weeks of prednisone treatment was insufficient in a subset, and they may require more gradual tapering of steroids over a few months (BIII). Tapering of corticosteroids should be guided by repeated clinical assessment of symptoms (BIII). Corticosteroids should be avoided in patients with Kaposi’s sarcoma, as life-threatening exacerbations can occur, and also where the diagnosis of paradoxical TB-IRIS is not certain. There are case reports of patients with steroid-refractory and prolonged IRIS responding to TNF-blockers or thalidomide.

Some clinicians use non-steroidal anti-inflammatory drugs to provide symptomatic relief in patients with mild TB-IRIS. Needle aspiration of enlarging serous effusions, large tuberculous abscesses, or suppurative lymphadenitis may provide symptom relief. Repeated aspirations may be required as abscesses and effusions often re-accumulate.

**Unmasking TB-IRIS**

Unmasking TB-IRIS may occur in patients who have unrecognized TB at the start of ART (because it is oligo-symptomatic or because the diagnosis has been missed). These patients may present with a particularly accelerated and inflammatory presentation of TB in the first weeks of ART. 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. Focal inflammatory manifestations such as abscesses and lymphadenitis may also develop. The treatment should be standard TB treatment and corticosteroids, if the manifestations are life-threatening, although there is no clinical trial evidence to support steroid use (BIII).

**Prevention of Recurrent TB**

The risk of recurrent TB among patients with HIV co-infection appears to be somewhat higher than in HIV-uninfected patients treated with the same TB treatment regimen in the same setting. 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. In settings with low rates of TB (such as the United States), recurrent TB due to re-infection is uncommon, even among HIV-infected patients.
Several interventions have been suggested to decrease the risk of recurrent TB among patients with HIV co-infection: longer TB treatment regimens, more frequent dosing of TB therapy, 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, 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 its beneficial effects on the risk of initially developing TB disease, it is very likely that ART decreases the risk of re-infection with TB disease.

**Special Considerations During Pregnancy**

HIV-infected pregnant women 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 should be tested during pregnancy (AIII). The frequency of anergy is not increased during pregnancy, and routine anergy testing for HIV-infected pregnant women is not recommended. There are several studies examining the performance of the IGRAIs for diagnosis of LTBI in pregnant women. In a study in HIV-infected pregnant women 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/μL, a positive IGRA result was associated with a 5-fold increased risk of maternal mortality or active TB and a 3-fold increased risk of either active TB or mortality in infants. Antenatal IGRA testing has also been demonstrated to correlate with postpartum IGRA test positivity (i.e., TB infection) in HIV-infected women. In women without HIV infection, the test appears to perform well but cost issues for routine screening are an area of debate. If LTBI is diagnosed during pregnancy and active TB has been ruled out, preventive treatment should be considered during pregnancy (BIII). The potential risk of isoniazid toxicity must be weighed against the consequences of active TB developing during pregnancy and postpartum. Studies in HIV/TB co-infected individuals who are not receiving ART have found a high risk of progression from LTBI to active TB (10% per year) and there is a high risk of maternal and infant mortality in HIV-infected pregnant women with active TB. However, the risk of progression from LTBI to active TB in individuals on ART is significantly decreased. Given that HIV-infected pregnant women should be receiving ART for prevention of mother-to-child transmission, the risks and benefits of isoniazid therapy should be discussed. The risk of isoniazid-associated hepatotoxicity may be increased in pregnancy and frequent monitoring is needed for women receiving therapy. Pregnant women receiving isoniazid should receive daily pyridoxine supplementation as they are at risk of isoniazid-associated peripheral neuropathy.

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 treatment is not begun until late in pregnancy. Congenital TB infection of the infant has been reported, although it appears relatively uncommon. However, in one study of 107 women with active TB during pregnancy in South Africa, *M. tuberculosis* was detected in 16% of neonates (12 by culture and 4 by smear microscopy) sampled within the first 3 weeks of life.

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

- Although isoniazid is not teratogenic in animals or humans, hepatotoxicity caused by isoniazid might occur more frequently in pregnancy and the postpartum period. 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 born after exposure *in utero*.

- Pyrazinamide is not teratogenic in animals. Experience is limited with use in human pregnancy. Although WHO and the International Union Against Tuberculosis and Lung Diseases\textsuperscript{250,251} have made recommendations for the routine use of pyrazinamide in pregnant women, it has not been recommended for general use during pregnancy in the United States because data characterizing its effects in this setting are limited.\textsuperscript{252} If pyrazinamide is not included in the initial treatment regimen, the minimum duration of TB therapy should be 9 months (CIII). The decision regarding whether to include pyrazinamide for treatment should be made after consultation among obstetricians, TB specialists, and patients, taking into account gestational age and likely susceptibility pattern of the infecting strain.

Considering the information above, the preferred first-line treatment for TB in pregnancy is isoniazid, rifampin, and ethambutol.\textsuperscript{253} Experience with using the majority of the second-line drugs for TB during pregnancy is limited.\textsuperscript{254-257} MDR TB in pregnancy should be managed in consultation with a specialist. 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 *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 otoxicity 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 musculoskeletal abnormalities.\textsuperscript{258,259} Thus, fluoroquinolones can be used in pregnancy for drug-resistant TB if they are required on the basis of susceptibility testing (CIII).\textsuperscript{260}

- Para-aminosalicylic acid is not teratogenic in rats or rabbits.\textsuperscript{252} In one study, a possible increase in limb and ear anomalies was reported among 143 infants delivered by women who were exposed during the first trimester.\textsuperscript{261} No specific pattern of defects and no increase in rate of defects have been detected in subjects 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 mice and rabbits.\textsuperscript{262-264} Case reports have documented cases of CNS defects in humans but overall experience is limited with use during human pregnancy.\textsuperscript{265} 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.
### Treating LTBI (to prevent TB disease)

**Indications:**
- (+) screening test\(^a\) for LTBI, no evidence of active TB, and no prior history of treatment for active or latent TB (AI);
- Close contact with a person with infectious TB, regardless of screening test result (AII)

**Preferred Therapy (Duration of Therapy = 9 Months):**
- INH 300 mg PO daily + pyridoxine 25-50 mg PO daily (AII) or
- INH 900 mg PO twice weekly (by DOT) + pyridoxine 25-50 mg PO daily (BII)

**Alternative Therapies:**
- RIF 600 mg PO daily x 4 months (BIII) or
- RFB (dose adjusted based on concomitant ART) x 4 months (BIII) or
- RPT (weight-based, 900 mg max) PO weekly + INH 15 mg/kg weekly (900 mg max) + pyridoxine 50 mg weekly x 12 weeks – in patients receiving an EFV- or RAL-based ART regimen (BIII)
  - 32.1–49.9 kg 750 mg
  - ≥50.0 kg 900 mg
- 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 HIV-infected persons with clinical and radiographic presentation suggestive of HIV-related TB (AIII).
- DOT is recommended for all patients requiring treatment for HIV-related TB (AII).
- Please refer to the table below for TB drug dosing recommendations and to the Adult and Adolescent ARV Guidelines for dosing recommendations of ARV drugs when used with RIF or RFB.

#### For Drug-Sensitive TB

**Intensive Phase (2 Months)**
- INH + (RIF or RFB) + PZA + EMB (AI); if drug susceptibility report shows sensitivity to INH & RIF, then EMB may be discontinued.

**Continuation Phase (For Drug-Susceptible TB)**
- INH + (RIF or RFB) daily (5–7 days per week) (AII)

**Total Duration of Therapy:**
- Pulmonary, drug-susceptible TB—6 months (BII)
- Pulmonary TB & positive culture at 2 months of TB treatment—9 months (BII)
- Extrapulmonary TB w/CNS involvement—9 to 12 months (BII)
- Extrapulmonary TB w/bone or joint involvement—6 to 9 months (BII)
- Extrapulmonary TB in other sites—6 months (BII)

#### For Drug-Resistant TB

**Empiric Therapy for Suspected Resistance to Rifamycin +/- Resistance to Other Drugs:**
- INH + (RIF or RFB) + PZA + EMB + (moxifloxacin or levofloxacin) + (an aminoglycoside or capreomycin)
- Therapy should be modified based on drug susceptibility results
- A TB expert should be consulted

**Resistant to INH**
- (RIF or RFB) + EMB + PZA + (moxifloxacin or levofloxacin) for 2 months (BIII); followed by (RIF or RFB) + EMB + (moxifloxacin or levofloxacin) for 7 months (BII)

**Resistant to Rifamycins +/- Other Antimycobacterial Agents:**
- Therapy and duration of treatment should be individualized based on drug susceptibility, clinical and microbiological responses, and with close consultation with experienced specialists (AIII).
Other Considerations in TB Management

- Adjunctive corticosteroid improves survival for patients with HIV-related TB involving the CNS and pericardium (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 0 mg per day and taper by 1 mg/week; total duration of 12 weeks.
- Prednisone or prednisolone may be used in pericardial disease (e.g., 60 mg PO daily and taper by 10 mg per day weekly; total duration 6 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 there is rifamycin-resistant isolate or the patient has a severe adverse effect that is likely to be due to the rifamycin (please refer to the table below and to the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents for dosing recommendations involving concomitant use of RIF or RFB and different antiretroviral drugs).
- If NVP is to be added to a patient who is receiving RIF, the lead-in dose for NVP should be omitted.
- RFB is a less potent CYP 3A4 inducer than RIF and is preferred in patients receiving HIV PIs (BIIi).
- Rifamycins administered once or twice weekly can result in development of resistance in HIV-infected patients and is not recommended for patients with TB disease (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

- In patients on a RIF-based regimen: prednisone 1.5 mg/kg/day x 2 weeks, then 0.75 mg/kg x 2 weeks
- In patients on a RFB + boosted PI based regimen: prednisone 1.0 mg/kg/day x 2 weeks, then 0.5 mg/kg/day x 2 weeks
- A more gradual tapering schedule over a few months may be necessary in some patients.

Key to Abbreviations:

- ART = antiretroviral therapy
- ARV = antiretroviral
- CNS = central nervous system
- DOT = directly observed therapy
- EFV = efavirenz
- EMB = ethambutol
- INH = isoniazid
- LTBI = latent tuberculosis infection
- NVP = nevirapine
- PI = protease inhibitor
- PO = per os (oral)
- PZA = pyrazinamide
- RAL = raltegravir
- RFB = rifabutin
- RIF = rifampin
- RPT = rifapentine
- TB = tuberculosis
- TIW = thrice weekly
- TST = tuberculin skin test
- IGRA = interferon-gamma release assays

Dosing Recommendations for Anti-Tuberculosis Drugs for Treatment of Active TB

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>5 mg/kg (usual dose 300 mg)</td>
</tr>
<tr>
<td>Rifampin*</td>
<td>10 mg/kg (usual dose 600 mg)</td>
</tr>
<tr>
<td>Note: Rifampin is not recommended in patients receiving HIV PIs, ETR, RPV, EVG/CObI, or TAF</td>
<td></td>
</tr>
<tr>
<td>Rifabutin*</td>
<td>5 mg/kg (usual dose 300 mg)</td>
</tr>
<tr>
<td>without HIV PIs, EFV, RPV</td>
<td></td>
</tr>
<tr>
<td>with HIV PIs</td>
<td>150 mg&lt;sup&gt;ia&lt;/sup&gt;</td>
</tr>
<tr>
<td>with EFV</td>
<td>450–600 mg</td>
</tr>
<tr>
<td>with TAF or EVG/CObI containing regimens</td>
<td>not recommended</td>
</tr>
<tr>
<td>Pyrazinamide (weight-based dosing)</td>
<td></td>
</tr>
<tr>
<td>40–55 kg</td>
<td>1000 mg (18.2–25.0 mg/kg)</td>
</tr>
<tr>
<td>56–75 kg</td>
<td>1500 mg (20.0–26.8 mg/kg)</td>
</tr>
<tr>
<td>76–90 kg</td>
<td>2000 mg (22.2–26.3 mg/kg)</td>
</tr>
<tr>
<td>&gt;90 kg</td>
<td>2000 mg&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ethambutol</td>
<td></td>
</tr>
<tr>
<td>40–55 kg</td>
<td>800 mg (14.5–20.0 mg/kg)</td>
</tr>
<tr>
<td>56–75 kg</td>
<td>1200 mg (16.0–21.4 mg/kg)</td>
</tr>
<tr>
<td>76–90 kg</td>
<td>1600 mg (17.8–21.1 mg/kg)</td>
</tr>
<tr>
<td>&gt;90 kg</td>
<td>1600 mg&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
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