Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children

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Mycobacterium tuberculosis (Last updated November 6, 2013; last reviewed November 6, 2013)

Panel's Recommendations

Detection of Latent TB Infection

- Diagnostic methods for latent tuberculosis (TB) infection (LTBI) include the tuberculin skin test (TST), administered by the Mantoux method with an Food and Drug Administration (FDA)-approved purified protein derivative, or FDA-approved interferon gamma release assays (IGRA) (QuantiFERON®-TB Gold In-Tube, and T SPOT®.TB); TST is preferred over IGRA in children aged <5 years **(BII)**.
- TST and IGRA **should NOT** be used to rule out disease and cannot replace regular screening for TB exposure **(AII)**. In high-TB-burden settings, screening for TB exposure and for signs or symptoms suggestive of TB disease is universally applicable and should occur at every health care visit **(AII)**.

Treatment for LTBI

- HIV-infected children should receive preventive therapy if they have a positive TST or IGRA result or if they are exposed to an individual with infectious TB (regardless of previous treatment for TB or the TST or IGRA result), after TB disease has been excluded **(AII)**.
- The preferred preventive therapy regimen is isoniazid daily for 9 months **(AII)**. If adherence with daily isoniazid cannot be ensured, then consider twice-weekly isoniazid by directly observed therapy (DOT) by a trained worker, not a family member **(BII)**.
- With exposure to an isoniazid mono-resistant source case, preventive therapy consisting of daily rifampin for 6 months is recommended, with adjustment of combination antiretroviral therapy (cART) as required **(BII)**.
- A 12-dose combination regimen of once-weekly isoniazid and rifapentine by DOT is as safe and effective as other regimens in preventing TB disease, and the completion rate is greater than for longer regimens. However, pediatric experience with this regimen is limited, and drug-drug interactions between rifapentine and other antiretroviral drugs have not been determined. This regimen is not recommended for children aged <2 years, nor for HIV-infected adults or children who are receiving cART or individuals who have LTBI with presumed isoniazid or rifampin resistance; the preferred regimen for children aged 2 to 11 years remains daily isoniazid for 9 months.

Treatment of TB Disease

- In children diagnosed with TB, DOT must be started immediately **(AII)** and all cases of suspected and confirmed TB disease must be reported to the relevant health authorities.
- All children diagnosed with TB should be tested for HIV infection **(AIII)**.
- In HIV-infected children, the recommended treatment for fully-drug-susceptible TB is a 4-drug regimen consisting of isoniazid, rifampin, pyrazinamide, and ethambutol given daily during the 2-month intensive phase, followed by a 7-month continuation phase using only isoniazid and rifampin **(AII)**, with adjustment of cART as required. With good adherence and treatment response, thrice-weekly treatment under DOT during the continuation phase can be considered **(CII)**.
- For children with extrapulmonary disease caused by drug susceptible TB involving the bones or joints, central nervous system (CNS), or disseminated/miliary disease, the recommended duration of treatment is 12 months **(AIII)**.
- For TB meningitis (TBM), pending drug-susceptibility testing results, ethionamide can replace ethambutol (or an injectable aminoglycoside) as the fourth drug because of its superior cerebrospinal fluid penetration **(CII)**.
- Children with suspected and confirmed multidrug resistant (MDR) TB (i.e., resistance to both isoniazid and rifampin) should be managed in consultation with an expert. In the United States, treatment of MDR-TB should be individualized based on drug susceptibility test (DST) results (in cases where DST results for the child are not available, then DST results for the source case should be used to guide initial choice of regimen) **(AII)**.
- Treatment for TB must commence as soon as the diagnosis is established in HIV-infected children, both those who are already on cART and those not yet receiving cART; those not yet on cART should be evaluated for early cART initiation, preferably within 2 to 8 weeks of starting TB therapy **(AII)**.
- Depending on age and previous cART exposure, an efavirenz-based regimen usually is preferable because such regimens are associated with better treatment outcomes **(AII)**. Nevirapine with potential dose adjustment with concomitant rifampin administration can also be considered **(CIII)**.
- If a protease inhibitor-based regimen is used, superboosting with ritonavir (using a ritonavir dose equal to the lopinavir dose) for the full duration of rifampin treatment (and 2 weeks after termination) is required **(AII)**.
- Pyridoxine supplementation (1-2 mg/kg body weight/day, max 50 mg/day) is recommended for all HIV-infected children who are taking isoniazid **(AII)** or cycloserine **(AIII)**.
- Adjunctive corticosteroids treatment (with ongoing treatment for TB) is indicated for children with TBM or pericardial effusion **(AII)**. It can also be considered with severe immune reconstitution inflammatory syndrome, airway compression, or pleural effusion **(BII)**.

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Panel's Recommendations, continued

- Liver chemistry tests should be performed before initiation and after 2, 4, and 8 weeks of treatment for TB (the same for cART initiation while receiving treatment for TB) **(BIII)**. Beyond 2 months, routine testing every 2 to 3 months is advisable for all children receiving cART, or more frequently if clinically indicated **(BIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion*

† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Epidemiology

Of the 11,182 cases of tuberculosis (TB) reported in the United States in 2010, 637 (6%) occurred in children aged <15.[1] Information on the epidemiology of TB in the United States can be found at http://www.cdc.gov/tb/statistics/default.htm. Among TB cases with known HIV tests results reported in the United States between 1994 and 2007, HIV coinfection was reported in 20% of adults and 3% of children and adolescents (<18 years) overall.[2] The actual rate of HIV coinfection in U.S. children and adolescents with TB is unknown because of the very low rate of HIV testing in this population—more than 70% did not have an HIV result reported to the National TB Surveillance System;[2] however, routine HIV testing is indicated in all individuals with confirmed or suspected TB.

Numerous studies have documented the increased risk of TB in HIV-infected adults. Domestic and international studies have documented a similar increased risk of TB in HIV-infected children.[3-5] Unlike other AIDS-related opportunistic infections, a decreasing or low CD4 T lymphocyte (CD4) cell count is not necessary for increased risk of TB in HIV-infected children. Congenital TB is rare, but has been reported with possible increased frequency in children born to HIV-infected mothers with TB.[6,7]

Children with TB usually have been infected by an adult in their immediate environment, and their disease represents progression of primary infection rather than reactivation disease.[8] Discovery and treatment of the source case and evaluation of all exposed members of the household are particularly important to terminate ongoing transmission (from primary and secondary cases) and to find and diagnose high-risk individuals with latent *Mycobacterium tuberculosis* infection who may benefit from preventive therapy.[9] All confirmed and suspected cases of TB disease must be reported to state and local health departments, which will assist in contact evaluation.

Disease caused by *Mycobacterium bovis* is less common than disease caused by *M. tuberculosis* in the United States, but pediatric cases have been reported.[10,11] Among 11,860 TB cases reported in the United States between 1995 and 2005 for which genotyping information was available, 165 (1.4%) were caused by *M. bovis*; of these, 12 (7.3%) of the patients were aged 0 to 4 years and 19 (11.5%) were aged 5 to 14 years. Risk factors for *M. bovis* disease in the United States include Hispanic ethnicity, age <15 years, HIV infection, and extrapulmonary TB (EPTB).[12] Several reports demonstrate that *M. bovis* is primarily transmitted via ingestion of unpasteurized dairy products,[10,12] which may have been consumed outside the United States or imported casually. Although ingestion is the usual route of entry, human-to-human airborne transmission has been observed and its likelihood may be increased by HIV coinfection. Distinction between *M. tuberculosis* and *M. bovis* is important, because nearly all *M. bovis* isolates are resistant to pyrazinamide and the public health interventions are different.

The emergence and effective transmission of drug-resistant TB is a major obstacle to global TB control.[13-15] In the United States, comprehensive public health measures successfully reduced the rates of drug-resistant

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TB; the proportion of primary multidrug-resistant TB (MDR-TB) cases declined from 2.5% in 1993 to approximately 1.1% in 1997 and has remained at about 1% since.[16] Between 1994 and 2007, *M. tuberculosis* resistance to any first-line TB drug was found in 17% of children and adolescents (<18 years) who had culture-confirmed TB and drug-susceptibility testing results reported to the Centers for Disease Control and Prevention (CDC), with higher rates in foreign-born (20%) than in U.S.-born children (15%).[2] The fraction of culture-confirmed TB that was MDR-TB (resistant to at least isoniazid and rifampin) was 2% in foreign-born and 1% in U.S.-born children.[2] However, the fraction of foreign-born TB patients in the United States continues to rise,[16] many originating from countries with high rates of drug-resistant TB. Parents, guardians, or visiting relatives may expose children to drug-resistant infection.

Extensively drug-resistant TB (XDR-TB), defined as resistance to isoniazid and rifampin (MDR-TB) with additional resistance to any fluoroquinolone and at least one of three second-line injectable drugs (capreomycin, kanamycin, and amikacin), emerged globally as an important new threat, particularly in HIV-infected individuals.[13,14,17] Of the 49 cases of XDR-TB reported in the United States from 1993 to 2006, one (2%) was in a child aged <15 years.[18] However, this number possibly underestimates the burden in children, because most TB cases in children are not culture-positive; thus, a definitive diagnosis of drug-resistant TB is not achieved.

Clinical Manifestations

Once infected with TB, young (aged <5 years) and/or immunocompromised children such as those who are HIV-infected are highly susceptible to developing TB disease, with the first 12 months after primary infection representing the period of greatest risk for progression to TB disease.[5,19] Generally, the clinical features of TB in HIV-infected and HIV-uninfected children are similar, with non-localizing signs such as failure to thrive, cough, and intermittent fever present, although disease progression may be more rapid and the development of complicated or disseminated disease more likely in HIV-infected children.[8,20,21] Both HIV-infected and HIV-uninfected children may present with characteristic pulmonary involvement such as hilar and/or mediastinal adenopathy, which may cause airway compression. Immunocompromised children, including those who are HIV-infected, may also have atypical findings, such as multi-lobar infiltrates and diffuse interstitial disease.[4] Rapidly progressive disease, including meningitis or mycobacterial sepsis, is more likely in the very young and/or immunocompromised, including HIV-infected children. Descriptions of the disease's natural history provide the following general patterns that characterize childhood TB, although exceptions to the rule are common and HIV-infected children of all ages are more likely to have disease manifestations similar to those seen in very young (immune immature) children:[8]

- **Aged <1 year:** Greatest risk of disease progression and disease manifestations reflecting poor containment such as disseminated (miliary) TB, tuberculous meningitis (TBM), extensive pneumonic infiltration.
- **Aged 1–4 years:** Persistent but declining risk of disseminated forms of disease. Children <5 years are at greatest risk of complications resulting from airway compression, because of their small, pliable airways and exuberant lymph node responses. Extra-thoracic manifestations are not uncommon (see below).
- **Aged 5–9 years:** Period of lowest risk for immunocompetent children, but they may contribute significantly to the total case load, depending on the average age at which primary infection occurs in the epidemiological setting. In this age group, a wide range of disease manifestations is seen, including disease patterns seen in young children and adult-type disease. Adult-type pulmonary disease, with upper lobe infiltration, cavitation, and sputum production, is more common starting at age 8 years, and in high-TB-burden settings, and is seen more frequently in adolescent girls than in boys.
- **Aged >10 years:** Adult-type pulmonary disease is more common. Children in this age group are more likely to have positive results from acid-fast bacteria (AFB) sputum-smear microscopy and should be regarded as a potential infectious source.[22]

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Approximately 25% of children with TB have extra-thoracic involvement, with disseminated forms more common in HIV-infected children.[20,23-25] Extra-thoracic disease manifestations include:

- Peripheral lymphadenitis (usually cervical). Features include a matted mass of lymph nodes >2x2 cm.[26] Axillary adenitis ipsilateral to bacille calmette Guerin (BCG) vaccination site is suggestive of BCG adenitis (also see immune reconstitution inflammatory syndrome [IRIS] discussion).
- TBM is most common in children aged <3 years, but especially with HIV coinfection, can occur at any age. Disease manifestations are often similar, but the list of differential diagnoses is greatly expanded in immunocompromised individuals, including HIV-infected children.[27,28]
- Osteo-articular disease can involve any bone or joint, but vertebral involvement with typical TB gibbus formation with/without para-vertebral abscess formation is most common.
- Cold abscesses can occur at any site, but often develop in association with bone involvement or in deep muscle groups, such as psoas muscle.
- A great variety of disease manifestations are possible, including hypersensitivity reactions such as erythema nodosum and phlyctenular keratoconjunctivitis.[29]

Diagnosis

TB Infection

Latent TB infection (LTBI), which by definition is a symptomless condition, can be diagnosed using the tuberculin skin test (TST), administered by the Mantoux method, or by interferon-gamma release assays (IGRAs). Both categories of testing methods are indirect ways of detecting *M. tuberculosis* infection and require T-cell immune activity; thus, HIV infection and the degree of immune alteration diminish the utility of these tests and change interpretation of results. A negative result with any of these tests cannot be regarded as exclusionary for *M. tuberculosis* infection **(AII)**, whether latent or active, especially in the context of HIV infection, and the interpretation of any result with any of these tests must take into account an individual patient's epidemiological and medical factors and the circumstances of testing. The QuantiFERON-TB Gold In-Tube (QFT) (Cellestis Limited, Valencia, California) and the T SPOT®.TB assay (Oxford Immunotec, Marlborough, Massachusetts) are U.S. Food and Drug Administration (FDA)-approved. An IGRA is preferred for testing BCG-vaccinated patients and for use in settings when the return rate for TST reading is poor; however, studies of IGRA performance in HIV-infected children and in very young children are limited, and results from these studies have shown inconsistent results, with data on sensitivity and specificity in this age group not available.[30] TST is preferred over IGRAs for children younger than age 5 years **(AII)**.[31] When increased sensitivity for diagnosing *M. tuberculosis* infection is sought, TST and an IGRA can be done simultaneously, with a positive result from either being diagnostic. Younger age, HIV infection, and reduced numbers of CD4 cells increase the rate of indeterminate IGRA results.[32] A recent systematic review and meta-analysis also found reduced QFT sensitivity in young children with greatly reduced diagnostic utility in TB-endemic areas.[33]

Because HIV-infected children are at high risk of TB, annual LTBI testing is recommended beginning at ages 3 to 12 months and annually thereafter for those who tested negative in the past **(AIII)**,[34] depending on the local epidemiology, region of birth, and travel history. In HIV-infected patients, a TST induration ≥5 mm is considered positive, but even with this reduced cut-off, sensitivity remains poor; in U.S. recommendations, cut-off points for IGRAs are not adjusted for HIV infection. It is important that skin tests be administered and read correctly (http://www.cdc.gov/tb/education/Mantoux/default.htm).[34] The use of control skin antigens to assess cutaneous anergy is of uncertain value and not recommended **(AII)**. Sensitivity to tuberculin is reduced by severe malnutrition and some viral infections, including measles; the additive effect of HIV infection in these circumstances has not been determined. As a precaution, skin testing scheduled around the time of live-virus vaccination should be done at the same time as, or delayed until 4 weeks after

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vaccination to avoid potentially suppressed sensitivity **(AIII)**. Test characteristics for IGRAs in these situations have not been determined, but the same scheduling adjustments as for TST are advisable.[31] Two-step skin testing may boost sensitivity in adults, but its utility has not been assessed in children nor in the presence of HIV infection and its use is not recommended. Patients who test positive should undergo chest radiography and clinical evaluation to exclude TB disease.

TB Disease

The most rigorous diagnosis of TB requires culture confirmation. However, in clinical practice, a diagnosis of TB in children frequently depends on a combination of TB exposure or infection together with symptoms and clinical signs suggestive of TB and chest imaging studies with findings suggestive of active disease; where EPTB is suspected, histopathology and other laboratory results (such as evidence of granuloma formation on histological examination of biopsy specimens) also may aid diagnosis. Chest radiography should include both posteroanterior (or anteroposterior) and lateral views for optimal assessment of hilar adenopathy; in cases of uncertainty, ongoing symptom review and repeat radiography in 1 to 2 weeks may be highly informative. All children diagnosed with TB should be tested for HIV infection **(AIII)**.

Direct methods for detection of *M. tuberculosis* include AFB microscopy, nucleic-acid amplification tests (NAATs), and isolation in culture. Sputum smears are positive on AFB microscopy in 50% to 70% of adults with pulmonary TB; however, young children and children infected with HIV often have paucibacillary disease (low bacterial load), resulting in lower yield from sputum smear microscopy and culture, and specimens may be difficult to obtain because young children are unable to expectorate.[35] A positive smear result is suggestive of TB, but it does not differentiate *M. tuberculosis* from other mycobacterial species. Mycobacterial culture improves both sensitivity and specificity beyond that of AFB microscopy and permits species identification, drug-susceptibility testing, and genotyping. Confirming the presence of *M. tuberculosis* is most helpful in HIV-infected children because of the expansive differential diagnosis.[36] Obtaining a total of 3 sputum specimens[37] for microscopic evaluation and mycobacterial culture is advisable.[38-40] Performing NAAT on at least one respiratory specimen is advisable in adults and also has added value in children.[41,42] For children who are unable to produce sputum spontaneously, specimens should be collected via early-morning gastric aspirates or sputum induction; the first gastric aspirate collected gives the very highest yield and should be undertaken carefully.[43] The sensitivity and specificity of AFB microscopy of gastric aspirate specimens is poor. Bronchoscopy can be considered for patients unable to produce sputum.[37] When extrapulmonary involvement is suspected, relevant specimens should be obtained as clinically indicated and sent for histology and culture carefully.[43] Overall yield is increased by collecting multiple specimens.

A single FDA-approved commercial NAAT for direct detection of *M. tuberculosis* in sputum samples with positive or negative smear-microscopy results is available in the U.S. market: Amplified *M. tuberculosis* Direct Test (Gen-Probe). Newer direct tests that also can detect genetic markers of drug resistance, such as GenXpert (Cepheid), have been developed for point-of-care applications; these tests have been adopted at some sites in the United States after local validation but are not yet FDA-approved. GeneXpert testing of non sputum samples is not recommended. Data on the use of urine lipoarabinomannan (LAM) in children is unavailable. For children who can produce sputum, consideration should be given to performing NAAT on at least one respiratory specimen if a diagnosis of TB is being considered and if a positive test result would alter case management; however, further research is needed before specific recommendations can be made on the use of NAAT in the diagnosis of TB in children who cannot produce sputum and in the diagnosis of EPTB. Individual case reports have shown the utility of such testing without determining the overall test characteristics for this off-label usage.[41] Use of NAATs on gastric aspirate and cerebrospinal fluid specimens proved disappointing in the past;[44-46] they may be useful for increasing specificity of diagnosis (confirming disease) but sensitivity is inadequate to exclude disease.[47]

Because of the challenges of specimen collection and poor bacteriologic yield in children including those who are HIV-infected, the epidemiologic risk factors and a TB exposure history are critical determinants for making the diagnosis. In clinical practice, diagnosis often rests on indirect tests for TB infection (positive

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result from TST or IGRA) together with symptoms and chest radiograph findings suggestive of active disease.[19] A high index of suspicion is important, together with awareness that the stage of HIV infection affects the frequency of symptoms and radiologic signs and the characteristic performance of the indirect tests for infection such as TST, as well as the likelihood of alternative diagnoses (such as chronic lymphoid interstitial pneumonitis or recurrent bacterial infections).[4]

Drug-resistant TB should be suspected in the following situations:[43]

- Exposure to a person with drug-resistant TB,
- Residence in or travel to a region with high rates of drug-resistant TB,
- Residence in or work in an institution or setting in which drug-resistant TB is documented,
- Treatment of pulmonary problems with a prolonged course of multiple medicines or an injectable agent for more than a few weeks in a foreign country (i.e., the patient may not realize that he or she was treated for TB),
- Treatment of a pulmonary illness with a fluoroquinolone, and
- Treatment for LTBI when TB disease was not recognized.

Careful inquiry about the drug susceptibility pattern and treatment history of the likely source case (this should be routinely available for all newly diagnosed adult TB cases)[48] is essential to guide clinical management and choice of treatment regimen in children. TB drug-susceptibility testing (genotypic and phenotypic) should be performed in all cases where *M. tuberculosis* is isolated from a child; obtaining specimen(s) for mycobacterial culture and TB-drug susceptibility testing is particularly important for those who meet any of the risk criteria for drug resistance or if treatment failure occurs. A service for the molecular (i.e., genotypic) detection of drug resistance, provided by CDC through public health microbiology laboratories, provides rapid assessment of drug resistance, but phenotypic testing, using well standardized techniques, remains the reference standard.[41]

Prevention Recommendations

The most effective way to reduce TB-related morbidity and mortality is to prevent TB disease, which can be achieved by preventing TB exposure, minimizing HIV-related immunocompromise with early initiation of combination antiretroviral therapy (cART),[49,50] and preventing progression to disease by diagnosing infection or high-risk exposure early and treating it.[36] TB infection control has proven to be critical in healthcare and high-risk congregate settings.

Preventing Exposure

Most childhood infections with *M. tuberculosis* come from exposure in the immediate environment, often the household. Risk factors for TB disease (such as homelessness, incarceration, exposure to institutional settings, birth or residence in a high TB burden region) in close contacts of HIV-infected children also should be considered. The peripartum period seems to be a particularly vulnerable period for HIV-infected mothers; they should be evaluated for TB if they develop any symptoms suggestive of disease.[51]

Preventing Disease

BCG vaccine, which is not routinely administered in the United States, should not be administered to HIV-infected infants and children **(AII)**.

In the United States, where TB exposure is uncommon and BCG is not routinely administered at birth, HIV-infected children should have a TST (IGRA has uncertain value) during infancy (3–12 months of age) and annually thereafter **(AIII)**.[34] However, the value of this strategy will depend on the local TB epidemiology, region of birth, and travel history. After TB disease has been excluded, all HIV-infected children who have

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had close contact with an infectious TB case (regardless of their TST or IGRA result or previous history of TB diagnosis) or who test positive for the first time **(AI)** should receive preventive therapy **(AII)**. The preferred regimen is isoniazid (10–15 mg/kg body weight/day for 9 months) **(AII)**; if adherence with daily treatment supervised by the parent or other family member cannot be ensured, then isoniazid (20–30 mg/kg body weight twice weekly as directly-observed therapy [DOT] by a trained worker, not a family member) can be considered **(BII)**. For HIV-infected children, liver chemistry tests (serum alanine aminotransferase [ALT] concentration at a minimum) should be performed before initiating isoniazid **(AII)** and monthly thereafter or if any symptoms or signs suggestive of possible hepatotoxicity develop; medical providers should emphasize to patients that isoniazid treatment should be stopped immediately upon the earliest onset of toxicity (such as excess fatigue, nausea, vomiting, abdominal pain, or jaundice), even before a clinical evaluation has been conducted, and that initial symptoms can be subtle and may not include jaundice.[52] If isoniazid mono-resistance is known or suspected in the source case, daily rifampin for 6 months is recommended **(BII)**. A 2-month regimen of rifampin and pyrazinamide has been associated with severe and fatal hepatotoxicity in adults and was never recommended for children **(AII)**. Children exposed to other drug-resistant TB should receive individualized medical management in consultation with an expert, taking into account the susceptibility pattern and treatment history of the likely source-case.[53,54]

As noted above, in the United States, treatment for LTBI should be given to all HIV-infected patients following exposure to an infectious TB case or who test positive for the first time (i.e., positive on TST or IGRA) after TB disease has been excluded.

Ongoing prophylaxis after treatment for TB is completed (secondary or post-treatment prophylaxis) is not recommended. TB exposure screening should be ongoing and post-exposure prophylaxis provided following documented close contact with an infectious TB case, irrespective of previous exposure or treatment.

A 12-dose combination regimen of once-weekly isoniazid and rifapentine by DOT is safe and as effective as other regimens in preventing TB disease, and the completion rate is greater than for longer regimens.[1,55-57] However, pediatric experience with this regimen is limited, and the drug-drug interactions between rifapentine and antiretroviral drugs have not been determined. This regimen is not recommended for children aged <2 years, for HIV-infected adults or children who are receiving cART, or for individuals who have LTBI with presumed isoniazid or rifampin resistance; the preferred regimen for children aged 2 to 11 years remains daily isoniazid for 9 months.[1]

Treatment Recommendations

Treating Disease

Empiric therapy for TB should be started in HIV-infected infants and children in whom the diagnosis is strongly suspected and continued until the diagnosis is definitively excluded. The use of DOT (by a trained worker, not a family member) is recommended to maximize adherence **(AII)**. Principles for treatment of TB are similar in HIV-infected and HIV-uninfected children. However, treating TB in an HIV-infected child is complicated by cART interactions and overlapping toxicities. Once TB is diagnosed, treatment must be started immediately **(AII)**. The recommended total treatment duration is a minimum of 9 months for HIV-infected children **(AIII)**.[34,58] An overview of dosing recommendations for the prevention and treatment of TB in HIV-infected children is provided in the Dosing Recommendations Table.

In HIV-infected children, treatment of drug-susceptible TB consists of a 4-drug regimen: isoniazid, rifampin, pyrazinamide, and ethambutol given daily during the 2-month intensive-therapy phase, followed by a 7-month continuation phase using only isoniazid and rifampin **(AII)**.[34] Therapy for HIV-infected children should be given as daily DOT. With good adherence and treatment response, thrice-weekly treatment during the continuation phase can be considered **(CIII)**; once- or twice-weekly dosing has been associated with an increased rate of relapse or treatment failure with rifamycin resistance in HIV-infected adults with low CD4 counts and, therefore, is not recommended.[59,60] For children without significant immune compromise and

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with minimal disease with fully drug-susceptible TB, some experts would consider a standard 3-drug regimen (isoniazid, rifampin, pyrazinamide) during the 2-month intensive phase and a continuation phase (using isoniazid and rifampin) of 4 months **(BII)**.

Ethionamide can be used as an alternative to ethambutol (or an injectable aminoglycoside) in TBM cases **(CII)**, because of its superior cerebrospinal fluid penetration.[61-64] For children with extrapulmonary disease involving the bones or joints, central nervous system (CNS), or miliary disease, the minimum recommended total duration of treatment is 12 months (2-month intensive phase followed by 10-month continuation phase) **(AIII)**;[34,62,65] see the Dosing Recommendations Table. These recommendations assume that the organism is believed to be fully susceptible, that adherence is ensured by DOT, and that a child responds well clinically (and, if laboratory confirmed, microbiologically) to therapy.

Co-Treatment of TB and HIV

Concomitant treatment of TB and HIV is complicated by unfavorable pharmacokinetic (PK) interactions and overlapping toxicities and should be managed by a specialist with expertise in treating both conditions. Issues to consider when treating both conditions include:

- The critical role of rifampin because of its bactericidal and sterilizing properties, but also its potent induction of the CYP3A enzyme system and p-glycoprotein-mediated efflux that lowers cART drug levels, especially those of the protease inhibitors (PIs);
- Overlapping toxicities; and
- The challenges of adhering to a medication regimen that may include seven or more drugs. See the Summary of Recommendations Table.

Standard anti-TB treatment must start as soon as TB is diagnosed **(AII)**. For children already receiving cART, the cART regimen should be reviewed to minimize potential toxicities and drug-drug interactions. For children not yet receiving cART, early cART initiation should be planned, preferably within 2 to 8 weeks of starting treatment for TB **(AII)**. Results from treating TB/HIV coinfection in adults suggest that early initiation of cART after the start of treatment for TB (within 2–8 weeks) may increase the risk of IRIS, but it is associated with a significant reduction in mortality.[66] Results from treating TB/HIV coinfection in children also support early cART initiation.[49] For severely ill children, immediate cART initiation may be advisable **(CIII)**. The timing of cART initiation with CNS TB remains more controversial because of the potentially devastating effects of CNS IRIS.[67,68]

The choice of cART regimen in an HIV-infected child receiving a rifampin-based TB treatment regimen should be carefully considered. Rifampin is a potent inducer of the CYP3A enzyme system, with resultant severe reductions in PI levels (except ritonavir, which partially reverses this effect) and moderate reductions in nevirapine levels; nucleoside reverse transcriptase inhibitor (NRTIs) and efavirenz drug levels are least affected. Rifabutin, a rifamycin-class semi-synthetic antibiotic related to rifampin, exhibits minimal CYP3A induction and has been used in this context. However, drug dose adjustments are still required and data on its use in children remain limited; use only with expert guidance. NRTI drug levels are least affected by rifampin; therefore, a classic double NRTI backbone is maintained. However, because a triple NRTI strategy is associated with inferior virologic outcomes[69] (unless the viral load is sufficiently suppressed), the third drug of choice is usually a non-nucleoside reverse transcriptase inhibitor (NNRTI); efavirenz is the preferred NNRTI, but alternative options need to be considered in children in whom efavirenz is contraindicated or intolerable. Efavirenz is the preferred NNRTI in children and evidence suggests that no dosage adjustment is necessary **(AII)**.[70] Efavirenz was FDA approved in 2013 for children aged 3 months (and at least 3.5 kg) to 3 years old, but experience in this age group remains very limited. Nevirapine can be considered, but serum drug levels are reduced by more than 30% to 40% during rifampin co-treatment.[71] Adult data suggest that no dosage adjustment is necessary, apart from omitting the lead-in dose,[32] but many pediatric experts still recommend a ≈30% increase in the nevirapine dose in children, given the low risk of hepatic toxicity (a

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particular concern in healthy in young women) and the need to ensure optimal drug levels in young children with high viral loads **(CIII)** (See the Summary of Recommendations Table).

If a PI-based regimen is used, then a super-boosted PI regimen is advised, such as lopinavir/ritonavir with additional ritonavir to equal the lopinavir dose.[73] The super-boosted PI regimen should be continued for the full duration of rifampin treatment and 2 weeks after termination of TB therapies **(AIII)**. For children already receiving cART, the issues are similar. cART must continue and concurrent treatment of TB must be started immediately **(AII)**. The cART regimen should be reviewed to ensure optimal treatment of both TB and HIV and to minimize potential toxicities and drug-drug interactions. Combined use of integrase inhibitors and other cART classes with rifampin-based treatment has not been evaluated in children. Ongoing studies in adults suggest that dosage adjustment also is required with integrase inhibitors (See the Summary of Recommendations Table).

When available, therapeutic drug monitoring can be used to help guide drug dose adjustments during HIV/TB co-treatment.

Treatment of Drug-Resistant TB

For treatment of drug-resistant TB, a minimum of 4 drugs to which the isolate is susceptible should be administered, including two or more bactericidal drugs **(AII)**. Therapeutic regimens are individualized on the basis of the resistance pattern of the *M. tuberculosis* isolate and treatment history of the patient and the likely source case, considering the relative activities of each drug, the extent of disease, and any comorbid conditions. Children with suspected or confirmed drug-resistant TB should be managed in consultation with an expert.

Mono-Drug Resistance

If the strain is resistant only to isoniazid, isoniazid should be discontinued and the patient treated with 9 to 12 months of a rifampin-containing regimen (e.g., rifampin, pyrazinamide, ethambutol) **(BII)**. Rifampin mono-resistance is rare, and rifampin resistance usually is a marker of MDR-TB. Therefore, if rifampin mono-resistance is detected with a rapid test, it should be regarded as MDR-TB until the susceptibility or resistance to both isoniazid and rifampin is confirmed by phenotypic testing, because the rapid molecular (genotypic) methods for detecting resistance are not as sensitive to isoniazid as they are to rifampin.

MDR-TB

Children with suspected and confirmed MDR-TB (resistance to both isoniazid and rifampin) should be managed in consultation with an expert. In the United States, treatment of MDR-TB should be individualized based on drug susceptibility test (DST) results. In cases where DST results for a child are unavailable, DST results for the source case should be used to guide initial choice of regimen. For treatment of drug-resistant TB, a minimum of 3 to 4 drugs to which the isolate is susceptible should be administered, including two or more bactericidal drugs **(AII)**. Children with extensive or disseminated disease should be treated with at least 5 active drugs, because early aggressive treatment provides the best chance for cure.[14,53,54] All treatment for MDR-TB in HIV-infected children should be given daily with DOT.[34,74]

XDR-TB

Children with suspected or confirmed XDR-TB should be managed in consultation with an expert. XDR-TB is a form of MDR-TB for which the principles of management are similar, albeit with even greater challenges.[53]

Adjunctive Treatment

Adjunctive treatment with corticosteroids is indicated for children with TBM, since it reduces mortality and long-term neurologic impairment **(AII)**. Adjunctive corticosteroid use reduces long-term constrictive

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complications in TB pericarditis **(AII)** and is associated with more rapid symptom resolution in TB pleural effusion (relative indication). It also can be considered with severe airway obstruction related to endobronchial TB and highly symptomatic TB IRIS **(BIII)**. Prednisone (1–2 mg/kg body weight/day) for 4 to 6 weeks is advisable, tapered over 2 weeks. Pyridoxine (1–2 mg/kg body weight/day, max 50 mg/day) is recommended for all HIV-infected children treated with isoniazid, because of persistent low pyridoxine levels and possible increased risk of peripheral neuropathy **(AII)**.[75]

Monitoring of Adverse Events (Including IRIS)

Regular monitoring of clinical and bacteriologic response to therapy is important **(AII)**. For children with pulmonary TB, chest radiographs should be obtained 2 months after the start of treatment to evaluate acute response to therapy and then serially as needed, judging by clinical response.[34] Hilar adenopathy may persist or even worsen despite successful treatment, and normalization of the chest radiograph is not a criterion for shortening or discontinuing therapy. The most important indicators of treatment response are bacteriologic conversion, symptom resolution, and weight gain; all children with culture-confirmed disease should be monitored regularly for bacteriologic response;[37] this is critical in all children with extensive lung disease or culture-confirmed drug-resistant TB **(CIII)**.

Gastric upset can occur during the initial weeks of isoniazid treatment, but it usually can be avoided by having some food in the stomach when the drug is administered. Hepatotoxicity is the most common serious adverse effect. It includes subclinical hepatic enzyme elevation, which usually resolves spontaneously during continuation of treatment, and clinical hepatitis that usually resolves when the drug is discontinued. It rarely progresses to hepatic failure, but the likelihood increases when isoniazid is continued despite hepatitis symptoms (jaundice; tender, enlarged liver). Hepatotoxicity is less frequent in children than in adults, but no age group is risk-free. Transient asymptomatic serum transaminase elevations have been noted in 3% to 10% and clinical hepatitis in <1% of children receiving isoniazid; <1% required treatment discontinuation.[65,76] The rate of hepatotoxicity may be higher in children who take multiple hepatotoxic medications.

Although the risk in HIV-infected children has not been quantified, excessive hepatotoxicity has not been documented. Liver chemistry tests (serum ALT at a minimum; AST and bilirubin also should be considered) should be performed before initiation and after 2, 4, and 8 weeks of treatment for TB (the same for cART initiation while receiving treatment for TB) **(BIII)**. Beyond 2 months, routine testing every 2 to 3 months is advisable for all children receiving ART, and more frequently if clinically indicated **(BIII)**. Patients and their families should be educated about the signs and symptoms of hepatotoxicity; for children who develop them, treatment should be stopped and evaluation done on an urgent basis and liver enzymes measured **(AIII)**. Mild elevations in serum transaminase concentration (i.e., less than 3 times the upper limit of normal [ULN]) do not require drug discontinuation in children who are asymptomatic and in whom other findings (including bilirubin) are normal **(AII)**. If transaminase levels exceed five times the ULN or three times the ULN in the presence of any symptoms or signs indicative of hepatotoxicity (e.g., anorexia, jaundice, raised bilirubin), then all hepatotoxic drugs should be immediately discontinued. Discussion with an expert on further management using non-hepatotoxic drugs, and future careful re-challenge with first-line TB drugs should be considered. With transaminase levels three to five times the ULN in the absence of any symptoms or signs indicative of hepatotoxicity, treatment can cautiously continue with regular (at least weekly) liver chemistry tests and ongoing expert consultation.[52,77]

Rifampin is also associated with hepatotoxicity. If transaminase levels exceed 5 times ULN or 3 times the ULN in the presence of any symptoms or signs indicative of hepatotoxicity (e.g., anorexia, jaundice, raised bilirubin), then all hepatotoxic drugs should be immediately discontinued. Discussion with an expert on further management using non-hepatotoxic drugs, and future careful re-challenge with first-line TB drugs should be considered. Rifampin may lead to color changes in secretions including urine and saliva, and may lead to discoloration of contact lenses. Ethambutol can cause optic neuritis, with symptoms of blurry vision, central scotomata, and red-green color blindness, but it is rare at the recommended daily dose of 20 to 25 mg/kg body weight[34,37,62] and is usually reversible[78,79] (see http://whqlibdoc.who.int/hq/2006/WHO_HTM_TB_2006.365_eng.pdf). Because

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ethambutol should be given daily as part of a 4-drug regimen for TB treatment, intermittent dosing (i.e., two or three times weekly) in children is not recommended. The maximum recommended dose of ethambutol given as daily dosing is 1.6 g. Visual acuity should be evaluated before starting ethambutol and monitored regularly during treatment **(AIII)**. Use of ethambutol in very young children whose visual acuity cannot be monitored requires careful consideration of risks and benefits.[34]

Hypothyroidism has been associated with ethionamide and 4 (para)-aminosalicylic acid use;[80] periodic (i.e., every 3 months) monitoring of thyroid function is recommended **(AIII)**. Major adverse effects of aminoglycoside drugs are ototoxicity and nephrotoxicity; periodic (i.e., every 3 months) audiometry and blood urea and creatinine measurements are recommended **(AIII)**. Audiometry should be continued until 6 months after treatment completion, because ototoxicity can progress after termination of prolonged aminoglycoside use. Co-administration of pyridoxine (1–2 mg/kg body weight/day) with cycloserine is recommended to reduce CNS side-effects **(AIII)**.

Immune Reconstitution Inflammatory Syndrome (IRIS)

TB IRIS after initiation of cART was first reported in HIV-infected adults.[81-83] It may present with new onset of systemic symptoms, especially high fever; expanding CNS lesions; and worsening adenopathy, pulmonary infiltrates, or pleural effusions. Similar cases in children have been reported.[65,84,85] IRIS should be suspected in children with advanced immunosuppression who initiate cART and develop new symptoms shortly thereafter (within 3–6 months), despite evidence of good HIV control (increased weight and CD4 count, reduced viral load). It represents a temporary exacerbation of symptoms and occurs in two clinical scenarios. In patients who have occult TB before cART initiation, TB may be unmasked by subsequent immune recovery.[86] This unmasking or incident TB-IRIS usually occurs within 3 months of cART initiation and the pathogen typically is detectable.[87] IRIS also can result in paradoxical worsening of TB disease in HIV/TB-coinfected patients after cART initiation; treatment failure because of microbial resistance or poor adherence also must be excluded in these cases. In prospective observational studies, IRIS occurred in nearly 20% of children, usually within 4 weeks of cART initiation, resulting mostly from atypical mycobacteria, BCG (in young vaccinated infants) and TB (more prevalent in older children).[88,89] Mild-to-moderate symptoms of IRIS can be treated symptomatically with nonsteroidal anti-inflammatory agents, while short-term use of systemic corticosteroids can be considered in more severe cases **(BIII)**;[81-83,90] treatment for TB and ART should not be discontinued.

Managing Treatment Failure

Most children with TB, including those who are HIV-infected, respond well to standard treatment. If clinical response is poor, then adherence to therapy, drug absorption, and the possibility of drug resistance should be addressed. Mycobacterial culture, drug-susceptibility testing, and serum concentrations of TB drugs should be done whenever possible. Drug resistance should be suspected in any child whose smear or culture fails to convert after 2 months of DOT or in any of the situations previously emphasized. Also consider possible alternative diagnoses or dual pathology.

Preventing Recurrence

TB recurrence can represent relapse or re-infection disease. The relapse rate is low in children with drug-susceptible TB who receive DOT and cART. Recurrence within 6 to 12 months of treatment completion should be regarded as relapse and managed the same as treatment failure. Recurrence more than 6 to 12 months after treatment completion is probably re-infection disease, especially after new TB exposure or a visit to a TB endemic setting. Re-infection disease should be managed the same as first-time TB. Secondary (post-treatment) prophylaxis is not recommended. However, regular TB exposure screening should continue after completion of treatment, and preventive therapy should be considered whenever repeat exposure occurs.

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International Guidelines

These guidelines were developed for the United States. Guidelines for resource-limited countries may be different and are available from the World Health Organization and International Union Against Tuberculosis and Lung Disease.[91]

Additional Resources:

- CDC Division of TB Elimination
  - http://www.cdc.gov/tb/
  - 800-CDC-INFO
    (800-232-4636)
    TTY: (888) 232-6348
    24 Hours/Every Day
  - cdcinfo@cdc.gov
- U.S. Regional Training and Medical Consultation Centers
  - http://www.cdc.gov/tb/education/rtmc/default.htm
- Drug-Resistant Tuberculosis: A Survival Guide for Clinicians
  - http://www.currytbcenter.ucsf.edu/drtb/
- World Health Organization Childhood TB website
  - http://www.who.int/tb/challenges/children/en/index.html
- International Union Against TB and Lung Disease Childhood TB website
  - http://www.theunion.org/index.php/en/what-we-do/child-lung-health-/childhood-tb

Table: Summary of Recommendations for Concurrent Use of Antiretroviral Therapy and TB Treatment (page 1 of 2)

Age/Weight	Combination Antiretroviral Therapy (cART)[a]
Aged <3 years or weight <10 kg	Retain or Start the Following Regimens: • NRTI backbone; use 2 NRTIs Third Drug *If Receiving NVP, Consider:* • Switching to lopinavir/ritonavir (Kaletra®) with additional ritonavir to achieve mg-for-mg parity with lopinavir and continue for 1–2 weeks after treatment for TB has been stopped • If not possible, continue NVP dose at the upper end of the dosage scale *If Receiving Lopinavir/Ritonavir (Kaletra®):* • Use additional ritonavir as above • If ritonavir boosting is not possible, substitute NVP for lopinavir/ritonavir (preferably only if undetectable viral load and if not previously exposed to NVP through PMTCT or prior treatment regimen) dose at the upper end of the dosage scale For cART Initiation: • Triple NRTI therapy is an option, if baseline viral load <100,000 copies/mL

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Table: Summary of Recommendations for Concurrent Use of Antiretroviral Therapy and TB Treatment (page 2 of 2)

Age/Weight	Combination Antiretroviral Therapy (cART)[a]
Aged ≥3 years and weight ≥10 kg	Retain or Start the Following Regimens: • 2 NRTIs as backbone Third drug *If Receiving EFV:* • Retain efavirenz (no dosage adjustment necessary) *If Receiving NVP:* • Substitute efavirenz for nevirapine • If efavirenz not available, continue nevirapine; dose at the upper end of the dosage scale *If Receiving Lopinavir/Ritonavir (Kaletra®):* • Consider substituting efavirenz for lopinavir/ritonavir, preferably only if viral load is undetectable[b] and no prior NNRTI exposure • Alternatively use additional ritonavir as above • If starting efavirenz or ritonavir boosting is not possible, start NVP in place of lopinavir/ritonavir, preferably only if undetectable viral load and no prior NNRTI exposure; dose at the upper end of the dosage scale For Initiation: • Triple NRTI therapy is an option if baseline viral load <100,000 copies/mL
Treatment for TB is not adjusted and should be initiated as soon as the diagnosis is made. No cART adjustment is necessary with INH preventive therapy Monitoring: • If previously on cART, monitor clinically for signs of drug toxicity; routine liver function testing every 2-3 months is advisable for all children on cART; no routine additional testing beyond what is done for routine HIV care and treatment is advised unless clinically indicated **(BIII)**. • If cART newly initiated—Liver chemistry tests (such as serum ALT concentration) should be performed before initiation and after 2, 4, and 8 weeks of treatment for TB (the same for cART initiation while receiving treatment for TB) **(BIII)**. Beyond 2 months, routine testing every 2-3 months is advisable for all children on cART; no routine additional testing beyond what is done for routine HIV care and treatment is advised unless clinically indicated **(BIII)**.	

[a] TB patients newly diagnosed with HIV should receive cART as soon as possible, after completing the first 2 weeks of treatment for TB (earlier if clinically justified); efavirenz is preferred third drug with concurrent rifampin-based treatment for TB, but alternative options need to be considered in children aged <3 years and in those for whom efavirenz is not a preferred option.

[b] Children established on cART should be assessed for therapeutic failure. Do not exchange only a single drug in children whose viral load is not suppressed; rather, consider a full regimen change.

Adapted from Marais, Rabie, Cotton (2011)

Key to Acronyms: cART = combined antiretroviral therapy; EFV = efavirenz; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; TB = tuberculosis

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Table: Dosing Recommendations for Preventing and Treating TB in HIV-infected Children (page 1 of 2)

Indication	First Choice	Alternative	Comments/Special Issues
Prophylaxis Post-exposure	Source Case Drug Susceptible: • Isoniazid 10–15 mg/kg body weight (maximum 300 mg/day) by mouth daily for 9 months Source Case Drug Resistant: • Consult expert and local public health authorities.	• If adherence with daily isoniazid cannot be ensured, consider isoniazid 20–30 mg/kg body weight (maximum 900 mg/day) by mouth 2 times a week by DOT for 9 months • Isoniazid 10–15 mg/kg body weight (maximum 300 mg/day) and rifampin 10–20 mg/kg body weight (maximum 600 mg/day) by mouth daily for 3–4 months • Rifampin 10–20 mg/kg body weight (maximum 600 mg/day) by mouth daily for 4–6 months	Drug-drug interactions with cART should be considered for all rifamycin containing alternatives. Indication: • Positive TST (TST ≥5 mm) or IGRA without previous TB treatment • Close contact with any infectious TB case (repeated exposures warrant repeated post-exposure prophylaxis) • TB disease must be excluded before starting treatment. • No indication for pre-exposure and post-treatment prophylaxis. Criteria for Discontinuing Prophylaxis: • Only with documented severe adverse event, which is exceedingly rare. Adjunctive Treatment: • Pyridoxine 1–2 mg/kg body weight once daily (maximum 25–50 mg/day) with isoniazid; pyridoxine supplementation is recommended for exclusively breastfed infants and for children and adolescents on meat- and milk-deficient diets; children with nutritional deficiencies, including all symptomatic HIV-infected children; and pregnant adolescents and women.
Treatment	Intrathoracic Disease *Drug-Susceptible TB* *Intensive Phase (2 Months):* • Isoniazid, 10–15 mg/kg body weight (maximum 300 mg/day) by mouth once daily, **plus** • Rifampin 10–20 mg/kg body weight (maximum 600 mg/day) by mouth once daily, **plus** • Pyrazinamide 30–40 mg/kg body weight (maximum 2 g/day) by mouth once daily, **plus** • Ethambutol 15–25 mg/kg body weight (maximum 2.5 g/day) by mouth once daily *Continuation Phase (7 Months):* • Isoniazid 10–15 mg/kg body weight (maximum 300 mg/day) by mouth once daily, **plus** • Rifampin 10–20 mg/kg body weight (maximum 600 mg/day) by mouth once daily Extrathoracic Disease: **Note:** Depends on disease entity	Alternative for Rifampin: • Rifabutin 10–20 mg/kg body weight (maximum 300 mg/day) by mouth once daily (same dose if 3 times a week) • Discuss with an expert. Alternative Continuation Phase *If Good Adherence and Treatment Response:* • Isoniazid 20–30 mg/kg body weight (maximum 900 mg/day) by mouth, plus • Rifampin 10–20 mg/kg body weight (maximum 600 mg/day) three times a week. • In children with minimal disease with fully drug-susceptible TB in the absence of significant immune compromise, a 3-drug intensive phase regimen (excluding ethambutol) and a continuation phase of 4 months can be considered (total duration of therapy of 6 months).	Only DOT. If cART-naive, start TB therapy immediately and initiate cART within 2–8 weeks. Already on cART; review to minimize potential toxicities and drug-drug interactions; start TB treatment immediately. Potential drug toxicity and interactions should be reviewed at every visit. Adjunctive Treatment: • Co-trimoxazole prophylaxis • Pyridoxine 1–2 mg/kg/ body weight/day (maximum 25–50 mg/day) with isoniazid or cycloserine/terizidone or, if malnourished; pyridoxine supplementation is recommended for exclusively breastfed infants and for children and adolescents on meat- and milk-deficient diets; children with nutritional deficiencies, including all symptomatic HIV-infected children; and pregnant adolescents and women. • Corticosteroids (2 mg/kg body weight per day of prednisone [maximum, 60 mg/day] or its equivalent for 4–6 weeks followed

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Table: Dosing Recommendations for Preventing and Treating TB in HIV-infected Children (page 2 of 2)

Indication	First Choice	Alternative	Comments/Special Issues
Treatment, continued	• Lymph node TB—treat as minimal intrathoracic disease • Bone or joint disease–consider extending continuation phase to 10 months (for total duration of therapy of 12 months). TB Meningitis: • As alternative to ethambutol or streptomycin, 20–40 mg/kg body weight (maximum 1 g/day) IM once daily—during intensive phase, consider ethionamide, 15–20 mg/kg body weight by mouth (maximum 1 g/day), initially divided into 2 doses until well tolerated • Consider extending continuation phase to 10 months (for total duration of therapy of 12 months). • Discuss with an expert. *Drug-Resistant TB* *MDR-TB:* • Therapy should be based on resistance pattern of child (or of source case where child's isolate is not available); consult an expert. Treatment Duration: • 18–24 months after non-bacteriological diagnosis or after culture conversion; ≥12 months if minimal disease • Discuss with an expert.		by tapering) with CNS disease or pericardial effusion; may be considered with pleural effusions, severe airway compression, or severe IRIS. Second-Line Drug Doses: • Amikacin 15–30 mg/kg body weight (maximum 1 g/day) IM or IV once daily • Kanamycin 15–30 mg/kg body weight (maximum 1 g/day) IM or IV once daily • Capreomycin 15–30 mg/kg body weight (maximum 1 g/day) IM once daily • Ofloxacin 15–20 mg/kg body weight (maximum 800 mg/day), or levofloxacin 7.5–10 mg/kg body weight (maximum 750 mg/day) by mouth once daily. Because some fluoroquinolones are approved by the FDA for use only in people aged 18 years and older, their use in younger patients necessitates careful assessment of the potential risks and benefits. • Cycloserine/Terizidone 10–20 mg/kg body weight (maximum 1 g/day) by mouth once daily • Ethionamide/prothionamide, 15–20 mg/kg body weight (maximum 1 g/day) by mouth in 2–3 divided doses • Para-aminosalicylic acid 200–300 mg/kg body weight by mouth divided into 3–4 doses per day (maximum 10 g/day). • Thiacetazone can cause severe reactions in HIV-infected children including rash and aplastic anemia, and should not be used.

Key to Acronyms: cART = combined antiretroviral therapy; CNS = central nervous system; DOT = directly observed therapy; FDA = Food and Drug Administration; IGRA = interferon-gamma release assay; IM = intramuscular; IRIS = immune reconstitution inflammatory syndrome; IV = intravenous; MDR-TB = multi-drug-resistant tuberculosis; TB = tuberculosis; TST = tuberculin skin test

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