Mycobacterium tuberculosis

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Panel's Recommendations

I. Among children <15 years old with HIV, do interferon-gamma release assays (IGRAs) compared to tuberculin skin test (TST) reliably identify latent tuberculosis (TB) infection (LTBI)?

- IGRAs and TSTs can be used to diagnose LTBI in children 5 years or older (strong, moderate). IGRAs are preferred for diagnosing LTBI in Bacille Calmette-Guerin–vaccinated people and those who are not likely to return for interpretation of TST results (strong, moderate).
- Centers for Disease Control and Prevention (CDC) currently recommends TSTs for diagnosing LTBI in children 2–5 years old (strong, low); some experts and the American Academy of Pediatrics (AAP) Red Book recommend using IGRAs to diagnose LTBI in children ≥2 years old (strong, low).
- CDC and the AAP Red Book recommend TSTs for diagnosing LTBI in children <2 years old (expert opinion).
- Younger age (<5 years), HIV infection itself, and lower CD4 T lymphocyte (CD4) cell counts have been associated with indeterminate IGRA results and false negative TST results.

II. Among children <15 years old with HIV, does a negative TST or IGRA reliably exclude TB infection or disease?

- Neither TST nor IGRA results definitively exclude LTBI or TB disease. Therefore, testing for LTBI with TST or IGRA should not replace regular screening questions to ascertain exposures to TB disease and presence of clinical, epidemiologic, and social risk factors for LTBI or TB disease in addition to HIV infection (strong, moderate).

III. Among children <15 years old with HIV, does LTBI treatment result in fewer cases of TB disease, compared to no treatment?

- LTBI treatment is highly effective for preventing TB disease. Therefore, after TB disease (also referred to as "active TB disease") has been excluded, children with HIV should receive treatment for LTBI as soon as possible after a positive TST or IGRA result and presumptive LTBI treatment after exposure to infectious TB (regardless of whether the child has a negative TST or IGRA result or was previously treated for TB) (strong, high).

IV. Among children <15 years old with HIV, does a 12-dose combination of once-weekly isoniazid and rifapentine in place of 9 months of daily isoniazid result in comparable outcomes for TB prevention?

- Clinical trials have demonstrated that LTBI treatment with a 12-dose combination of once-weekly isoniazid and rifapentine has similar efficacy to 9 months of daily isoniazid for preventing TB disease; in practice, treatment adherence with the 12-dose regimen might be higher, resulting in higher real-world effectiveness. Therefore, the 12-dose regimen of once-weekly isoniazid and rifapentine for treatment of LTBI can be used in adults and children ≥2 years old with HIV who are on antiretroviral regimens with acceptable drug–drug interactions with rifapentine (strong, moderate).

V. Among children <15 years old with HIV and exposure to a person with drug-resistant TB, would 9 months of daily isoniazid compared to other regimens result in fewer cases of TB disease?

- Some studies have demonstrated successful prevention of presumed drug-resistant TB through treatment of LTBI with regimens informed by the drug-susceptibility test (DST) results of the presumed source case.
- After exposure to TB caused by isoniazid mono-resistant organisms, preventive therapy with 4 months of daily rifampin is recommended for children with HIV. Adjustment of antiretroviral therapy to consider drug–drug interactions between rifampin and antiretroviral therapy (ART) might be necessary (expert opinion).

- After exposure to TB caused by organisms with other drug resistance patterns (e.g., multidrug-resistant [MDR]), expert consultation should be obtained to determine optimal LTBI treatment regimens. DST results for the TB index patient are important considerations in the management of children exposed to drug-resistant TB (expert opinion).

VI. Among children <15 years old with HIV who are diagnosed with TB while not yet on ART, does early initiation of ART (2–8 weeks) compared to delayed ART initiation result in improved treatment outcomes?

- Children with HIV who are diagnosed with non–central nervous system (CNS) TB disease and who are not yet receiving ART should be evaluated for early ART initiation, preferably within 2 to 8 weeks of starting TB therapy (strong, moderate).
- Children with HIV who are diagnosed with CNS TB disease, including TB meningitis, should be evaluated for ART initiation within 2 to 8 weeks (expert opinion).

VII. Among children <15 years old with HIV diagnosed with TB disease, does therapy administered by directly observed therapy (DOT) or administered by self or family members result in improved medication adherence?

- Daily DOT (by a trained health care worker) should be used to maximize adherence and minimize treatment failures, relapse rates, and emergence of acquired drug resistance (strong, moderate).

VIII. Among children <15 years old with HIV who are diagnosed with intrathoracic TB disease (e.g., pulmonary or intrathoracic lymph nodes), does treatment with a four-drug regimen during the 2-month intensive phase compared to a three-drug regimen during the 2-month intensive phase result in better treatment outcomes? Among children <15 years old with HIV who are diagnosed with TB disease and treated with a four-drug regimen during the 2-month intensive phase, does a 7-month continuation phase using isoniazid and rifampin or a 4-month continuation phase using isoniazid and rifampin result in better treatment outcomes?

- In children with HIV, the recommended treatment for drug-susceptible TB is a four-drug regimen consisting of isoniazid, rifampin, pyrazinamide, and ethambutol given daily during the 2-month intensive phase, followed by a ≥4-month continuation phase using only daily isoniazid with daily rifampin (strong, moderate) and adjusting of ART as required for drug–drug interactions (expert opinion).
- For children with well-controlled HIV, minimal TB disease, and confirmed drug-susceptible TB, some experts would consider a standard three-drug regimen (isoniazid, rifampin, pyrazinamide) during the 2-month intensive phase followed by a ≥4-month continuation phase using only isoniazid and rifampin (expert opinion).

IX. Among children <15 years old with HIV who are taking isoniazid or cycloserine, should adjunctive pyridoxine supplementation versus no adjunctive pyridoxine supplementation be recommended routinely to improve clinical outcomes?

- Pyridoxine supplementation (1–2 mg/kg body weight/day, maximum 50 mg/day) is recommended for all children with HIV who are taking isoniazid or cycloserine (expert opinion).

X. Among children <15 years old with HIV in whom TB disease is diagnosed, what evidence-based antiretroviral treatment regimens result in better treatment outcomes?

- Among children >20 kg, dolutegravir (DTG)-based ART (dose increased to 50 mg twice daily) is preferred during TB treatment because DTG-based regimens are associated with better HIV treatment outcomes in the absence of TB (strong, moderate). Twice-daily DTG is safe and has favorable pharmacokinetic parameters in children >20 kg when co-administered with rifampin (strong, moderate).
- Children <20 kg receiving raltegravir (RAL)-based ART who begin TB treatment should increase RAL dose to 12 mg/kg twice daily for the duration of TB treatment. Among children <20 kg who are receiving lopinavir (LPV)/ritonavir-based ART regimens, LPV should be super-boosted to achieve a 1:1 ratio between LPV and ritonavir (strong, moderate). Alternately, children <20 kg can receive an efavirenz (EFV)-based regimen (expert opinion).
- If the EFV-based regimen is used, CYP2B6-516 genotype-directed EFV dosing is recommended.

XI. Among children <15 years old with HIV who are diagnosed with extrapulmonary TB disease, does TB treatment for 12 months compared to standard 9-month treatment result in better treatment outcomes?

- For children with extrapulmonary disease caused by drug-susceptible TB involving the bones or joints, CNS, or disseminated/miliary disease, the recommended duration of treatment is ≥12 months (expert opinion).

XII. Among children <15 years old with HIV who are diagnosed with TB meningitis (TBM), does the standard four-drug TB regimen compared to a regimen using ethionamide result in better treatment outcomes?

- For TBM, while DST results are pending, ethionamide can replace ethambutol (or an injectable aminoglycoside) as the fourth drug because of its superior cerebrospinal fluid penetration (expert opinion).
- For TBM, some experts recommend adding a fluoroquinolone to the treatment regimen pending the results of DST (expert opinion).

XIII. Among children <15 years old with HIV who are diagnosed with TBM, pericardial or pleural effusion, airway compression, or severe immune reconstitution inflammatory syndrome, does adjunctive treatment with corticosteroids result in improved clinical outcomes?

- Adjunctive corticosteroids (with concurrent treatment for TB disease) should be considered for children with TBM (strong, moderate). Adjunctive corticosteroids should also be considered in the context of severe immune reconstitution inflammatory syndrome, airway compression, pleural effusion, or pericarditis (expert opinion).

XIV. Among children <15 years old who are diagnosed with MDR-TB disease, does the use of individualized treatment regimens based on DST results compared to a standardized regimen result in better treatment outcomes?

- Whenever possible, treatment regimens for MDR-TB should be individualized (expert opinion); considerations include phenotypic and molecular DST results for the child or the presumed source case (when results of DST results are not available for the child) (strong, moderate). Expert consultation should be obtained for clinical management of suspected and laboratory-confirmed MDR-TB (i.e., resistance to both isoniazid and rifampin) (expert opinion).
- For treatment of drug-resistant TB, a minimum of five drugs to which the isolate is susceptible should be administered, including two or more bactericidal drugs (strong, moderate). Fluoroquinolones can be used to treat MDR-TB in children (strong, moderate).
- For treatment of TB that is resistant only to isoniazid, isoniazid should be discontinued, and the patient should be treated with 6 to 9 months of a rifampin-containing regimen (e.g., rifampin, pyrazinamide, ethambutol, and levofloxacin or moxifloxacin) (expert opinion).

XV. Among children <15 years old with HIV who are receiving treatment for TB disease, does liver chemistry testing at 2-week intervals during the first 2 months of treatment compared to less frequent monitoring result in better clinical outcomes?

- Routine monitoring of liver enzymes is not necessary in children who have no risk factors for hepatotoxicity. For children with additional risk factors (such as concomitant ART), routine monitoring of liver enzymes should be performed before initiation and 2, 4, and 8 weeks after starting TB treatment (the same monitoring schedule as for ART initiated while a patient is receiving treatment for TB) (expert opinion). Beyond 2 months, routine testing every 2 to 3 months is advisable for all children receiving ART, or more frequently if clinically indicated (expert opinion).
- Mild elevations in serum transaminase concentration (i.e., less than five times the upper limit of normal) do not require drug discontinuation in children who are asymptomatic and in whom other findings (including bilirubin) are normal (expert opinion).

XVI. Among children <15 years old who are diagnosed with TB disease, does routine HIV testing compared to HIV testing and counseling upon request identify more cases of HIV?

- All people diagnosed with TB disease should be tested for HIV (expert opinion).

Rating System

Strength of Recommendation: Strong or Weak

Quality of Evidence: High, Moderate, Low, or Very Low

Definitions

Latent Tuberculosis Infection

Latent tuberculosis (TB) infection (LTBI), as referred to by the Centers for Disease Control and Prevention (CDC), or TB infection (TBI), as indicated by the American Academy of Pediatrics' Red Book, is defined as a state of persistent immune response to stimulation by antigens of bacteria in the *Mycobacterium tuberculosis* complex (MTBC; e.g., *Mycobacterium tuberculosis*, *Mycobacterium bovis*, *Mycobacterium africanum*) without any clinical, radiographic, or microbiologic evidence of disease. People with LTBI/TBI are not contagious and have no signs or symptoms of tuberculosis (TB) disease. Nonetheless, they are at increased risk for developing TB disease and becoming contagious; diagnosing and treating LTBI/TBI can help prevent progression to TB disease.

Tuberculosis Disease (Also Called "Active Disease")

TB disease occurs when a person with MTBC has clinical signs and/or symptoms, radiographic evidence, or viable mycobacteria recovered from a clinical specimen. Disease can be pulmonary, extrapulmonary, or both.

Note: The terms "active" and "latent" are not universally accepted, because they imply a clear distinction between two states when there is instead a continuum from infection to disease, particularly in children who often have paucibacillary disease.

Introduction

Epidemiology

Information on the epidemiology of TB in the United States is available from the CDC.[1,2] Of the 8,300 TB cases provisionally reported in the United States during 2022, 362 (4.3%) occurred in children aged <15 years.[1] Among TB cases with known HIV status reported in the United States between 2008 and 2010, HIV coinfection was reported in 1.1% of children and adolescents <18 years old.[3] The actual rate of HIV coinfection in children and adolescents with TB in the United States is unknown during this period because of the low rate of HIV testing documented in national surveillance for this population—approximately 55% of TB cases did not have an HIV result reported to the National TB Surveillance System despite recommendations for routine HIV testing in all individuals with confirmed or suspected TB.

Numerous studies have documented an increased risk of TB in children and adults with HIV.[4-6] A decreasing or low CD4 T lymphocyte (CD4) cell count is not necessary for an increased risk of TB in children with HIV. However, decreasing CD4 cell counts reflect diminishing immunity, which further increases the risk for TB disease. Multiple studies conducted in resource-limited settings have demonstrated that among children with HIV, those with TB disease tend to have lower CD4 cell counts and percentages than those without TB disease.[7-9] In addition, while rare, congenital TB might be more common among children born to mothers with TB/HIV coinfection,[10,11] especially when those children have also perinatally acquired HIV.[11]

Most often, children with TB acquired the infection from an adult in their immediate environment; frequently, TB in children, especially young children, represents progression of a primary infection rather than the reactivation of an infection acquired in the past.[12] Diagnosis and treatment of the

source cases and evaluation of household contacts exposed to TB disease are important measures to identify individuals at high risk of infection, diagnose LTBI and TB disease promptly, and prevent more transmission.[13-15] All confirmed and suspected cases of TB disease should be reported to state and local health departments.[15]

In the United States, disease caused by *Mycobacterium bovis* (*M. bovis*) is thought to be far less common than disease caused by *M. tuberculosis*, but pediatric *M. bovis* cases have been reported, and children might have an increased relative prevalence of *M. bovis* disease.[16,17] Of the 165 cases of TB known to be caused by *M. bovis* in the United States between 1995 and 2005, 12 (7.3%) were in children aged 0 to 4 years, and 19 (11.5%) were in children aged 5 to 14 years.[16] Several reports suggest that *M. bovis* is primarily transmitted via ingestion of unpasteurized dairy products[16,18]; however, human-to-human airborne transmission has been reported.[19-21] *M. bovis* is considered intrinsically resistant to pyrazinamide, a characteristic that could influence treatment decisions.[22,23]

The emergence and effective transmission of drug-resistant TB is a major obstacle to global TB control.[24-26] In the United States, comprehensive public health measures have successfully reduced the rates of drug-resistant TB; among reported cases of TB, the proportion of primary multidrug-resistant (MDR)-TB cases, defined as cases resistant to at least isoniazid and rifampin, declined from 2.5% in 1993 to less than 1% since 1996.[2] Between 2008 and 2010, resistance to isoniazid was found for 7.8% of culture-confirmed TB cases occurring in children and adolescents (aged <18 years) and MDR-TB was found in 4% of non-U.S.–born and 1% of U.S.-born children in the United States who had culture-confirmed TB and drug-susceptibility testing (DST) results reported to the CDC.[3]

Extensively drug-resistant TB (XDR-TB) was traditionally defined as resistance to isoniazid and rifampin (i.e., MDR-TB), with additional resistance to any fluoroquinolone and at least one of three second-line injectable drugs (capreomycin, kanamycin, and amikacin). In 2021, the World Health Organization (WHO) updated the XDR-TB definition; according to WHO, XDR is TB caused by MDR or rifampin-resistant (RR) *M. tuberculosis* strains that are also resistant to any fluoroquinolone and at least one additional Group A drug (i.e., bedaquiline or linezolid); CDC has also updated the United States definition of XDR-TB.[27,28] CDC defines XDR as TB caused by *M. tuberculosis* strains that are resistant to isoniazid, rifampin, a fluoroquinolone and a second-line injectable agent (e.g., amikacin, capreomycin, and kanamycin).[28] CDC also considers *M. tuberculosis* strains resistant to isoniazid, rifampin, a fluoroquinolone, bedaquiline, and linezolid to be XDR.[28] XDR-TB has emerged globally as an important new threat.[24,26,29] 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.[30]

Clinical Manifestations

After acquiring *M. tuberculosis* complex, children aged <5 years old and children with immune-compromising conditions, such as HIV, are highly susceptible to developing symptomatic TB disease; the first 12 months after primary infection represents the period of greatest risk for progression to TB disease.[6,12,31] Children <5 years old and children with HIV can also develop TB disease after a primary infection of *M. tuberculosis* complex. Generally, the clinical features of TB disease in children with and without HIV are similar, with non-localizing signs such as failure to thrive, cough, and intermittent fever present. Disease progression, however, may be more rapid, and the development of complicated or disseminated disease is more likely in children with HIV.[12,32-34] Regardless of HIV status, children may present with characteristic pulmonary involvement such as hilar and/or mediastinal adenopathy, which may cause airway compression. In addition, children who are immunocompromised, including those with HIV, might have atypical findings such as

multi-lobar infiltrates and diffuse interstitial disease.[5,35] Rapidly progressive disease, including meningitis or mycobacterial sepsis, is more likely among very young children or those who are immunocompromised, including in children with HIV.

The following describes the natural history of childhood TB, although children with HIV of all ages are more likely to have disease manifestations similar to those seen in very young children.[12,36,37]

- **Aged <1 year:** Infants are at the highest risk for disease following primary infection with *M. tuberculosis*: as many as 50% of infants under 12 months of age might progress to active TB disease. Infants with TB are at high risk for extrapulmonary and disseminated disease, such as miliary TB, tuberculous meningitis (TBM), and extensive pneumonic infiltration.
- **Aged 1 to 4 years:** Compared to adults, young children have an elevated risk of disseminated forms of disease. However, this risk is lower than in infants under 1 year old. Children <5 years are at the greatest risk of complications resulting from airway compression because of their small, pliable airways and exuberant lymph node responses. Extrathoracic manifestations are also common (see below).
- **Aged 5 to 9 years:** Immunocompetent children in this age group have the lowest risk of progression to TB disease after primary infection. Still, depending on the average age at which primary infection occurs, TB among children in this age group may contribute substantially to the total case load of pediatric TB. Clinical manifestations in this age group vary; some patients present clinically with disease patterns more commonly seen in young children while others present with adult-type pulmonary disease, upper lobe infiltration, cavitation, and sputum production.
- **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 considered potential infectious sources.[38]

The reported proportion of children with TB who have extra-thoracic involvement has ranged widely, from approximately 10% to more than 50%, which is likely due to variations in diagnostic capacity and the timing of presentation; disseminated forms appear to be more common in children with HIV.[33,34,36,37,39,40] Extra-thoracic disease manifestations include:

- **Peripheral lymphadenitis (usually cervical):** Features include a matted mass of lymph nodes >2×2 cm.[41] Axillary adenitis ipsilateral to Bacille Calmette-Guerin (BCG) vaccination site is suggestive of BCG adenitis (also see the Immune Reconstitution Inflammatory Syndrome [IRIS] section below).
- **TBM** is most common in children aged <3 years, but can occur at any age, especially in children with HIV. Although the disease manifestations of TBM in immunocompetent and immunocompromised children are often similar, the list of differential diagnoses is greatly expanded in immunocompromised individuals, including children with HIV.[42,43]
- **Osteo-articular disease** can involve any bone or joint, but vertebral involvement with typical TB gibbus formation with or 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.[44]

Diagnosis

Latent TB Infection

Because children with HIV are at high risk for developing TB disease, screening questions about exposure to TB should occur at each health care visit; testing for LTBI is recommended beginning at ages 3 to 12 months and annually thereafter for those with negative results **(expert opinion).**[23] More frequent LTBI testing may be needed depending on epidemiologic risk factors, travel history, contact with people with suspected or confirmed TB, or clinical symptoms.

LTBI, which is a symptomless condition in which no viable mycobacteria are recovered from clinical specimens, can be diagnosed using the tuberculin skin test (TST) administered by the Mantoux method or by interferon-gamma release assays (IGRAs). Both testing methods depend on T-cell mediated immune activity; therefore, HIV and the degree of immune alteration influence the accuracy of these tests. Neither TST nor IGRA can be used to definitively exclude TB infection or disease, especially in the context of HIV **(strong, moderate).**[23,45,46]

The interpretation of TST or IGRA results must include consideration of an individual patient's epidemiological and medical factors and the circumstances of testing. The QuantiFERON-TB Gold (QFT) and QFT-Plus (Cellestis Limited, Valencia, California) and the T SPOT.TB assay (Oxford Immunotec, Marlborough, Massachusetts) are U.S. Food and Drug Administration (FDA)-approved. According to CDC guidelines, either an IGRA or TST can be used in children 5 years or older and will perform well in children with well-controlled HIV who are sufficiently nourished **(strong, moderate);** in addition, some experts and the AAP Red Book recommend IGRA use in children ≥2 years old.[23,47-50] Nonetheless, current CDC guidance recommends the use of TST in children 2 to 5 years old. An IGRA is preferred for testing BCG-vaccinated patients and for use in settings when the return rate for TST reading is poor **(strong, moderate).**[50] However, studies of IGRA performance in children with HIV and in very young children are limited, and results from these studies have been inconsistent; data on the sensitivity and specificity of IGRAs in children <2 years are not available.[51] CDC and the AAP Red Book preferentially recommend TSTs over IGRAs to test for LTBI in children younger than 2 years **(expert opinion).**[23,26,50,52,53]

When increased sensitivity for diagnosing *M. tuberculosis* infection is sought, both a TST and an IGRA can be done, with a positive result from either test being diagnostic **(expert opinion).** If the tests are performed simultaneously, blood for IGRA testing should be drawn before the TST is administered **(expert opinion).** Younger age, HIV infection, and reduced numbers of CD4 cells increase the rate of indeterminate IGRA results.[54] A recent systematic review and meta-analysis of IGRA use in children also found reduced QuantiFERON-TB Gold sensitivity in young children, which greatly reduced the diagnostic utility of the assay in TB-endemic areas.[53]

Interpretation of Tests for M. tuberculosis Infection

In patients with HIV, ≥5 mm of induration after TST placement is considered a positive test. However, even with this lower cutoff, sensitivity remains poor. It is important that skin tests be administered and interpreted by trained professionals.[23] The CDC offers resources and training materials for administering and interpreting skin tests. The use of control skin antigens to assess

cutaneous anergy is not routinely recommended **(expert opinion).** Sensitivity to tuberculin is reduced by severe malnutrition and some viral infections, including measles; the additive effect of HIV in these circumstances has not been determined.[23] As a precaution, skin testing scheduled around the time of live-virus vaccination should be done at the same time as vaccination, or delayed until 4 weeks after, to avoid potentially suppressed sensitivity **(expert opinion).**[23] Test characteristics for IGRAs in the situations described (i.e., severe malnutrition or viral infection in the setting of immunosuppression) have not been determined, but the same scheduling adjustments as for TST are advisable.[50] Two-step skin testing may boost sensitivity in adults, but its utility has not been assessed in children nor in the presence of HIV, and its routine use is not recommended **(expert opinion).** Patients with positive TST or IGRA results should undergo chest radiography and clinical evaluation to exclude TB disease.[23,45,46]

TB Disease

Direct methods for detection of *M. tuberculosis* complex include AFB microscopy, nucleic acid amplification tests (NAATs), and culture. However, the effectiveness of sputum smear microscopy and culture in young children and children with HIV may be limited because these children often have paucibacillary TB disease, which yields sputum with a low bacterial load. In addition, sputum specimens may be difficult to obtain from young children because they cannot expectorate.[23] A positive smear result is suggestive of TB, but it does not differentiate *M. tuberculosis* from other AFB, such as *M. fortiuitum or M. avium*. A positive mycobacterial culture result for MTBC provides a definitive diagnosis of TB disease; culture yield is less than optimal, especially among people with HIV and children. When organisms are successfully grown, culture permits species identification, DST, and genotyping. Because there are many possible causes of similar illness, especially among children with HIV, obtaining a definitive diagnosis by confirming the presence of *M. tuberculosis* complex is helpful in children with HIV.[55] For children who are unable to produce sputum spontaneously, specimens should be collected via sputum induction, nasopharyngeal aspiration or early-morning gastric aspiration. Because the first specimen collected gives the very highest yield, the sample collection should be undertaken carefully. When extrapulmonary involvement is suspected, relevant specimens should be obtained as clinically indicated and sent for histology and culture.[56] Overall diagnostic yield is increased by collecting multiple specimens.[56]

Two FDA-approved commercial NAATs for direct detection of *M. tuberculosis* in sputum samples with positive or negative smear-microscopy results are available in the United States: Amplified Mycobacterium Tuberculosis Direct Test (Gen-Probe) and Xpert MTB/RIF (Xpert, Cepheid), which can also detect rifampin resistance. FDA approval of Xpert MTB/RIF is based on the evaluation of the test's performance on sputum specimens. WHO endorsed use of Xpert MTB/RIF for testing in children, including testing of extrapulmonary specimens, in 2013.[57] NAATs are also recommended for diagnosis of TB in the United States.[58] A meta-analysis of studies that compared the performance of Xpert MTB/RIF to culture on respiratory specimens from children showed sensitivities, compared to culture, of approximately 62% for expectorated or induced sputum and 66% for gastric lavage specimens.[59] A recent meta-analysis showed that the sensitivity of Xpert MTB/RIF relative to culture on extrapulmonary specimens varies by specimen type.[60] Tests for urine lipoarabinomannan (LAM) in children have poor sensitivity and specificity.[61,62]

Drug-resistant TB should be suspected in the following situations[23]:

- History of inadequate previous treatment for TB disease (or exposure to a person who received previous treatment for TB disease)

- Exposure to a person with drug-resistant TB
- Residence in or travel to regions or setting (e.g., an institution such as an orphanage) with high prevalence of drug-resistant TB
- Treatment of pulmonary problems with a prolonged course of multiple medicines or an injectable agent for more than a few weeks while in a foreign country (i.e., the patient or guardian may not realize that the treatment was for TB)
- Putative source case has positive smears for acid-fast bacilli or cultures after 2 months of an appropriate antituberculosis regimen
- Relapse of TB following a completed course of treatment
- Failure to respond to adequate treatment

Careful inquiry about the drug-susceptibility pattern and treatment history of the likely source case (which should be routinely available for all newly diagnosed adult, culture-confirmed TB cases) is essential to guide clinical management and the choice of treatment regimen in children. TB DST (molecular and phenotypic) should be performed in all cases where *M. tuberculosis* is isolated from a child; obtaining specimen(s) for mycobacterial culture and TB DST 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 detection of drug resistance, provided by CDC through public health microbiology laboratories, provides rapid assessment of drug resistance.[63]

Prevention Recommendations

Several strategies are necessary for preventing TB-related morbidity among children with HIV, including preventing exposures to infectious TB, minimizing HIV-related immunocompromise with early initiation of antiretroviral therapy (ART),[64-66] and providing prompt diagnoses and treatment for people with LTBI or exposures to infectious TB.[55,67] TB infection control is also critical in health care and congregate settings.[68]

Preventing Exposure

Most childhood infections with MTBC result from exposure to an individual with infectious TB in a child's immediate environment, often within a household. Families should be educated about epidemiologic and social risk factors for TB disease (such as homelessness, congregation in high-risk settings, and birth or residence in a region with a high TB burden), and children with HIV who have been in close contact with people with these risk factors should receive heightened attention. During the peripartum period, women with HIV seem particularly vulnerable to TB, and they should be evaluated for TB disease if they develop any symptoms suggestive of disease, such as unexplained cough, fever, weight loss, or failure to thrive.[69,70]

Preventing Disease

BCG vaccine, which is commonly used to reduce the risk of disseminated TB in high-TB burden countries, should not routinely be administered to infants and children with HIV in the United States **(expert opinion).**[23] BCG is not thought to prevent against pulmonary TB, the most common form of TB in the United States. In the United States, children with HIV should be tested for TB infection

beginning during infancy (3–12 months of age) and annually thereafter **(expert opinion).**[23] TST is preferred over IGRA for children aged <2 years **(strong, low).**[23,50]

CDC guidelines stipulate that both TSTs and IGRAs can be used for testing children with HIV for LTBI who are ≥5 years old.[50] In addition, some experts and the AAP Red Book provide recommendations for testing children ≥2 years with IGRAs. TSTs are preferred in children <2 years.[23] IGRAs are preferred for testing BCG-vaccinated people and for use in settings when the return rate for TST reading is low **(strong, moderate).**[50] The value of an annual TB infection testing strategy will depend on the local TB epidemiology, a child's region of birth and travel history, and whether the child has any additional social risk factors for exposure to *M. tuberculosis* (e.g., residence in a congregate setting). After TB disease has been excluded, all children with HIV who have a positive TST or IGRA or who have had close contact with a person with infectious TB (regardless of their TST or IGRA result or previous treatment for TB) should receive preventive therapy **(strong, high).**[46,67,71,72]

In adults and children 2 years and older, including those with HIV, a 12-dose combination regimen of once-weekly isoniazid and rifapentine (3HP) is as safe and effective as 9 months of isoniazid in preventing TB disease.[73-76] Completion rates are high whether given as directly observed therapy (DOT) or self-administered therapy.[77] Therefore, the 3HP regimen can be used for the treatment of LTBI in adults and children ≥2 years old with HIV who are receiving ART, with acceptable drug–drug interactions with rifapentine **(strong, moderate).**[46] The preferred regimens for LTBI from presumed drug-susceptible TB include—

- Twelve doses of weekly isoniazid (for medication dosing recommendations, see the Dosing Recommendations Table) and rifapentine for children and adolescents >2 years old.[46]
- Four months of daily rifampin for children of all ages.
- Three months of daily isoniazid and rifampin for children of all ages.[46]

Alternative regimens include 6 or 9 months of isoniazid for children of all ages.[23] If adherence with treatment cannot be ensured, then DOT by a trained worker can be considered **(expert opinion).**[23,72] There is some evidence to suggest that the risk of isoniazid-related severe liver injury is lower in children with HIV than in adults with HIV.[78] However, it may be necessary to monitor serum transaminases in children with HIV receiving ART and/or with any symptoms or signs suggestive of possible hepatotoxicity. Patients (or their caregivers) should be counseled to discontinue taking the medication and contact their physicians immediately if any symptoms such as excess fatigue, nausea, vomiting, abdominal pain, or jaundice occur.[79] Drug–drug interactions between LTBI medications (particularly rifamycins) and ART should be considered; these interactions might require adjustment of ART.

Dose adjustments with dolutegravir and raltegravir should be considered when administering 4 months of daily rifampin or 3 months of daily rifampin with isoniazid. In children with HIV being treated for TB disease, twice-daily dolutegravir is safe and achieves adequate pharmacokinetic (PK) targets in children >20 kg when co-administered with rifampin **(strong, moderate).**[80] Similarly, raltegravir dosing of 12 mg/kg twice daily is safe and achieves adequate PK targets in children <20 kg when co-administered with rifampin for TB treatment **(expert opinion).**[81]

If isoniazid mono-resistance is known or suspected in the TB source case, daily rifampin for 4 months is recommended, with adjustment of ART as needed **(strong, moderate)** to account for

potential drug–drug interactions with rifampin.[23] Children exposed to other drug-resistant TB should receive individualized medical management in consultation with an expert, considering the susceptibility pattern and treatment history of the likely source case.[23,67,82,83]

Treatment Recommendations

Treating Disease

Empiric therapy for TB disease should be started in infants and children with HIV in whom TB is strongly suspected and continued until treatment is completed or TB disease is excluded **(strong, low).** The use of DOT by a trained health care worker is recommended to maximize adherence and to decrease rates of relapse, treatment failures, and drug resistance **(strong, moderate).**[23,45,84] Principles for treatment of TB are similar for children with and without HIV. However, treating TB in a child with HIV is complicated by ART interactions and overlapping toxicities. The recommended total treatment duration is a minimum of 6 months for children with HIV **(strong, moderate).**[23,45,85]

An overview of dosing recommendations for the prevention and treatment of TB in children with HIV is provided in the Dosing Recommendations Table at the end of this section. In children with HIV, treatment of drug-susceptible TB often involves a four-drug regimen: isoniazid, rifampin, pyrazinamide, and ethambutol given daily during a 2-month intensive-therapy phase, followed by a 4-month (or more) continuation phase using only isoniazid and rifampin **(strong, moderate).**[23,45,85] For children with well-controlled HIV, minimal TB disease, and confirmed drug-susceptible TB, some experts would consider a standard three-drug regimen (isoniazid, rifampin, pyrazinamide) during the 2-month intensive phase and a continuation phase (using isoniazid and rifampin) of 4 months (or more).[23,85]

Ethionamide should be used as an alternative to ethambutol (or an injectable aminoglycoside) for treatment of TBM, because of its superior cerebrospinal fluid penetration **(expert opinion).**[23,85-89] Some experts also routinely add a fluoroquinolone to the initial regimen.[23] For children with extrapulmonary disease involving the bones or joints or central nervous system (CNS), or who have miliary disease, the recommended total duration of treatment is at least 12 months (2-month intensive phase followed by a ≥10-month continuation phase) **(expert opinion).**[23,85,90,91] These recommendations assume that the organism is 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 PK interactions and overlapping toxicities and should be managed by a specialist with expertise in treating both conditions.

For children already receiving ART, ART should be reviewed to minimize potential toxicities and drug interactions. For children not yet receiving ART, early ART initiation should be planned, preferably beginning within 2 to 8 weeks of starting treatment for TB **(strong, moderate).** Children with HIV who are diagnosed with CNS TB disease, including TB meningitis, should be evaluated for ART initiation within 2 to 8 weeks **(expert opinion).** Results from treating TB/HIV coinfection in adults suggest that early initiation of ART 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 among those with a CD4 count below 50 cells/mm^3.[92-95] Results from treating TB/HIV coinfection in children also

support early ART initiation.[66,94] Early ART initiation is especially important for children who are severely immunocompromised, and ART initiation within 2 weeks of beginning TB treatment might be advisable, depending on the clinical circumstances **(expert opinion).**[96] The optimal timing of ART initiation in patients with CNS TB has not been established and remains controversial because of the potentially devastating effects of CNS IRIS.[97,98]

Drug–Drug Interactions in TB and HIV Co-treatment

Rifampin is a potent inducer of the CYP3A enzyme system with moderate to significant interactions with nevirapine and protease inhibitors (PIs), respectively, reducing corresponding plasma drug concentrations. Rifabutin, a rifamycin-class semi-synthetic antibiotic related to rifampin, exhibits minimal CYP3A induction and can be used instead of rifampin to reduce drug interactions.[23]

Preliminary results from the ODYSSEY trial in children aged 6 to 18 years receiving TB treatment with rifampin demonstrated that twice-daily DTG dosing was safe and achieved adequate dolutegravir pharmacokinetic targets.[80] Therefore, in children >20 kg, DTG-based ART is the preferred regimen in the context of TB/HIV co-treatment, with 50 mg DTG given twice daily throughout TB treatment. While the FDA has approved twice-daily DTG during TB treatment for children as young as 4 weeks old and ≥3 kg, additional evidence on safety and PK parameters in children <20 kg is needed to inform formal U.S. Department of Health and Human Services recommendations.[99] There are insufficient pharmacokinetic data for the use of bictegravir during TB treatment for children with HIV.

Children <20 kg receiving raltegravir (RAL)-based ART who begin TB treatment should increase RAL dose to 12 mg/kg twice daily for the duration of TB treatment. Safety and adequate PK targets in children receiving RAL 12 mg/kg twice-daily dosing with concurrent rifampin administration have been demonstrated among children as young as 4 weeks of age.[81,100]Among children <20 kg who are receiving lopinavir (LPV)/ritonavir (LPV/r)-based ART, LPV should be super-boosted to achieve a 1:1 ratio between LPV and ritonavir (RTV) **(strong, moderate).** Non-inferiority of super-boosted LPV/r PK targets during rifampin treatment was demonstrated in a clinical trial of South African children between 3 to 15 kg receiving rifampin for TB treatment.[101] Alternatively, children <20 kg can receive an efavirenz (EFV)-based regimen **(expert opinion).** If an EFV-based regimen is used, CYP2B6-516 genotype-directed EFV dosing is recommended.

Treatment of Drug-Resistant TB

Children with clinically diagnosed or microbiologically confirmed drug-resistant TB should be managed in consultation with an expert. Therapeutic regimens are individualized based on 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 **(expert opinion).**[23,102]

Mono-Drug Resistant TB

If the TB strain is resistant only to isoniazid, isoniazid should be discontinued and the patient treated for 6 to 9 months with a rifampin-containing regimen (e.g., rifampin, pyrazinamide, ethambutol) **(expert opinion).**[23,85] The addition of a late-generation fluoroquinolone for the duration of treatment is also now suggested.[23,102] Rifampin mono-resistance is thought to be uncommon; therefore, rifampin resistance is considered a reliable marker of MDR-TB (see below). 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 for isoniazid resistance as they are for rifampin resistance **(expert opinion).**

Multidrug-Resistant TB

Children with suspected and confirmed MDR-TB should be managed in consultation with an expert **(expert opinion).**[23,102] Treatment should be guided by DST; use of medications to which the *M. tuberculosis* strain is susceptible is associated with better treatment outcomes whereas use of medications to which the *M. tuberculosis* strain is resistant is associated with treatment failure, additional acquired resistance, and unnecessary toxicity.[103-105] In the United States, where DST is widely available, treatment of MDR-TB should be individualized based on results of DST rather than on standardized or empiric regimens which may include ineffective agents.[102,106] In cases where DST results for a child are unavailable, DST results for the presumed source case should be used to guide initial choice of regimen **(strong, moderate).**[23,102] For treatment of MDR-TB, a minimum of five drugs to which the isolate is susceptible should be administered, including two or more bactericidal drugs **(strong, moderate).**[23,102] Children with extensive or disseminated disease should be treated with at least five active drugs, because early aggressive treatment provides the best chance for cure.[82,83,102,107] When molecular or phenotypic DST demonstrates susceptibility (or is presumed based on the putative source case), a late-generation fluoroquinolone should be included in treatment regimens for MDR-TB **(strong, moderate).**[85,102] Recommendations on designing an individualized regimen for MDR-TB are provided in updated guidance.[102] Due to medication-related toxicity and modest efficacy, current guidance recommends avoiding injectable agents for routine MDR-TB care.[102] Injectable agents should be reserved for situations requiring injectables to assemble five effective drugs; amikacin or streptomycin should only be considered for inclusion in the regimen if there is documented susceptibility and an effective regimen cannot otherwise be constructed **(strong, moderate).**[102] Kanamycin and capreomycin should be avoided as these drugs have been associated with increased toxicity and adverse treatment outcomes **(strong, moderate).**[102] Bedaquiline, now increasingly a priority medication for treatment of MDR-TB in adults and children, has clinically significant drug–drug interactions with ART that should be considered when treating MDR-TB in the context of HIV. Co-treatment of TB with bedaquiline and HIV with EFV results in clinically significantly lower bedaquiline levels.[102,108] Co-treatment with lopinavir/ritonavir, specifically, and other boosted PIs, generally, can result in increased bedaquiline levels, although the clinical relevance is not clear.[109-111] Co-treatment of HIV with EFV or lopinavir/ritonavir and TB with delamanid does not result in clinically significant drug–drug-interactions.[112] All treatment for MDR-TB in children with HIV should be given daily with DOT **(strong, low).**[23,85,102]

Extensively Drug-Resistant TB

In 2021, the definition of XDR-TB was updated.[27,28] WHO defines XDR-TB as caused by *M. tuberculosis* strains that fulfill the definition of MDR/RR-TB and which are also resistant to any fluoroquinolone and at least one additional Group A drug (e.g., bedaquiline or linezolid); CDC has also updated the United States definition of XDR-TB. CDC defines XDR as TB caused by *M. tuberculosis* strains that are resistant to isoniazid, rifampin, a fluoroquinolone and a second-line injectable agent (e.g., amikacin, capreomycin, and kanamycin).[28] CDC also considers *M. tuberculosis* strains resistant to isoniazid, rifampin, a fluoroquinolone, bedaquiline, and linezolid to be XDR.[28] 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.[83,102]

Adjunctive Treatment

Adjunctive treatment with corticosteroids is indicated for children with TBM **(strong, moderate),** as evidence suggests that it reduces mortality and long-term neurologic impairment in patients with TBM.[113,114] Adjunctive corticosteroids can also be considered for management of patients with severe IRIS, airway compression, pleural effusion, or pericarditis **(expert opinion).** Adjunctive corticosteroid use appears to reduce long-term constrictive complications in TB pericarditis[115] and is associated with more rapid symptom resolution in TB pleural effusion (relative indication).[116] Prednisone (1–2 mg/kg body weight/day) for 4 to 6 weeks is advisable, with tapered dosing during the final 2 weeks.

Treatment with isoniazid or cycloserine can result in neurologic adverse events, which are related to relative pyridoxine deficiency. Prophylaxis with pyridoxine has been recommended in at-risk patients for decades.[117] Recent evidence supports the idea that children with nutritional deficiencies and those with HIV are at particular risk of isoniazid-associated neuropathy.[118,119] Pyridoxine (1–2 mg/kg body weight/day, maximum 50 mg/day) is recommended for all children with HIV treated with isoniazid or cycloserine **(expert opinion).**

Monitoring of Adverse Events (Including IRIS)

Regular monitoring of clinical and bacteriologic response to therapy is important. For children with pulmonary TB, chest radiographs should be obtained 2 months after the start of treatment to evaluate acute response to therapy **(expert opinion).**[23,45] 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.[23,45] 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.[45]

Gastric upset can occur during the initial weeks of isoniazid treatment; however, this can usually be avoided when the medication is given with food. While the overall incidence of hepatoxicity is low, it is the most common serious adverse effect of isoniazid treatment. This toxicity includes subclinical hepatic enzyme elevation, which usually resolves spontaneously during continuation of treatment, and clinical hepatitis that usually resolves when the drug is discontinued. Drug-induced hepatic failure is rare, but the likelihood increases when isoniazid is continued despite hepatitis symptoms (jaundice or tender, enlarged liver). Hepatotoxicity is less frequent in children than in adults, but no age group is risk free.[78,89] Among children receiving isoniazid, 3% to 10% experienced transient asymptomatic serum transaminase elevations and <1% had clinical hepatitis; <1% of the cases required treatment discontinuation.[90,120] The rate of hepatotoxicity may be higher in children who take multiple hepatotoxic medications.[23]

Although the risk in children with HIV has not been quantified, excessive hepatotoxicity has not been documented. Routine monitoring of liver enzyme is not necessary in children who have no risk factors for hepatotoxicity. For children with additional risk factors (such as concomitant ART), routine monitoring of liver enzymes (serum alanine aminotransferase at a minimum; aspartate aminotransferase and bilirubin also should be considered) should be performed before initiation and after 2, 4, and 8 weeks of treatment for TB (which is the same monitoring schedule as for ART

initiated while a patient is receiving treatment for TB) **(expert opinion).**[23] Beyond 2 months, routine testing every 2 to 3 months is advisable for all children receiving ART, and more frequently if clinically indicated **(expert opinion).**[23] Patients and their families should be educated about the signs and symptoms of hepatotoxicity; for children who develop abnormal symptoms, treatment should be stopped immediately and an urgent evaluation for hepatotoxicity should be performed that includes measuring liver enzymes **(expert opinion).**[85] Mild elevations in serum transaminase concentration (i.e., less than 5 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 **(expert opinion).**[45,85] 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 hepatotoxic drugs should be discontinued immediately **(expert opinion).**[23] 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 is also associated with hepatotoxicity. If transaminase levels exceed five times 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 **(expert opinion).** 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 causes color changes in body 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[23,45,85] and is usually reversible.[121,122] Because ethambutol should be given daily as part of a four-drug regimen for TB treatment, intermittent dosing (i.e., two or three times weekly) in children is not recommended **(expert opinion).** The maximum recommended dose of ethambutol given as daily dosing is 1.6 g/day **(expert opinion).** Use of ethambutol in very young children whose visual acuity cannot be monitored requires careful consideration of risks and benefits.[23,45] Color vision screening should be performed prior to starting ethambutol for children who are old enough to cooperate with testing.

Other TB drugs have known side effects which should be monitored.[23,45,102] Hypothyroidism has been associated with ethionamide and 4 (para)-aminosalicylic acid. Major adverse effects of aminoglycoside drugs are ototoxicity[123] and nephrotoxicity. Ototoxicity can progress after termination of prolonged aminoglycoside use, and monitoring may be needed for 6 months after treatment completion. QT interval prolongation is an adverse effect of many new and newly repurposed medications used for MDR-TB treatment, including bedaquiline, delamanid, clofazimine, and the fluoroquinolones, especially moxifloxacin.[124] Although the risk of severe QT interval prolongation (≥500 ms) appears to be low, regular electrocardiogram monitoring should be considered, especially when multiple QT-prolonging medications are combined in regimens. Linezolid is associated with frequent dose and duration dependent adverse effects that can be severe, including cytopenias (anemia, neutropenia, thrombocytopenia) and peripheral neuropathy; careful monitoring, especially for cytopenias in children, should be considered.

Immune Reconstitution Inflammatory Syndrome

TB IRIS after initiation of ART was first reported in adults with HIV, and data on TB IRIS among children with HIV remains limited.[125-128] TB IRIS may present with new onset of systemic symptoms, especially high fever, expanding CNS lesions, and worsening adenopathy, pulmonary infiltrates, or pleural effusions.[90,129,130] IRIS should be suspected in children with advanced

immunosuppression who develop new symptoms shortly after ART is initiated (within 3–6 months), despite evidence of good HIV control (increased weight and CD4 count, reduced viral load). TB IRIS represents a temporary exacerbation of symptoms and occurs in two clinical scenarios. In patients who have occult TB before ART initiation, TB may be unmasked by subsequent immune recovery.[131] This unmasking or incident TB IRIS usually occurs within 3 months of ART initiation, and the pathogen typically is detectable.[132] TB IRIS also can result in paradoxical clinical worsening of TB disease after ART initiation in patients with TB/HIV coinfection; treatment failure because of microbial resistance or poor adherence also must be excluded in these cases. In prospective observational studies, IRIS occurred in nearly 5% to 10% of children, usually within 4 weeks of ART initiation, resulting mostly from atypical mycobacteria, BCG (in young vaccinated infants) and TB (more prevalent in older children).[133,134] 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 **(expert opinion)**[125-128,135,136]; treatment for TB and ART should not be discontinued.

Managing Treatment Failure

Most children with TB, including those with HIV, respond well to standard treatment. If clinical response is poor, then adherence to therapy, drug absorption, and the possibility of drug resistance should be carefully considered. Mycobacterial culture, DST, and assessment of 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 from positive to negative after 2 months of DOT, and alternative diagnoses or dual pathology should also be considered.

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 ART. Recurrence within 6 to 12 months of treatment completion should be regarded as relapse and managed the same as treatment failure **(expert opinion).** Recurrence more than 6 to 12 months after treatment completion might be due to re-infection with *M. tuberculosis*, especially after a new exposure to a person with TB disease or a visit to a TB-endemic setting. Re-infection should be managed the same as the first episode of TB disease. Regular TB exposure screening should continue after completion of treatment, and preventive therapy should be considered whenever repeat exposure occurs.

International Guidelines

These guidelines were developed for the United States. Guidelines for resource-limited countries may be different and are available from WHO.[26]

Additional Resources

- CDC Division of TB Elimination
  https://www.cdc.gov/tb
  800-CDC-INFO (800-232-4636)
  TTY: 888-232-6348
  24 Hours/Every Day
  cdcinfo@cdc.gov

- TB Centers of Excellence for Training, Education, and Medical Consultation https://www.cdc.gov/tb/education/tb_coe/default.htm
- Drug-Resistant Tuberculosis: A Survival Guide for Clinicians https://www.currytbcenter.ucsf.edu/products/view/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition
- WHO Ending TB in Children and Adolescents https://www.who.int/activities/ending-tb-in-children-and-adolescents
- International Union Against TB and Lung Disease Child & Adolescent TB website https://theunion.org/our-work/tuberculosis/child-adolescent-tuberculosis

PICO Questions

Detection of Latent TB Infection

I. Among children <15 years old with HIV, do interferon-gamma release assays (IGRA) compared to tuberculin skin test (TST) reliably identify latent tuberculosis infection (LTBI)?

IGRAs and TSTs can be used to diagnose LTBI in children 5 years or older **(strong, moderate).**[23] Although CDC guidelines currently recommend TSTs for diagnosing of LTBI in children 2 to 5 years old, some experts and the AAP Red Book recommend using IGRAs to diagnose LTBI in children ≥2 years old.[23,50] When applicable, IGRAs are preferable for diagnosing LTBI in Bacille Calmette-Guerin (BCG)–vaccinated people and those who are unlikely to return for interpretation of TST results **(strong, moderate).**[50] However, younger age (<5 years), HIV itself, and lower CD4 cell counts have been associated with indeterminate IGRA results (and false negative TST results). CDC guidelines and the AAP Red Book recommend TSTs for diagnosing LTBI in children <2 years old **(expert opinion).**[23,50]

Diagnostic methods for LTBI include the TST administered by the Mantoux method using 5 tuberculin units of an FDA-approved purified protein derivative, or an FDA-approved IGRA (QuantiFERON-TB Gold, QuantiFERON-Plus, and T-SPOT.*TB*). Evidence suggests that TST and IGRAs have comparable sensitivity in immune-competent adults.[50]

II. Among children <15 years old with HIV, does a negative TST or IGRA reliably exclude TB infection or disease?

Neither TST nor IGRA results can definitively exclude LTBI or TB disease **(strong, moderate).**

A negative result by either TST or IGRA does not exclude *M. tuberculosis* infection or TB disease, especially in the context of HIV infection.[23,53] AAP reports that 10% to 40% of children with TB disease who are immunocompetent do not react to a TST; TST reactivity has been shown to be even lower among those with HIV, particularly in the context of low CD4 counts and severe malnutrition.[48] IGRAs and TSTs have similar sensitivities; however, because IGRAs can distinguish between BCG and *M. tuberculosis*, they have higher specificity in many clinical settings.[23] Clinicians should screen for possible exposure to TB disease through a detailed history and for signs of TB disease through a physical exam. Documentation of exposure to an infectious source of TB disease should prompt further diagnostic investigation and, regardless of TST or IGRA result, may prompt a decision to treat for TB infection or TB disease.

Treatment

Treatment for Latent TB Infection

III. Among children <15 years old with HIV, does LTBI treatment result in fewer cases of TB disease, compared to no treatment?

LTBI treatment is highly effective for preventing TB disease. Therefore, after TB disease has been excluded, children with HIV should receive treatment for LTBI as soon as possible after a positive TST or IGRA result and presumptive LTBI treatment after exposure to infectious TB (regardless of whether the child has a negative TST or IGRA result or was previously treated for TB) **(strong, high).**[23,46]

Young children and children with HIV who acquire TB have a high rate of progression to active disease. Studies have demonstrated that treatment of TB infection with isoniazid greatly diminishes the likelihood of progression to TB disease[66,70,71,136]; on a population level, screening for and treatment of LTBI should result in fewer TB cases over time.[66] Although isoniazid has been shown to prevent TB disease among those with known TB exposure or TB infection, evidence does not support its use for primary prevention in infants with low risk of TB exposure, such as in low incidence settings like the United States. One randomized controlled trial evaluated the use of isoniazid for **primary** prevention of TB infection and disease in infants with and without HIV who had no known TB exposure and showed no difference in TB incidence, infection, or death.[26]

IV. Among children <15 years old with HIV, does a 12-dose combination of once-weekly isoniazid and rifapentine in place of 9 months of daily isoniazid result in comparable outcomes for TB prevention?

Clinical trials have demonstrated that LTBI treatment with a 12-dose combination of once-weekly isoniazid and rifapentine has similar efficacy to 9 months of daily isoniazid for preventing TB disease; in practice, treatment adherence with the 12-dose regimen might be higher resulting in higher real-world effectiveness. Therefore, the 12-dose regimen of once-weekly isoniazid and rifapentine regimen for treatment of LTBI can be used in adults and children ≥2 years old with HIV who are receiving ART regimens with acceptable drug–drug interactions with rifapentine **(strong, moderate).**

A 12-dose combination regimen of once-weekly isoniazid and rifapentine appears to be as safe and effective as other regimens in preventing TB disease, and the completion rate is greater than for regimens of longer duration.[46,71,73,75] There are no commercially available dispersible formulations of rifapentine and dosing has not yet been determined for children <2 years old. The experience in children with HIV is limited and drug interactions between weekly rifapentine and many antiretroviral drugs, including integrase strand transfer inhibitors (INSTIs), have not yet been determined in children. For children ≥2 years old, when drug–drug interactions allow, the 12-dose combination regimen of once-weekly isoniazid and rifapentine is the preferred regimen. Daily isoniazid for 6 to 9 months can be used when drug interactions preclude the use of the preferred rifamycin-based preventive treatment regimens.

V. Among children <15 years old with HIV and exposure to a person with drug-resistant TB, would 9 months of daily isoniazid compared to other regimens result in fewer cases of TB disease?

Some studies have demonstrated successful prevention of presumed drug-resistant TB through treatment of LTBI with regimens informed by the drug-susceptibility results of the presumed source case. After exposure to TB caused by isoniazid mono-resistant organisms, preventive therapy with 4 months of daily rifampin is recommended for children with HIV. Adjustment of antiretroviral therapy to consider drug–drug interactions between rifampin and ART might be necessary **(expert opinion).** After exposure to TB caused by organisms with other drug resistance patterns (e.g., MDR), expert consultation should be obtained to determine optimal LTBI treatment regimens. DST results for the TB index patient are important considerations in the management of children exposed to drug-resistant TB **(expert opinion).**[137]

The optimal prophylaxis regimen for children with HIV and exposure to or TB infection from a person with MDR-TB or XDR-TB has not been defined.[23,66,137] Treatment for that child's infection should be tailored in consultation with an expert. A guiding principle is to use therapy to which the source case demonstrated susceptibility, at a dose that is safe and effective in the child. There is evidence that rifampin is safe and effective at preventing TB disease in adults and children, and this would be the preferred agent if the source case was known to be resistant to isoniazid but susceptible to rifampin.[23,66,81,82,138,139] Rifampin, however, has drug–drug interactions with several antiretroviral drugs used to treat HIV infection, and dose adjustment may be needed.

Treatment of TB Disease

VI. Among children <15 years old with HIV who are diagnosed with TB while not yet on ART, does early initiation of ART (2–8 weeks) compared to delayed ART initiation result in improved treatment outcomes?

Children with HIV who are diagnosed with non-central nervous system (CNS) TB disease and who are not yet receiving ART should be evaluated for early ART initiation, preferably within 2 to 8 weeks of starting TB therapy **(strong, moderate).**

Children with HIV who are diagnosed with CNS TB disease, including TB meningitis, should be evaluated for ART initiation within 2 to 8 weeks **(expert opinion).**

In adults with HIV who are not on ART at the time of TB diagnosis, early initiation of ART reduces mortality, especially among those with CD4 counts below 50 cell/mm^3, but increases risk of IRIS.[92,94] Data for children, although limited, support early ART initiation, especially in those with severe immune suppression,[66,93] and WHO recommends that all children with HIV and TB disease who are not already receiving ART should begin ART within 8 weeks of starting TB treatment.[94,140] The recommended timing of ART initiation with TB involving the CNS remains more uncertain because of the potentially devastating effects of CNS IRIS.[96,97]

VII. Among children <15 years old with HIV diagnosed with TB disease, does therapy administered by directly observed therapy (DOT) or administered by self or family members result in improved medication adherence?

Daily DOT (by a trained health care worker) should be used to maximize adherence and minimize treatment failures, relapse rates, and emergence of acquired drug resistance **(strong, moderate).**

To effectively treat TB disease and diminish the risk of acquired drug resistance, it is important that patients adhere to proven treatment regimens, which generally require at least 6 months of treatment with multiple drugs. Sustained adherence is difficult for anyone, and this may be particularly true for

young children. Some recent analyses have demonstrated that self-administered therapy compares favorably with DOT, but these studies did not include many children or adolescents, who represent a markedly different patient cohort for this intervention. The most relevant study for the United States was conducted in 1998 and showed that DOT was clearly associated with better treatment completion.[83] For this reason, DOT by a trained health care worker is recommended to maximize adherence.[23]

VIII. Among children <15 years old with HIV who are diagnosed with intrathoracic TB disease (e.g., pulmonary or intrathoracic lymph nodes), does treatment with a four-drug regimen during the 2-month intensive phase compared to a three-drug regimen during the 2-month intensive phase result in better treatment outcomes? Among children <15 years old with HIV who are diagnosed with TB disease and treated with a four-drug regimen during the 2-month intensive phase, does a 7-month continuation phase using isoniazid and rifampin or a 4-month continuation phase using isoniazid and rifampin result in better treatment outcomes?

In children with HIV, the recommended treatment for drug-susceptible TB is a four-drug regimen consisting of isoniazid, rifampin, pyrazinamide, and ethambutol given daily during the 2-month intensive phase, followed by a ≥4-month continuation phase using only daily isoniazid with daily rifampin **(strong, moderate)** and adjusting of ART as required for drug–drug interactions **(expert opinion).**

For children with well-controlled HIV, minimal TB disease, and confirmed drug-susceptible TB, some experts would consider a standard three-drug regimen (isoniazid, rifampin, pyrazinamide) during the 2-month intensive phase followed by a ≥4-month continuation phase using only isoniazid and rifampin **(expert opinion).**[23,45]

WHO recommends a standard treatment regimen for drug-susceptible TB disease in children with HIV, consisting of four-drug therapy for a 2-month intensive phase followed by a 4-month continuation phase of isoniazid and rifampin **(expert opinion).**[23,45,85] This guidance is supported by AAP. Alternative regimens have not been as well studied although some experts would consider a three-drug regimen (isoniazid, rifampin, pyrazinamide) during the 2-month intensive phase followed by a continuation phase using isoniazid and rifampin for 4 months to be appropriate for children with well-controlled HIV, minimal TB disease, and confirmed drug-susceptible TB **(expert opinion).**[23,85]

IX. Among children <15 years old with HIV who are taking isoniazid or cycloserine, should adjunctive pyridoxine versus no adjunctive pyridoxine supplementation be recommended routinely to improve clinical outcomes?

Pyridoxine supplementation (1–2 mg/kg body weight/day, max 50 mg/day) is recommended for all children with HIV who are taking isoniazid or cycloserine **(expert opinion).**[23]

Treatment with isoniazid or cycloserine can result in relative pyridoxine deficiency and neurologic adverse events. For decades, prophylaxis with pyridoxine has been recommended for patients at risk of isoniazid neuropathy. Recent evidence supports the idea that children with nutritional deficiencies and those with HIV are at particular risk.[117,118] Consequently, adjunctive treatment with pyridoxine is recommended in these groups to reduce the likelihood of neurologic adverse events.[23]

X. Among children <15 years old with HIV in whom TB disease is diagnosed, what evidence-based ART regimens result in better treatment outcomes?

Among children weighing >20 kg, dolutegravir (DTG)-based ART (dose increased to 50 mg twice daily) is preferred during TB treatment because DTG-based regimens are associated with better HIV treatment outcomes in absence of TB **(strong, moderate).** Twice-daily DTG is safe and has favorable pharmacokinetic parameters in children >20 kg when co-administered with rifampin **(strong, moderate).**

Children <20 kg receiving raltegravir (RAL)-based ART who begin TB treatment should increase RAL dose to 12 mg/kg twice daily for the duration of TB treatment. Among children <20 kg who are receiving lopinavir (LPV)/ritonavir (LPV/r)-based ART, LPV should be super-boosted to achieve a 1:1 ratio between LPV and ritonavir (RTV) **(strong, moderate).** Alternately, children <20 kg can receive an efavirenz (EFV)-based regimen **(expert opinion).**

If the EFV-based regimen is used, CYP2B6-516 genotype-directed EFV dosing is recommended. Simultaneous treatment of TB disease and HIV infection is difficult, because of known drug interactions in the recommended regimens. Rifampin increases elimination of INSTIs through UDP-glucuronosyltransferase upregulation and therefore dose adjustments of both raltegravir and dolutegravir are needed during TB/HIV co-treatment.[141] Rifampin potently induces the CYP3A enzyme system, which increases metabolism of protease inhibitors and nevirapine; co-administration of rifampin requires dose adjustment of these antiretroviral drugs as well. Interactions between rifampin and efavirenz are less significant, allowing achievable serum levels of EFV without dose adjustment.[98]

DTG is one of the preferred first-line ART options for children with HIV $\geq$4 weeks or $\geq$3 kg, given its superior efficacy compared to PI- or non-nucleoside-based ART in adults.[142,143] Preliminary results from the ODYSSEY trial in children aged 6 to 18 years receiving TB treatment with rifampin demonstrated that twice-daily DTG dosing was safe and achieved adequate dolutegravir pharmacokinetic targets.[80] Therefore, in children >20 kg, DTG-based ART is the preferred regimen in the context of TB/HIV co-treatment, with 50 mg DTG given twice daily throughout TB treatment. While the FDA has approved twice-daily DTG during TB treatment for children as young as 4 weeks old and ≥3 kg, additional evidence on safety and PK parameters in children <20 kg is needed to inform formal U.S. Department of Health and Human Services recommendations.[99] There are insufficient pharmacokinetic data for the use of bictegravir during TB treatment for children with HIV.

For children <20 kg who are receiving a RAL-based regimen, RAL dosing should be increased to 12 mg/kg twice daily for the duration of TB treatment. Safety and adequate PK targets in children receiving RAL 12 mg/kg twice-daily dosing with concurrent rifampin administration have been demonstrated among children as young as 4 weeks of age.[81,100] For children <20 kg receiving a LPV/r-based regimen, the dose of RTV should be increased to achieve a 1:1 ratio between LPV and RTV. Non-inferiority of super-boosted LPV/r PK targets during rifampin treatment was demonstrated in a clinical trial of South African children between 3 to 15 kg receiving rifampin for TB treatment.[101]

Efavirenz maintains serum levels better than nevirapine when co-administered with anti-TB therapy; as such, regimens that contain efavirenz are preferred compared to nevirapine-based regimens in the setting of TB/HIV.[144,145]

There have been no head-to-head comparisons of ART on treatment outcomes during TB/HIV co-treatment. A high proportion of young children (11 of 12) achieved virologic success (>1 log

decrease or viral load <400 copies/mL) in a trial of super-boosted LPV/r during TB co-treatment, but few children (2 of 12) achieved a more stringent definition of viral suppression (<50 copies/mL).[80] Lower rates of virologic suppression during the TB/HIV co-treatment period were observed in a trial of children on EFV-based therapy.[146] For this reason, in the United States, therapeutic drug monitoring should be used to guide dose adjustments to antiretroviral treatment and close virologic monitoring during TB/HIV co-treatment is recommended; consultation with an expert experienced in treatment of TB and HIV in children is also recommended.[23,147]

XI. Among children <15 years old with HIV who are diagnosed with extrapulmonary TB disease, does TB treatment for 12 months compared to standard 9-month treatment result in better treatment outcomes?

For children with extrapulmonary disease caused by drug-susceptible TB involving the bones or joints, CNS, or disseminated/miliary disease, the recommended duration of treatment is ≥12 months **(expert opinion).**[23]

Extrapulmonary TB disease, especially involving the CNS or bones and joints, can be associated with higher morbidity or mortality. Additionally, extrapulmonary TB of the CNS or bones and joints can be more difficult to treat because drug penetration into infected tissues or spaces is often reduced. As a consequence, the treatment should be extended to 12 months (a 2-month intensive phase, followed by a 10-month continuation phase) **(expert opinion).**[23,85] A recent prospective cohort demonstrated good results treating meningeal TB with conventional regimens (substituting ethionamide for ethambutol)[90]; but this study did not have a comparison to longer treatment, and the results have not been validated with repeat investigation. Given the potentially dire consequences of insufficiently treated disease, the recommendation for 12 months of treatment remains unchanged.

XII. Among children <15 years old with HIV who are diagnosed with TB meningitis (TBM), does the standard four-drug TB regimen compared to a regimen using ethionamide result in better treatment outcomes?

For TBM, while DST results are pending, ethionamide can replace ethambutol (or an injectable aminoglycoside) as the fourth drug because of its superior cerebrospinal fluid penetration **(expert opinion).**[23]

For TBM, some experts recommend adding a fluoroquinolone to the treatment regimen pending the results of DST **(expert opinion).**

TBM is a potentially devastating disease, associated with high morbidity and mortality. It is critical that the most effective agents are used during treatment. This requires drugs that are both effective against the organism and able to penetrate the blood–brain barrier. Ethionamide has been shown to cross the blood–brain barrier in higher concentrations than ethambutol and is recommended for the treatment of TBM in adults and children.[23,88]

XIII. Among children <15 years old with HIV who are diagnosed with TBM, pericardial or pleural effusion, airway compression, or severe IRIS, does adjunctive treatment with corticosteroids result in improved clinical outcomes?

Adjunctive corticosteroids (with concurrent treatment for TB disease) should be considered for children with TBM **(strong, moderate).** Adjunctive corticosteroids should also be considered in the context of severe IRIS, airway compression, pleural effusion, or pericarditis **(expert opinion).**

In children with certain forms of extrapulmonary TB disease, particularly TBM and TB-related pleural or pericardial effusions, the inflammatory response to disease can cause severe deleterious clinical consequences. Corticosteroids reduce the exuberance of the inflammatory response but may also diminish the immune response to disease. Evidence strongly suggests that adjunctive treatment with corticosteroids reduces mortality and disabling neurologic deficits in patients with TBM[112,113]; one systematic review has suggested that corticosteroids may reduce mortality in any form of TB,[148] but additional evidence is needed. While a mortality benefit has not been clearly demonstrated for other forms of TB disease, adjunctive corticosteroids have been shown to reduce constrictive pericarditis in patients with TB pericarditis and are associated with more rapid symptom resolution in TB pleural effusion.[114,115,127,149] There are limited data on the use of corticosteroids in children, and these recommendations are largely based on studies involving adults.

XIV. Among children <15 years old who are diagnosed with MDR-TB disease, does the use of individualized treatment regimens based on DST results compared to a standardized regimen result in better treatment outcomes?

Expert consultation should be obtained for clinical management of suspected and laboratory-confirmed MDR-TB (i.e., resistance to both isoniazid and rifampin) **(expert opinion).** Whenever possible, treatment regimens for MDR-TB should be individualized **(expert opinion);** considerations include phenotypic and molecular DST results for the child or the presumed source case (when results of DST are not available for the child) **(strong, moderate).**

For treatment of drug-resistant TB, a minimum of five drugs to which the isolate is susceptible should be administered, including two or more bactericidal drugs **(strong, moderate).** Fluoroquinolones can be used to treat MDR-TB in children **(strong, moderate).**

For treatment of TB that is resistant only to isoniazid, isoniazid should be discontinued, and the patient should be treated with 6 to 9 months of a rifampin-containing regimen (e.g., rifampin, pyrazinamide, ethambutol, and levofloxacin or moxifloxacin) **(expert opinion).**[137]

Treatment of drug-resistant TB disease can be complex, and consultation with an expert in drug-resistant TB is important. When the disease-causing organism is resistant to both isoniazid and rifampin, the two most active agents against *M. tuberculosis*, treatment requires multiple alternative agents, which often have compounding toxicities and are less effective, requiring prolonged therapy for up to 24 months. Using agents that have been shown by DST to have efficacy is clinically meaningful and associated with better treatment success allowing clinicians to tailor regimens appropriately.[102,104,105,137] For these reasons, clinicians are advised to treat drug-resistant TB based on DST results for the infecting organism or the DST results from the organism of the presumed source case.[23,137] In all cases of MDR-TB in children with HIV, at least five drugs to which the infecting organism is known or presumed to be susceptible should be used, including two or more bactericidal drugs.[23,137] For children with a TB strain resistant to only isoniazid, isoniazid should be discontinued, and experts recommend the use of rifampin, pyrazinamide, and ethambutol for six months or up to nine months; a late-generation fluoroquinolone should also be added to the treatment regimen.[137] Late-generation fluoroquinolones are key components of current MDR-TB treatment approaches, and in almost all cases should be included as part of a treatment regimen for MDR-TB, in consultation with a clinical expert.[85]

XV. Among children <15 years old with HIV who are receiving treatment for TB disease, does liver chemistry testing at 2-week intervals during the first 2 months of treatment compared to less frequent monitoring result in better clinical outcomes?

Routine monitoring of liver enzyme is not necessary in children who have no risk factors for hepatotoxicity. For children with additional risk factors (such as concomitant ART), routine monitoring of liver enzymes should be performed before initiation and 2, 4, and 8 weeks after starting TB treatment (the same monitoring schedule as for ART initiated while a patient is receiving treatment for TB) **(expert opinion).** Beyond 2 months, routine testing every 2 to 3 months is advisable for all children receiving ART, or more frequently if clinically indicated **(expert opinion).**

Mild elevations in serum transaminase concentration (i.e., less than 5 times the upper limit of normal) do not require drug discontinuation in children who are asymptomatic and in whom other findings (including bilirubin) are normal **(expert opinion).**

While the overall incidence of hepatotoxicity is low, it is the most common serious adverse effect during treatment of TB disease. This toxicity includes subclinical hepatic enzyme elevation, which usually resolves spontaneously during continuation of treatment, and clinical hepatitis that usually resolves when the drug is discontinued. Hepatotoxicity rarely progresses to hepatic failure, but the likelihood increases when isoniazid is continued despite hepatitis symptoms (jaundice; tender, enlarged liver). Hepatotoxicity is even less frequent in children than in adults,[77,150] but no age group is risk free. The rate of hepatotoxicity may be higher in children who take multiple hepatotoxic medications. There is a lack of data comparing the clinical consequences of routine versus clinically directed measurement of liver enzymes, and no studies which conclusively demonstrate that routine measurements reduce the incidence of liver disease in children on antituberculosis therapy. AAP recommends routine liver transaminase monitoring for children receiving ART.[23,85] Mild elevations in serum transaminases do not require drug discontinuation.[85]

XVI. Among children <15 years old who are diagnosed with TB disease, does routine HIV testing compared to HIV testing and counseling upon request identify more cases of HIV?

All children in whom TB is diagnosed should be tested for HIV infection **(expert opinion).**

WHO and CDC both recommend routine HIV testing for all people in whom TB disease is diagnosed given the increased risk of disease among those who are immunocompromised.[45,85] WHO explicitly recommends HIV testing for children as the diagnosis of HIV has important implications for the management of both TB and HIV. Excluding HIV infection also has implications for confirming the clinical diagnosis of TB.[85]

Dosing Recommendations for Preventing and Treating TB in Children with HIV

Indication	First Choice	Alternative	Comments/Special Issues
Treatment of LTBI *Also Known as TB Preventive Therapy*	Source Case Drug Susceptible *Age 2 to <12 years* • 12 weekly doses of isoniazid (25 mg/kg for children aged 2–12 years) and rifapentine (10–14.0 kg: 300 mg; 14.1–25.0 kg: 450 mg; 25.1–32.0 kg: 600 mg; 32.1–49.9 kg: 750 mg; ≥50.0 kg: 900 mg maximum) *Age ≥12 years* • 12 doses of weekly isoniazid (15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum) and rifapentine (10–14.0 kg: 300 mg; 14.1–25.0 kg: 450 mg; 25.1–32.0 kg: 600 mg; 32.1–49.9 kg: 750 mg; ≥50.0 kg: 900 mg maximum) Source Case Drug Resistant • For isoniazid-resistant source cases, daily rifampin 15–20 mg/kg (maximum 600 mg/day) for 4 months is recommended. • For isoniazid- and rifampin-resistant (i.e., MDR-TB) source cases, consult a TB expert and local public health authorities.	Rifampin 15–20 mg/kg (max 600 mg) daily for 4 months duration *or* Isoniazid 10–15 mg/kg (max 300 mg) daily and rifampin 15–20 mg/kg (maximum 600 mg/day) for 3 months duration *or* Isoniazid 10–15 mg/kg (max 300 mg) daily for 6–9 months	Indications • Positive TST (TST ≥5 mm in children with HIV) or IGRA without previous TB treatment • Close contact with any infectious TB case (repeated exposures warrant repeated post-exposure prophylaxis) Considerations • TB disease must be excluded before starting treatment for latent TB infection. • Drug-drug interactions with ART should be considered for all rifamycin-containing alternatives. Criteria for Discontinuing Prophylaxis • Only with documented severe adverse event, such as hepatotoxicity, hypersensitivity, or other adverse drug reactions, which are rare in children and adolescents. 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 children with HIV; and pregnant adolescents and adults.

Dosing Recommendations for Preventing and Treating TB in Children with HIV

Indication	First Choice	Alternative	Comments/Special Issues
Treatment of TB Disease	Intrathoracic Disease *Drug-Susceptible TB* • Intensive Phase (2 Months) o Isoniazid 10–15 mg/kg body weight (maximum 300 mg/day) by mouth once daily, plus o Rifampin 15–20 mg/kg body weight[a] (maximum 600 mg/day) by mouth once daily, plus o Pyrazinamide 30–40 mg/kg body weight (maximum 2 g/day) by mouth once daily, plus o Ethambutol 15–25 mg/kg body weight (maximum 1 g/day) by mouth once daily o In children with minimal disease with fully drug-susceptible TB, some experts recommend a three-drug intensive phase regimen excluding ethambutol. • Continuation Phase (4 Months) o Isoniazid 10–15 mg/kg body weight (maximum 300 mg/day) by mouth once daily, plus o Rifampin 15–20 mg/kg body weight[a] (maximum 600 mg/day) by mouth once daily Extrathoracic Disease Note: Depends on disease entity • Lymph node TB—treat as minimal intrathoracic disease • Bone or joint disease—consider extending the continuation phase to 10 months (for total duration of therapy of 12 months).	Alternative for Rifampin • Rifabutin 10–20 mg/kg body weight (maximum 300 mg/day) by mouth once daily (same dose if three times a week) • Discuss with an expert. Alternative Continuation Phase with Three Times Weekly Dosing *If Good Adherence and Treatment Response (4 months)* • Isoniazid 20–30 mg/kg body weight (maximum 900 mg/day) by mouth three times per week, plus • Rifampin 15–20 mg/kg body weight (maximum 600 mg/day) three times per week • In children with minimal disease with fully drug-susceptible TB, some experts recommend a continuation phase of 4 months (total duration of therapy of 6 months).	Treatment for TB disease should always be provided by DOT. If ART-naive, start TB therapy immediately and initiate ART within 2 to 8 weeks. If already on ART, review regimen to minimize potential toxicities and drug interactions; start TB treatment immediately. Potential drug toxicity and interactions should be reviewed at every visit. Drug interactions with ART should be considered for all rifamycin-containing alternatives. Adjunctive Treatment • Co-trimoxazole prophylaxis • Pyridoxine 1–2 mg/kg body weight/day (maximum 25–50 mg/day) with isoniazid or cycloserine/terizidone, 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 children with HIV; and pregnant adolescents and people. • Corticosteroids (2 mg/kg body weight per day of prednisone [maximum 60 mg/day] or its equivalent for 4–6 weeks followed by tapering) with TB meningitis; may be considered with pleural effusions, pericarditis, severe airway compression, or severe IRIS.

Dosing Recommendations for Preventing and Treating TB in Children with HIV

Indication	First Choice	Alternative	Comments/Special Issues
	TB Meningitis • As an alternative to ethambutol, 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 two doses until well tolerated. • Many experts recommend rifampin doses of 20–30 mg/kg daily for treatment of TB meningitis. See the AAP Red Book and WHO Operational Handbook on Tuberculosis for more information. • Consider extending the continuation phase to 10 months (for a total duration of therapy of 12 months). • Discuss with an expert. Drug-Resistant TB • Therapy should be based on the resistance pattern of the child (or of the source case where the child's isolate is not available); consult an expert.		Second-Line Drug Doses • Consult with an expert as dosing guidelines continue to evolve with emerging data.

[a] Some experts recommend using a daily rifampin dose of 20–30 mg/kg/day for infants and toddlers.

Key: AAP = American Academy of Pediatrics; ART = antiretroviral therapy; ATS = American Thoracic Society; CDC = Centers for Disease Control and Prevention; DOT = directly observed therapy; ERS = European Respiratory Society; IDSA = Infectious Diseases Society of America; IGRA = interferon-gamma release assay; IM = intramuscular; IRIS = immune reconstitution inflammatory syndrome; LTBI = latent TB infection; MDR-TB = multidrug-resistant TB; TB = tuberculosis; TST = tuberculin skin test; WHO = World Health Organization

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