Treatment of Latent Tuberculosis Infection in Children

Andrea T. Cruz,1,2,3 Amina Ahmed,5 Anna M. Mandalakas,1,4 and Jeffrey R. Starke1,2

1The Tuberculosis Initiative of Texas Children’s Hospital, and Sections of 2Infectious Diseases, 3Emergency Medicine and 4Retrovirology, Department of Pediatrics, Baylor College of Medicine, Houston, Texas; and 5Division of Infectious Diseases, Department of Pediatrics, Carolinas Medical Center, Charlotte, North Carolina

Corresponding Author: Andrea T. Cruz, MD, MPH, 6621 Fannin St, Ste A2210, Houston, TX 77030. E-mail: acruz@bcm.edu.

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Treatment of latent tuberculosis infection (LTBI) is an effective way of preventing future cases of tuberculosis disease. We review pediatric and adult studies of LTBI treatment (isoniazid and rifampin monotherapy, isoniazid plus rifapentine, and rifampin plus pyrazinamide). Based upon this review and our pediatric experience, we can offer recommendations for routine (isoniazid) and alternative courses of therapy.

Key words. Latent Tuberculosis Infection; Directly Observed Preventive Therapy; Adherence

Treatment of latent tuberculosis infection (LTBI) is the most effective strategy to prevent future cases of disease [1]. Most cases of childhood tuberculosis (TB) disease in low-prevalence countries are preventable by screening for risk factors, testing for LTBI, and offering therapy [2, 3]. Although LTBI therapy has been available and emphasized in industrialized nations, its use has been limited in most resource-limited settings.

Regimens for LTBI have been evaluated and used for over 6 decades. Over the last decade, however, concerns about low completion rates [4], costs [5], and increasing rates of drug resistance [6] have prompted research on shorter-course LTBI regimens and the use of multidrug regimens. In this review, we discuss available treatment regimens for children with LTBI, as documented by either the tuberculin skin test (TST) or an interferon gamma release assay (IGRA). For each regimen, data for safety and tolerability, efficacy, adherence, and scenarios in which a clinician might consider using the regimen will be discussed. English-language articles on the treatment of LTBI in children were included: because many of the studies regarding non-isoniazid (INH)–based regimens were performed in adults and minimal or no pediatric data are available in some instances, studies conducted in adults were included as well. The method of LTBI diagnosis, preventive therapy in the human immunodeficiency virus (HIV)–infected child, and treatment of children with LTBI due to drug-resistant Mycobacterium tuberculosis are outside the scope of this review.

REGIMENS

Several LTBI regimens are available (Table 1) [7–9]. Selection of a particular regimen should be based on drug-susceptibility data from the source of infection (if available), interaction with other medications the child is receiving, drug availability, the time frame the family has for completing therapy, costs, and adherence considerations. Advantages to combination therapy include shorter treatment duration and broadened coverage in the event of single-drug resistance.

Isoniazid, 6 and 9 Months

There have been 29 randomized (17 in HIV-uninfected persons and 12 in HIV-infected persons; 2 of the latter included children) [10, 11] trials of INH for LTBI.

Efficacy or Effectiveness. Since the 1950s, researchers conducted numerous studies to assess the efficacy of INH treatment regimens for LTBI. In 1958, the US Public Health Service (USPHS) conducted a seminal randomized trial in Alaskan boarding school children aged 5–20 years to compare the efficacy of 1.25 versus 5 mg/kg INH given daily or 5 times weekly for 6 months [12]. During the 10-year follow-up period, 1.9% (10 of 513) of participants who received the higher dose progressed to TB.
Table 1: Available Treatment Regimens for Latent Tuberculosis Infection in Children

<table>
<thead>
<tr>
<th>Regimen (months)</th>
<th>Dose (mg/kg per day)</th>
<th>Interval</th>
<th>Completion Rates</th>
<th>% AEs</th>
<th>% Hepatotoxicity</th>
<th>Estimated Efficacy</th>
<th>References (adult and pediatric)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9INH* or 6INH</td>
<td>10–15 (max: 300 mg)</td>
<td>Daily</td>
<td>20%–93%</td>
<td>1%–24%</td>
<td>1.2%–1.6%</td>
<td>9INH confers 20%–30% increased efficacy over 6INH</td>
<td>[12–19, 20–24, 43, 57]</td>
</tr>
<tr>
<td></td>
<td>20–30 (max: 900 mg)</td>
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</tr>
<tr>
<td>4RIF</td>
<td>10–20 (max: 600 mg)</td>
<td>Twice weekly†</td>
<td>72%–96%</td>
<td>11%–32%</td>
<td>0%–2%</td>
<td>Equivalent to 6–12 INH</td>
<td>[32–38, 57]</td>
</tr>
<tr>
<td>3INH/RIF</td>
<td>INH: 10–15 (max: 300 mg)</td>
<td>Daily</td>
<td>63%–97%</td>
<td>2%–64%</td>
<td>2%–17%</td>
<td>Equivalent to 6–12 INH</td>
<td>[32, 43, 44, 47, 51–54, 57]</td>
</tr>
<tr>
<td></td>
<td>RIF: 10–15 (max: 600 mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3INH/RFP§</td>
<td>INH: 900 mg</td>
<td>Weekly†</td>
<td>82%</td>
<td>4.9%</td>
<td>0.4%</td>
<td>Equivalent to 9 INH</td>
<td>[8, 9]</td>
</tr>
<tr>
<td></td>
<td>RFP: 900 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2RIF/PZA³</td>
<td>RIF: 10–15 (max: 600 mg)</td>
<td>Daily</td>
<td>61%–70%</td>
<td>20%–29%</td>
<td>6%–8%</td>
<td>Equivalent to 6–12 INH, but increased rates of AEs and/or hepatotoxicity</td>
<td>[1, 63, 64, 66, 72]</td>
</tr>
<tr>
<td></td>
<td>PZA: 30–40 (max: 2–4 g)</td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

Abbreviations: AEs, adverse events; INH, isoniazid; max, maximum; PZA, pyrazinamide; RIF, rifampin; RFP, rifapentine.

*Nine months of INH is the preferred duration in the United States.
†All intermittent therapy regimens should be administered via directly observed preventive therapy to ensure adherence [7].
‡Most adverse events in children (Table 2) involve nonspecific gastrointestinal complaints without associated transaminases or other evidence of hepatotoxicity (defined as AST/ALT 2–3 times the upper limit of normal (ULN) with abdominal complaints or > 5 times ULN even if asymptomatic) [1].
§Only recommended for children ≥12 years old [8, 9].
¶This regimen is only recommended for persons who are treated for TB disease and are later deemed to have latent TB infection.

The protective efficacy of INH should be substantially reduced in efficacy for patients treated for 12 versus 6 months. This suggests that INH should be administered for at least 9 months to achieve maximum efficacy. The International Union Against Tuberculosis and Lung Disease has published guidelines recommending 6 months of INH for the prevention of TB disease in household contacts of index cases. These guidelines are based on a meta-analysis of randomized controlled trials showing that 6 months of INH is as effective as 9 months in preventing TB disease. The efficacy of 6 months of INH is approximately 95%, whereas the efficacy of 9 months is approximately 98%. Therefore, for most indications, 6 months of INH is sufficient to achieve a high level of protection against TB disease.

Secondary analysis of INH trials including adults and children has shown that INH is highly effective in preventing TB disease. INH is generally well tolerated, and the most common side effects are gastrointestinal complaints. Although INH can cause hepatitis, this is uncommon and generally reversible with discontinuation of the drug. INH is also effective in preventing disseminated TB disease among patients with HIV infection. However, INH is not recommended for the treatment of active TB disease due to the risk of INH-induced hepatitis.

The use of INH in the prevention of TB disease has several advantages. INH is a safe and effective drug with a well-characterized pharmacokinetic profile. INH is also inexpensive and widely available. Therefore, INH is a preferred prophylactic agent for the prevention of TB disease in high-risk populations.

However, the use of INH for prophylaxis also has several challenges. INH has a narrow therapeutic index and can cause significant toxicity at high doses. INH is also associated with a high rate of drug resistance, particularly in settings with high prevalence of TB disease. INH prophylaxis is also associated with reduced growth and development in children, particularly those receiving long-term INH prophylaxis.

Despite these challenges, INH remains the prophylactic agent of choice for the prevention of TB disease. The combination of INH with other drugs, such as pyrazinamide and rifampin, can improve the efficacy and safety of INH prophylaxis. INH prophylaxis should be accompanied by close monitoring for signs of toxicity and drug resistance.

Pediatric Latent TB Infection Therapy
higher in young children because they have higher rates of disease progression without therapy.

**Adherence and Adverse Effects.** Despite long-standing recommendations for use of INH preventive therapy in child contacts, children’s adherence to treatment is consistently poor in high- and low-burden settings [7, 20–24]. At the Tuberculosis Clinic at Texas Children’s Hospital, despite counseling the family and child on the importance of LTBI therapy, recommending pharmacies dispensing inexpensively priced medications, and scheduling close follow-up, the completion rate for self-supervised therapy with 9 months of INH was only 49% [24]. Adherence rates in children are not solely associated with adverse events. Extensive evidence suggests that INH is well tolerated by children and adolescents [16, 20, 25–27]. One large meta-analysis showed that the rates of jaundice and mostly mild elevation in hepatic transaminases were 0.06% and 8%, respectively [28]. Given the low frequency of hepatotoxicity, children should be monitored for symptoms of hepatotoxicity, rather than by routine laboratory evaluation. Parents and other care givers must be educated regarding potential side-effects (Table 2) [7, 29]. Any child in whom hepatotoxicity is suspected should immediately stop taking INH until physician evaluation and laboratory analyses can occur. Children can be monitored via history and clinical examination at monthly follow-up visits.

**Recommendations.** Current US and international INH guidelines recommend similar daily or twice-weekly doses but variable duration of therapy (Table 1), with US guidelines recommending a 9-month duration and World Health Organization recommending 6-month regimens [30]. The level of protection offered by a 9-month INH regimen is 20%–30% higher than that afforded by a 6-month course [13]. Given the low rates of completion of LTBI therapy and the modest incremental benefit of 9 months versus 6 months of INH, it would not be unreasonable to accept 6 months of therapy rather than 9 months if adherence becomes an issue late in therapy. An alternative to daily therapy is twice-weekly therapy administered by direct observation, which has been shown to increase adherence when compared with self-administered therapy (96% vs 49% completion) [24], and is safe (0.4% had elevated hepatic transaminases; none had evidence of synthetic hepatic dysfunction) and effective (only 1 child who completed treatment in the cohort of 448 children with LTBI progressed to disease) [31].

**Table 2. Most Common Adverse Events Seen in Children Receiving Antituberculosis Medications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adverse Event</th>
<th>Details</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Hepatotoxicity</td>
<td>AST/ALT 2–3x ULN and symptoms or &gt;5x ULN even if asymptomatic; can see hyperbilirubinemia, and rarely coagulopathy and hepatic failure. Rate of INH-associated hepatotoxicity is 0%–6.3% if given as monotherapy and 0.7%–17% if given in combination with Rif.</td>
<td>[7, 29, 34, 44]</td>
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<tr>
<td></td>
<td>Peripheral neuropathy</td>
<td>More common in adolescents; preventable with pyridoxine (B6). Administration of B6 should be considered for exclusively breast-fed infants, HIV-infected patients, pregnant women, adolescents, and any patient with malabsorption.</td>
<td>[7, 29]</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal upset</td>
<td>Very common, especially if INH is given while the child is NPO. Many formulations of the suspension are sorbitol-based and can cause osmotic diarrhea. Consideration should be given to using crushed tablets in lieu of the suspension for even young infants if they are taking cereals or purred foods.</td>
<td>[7, 29]</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>Both urticarial and non-urticarial rashes seen in approximately 2% of HCWs and in patients receiving INH as part of multidrug therapy for disease.</td>
<td>[7, 29, 78, 79]</td>
</tr>
<tr>
<td>Rifampin, Rifapentine</td>
<td>Gastrointestinal upset</td>
<td>Very common (up to 26% in 1 adolescent study), especially if rifampin is given while the child is NPO.</td>
<td>[36]</td>
</tr>
<tr>
<td></td>
<td>Hepatotoxicity</td>
<td>AST/ALT 2–3x ULN and symptoms or &gt;5x ULN even if asymptomatic; can see hyperbilirubinemia, and rarely coagulopathy and hepatic failure. Rate of rifampin-associated hepatotoxicity is 0%–2% if given as monotherapy and 0.7%–1.2% if given in combination with isoniazid.</td>
<td>[32, 33, 36–38, 44]</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>Estimated to occur in 2% of patients receiving RIF as part of multidrug therapy for disease.</td>
<td>[80]</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>Seen in 3.4% of patients receiving RIF for LTBI monotherapy; no other cell lineages were suppressed, was asymptomatic in almost all cases, and resolved after RIF was stopped.</td>
<td>[82]</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Rash</td>
<td>Estimated to occur in 2% of patients receiving RIF as part of multidrug therapy for disease.</td>
<td>[78, 80]</td>
</tr>
<tr>
<td></td>
<td>Hepatotoxicity</td>
<td>Abdominal pain is seen in 4%–5% of children receiving PZA as part of multidrug therapy for disease, but hepatotoxicity is rare.</td>
<td>[81]</td>
</tr>
<tr>
<td></td>
<td>Joint pain</td>
<td>Serum uric acid increases in more than 90% of children receiving PZA, but remains within the normal range for the majority, and rarely is associated with joint pain or gout.</td>
<td>[81]</td>
</tr>
</tbody>
</table>

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCW, healthcare workers; HIV, human immunodeficiency virus; INH, isoniazid; LTBI, latent tuberculosis infection; NPO, nothing by mouth; RIF, rifampin; ULN, upper limit of normal.

*Gastrointestinal upset includes nausea, vomiting, abdominal pain.*
Rifampin, 4 Months
There have been 3 randomized [32–34] and 8 observational studies of rifampin (RIF) for LTBI [35–42].

**Efficacy and Effectiveness.** There have been 3 RCTs of RIF monotherapy for LTBI; all included only adults. An early study in Chinese adults with silicosis showed 3 months of RIF to be as efficacious as 6 months of INH [32]. The other 2 RCTs compared 4 months of RIF with 9 months of self-administered INH, and researchers found higher adherence rates (78%–91%) for the RIF arm compared with the INH arms (60%–76%). Subsequent studies have been largely observational [35–42]. One adolescent study of RIF prospectively followed 157 high school students who were prescribed 6 months of RIF after exposure to INH-resistant *M tuberculosis*. No cases of active TB were identified during a 2-year study period [36]. A large scale international trial comparing 4 months of RIF with 9 months INH for the treatment of LTBI is now underway with a separate pediatric arm.

**Adherence and Adverse Effects.** In two randomized trials, 4 months of treatment with RIF was compared with 9 months of treatment with INH, and the results indicated significantly better treatment completion with the shorter regimen [33, 34]. A retrospective review of 2149 patients under programmatic conditions found that 72% of those who received 4 months of RIF versus 53% of those who received 9 months of INH completed treatment (*P* < .001), and the treatment regimen was independently associated with treatment completion [37].

Serious adverse events (Table 2) leading to discontinuation of therapy occur significantly less often with 4 months of RIF treatment compared with 9 months of INH treatment [33, 34, 37, 38]. In a large retrospective study, adverse events resulting in permanent discontinuation of medication occurred in 4.6% and 1.9% of adults in the 9 months of INH and 4 months of RIF groups, respectively [37]. The incidence of adverse reactions is not as well delineated in children. In the trial evaluating 6 months of daily RIF for the treatment of LTBI in 157 adolescents, 26% reported anorexia, nausea, fatigue, or rash, but only 1.3% required permanent discontinuation of RIF due to abdominal pain or elevation in serum transaminases [36].

**Recommendations.** Four months of RIF is recommended as an acceptable alternative to a 9-month regimen of INH for the treatment of adults with LTBI [1]. For children with LTBI acquired from a source with INH-resistant, RIF-susceptible *M tuberculosis*, the American Academy of Pediatrics recommends a 6-month regimen of RIF [30]. The difference in duration recommended for pediatric patients is due to the lack of data on the optimal treatment duration in children, but there are minimal data to support the need for a 6-month regimen. In 2 case series, including the only efficacy study that included children (one with adolescents), no patients developed TB after completing 6 months of RIF [35, 36], compared with 1 case of disease among 1379 adults treated for 4 months with RIF in a second case series [37].

Although the optimal duration has not been established, the results of an ongoing international trial evaluating 4 months of RIF treatment in children should provide additional information. No comparative trial of 6-month versus 4-month regimens of RIF has been conducted, but the benefits of improved adherence and safety are largely demonstrated in trials using 4 months of RIF in adults [33, 34]. Based on this, we recommend 4 months of RIF for LTBI treatment in children truly intolerant of INH or children exposed to INH-resistant, RIF-susceptible *M tuberculosis*. In addition, 4 months of RIF is an acceptable regimen in children infected from persons with fully drug-susceptible *M tuberculosis* isolates, or for children with LTBI acquired from an unknown source, given that the improved adherence demonstrated with this shorter regimen will increase the effectiveness of LTBI therapy. Of note, RIF is substantially more expensive than INH for uninsured patients who are not receiving medication via directly observed preventive therapy (DOPT).

**Isoniazid + Rifampin, 3 Months**
There are 9 randomized trials [32, 43–50] and 6 observational studies [51–56] of combination therapy with INH and RIF for LTBI.

**Efficacy and Effectiveness.** A recent meta-analysis identified 5 high-quality RCTs comparing daily short-course treatment with INH and RIF (INH/RIF) to 6–12 months of INH [57]. The studies were conducted in Hong Kong, Spain, and Uganda, and 3 studies included patients infected with HIV. Among 1926 adults (972 treated with INH/RIF, and 954 treated with INH) who were followed for a mean of 13–37 months, the development of TB disease was equivalent for both regimens. In HIV–infected African adults with LTBI, there was no difference in death or progression to disease when 3 months of daily INH/RIF (administered via DOPT) was compared to either 6 months of INH or 3 months of INH/Rifapentine (RPT) [43].

A study conducted exclusively among Greek children compared 4 months of INH/RIF to 9 months of INH and subsequently 4 months of INH/RIF to 3 months of INH/RIF [44]. Some children had TB risk factors and were identified via contact investigations, whereas others were recruited based on a positive TST alone. Although the study was not adequately powered for efficacy, none of the 850 treatment-adherent patients progressed to clinical TB. The
authors concluded that 3 months of INH/RIF and 4 months of INH/RIF were equivalent to each other and superior to 9 months of INH for the treatment of LTBI in children given the improved adherence.

The largest programmatic experience using 3 months of INH/RIF is from British observational studies, where 3–6 months of INH/RIF has been used to treat pediatric LTBI since 1984 [51–53]. By comparing district notifications of TB to patients treated for LTBI, Ormerod [51] demonstrated a significantly reduced incidence of childhood TB with the introduction of INH/RIF compared with historical control groups who received 9 months of INH. No additional protection was offered by a 6-month versus a 3-month regimen of INH/RIF [52].

**Adherence and Adverse Effects.** Adherence with 3 months of INH/RIF is generally equivalent to or better than that of longer regimens [47, 54, 55]. The rate of completion in Greek children treated for LTBI was significantly lower for 9 months of INH (66%) compared with the shorter INH/RIF regimens (78%–90%) [44]. The adherence with 3 months of INH/RIF in high-burden settings was higher than for 6 months of INH (70% vs 28%) [55].

Serious adverse effects, including hepatotoxicity, have occurred with similar or lower frequency with 3 months of INH/RIF compared with 6–12 months of INH [32, 43, 47–49, 57]. In the Greek pediatric study, there were no serious adverse events noted among 926 participants, and modification of treatment was not required in any patient [44].

**Recommendations.** Programmatic experience in England and 1 Greek study suggest that 3 months of INH/RIF therapy is as effective as 4 months [44, 51–53]. We recommend 3 months of INH/RIF based on this experience in the United Kingdom and multiple studies establishing the safety and tolerability of this regimen in children and adults [43, 44, 48, 50].

**Isoniazid and Rifapentine, 3 Months (Once-Weekly Dosing)**

There have been 3 randomized trials [8, 43, 58] of combination therapy with INH and RPT.

**Efficacy and Effectiveness.** Rifapentine is a rifamycin with a long half-life (~13 h) and with greater potency against *M tuberculosis* than RIF. It has a US Food and Drug Administration-approved indication for treating TB disease, but RPT’s use for treating LTBI is off-label. Three studies were conducted to compare the use of once-weekly RPT in combination with INH given via directly observed therapy to treat LTBI [8, 43, 58]. In a small trial (206 close contacts on this regimen), 1.46% of adult subjects treated with this regimen developed TB disease compared with 0.52% of 193 subjects treated with 2 months of daily RIF and pyrazinamide (PZA) [58]. In the second study, of 328 HIV-infected adults who did not receive antiretroviral therapy and who also tested positive for TST, 24 developed TB disease, a rate of 2.0 per 100 patient years, compared with a rate of 1.9 per 100 patient years among similar patients treated for 6 months with self-administered, daily, INH [43]. The most rigorous and best designed comparative trial for treatment of LTBI was performed in a third study in Brazil, Canada, Spain, and the United States [8]. This trial compared 11 or 12 doses of INH (15–25 mg/kg, maximum 900 mg) and RPT (15 mg/kg, maximum 900 mg) given as weekly DOPT with 9 months of daily self-administered INH (5–15 mg/kg, maximum 300 mg). The modified intention-to-treat analysis included 7731 participants with LTBI: 5466 close contacts, 1925 subjects with TST conversion, 179 subjects with radiographic findings of healed pulmonary TB, and 161 subjects who were infected with HIV and were not taking antiretroviral drugs. The completion rates of therapy were 82% and 69% for the INH and RPT and INH regimens, respectively. Of the 22 cases of TB disease observed during the average 30-month follow-up period, 7 occurred in the INH and RPT group and 15 occurred in the INH group (hazard ratio of 0.38 for the INH and RPT regimen). Initially, only persons ≥12 years of age were enrolled. Although younger children were enrolled later in the study after some pediatric RPT pharmacokinetic data became available [59], there was insufficient power to determine the efficacy of treatment among children 2 to 11 years of age.

**Adherence and Adverse Effects.** In the large comparative trial, permanent drug discontinuation was more common with the INH regimen than with INH and RPT regimen (31% vs 18%) [8]. It was obvious that adherence with the INH and RPT regimen was enhanced by the use of DOPT for all doses. Permanent discontinuation ascribed to adverse effects was more common with INH and RPT (4.9% vs 3.7%) as was discontinuation attributed to hypersensitivity reactions (2.9% vs 0.4%), but hepatotoxicity requiring discontinuation of the regimen was significantly more common with the INH regimen (2.0% vs 0.3%). In a separate analysis, 1032 children (539 received INH and RPT and 493 received INH) aged 2–17 years were enrolled in the study. For this subset, completion of the regimen was significantly higher in the INH–RPT group (88% vs 80%), and the rates of discontinuation of either regimen due to an adverse effect were very low and not different (1.3% and 0.8% for INH plus RPT and INH, respectively) [60]. There were 7 cases of possible drug hypersensitivity in the INH and RPT group compared with none in the INH group; there were no cases of significant hepatotoxicity in either group.
Recommendations. In December 2011, the Centers for Disease Control and Prevention (CDC) stated that the combination of INH and RPT given as 12 weekly DOPT doses is recommended as an equal alternative to 9 months of daily self-administered INH for treating LTBI in otherwise healthy patients aged ≥12 years who are at high risk for progression to TB disease. These risk factors included recent exposure to contagious TB, conversion from a negative to a positive test for TB infection, and radiographic findings of healed pulmonary TB, including HIV-infected persons who are otherwise healthy and not taking antiretroviral medications [9]. The safety and tolerability data for children aged 2–11 years were not available when these recommendations were published, but the CDC stated that INH-RPT can be considered on a case-by-case basis for children aged 2–11 years when the circumstances make completion of 9 months of INH unlikely and the likelihood or the hazard of TB is great. It is unlikely that a well-powered study of the efficacy of INH-RPT will be conducted among young children aged 2–11 years. However, given the favorable results of the safety and tolerability data now available for this age group, INH-RPT should be considered an acceptable alternative when adherence with a self-administered regimen is difficult or unlikely. Because of the lack of data pertaining to the pharmacokinetics, safety, and tolerability of RPT in children <2 years of age, INH-RPT should be considered a secondary alternative to 9 months of INH.

Rifampin + Pyrazinamide, 2 Months

There have been 7 randomized [46, 48, 58, 61–64] and 7 observational trials [65–71] for the use of RIF and PZA for LTBI; all were in adults.

Efficacy and Effectiveness

Studies demonstrated efficacy equivalent to 6 months of INH in HIV-infected adults [61, 63] and higher rates of completion than standard LTBI regimens [61, 66]. This regimen was never recommended for LTBI treatment in children, and it is no longer recommended for adults due to high rates of hepatotoxicity [72].

Adherence and Adverse Events. The limitations to this regimen were elevated rates of hepatotoxicity among adults: 6%–8% of 2-month RIF/PZA recipients had grade 3–4 hepatotoxicity compared with 1%–2% of 6-month INH recipients [64, 68]. Rates of hepatotoxicity may vary by population; a retrospective study of Portuguese LTBI patients who received 2 months of treatment with INH/RIF/PZA showed comparable rates of hepatotoxicity (1.5% vs 1.6%) to those who received 6 months of treatment with INH [73]. Based on these data, the CDC recommended that 2 months of RIF/PZA may be used with caution in selected cases for the following patients: those without existing hepatic disease; those not taking other potentially hepatotoxic medications; those able to be cared for by an experienced clinician with close clinical and laboratory monitoring; and those in whom longer regimens are judged not likely to be completed [74].

Recommendations. Although it is not a recommended regimen, 2 months of RIF/PZA may be useful for children who are started on multidrug therapy for suspected TB disease (based in part upon on TST or IGRA positivity) and who are later found to have an alternative diagnosis. In these patients, receipt of at least 2 months of RIF/PZA constitutes an adequate course of LTBI therapy. Use of RIF/PZA outside this circumstance is not recommended given the risk of hepatotoxicity and availability of alternative regimens.

ADHERENCE AND MONITORING

Approximately 50% of adult Americans who start LTBI therapy do not complete it [4, 75], and a substantial number refuse to initiate therapy; the rates are similar for children [24, 75]. Completion rates are much higher for children who receive medications via DOPT [24]. Almost half of patients who do not complete therapy discontinue it in the first 1–2 months after initiation [76]. Risk factors for initiating but not completing therapy include initiation of a 9-month course of therapy (vs shorter courses) [4], residence in congregate settings [4], lack of insurance [77], and perceived side effects [77, 78].

Poor adherence should not be surprising: many cultures do not emphasize preventive care, and because the children, by definition, are asymptomatic at initiation of LTBI therapy, parents will only notice side effects, not improvement. A child’s adherence relates to numerous factors including the parents’ attitude regarding preventive therapy, perceived ability to provide their child with treatment, and social norms [79]. Predicting adherence in individual patients and families is challenging. Given the frequency of nonadherence, it would be unwise for healthcare providers to assume all children receive the intended regimen.

Strategies to address the most common reasons for nonadherence are listed in Table 3. One effective strategy to increase completion rates is to offer DOPT via local health departments or in schools regularly staffed by school nurses. Although DOPT may not be available for all children in all settings, it has been shown to increase adherence in children with LTBI irrespective of socioeconomic status, immigration status, and language of preference [24].

Children who receive LTBI therapy require frequent monitoring to assess adherence, address family concerns,
and assess for potential side effects (Tables 2 and 4) [80–82]. For the otherwise healthy child who only receives TB medication(s), baseline and serial laboratory evaluation is unnecessary. Results of studies have shown that 3% of children who receive TB medications have asymptomatic elevation in transaminases 2–3 times the upper limit of normal (ULN) [83]; in these cases, modification of therapy is not needed. Elevations >3 times ULN with accompanying symptoms or >5 times ULN without symptoms define hepatotoxicity. Hepatotoxicity may range from isolated transaminitis to hyperbilirubinemia to hepatic failure. If children are receiving other potentially hepatotoxic medications or have known or suspected hepatic dysfunction, measurement of baseline hepatic transaminases may be warranted. Obtaining transaminase concentrations is also warranted for the child who develops abdominal complaints, anorexia, or malaise while taking TB medication. Most children who receive TB medications with

<table>
<thead>
<tr>
<th>Category</th>
<th>Variable</th>
<th>Explanation</th>
<th>Strategy to Address Barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to initiate therapy</td>
<td>Knowledge</td>
<td>LTBI has never been explained to them</td>
<td>Explain risk of progression to disease if untreated</td>
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<td></td>
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<td></td>
<td>Explain abundance of data showing treatment is effective</td>
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<td></td>
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<td></td>
<td>Refer families to reputable websites to read about LTBI (eg, CDC)</td>
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<tr>
<td></td>
<td>Cultural</td>
<td>LTBI treatment not emphasized in many developing nations; stigma around TB</td>
<td>Emphasize that the US has resources to be able to invest in strategies, unlike many developing nations</td>
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<tr>
<td></td>
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<td></td>
<td>Explain that US recommendations are (for the most part) in line with WHO recommendations used in the families’ country of origin</td>
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<tr>
<td></td>
<td>Linguistic</td>
<td>Lack of explanatory materials in the family’s language of comfort</td>
<td>Explain rationale and recommended treatment plan via a translator (not the child translating for family)</td>
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<td>Provide family information sheets in their language of comfort</td>
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<td></td>
<td>Concern about adverse events</td>
<td>They may have heard about risk of hepatotoxicity for TB medications</td>
<td>Education lower risk of adverse events in children compared with adults</td>
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<td>List out potential adverse effects and formulate a plan about what the family will do if the child were to develop any symptoms</td>
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<td></td>
<td>Provide family ways to contact you if symptoms were to develop</td>
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<tr>
<td></td>
<td>Duration of therapy</td>
<td>Family uncomfortable given long duration of therapy</td>
<td>Offer shorter-course therapy</td>
</tr>
<tr>
<td></td>
<td>Financial constraints</td>
<td>Child lacks insurance and family reluctant to start medication without knowing cost</td>
<td>Offer health department-supervised therapy if available; if not, guide the family on where the medication can be purchased inexpensively</td>
</tr>
<tr>
<td>Failure to complete therapy</td>
<td>Forgetting the importance of taking the medication</td>
<td>Families need frequent reinforcement; by definition, they will not see an improvement in their child and may only notice side effects</td>
<td>Frequent clinic visits</td>
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<td>Reinforce child’s desire to take the medication by giving the child small gifts (eg, stickers, a book) at each clinic visit</td>
</tr>
<tr>
<td></td>
<td>Concern for perceived adverse effects</td>
<td>Parents may attribute esoteric side effects to the medication</td>
<td>Clearly state what medication effects may be (verbally and in written form in a language comprehensible to the family) and the spectrum of coverage for TB medications (eg, that they do not prevent child from developing other infectious diseases)</td>
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<td>Instruct family to connect medication administration to something else they do each day</td>
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<td>School-aged children may find it easier to take medication in the morning before school, because after school, schedules may vary each day</td>
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<tr>
<td></td>
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<td></td>
<td>Offer health department-supervised therapy, if available</td>
</tr>
<tr>
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<td></td>
<td>Administer the medicine outside the home (eg, school-based clinic)</td>
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<td>Be sure that forgetting the medicine is not a reflection of not prioritizing LTBI treatment</td>
</tr>
<tr>
<td></td>
<td>Forgetting to take medication</td>
<td>Chaotic home situation; children often do not take daily medication for long periods</td>
<td>Offer health department-supervised therapy, if available; if not, guide the family on where the medication can be purchased inexpensively</td>
</tr>
<tr>
<td></td>
<td>Financial constraints</td>
<td>Child lacks insurance and family reluctant to continue medication without knowing cost</td>
<td>Offer health department-supervised therapy, if available; if not, guide the family on where the medication can be purchased inexpensively</td>
</tr>
</tbody>
</table>

Abbreviations: CDC, Centers for Disease Control and Prevention; LTBI, latent tuberculosis infection; TB, tuberculosis; US, United States; WHO, World Health Organization.

*Adapted from references 24, 75–77.
abdominal complaints have normal laboratory evaluation. Even in children with transaminitis, many cases will be due to viral infections rather than medication toxicity.

**CONCLUSIONS**

The decision to initiate therapy for LTBI in children is made easier by the very favorable risk/benefit ratio compared with adults: risks are minimized because children tolerate TB medications better than adults, and children benefit more because they have increased risk of progression to disease.

Six treatment regimens for LTBI have been demonstrated to have efficacy based mainly on studies in adults, but only the effectiveness of INH alone has been studied extensively in children. For TB disease, drug regimens that have been shown to be effective in adults have been at least equally effective in children, and it is likely that the same would be true of regimens to treat LTBI. It is unlikely that large clinical trials of the newer regimens adequately powered to determine efficacy will be conducted in children because of cost. However, the safety and tolerability of additional or alternative drugs and regimens can be established with smaller numbers of children. There are ample data to confirm that RIF for all ages of children and RPT for children ≥2 years of age are safe and well tolerated by the large majority of children.

The American Academy of Pediatrics and the CDC currently recommend 9 months of INH as preferred therapy for children. However, there is increasing concern that the effectiveness of this regimen in clinical practice is far less than the efficacy demonstrated in clinical trials because the estimated completion rate for 9 months of self-administered INH often is less than 50%.

### Table 4. Common Symptoms When Children Are Receiving LTBI Therapy and Strategies to Address These Complaints

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Possible Cause</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain immediately after taking medication</td>
<td>Taking INH without food while NPO can cause self-limited gastric irritation</td>
<td>Instruct family to give child medication with food and see if symptoms resolve</td>
</tr>
<tr>
<td>Abdominal pain hours after taking medication or abdominal pain associated with vomiting, icterus, or other symptoms</td>
<td>May be due to hepatotoxicity</td>
<td>Stop the medication and see in clinic immediately for a more thorough history, physical examination, and laboratory evaluation. Although most children do not need baseline hepatic transaminases, if a child were to develop symptoms while on LTBI therapy, clinician threshold for obtaining transaminases should be low. Evaluation for other common causes of abdominal pain (eg, constipation) also should occur.</td>
</tr>
<tr>
<td>Diarrhea in association with INH</td>
<td>Many INH suspension formulations are sorbitol-based, causing an osmotic diarrhea</td>
<td>Change infants and children to tablets (which can be crushed and mixed with food) once they are eating cereal or some pureed foods</td>
</tr>
<tr>
<td>Numbness/tingling in hands/feet</td>
<td>INH can cause pyridoxine (vitamin B6) deficiency-associated peripheral neuropathy</td>
<td>Supplement the following groups with B6: Exclusively breastfed infants, Adolescents, HIV-infected persons, Persons with risk of malnutrition or malabsorption</td>
</tr>
<tr>
<td>Joint pain</td>
<td>PZA can increase serum uric acid, although this rarely results in symptoms</td>
<td>Check uric acid; if elevated, stop PZA and consider an alternative regimen</td>
</tr>
<tr>
<td>Rash</td>
<td>PZA is the most common TB medication causing rash</td>
<td>Strategy contingent upon extent and character of rash. Urticarial rashes or rashes associated with wheezing or angioedema should result in immediate cessation of the medication.</td>
</tr>
<tr>
<td>Other infectious diseases</td>
<td>Common childhood infections</td>
<td>Remind family that TB medications only kill TB; most have no spectrum of activity for other common infections. Instruct them that children can still receive common antibiotics (and antiviral drugs) while taking TB medications</td>
</tr>
<tr>
<td>Headache</td>
<td>Nonspecific, not traditionally associated with any of the first-line TB medications</td>
<td>After assuring a normal examination and being sure the history does not have “red flags,” explain to families that headaches are one of the most common locations for pediatric pain</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; INH, isoniazid; NPO, nothing by mouth; PZA, pyrazinamide; TB, tuberculosis.

*Please warn families about orange urinary (and occasionally, tears and sweat) discoloration with rifampin, and warn adolescent females that rifampin, among its many drug interactions, inactivates oral contraceptives. Other drug interactions include HIV protease inhibitors, non-nucleoside reverse-transcriptase inhibitors, corticosteroids, and phenytoin.*
regimens with single or multiple drugs should result in higher rates of adherence. Therefore, it is reasonable to consider shorter regimens for children when a 9-month regimen of INH is unlikely to be completed.

Regimen selection must balance efficacy (degree of protection described in trials) with the rates and types of adverse events (low in children for all the described regimens), adherence, and (if available) drug susceptibilities for the isolate obtained from the person with TB disease who has been in contact with the child. The increasing incidence of drug shortages also supports the wisdom of having several regimens. A highly efficacious regimen may have limited effectiveness in routine clinical use if a substantial number of patients do not complete the regimen. For children 12 years and older, the best alternative to 9 months of INH therapy for LTBI may be 12 weekly doses of INH + RPT administered by DOPT. This regimen is short, effective, well tolerated, and has the advantage of the fewest number of doses. Unfortunately, it is not currently recommended to give this regimen as self-administered treatment. Rifapentine has been in short supply, so many health departments have not yet been able to scale-up widespread use of this regimen. The next best alternative to 9 months of INH alone is 4 months of RIF (to optimize adherence). Acceptable but less well studied regimens are 3 months of daily INH + RIF or 6 months of INH. A regimen of 2 months of RIF + PZA should be considered acceptable only for children with TB LTBI in whom TB disease was suspected initially and who were treated with INH, RIF, PZA, and ethambutol therapy for 2 months. Historically, there has been a single recommended regimen for the treatment of LTBI for all children. However, numerous studies and programs have demonstrated that this monolithic approach is not sufficient to meet the needs and abilities of all patients and families. There are several safe, available regimens that can be used to serve the needs of both patients and providers in the various clinical and epidemiologic circumstances in which LTBI is identified and managed.

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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