

## Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection

Preventing tuberculosis (TB) by treating latent *Mycobacterium tuberculosis* infection (LTBI) is a cornerstone of the U.S. strategy for TB elimination (1,2). Three randomized controlled trials have shown that a new combination regimen of isoniazid (INH) and rifapentine (RPT) administered weekly for 12 weeks as directly observed therapy (DOT) is as effective for preventing TB as other regimens and is more likely to be completed than the U.S. standard regimen of 9 months of INH daily without DOT (2–5). This report provides CDC recommendations for using the INH-RPT regimen. The new regimen is recommended as an equal alternative to the 9-month INH regimen for otherwise healthy patients aged  $\geq 12$  years who have LTBI and factors that are predictive of TB developing (e.g., recent exposure to contagious TB). The new regimen also can be considered for other categories of patients when it offers practical advantages. Although the INH-RPT regimen was well tolerated in treatment trials, monitoring for adverse effects is recommended. Severe adverse effects should be reported to the Food and Drug Administration (FDA) and CDC.

### Background

*M. tuberculosis*, a bacterium transmitted by airborne droplet nuclei from patients with respiratory forms of the disease, causes TB, a contagious and potentially fatal disease. TB develops in 5%–10% of persons who get infected with *M. tuberculosis*, typically after a latency of 6–18 months, but after decades in some persons. Conditions that impair cellular immunity, especially HIV infection, increase the likelihood of TB developing at any interval after infection. Treatment during latency prevents TB during treatment and afterward (2).

INH is the only medication approved by the FDA for TB preventive therapy (i.e., treating LTBI). Regimens of INH monotherapy have been shown to prevent TB in diverse categories of patients, and use of these regimens has been extended based on expert opinion (2). However, self-supervised daily INH regimens have completion rates of 60% or less in typical settings, attributable largely to the duration of  $\geq 6$  months. Rare but severe liver injuries and the concerns over this risk have reduced acceptance of these regimens (2,6,7). Daily rifampin (RIF) for 4 months for adults and 6 months for children is recommended when the *M. tuberculosis* is presumed to be INH-resistant and RIF-susceptible or when INH is contraindicated or is not tolerated by the patient (2).

RPT, like RIF, is a rifamycin-class antibiotic with an FDA-approved indication for TB disease. Its use for treating LTBI is off label. RPT is microbicidal for susceptible *M. tuberculosis*.

Its long plasma half-life enables infrequent dosing, which can increase DOT convenience and thus adherence. Most RIF-resistant isolates also are resistant to RPT.

### Methods

In April 2011, CDC convened a panel of 23 consultants, each of whom had demonstrated TB-specific expertise in at least one of the following: diagnosis, treatment, prevention, nursing case management, public health programs, surveillance, epidemiology, clinical research, pulmonology, infectious diseases, pediatrics, mycobacteriology, health communication and education, migrant worker health, patient advocacy, and health economics. The panel reviewed findings from all three INH-RPT clinical trials that had been completed (3–5), interviewed the investigators in charge of the largest trial (5), and summarized the discussions of all evidence and opinions.

Each recommendation for use of INH-RPT was listed according to the quality of the evidence. High quality evidence came from randomized clinical trials that included the patient categories for which the recommendation was made. The three clinical trials of the INH-RPT regimen were limited by open-label (i.e., unblinded) design, and one was limited by small numbers of participants (3). The other evidence was of lower quality (i.e., indirect or generalized from treatment trials and observational studies of other regimens). Lower quality evidence, CDC expert opinion, and the conclusions of the panel supported other recommendations in these guidelines. Recommendations against the use of INH-RPT (without a reference to quality of evidence) were made for patient categories in which 1) previous experience with treatment of TB or LTBI with any regimen has revealed an increased risk for adverse effects, drug interactions, or low efficacy or 2) studies have not provided adequate evidence of safety or efficacy. Recommendations for precautions and guidance for monitoring treatment were based on the conclusions of the panel, TB epidemiology, methods of the INH-RPT clinical trials, and experience with other regimens for treating LTBI.

### Summary of Evidence from Clinical Trials of INH-RPT

A randomized clinical trial in Brazil compared 12 weekly doses of DOT INH-RPT with 2 months of daily, mostly self-supervised RIF and pyrazinamide (RIF-PZA) in tuberculin skin test-reactive household contacts aged  $\geq 18$  years (3). Enrollment was stopped at 399 participants because of hepatotoxicity in RIF-PZA recipients. Patients were followed  $\geq 2$  years after

treatment. TB was diagnosed in three INH-RPT recipients and one RIF-PZA recipient (incidence rate ratio: 2.8 for INH-RPT versus RIF-PZA, 95% confidence interval [CI] = 0.2–26.8).

A randomized clinical trial in South Africa assigned 1,148 human immunodeficiency virus (HIV)-infected tuberculin skin test–reactive participants aged  $\geq 18$  years who were not receiving antiretroviral treatment to one of four regimens: once-weekly INH-RPT or twice-weekly INH-RIF, both by DOT for 12 weeks; and daily self-supervised INH, for 6 months or indefinitely (4). For all four regimens, the median follow-up duration was approximately 4 years. The incidence rates of TB were 1.4–2.0 per 100 person-years, without significant differences between the four regimens. Treatment completion was greater for the two rifamycin-containing regimens, and grade 3 or 4 adverse effects\* were more common for INH taken indefinitely.

A randomized clinical trial in Brazil, Canada, Spain, and the United States compared 12 doses of INH-RPT given as weekly DOT with 9 months of self-supervised daily INH (5). The modified intention-to-treat analysis included 7,731 participants aged  $\geq 2$  years who had LTBI: 5,466 close contacts, 1,925 patients with tuberculin skin test conversions, 179 participants with radiographic findings of healed pulmonary TB, and 161 HIV-infected participants not taking antiretroviral drugs. Participants were followed until 33 months after enrollment. Completion of INH-RPT was defined as 11 or 12 doses within 16 weeks; doses had to be separated by  $>72$  hours to be counted. The completion rate was 82% (3,362 of 3,986) for INH-RPT and 69% (2,585 of 3,745) for INH ( $p < 0.01$ ). Of 22 TB cases, seven were in INH-RPT recipients, and 15 were in INH recipients (hazard ratio: 0.38 for INH-RPT, CI = 0.15–0.99, adjusted for TB risk factors). One case was caused by RIF-resistant *Mycobacterium bovis*<sup>†</sup> in an HIV-infected participant who had finished INH-RPT late; two cases were caused by INH-resistant *M. tuberculosis* in INH recipients. Permanent drug discontinuations were more common with INH than INH-RPT (31% versus 18%), as were grade 3 and 4 adverse events<sup>§</sup> (3.0% versus 1.6%) ( $p < 0.01$  for both). However, permanent drug discontinuations ascribed to adverse effects were more common for INH-RPT (4.9% versus 3.7%,  $p < 0.01$ ), as was discontinuation attributed to possible hypersensitivity (2.9% versus 0.4%,  $p < 0.01$ ); six of 152 possible INH-RPT hypersensitivity reactions included hypotension. Discontinuation because of hepatotoxicity was more common for INH (2.0% versus 0.3%,  $p < 0.01$ ). No deaths were attributed to study medications.

\*Additional information available at [http://www.hptn.org/web%20documents/hptn046/ssp/appendices/appendix-toxicitytables\\_daids\\_ae\\_gradingtable\\_finaldec2004.pdf](http://www.hptn.org/web%20documents/hptn046/ssp/appendices/appendix-toxicitytables_daids_ae_gradingtable_finaldec2004.pdf).

<sup>†</sup> *M. bovis* is part of the *M. tuberculosis*-complex and a cause of human TB.

<sup>§</sup>Additional information available at [http://www.eortc.be/services/doc/ctc/ctcv20\\_4-30-992.pdf](http://www.eortc.be/services/doc/ctc/ctcv20_4-30-992.pdf).

## Recommendations

**Patients for whom INH-RPT is recommended.** The combination regimen of INH and RPT given as 12 weekly DOT doses (Box 1) is recommended as an equal alternative to 9 months of daily self-supervised INH for treating LTBI in otherwise healthy patients aged  $\geq 12$  years who have a predictive factor for greater likelihood of TB developing, which includes recent exposure to contagious TB, conversion<sup>¶</sup> from negative to positive on an indirect test for infection (i.e., interferon- $\gamma$  release assay or tuberculin skin test), and radiographic findings of healed pulmonary TB (see Precautions). HIV-infected patients who are otherwise healthy and are not taking antiretroviral medications also are included in this category (see Precautions). (Recommendation based on high quality evidence, as defined in Methods).

Recommendations for using the previous regimens for treating LTBI are unchanged (2), and the RIF-PZA regimen is not recommended (8). The choice between INH and INH-RPT depends on feasibility of DOT, resources for drug procurement, program operations including patient monitoring, expectance of treatment completion as foreseen from medical and social circumstances of the patient, and preferences of the patient and the prescribing physician.

The broad use of INH monotherapy has relied on extending the findings from randomized clinical trials and long-term observations (2). Analogously, weekly INH-RPT can be considered for treating LTBI in patient categories that were not included in treatment trials if the individual patients are unlikely to complete 9 months of daily INH or they are in situations where INH-RPT offers practical advantages, such as correctional settings, clinics for recent immigrants, and homeless shelters. Patients who have underlying illnesses that are associated with TB (e.g., diabetes mellitus) or that might decrease the tolerability of INH-RPT should be considered on a case-by-case basis. (Recommendation based on expert opinion and lower quality evidence, as defined in Methods).

The preferred regimen for children aged 2–11 years is 9 months of daily INH (2). The number of children in this age range who have received INH-RPT is insufficient for assessing tolerability and efficacy. However, INH-RPT can be considered on a case-by-case basis when both 1) the circumstances make the completion of 9 months of daily INH unlikely and 2) the likelihood or the hazard of TB is great (e.g., recent *M. tuberculosis* infection in a preschool-aged child).

<sup>¶</sup> Tuberculin skin test conversion is defined by a change from a negative to a positive result and a  $\geq 10$  mm increase in induration, within a 2-year interval (2). Conversion of interferon- $\gamma$  release assays is defined by a change from a negative to a positive result.

**BOX 1. Dosage for a combination regimen of isoniazid and rifapentine in 12 once-weekly doses under direct observation for treating latent *Mycobacterium tuberculosis* infection.****Isoniazid**

15 mg/kg rounded up to the nearest 50 or 100 mg;  
900 mg maximum

**Rifapentine**

10.0–14.0 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

Isoniazid (INH) is formulated as 100 mg and 300 mg tablets. Rifapentine (RPT) is formulated as 150 mg tablets packed in blister packs that should be kept sealed until usage. New formulations with larger dosage per tablet and fixed-dose INH-RPT combinations are in development.

**Source:** Three months of weekly rifapentine and isoniazid for *Mycobacterium tuberculosis* infection (PREVENT TB). Information available at <http://clinicaltrials.gov/ct2/show/nct00023452?term=rifapentine&rank=9>.

**Patients for whom INH-RPT is not recommended.** INH-RPT is not recommended for the following patients: children aged <2 years, because the safety and pharmacokinetics of RPT have not been established for them; HIV-infected patients receiving antiretroviral treatment, because the drug interactions have not been studied; pregnant women or women expecting to become pregnant during treatment, because safety in pregnancy is unknown; and patients who have LTBI with presumed INH or RIF resistance.

**Precautions**

Treating for LTBI when TB is active could result in partial treatment and drug resistance. Some patients who have radiographic findings of presumed old “healed” TB might have active TB, and they should be examined for it before treating LTBI. A 4-drug regimen may be started while mycobacterial culture results are pending (2). A similar concern applies for HIV-infected patients, who are more likely than patients who are not HIV infected to have extrapulmonary TB or pulmonary TB with normal findings on the chest radiograph.

RPT reddens secretions, including urine and tears, and can stain contact lenses. Neutropenia and increased serum concentrations of liver enzymes are uncommon adverse effects. For other rifamycins, rare hypersensitivity reactions have been reported, with symptoms such as fever, headache, dizziness, musculoskeletal pain, petechiae, purpura, and pruritus (9). One participant in a treatment trial for active TB had thrombocytopenia associated with first RIF and then RPT (10). RPT induces increased metabolism of many medications, particularly those metabolized by cytochrome P450 isoenzyme 3A. RPT should not be used with affected medications having narrow therapeutic ranges (e.g., methadone or warfarin), except with careful monitoring. Women who use any form of hormonal birth control should be advised to add, or switch to, a barrier method.

Because missed doses or altered dosing intervals or amounts could jeopardize efficacy or safety, DOT is recommended. DOT workers should be trained to use a symptom checklist for adverse effects and to report problems to a clinician. At each encounter, patients should be instructed in their preferred language to seek medical attention immediately if they have fever, yellow eyes, dizziness, rash, or aches or >1 day of nausea, vomiting, weakness, abdominal pain, or loss of appetite. INH-RPT should be withheld while the cause of symptoms is being determined. Patients should undergo at least monthly clinical assessment, including inquiries about side effects and a physical examination. Although blood tests are not recommended for everyone, baseline and subsequent tests should be performed for certain patients (Box 2) (2,6).

Testing and treatment for LTBI should be planned for an optimal risk-benefit ratio (2). INH-RPT was well tolerated in treatment trials (3–5). However, with both INH and RIF-PZA, fatal liver injuries came to attention only after the regimens were widely adopted (6–8). To monitor adverse effects, CDC has established an LTBI treatment adverse effects surveillance system (7). Adverse effects leading to hospital admission or death should be reported to local or state health departments for inclusion in this system (e-mail: [ltbidrugs@cdc.gov](mailto:ltbidrugs@cdc.gov)). Adverse events or medication errors also should be reported to FDA MedWatch at <http://www.fda.gov/medwatch>, by submitting a MedWatch Form 3500 (available at [http://www.fda.gov/medwatch/safety/FDA-3500\\_fillable.pdf](http://www.fda.gov/medwatch/safety/FDA-3500_fillable.pdf)) or by calling 1-800-FDA-1088.

The American Thoracic Society, Infectious Diseases Society of America, and CDC are revising their joint guidelines for finding and treating LTBI (2). Those guidelines are expected to augment these recommendations.

**BOX 2. Guidance for early detection and management of adverse effects during treatment of latent *Mycobacterium tuberculosis* infection with a combination regimen of isoniazid (INH) and rifapentine (RPT) in 12 once-weekly doses under direct observation**

- Education of patients to seek medical attention upon the first symptom of a possible adverse event.
- Clinical assessment upon the first sign or symptom of a possible adverse event.
- Monthly interview and brief physical examination for the findings of treatment-associated adverse events (e.g., icterus, tenderness of the liver, or rash).
- Baseline hepatic chemistry blood tests (at least aspartate aminotransferase [AST]) for patients with specific conditions:
  - Human immunodeficiency virus infection
  - Liver disorders
  - In the immediate postpartum period ( $\leq 3$  months after delivery)
  - Regular alcohol usage
- Consideration of a baseline hepatic chemistry blood test for older patients on an individual basis, especially for those taking medications for chronic medical conditions.
- Blood tests at subsequent clinical encounters for patients whose baseline testing is abnormal and for others at risk for liver disease.
- Discontinuance of INH-RPT if a serum aminotransferase concentration is  $\geq 5$  times the upper limit of normal even in the absence of symptoms or  $\geq 3$  times the upper limit of normal in the presence of symptoms.
- Vigilance for drug hypersensitivity reactions, particularly hypotension or thrombocytopenia.
  - Severe condition (e.g., hypotension requiring intravenous fluid support): discontinuance of INH-RPT; supportive medical care
  - Mild to moderate condition (e.g., dizziness treated with rest or oral fluids): conservative management of constitutional symptoms, clinical and laboratory monitoring, the option for continuing treatment under observation

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