

Isoniazid-Rifapentine for Treatment of Latent TB Infection

Beth Gadkowski MD MPH MS
Assistant Professor
Eastern Virginia Medical School
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Preventing Tuberculosis

- Treatment for latent TB infection is the cornerstone of the US strategy for TB elimination
- Active TB develops in 5-10% of individuals who are infected with TB
- Those with impaired cellular immunity are at higher risk for developing active TB

Latent TB Infection Therapy

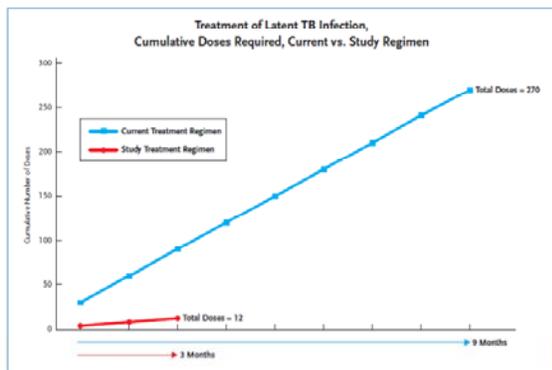
- Isoniazid:
 - 9 months of treatment
- Pros:
 - Inexpensive
 - Best efficacy and safety data
 - Hepatitis in 0.1-0.6% of patients
 - About 75-80% effective
- Cons:
 - low completion rates of 30-64%

Other LTBI Treatment Options

- Rifampin:
 - 4 months of therapy
 - to be used when contact to INH-resistant disease, INH contraindicated or is not tolerated by the patient
- Rifampin/PZA:
 - not recommended due to hepatotoxicity

PREVENT TB Trial

- Enrolled 8,053 patients
- Most participants were from the US and Canada, some from Spain and Brazil
- Participants either received 9 months of INH or a once-weekly dose of rifapentine and isoniazid for 3 months given via DOT
- Trial lasted for 10 years and participants were followed for approximately 33 months to evaluate for development of TB disease



PREVENT TB Trial

- 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

12-Weeks of once weekly INH/Rifapentine (1)

Pros:

- Shorter duration of treatment (12 doses vs. 270 doses)
- Individuals more likely to complete therapy (82% vs 69%)
- 7 cases of TB in INH-Rifapentine group vs. 15 cases in INH group
- Similar amount of adverse drug events in each group

12-Weeks of once weekly INH/Rifapentine (2)

Cons:

- More Expensive: \$503 vs \$237
- May have difficulty getting Rifapentine
- Trial results are applicable only in low-to-medium TB incidence countries
- Not clear how to use this regimen in special populations:
 - HIV positive
 - Children under 5

Morbidity and Mortality Weekly Report

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

- INH-RPT given as 12 weekly DOT doses is recommended as an equal alternative to 9 months of daily self-supervised INH for treating LTBI in otherwise healthy patients aged ≥ 12 years at risk for TB disease:
 - recent exposure to contagious TB
 - conversion of TST or IGRA
 - radiographic findings of healed pulmonary TB

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Choosing between INH and INH-RPT

- Feasibility of DOT
- Resources available for obtaining drugs
- Ability of the program to monitor patient
- Expectance of treatment completion based on medical/social circumstances
- Preferences of the patient and the prescribing physician

INH-RPT NOT Recommended

- Children <2 years old
- HIV-infected patients receiving HAART
- Pregnant women and women expecting to become pregnant during treatment
- Where LTBI is presumed to have INH or RIF resistance

Children

- Preferred regimen for children aged 2-11 years: 9 months of INH
- However, INH-RPT may be considered on a case-by-case basis when BOTH:
 - 1) completion of 9 months of therapy is unlikely
 - 2) the likelihood or hazard of TB is great

Dosing

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/study00023452?term=rifapentine&rank=9>.

Rifapentine (1)

- Longer half life than rifampin
- Orange discoloration of secretions, urine, tears
- Can stain contact lenses
- Rare adverse effects:
 - elevated liver function tests
 - thrombocytopenia
 - headache and dizziness

Rifapentine (2)

- Increases the metabolism of medications, particularly those metabolized by cytochrome P450 3A:
 - birth control
 - coumadin
 - methadone
 - glipizide, glimepiride, glyburide
 - levothyroxine

Directly-observed therapy

- DOT recommended as missed doses or altered dosing intervals can affect efficacy and safety of INH-RPT
- DOT workers need to be trained to look for adverse effects of medications and report them to clinician

Monitoring (1)

- At each encounter, patients need to be instructed to seek medical attention immediately if they have:
 - fever
 - yellow eyes (jaundice)
 - dizziness
 - rash
 - aches
 - >1 day of nausea, vomiting, weakness, abdominal pain or loss of appetite

Monitoring (2)

- Medications should be withheld while cause of symptoms is being determined
- Patients should undergo at least monthly clinical assessments, to include inquiries about side effects and a physical examination
- Laboratory tests:
 - baseline LFTS in HIV, liver disease, ETOH use, immediate post-partum period
 - repeat liver tests at subsequent visits for those with baseline abnormal tests or those at risk for liver disease

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 (≤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.
- Discontinuation of INH-RPT if a serum aminotransferase concentration is ≥5 times the upper limit of normal even in the absence of symptoms or ≥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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