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## **GUIDELINE FOR THE USE OF THE COMBINATION REGIMEN OF ISONIAZID AND RIFAPENTINE IN 12 ONCE-WEEKLY DOSES UNDER DIRECT OBSERVATION TO TREAT LATENT MYCOBACTERIUM TUBERCULOSIS INFECTION**

### **Summary**

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Preventing tuberculosis (TB) disease by treating latent *Mycobacterium tuberculosis* infection (LTBI) is a cornerstone of the U.S. strategy for TB elimination. 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 disease as other regimens and is more likely to be completed than the U.S. standard regimen of 9 months of INH daily without DOT. 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 developing TB disease (e.g., recent exposure to contagious TB disease). The new regimen also can be considered for other categories of patients when it offers practical advantages.

### **Background**

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On December 9, 2011 the Centers for Disease Control and Prevention (CDC) released recommendations on the use of a new treatment regimen for LTBI. This new regimen, referred to as the 12-dose regimen, represents a major advancement in preventing future cases of TB disease and puts us closer to our goal of TB elimination. The 12-dose regimen is a combination regimen of isoniazid and rifapentine given in 12 once-weekly doses under DOT. The 12-dose regimen reduces the required treatment for LTBI from 270 daily doses over 9 months to 12 once-weekly doses over 3 months.

CDC's recommendations are a result of a recent large randomized controlled trial that found the 12-dose regimen to be as effective for preventing TB disease as other regimens. The new regimen is also more likely to be completed than the current U.S. standard regimen of 9 months of daily isoniazid given without directly observed therapy. Two additional studies also found the 12-dose regimen to be as effective as other regimens in preventing new cases of TB disease.

Treating LTBI to prevent progression to TB disease is a cornerstone of the U.S. strategy for TB elimination. More than 11 million people in the United States are estimated to have LTBI, which is about 4 percent of the total population. Certain individuals with LTBI, such as those with

weakened immune systems (e.g., due to HIV, an organ transplant, immunosuppressant drugs, or other reasons) and persons recently infected with TB, are at increased risk of developing TB disease. About 5 to 10 percent of people with LTBI will develop TB disease if not treated. This equates to approximately 550,000 to 1.1 million people who will develop TB disease at some point in their life, unless they receive adequate treatment for LTBI.

Treating LTBI is essential to controlling and eliminating TB in the United States, because it substantially reduces the risk that the infection will progress to TB disease. Of those with LTBI, an estimated 300,000 to 400,000 people begin preventive treatment each year in the United States. Among those who begin treatment, up to 60 percent never complete the current standard treatment regimen. Patients are more likely to complete a once-weekly, shorter duration regimen. Clinicians may also be more inclined to prescribe a shorter regimen. Every effort should be made to ensure that people with LTBI who are at increased risk for progression to TB disease begin — and complete — the entire course of treatment. Premature termination of treatment, or missing a significant number of doses, can lead to treatment failure and the subsequent development of TB disease.

The choice between the 12-dose regimen and other approved for the treatment of LTBI depends on several factors, including:

- Feasibility of DOT
- Resources for drug procurement
- Program operations including patient monitoring
- Expectance of treatment completion considering medical and social circumstances
- Preferences of the patient and the prescribing physician

Although the new regimen will initially be more expensive for TB programs to administer (including the cost of the drugs and DOT), the public health benefits associated with the new regimen will be that more people will actually complete treatment to prevent progression to TB disease (therefore, also avoiding the potential cost of treating future cases of TB disease).

**INH-RPT is recommended for patients in whom TB disease has been ruled out who are:**

- Healthy persons 12 years or older
- Recently exposed contacts to infectious TB disease and new TB test converters
- Persons with radiographic findings of healed pulmonary TB (e.g., fibrotic disease)
- HIV infected persons who are NOT taking antiretroviral medications

**The regimen can be considered on a case by case basis for:**

- Persons with a co-existing medical condition (e.g., diabetes mellitus, immunosuppressive therapy)
- Children aged 2–11 years
- Persons not in the above category who are unlikely to complete 9 months of daily INH
- Persons in situations where INH-RPT offers practical advantages (e.g., correctional settings, clinics for recent immigrants, homeless shelters)

### **INH-RPT is not recommended for the following patients:**

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- Persons with confirmed or suspected TB disease
- Children under 2 years of age
- HIV infected persons taking antiretroviral medications (the drug interactions between rifapentine and antiretroviral medications have not been studied)
- Persons presumed to be infected with *M. tuberculosis* resistant to INH or rifampin
- Pregnant women or women planning to become pregnant during treatment
- Women who are breastfeeding
- Individuals who have had prior adverse events or hypersensitivity to INH or rifamycins (i.e., rifampin, rifabutin, rifapentine)

### **Directly observed therapy (DOT)**

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Because missed doses or altered dosing intervals or dosages 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 in-person clinical assessments, including inquiries about side effects and a physical examination. Although blood tests are not recommended universally, baseline and subsequent tests should be performed for certain at-risk patients.

### **Precautions**

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Treating for presumed LTBI when in fact active TB disease is present could result in the partial treatment of TB disease with subsequent acquisition of drug-resistance. Some patients who have radiographic findings of presumed old "healed" TB might have active TB disease, and this should be excluded before commencing treatment for LTBI treatment. In such situations, consideration may be given to starting a 4-drug regimen while mycobacterial culture results are pending. A similar concern applies for HIV-infected patients, who are more likely than non-HIV infected patients to have extrapulmonary TB disease or pulmonary TB disease with normal findings on the chest radiograph.

RPT reddens secretions, including urine, sweat, and tears, and can stain contact lenses. Neutropenia, increased serum concentrations of liver enzymes, and hyperbilirubinemia are uncommon adverse effects. For other rifamycins, rare hypersensitivity reactions have been reported, which may present with symptoms such as fever, headache, dizziness, musculoskeletal pain, petechiae, purpura, and pruritus. One participant in a treatment trial for active TB disease had thrombocytopenia associated with first RIF and then RPT. 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.

## Dosage

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Drug	Dosage	Maximum dose
Isoniazid	15 mg/kg rounded up to the nearest 50 or 100 mg	900 mg
Rifapentine	10.0–14.0 kg = 300 mg	900 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	

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.

### **Early detection, monitoring, and management of adverse effects**

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- 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 alanine aminotransferase [ALT]) 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

## Reporting of adverse events

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- Report adverse events to FDA MedWatch (<http://www.fda.gov/medwatch/safety/FDA-3500>)
- Report adverse events leading to death or hospitalization to LAC TBCP, who will report to the CDPH TB Control Branch (TBCB) and CDC.

## Patient education

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Pamphlets and videos are available at the CDC websites:

<http://www.cdc.gov/tb/publications/pamphlets/12DoseLTBITreatmentbrochure11x17.pdf>

[http://www.cdc.gov/tb/publications/PDF/3HP\\_508.pdf](http://www.cdc.gov/tb/publications/PDF/3HP_508.pdf)

<http://www.cdc.gov/Features/TuberculosisTreatment/>

[http://www.cdc.gov/tb/topic/treatment/12dose\\_video.htm](http://www.cdc.gov/tb/topic/treatment/12dose_video.htm)

Spanish language materials are also available:

Brochure: <http://www.cdc.gov/spanish/especialesCDC/TratamientoTB/>

Video: [http://www.cdc.gov/tb/topic/treatment/12dose\\_video\\_es.htm](http://www.cdc.gov/tb/topic/treatment/12dose_video_es.htm)

## References

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