



# Latent tuberculosis infection (LTBI) treatment guidance in Washington State

Promoting rifamycin-based, shorter-course regimens

**Version 3**



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## Background

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Historically, based on the U.S. Centers for Disease Control and Prevention (CDC) recommendations published in 2000, nine months of daily isoniazid (INH) was the most widely used regimen for treatment of latent TB infection (LTBI). In 2011, CDC recommended a short-course combination regimen of once-weekly isoniazid-and-rifapentine for 12 weeks (3HP) by directly observed therapy for treatment of LTBI. <sup>1</sup> This guidance was recently updated to support self-administration of 3HP. <sup>2</sup>

Furthermore, recent studies and accumulating practice experience encourage the use of rifamycin-based, shorter LTBI regimens (3HP and daily rifampin for 4 months). The two shorter LTBI regimens are now routinely used by many TB experts in the U.S., given concerns about INH-related hepatotoxicity, poor adherence due to longer duration of INH, and the increasing proportion of patients from TB endemic countries with INH-resistance. <sup>3-18</sup>

## Daily RIFAMPIN and Once-weekly ISONIAZID+RIFAPENTINE

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Recent literature suggests that two shorter LTBI regimens (daily rifampin for 4 months and once-weekly isoniazid and rifapentine [3HP] for 12 weeks) have higher rates of treatment completion and lower rates of side effects, especially drug-induced hepatitis. <sup>3-20</sup> Both daily rifampin and once-weekly INH-and-rifapentine can be self-administered rather than observed by a healthcare professional. <sup>21</sup> The choice between rifampin daily for 4 months, vs. INH and rifapentine once weekly for 12 weeks depends on the patient's and medical provider's preference.

For those who weigh 55 kg or more, rifampin 600 mg (two 300 mg capsules) or INH 900 mg and rifapentine 900 mg (three 300-mg INH tablets and six 150-mg rifapentine tablets) is recommended. Patients may have a preference for one regimen over another based on the frequency of dosing and/or the number of pills.

## Notes

- Children: The American Academy of Pediatrics considers any of the three regimen options adequate, depending on the circumstances for individual patients. Most experts consider 3HP to be the preferred regimen for treatment of LTBI for children 2 years and older. 3HP is not recommended for children under 2 years old because the safety and pharmacokinetics of rifapentine have not been established for this age group. (see Daily ISONIAZID)
- HIV infection: National guidelines for the prevention and treatment of opportunistic infections in patients infected with HIV cite INH as the preferred regimen for LTBI in the context of HIV infection, but the guidelines also acknowledge that the shorter rifamycin-based regimens are more likely to be completed and are acceptable alternatives in the absence of incompatible drug interactions or other contraindications.<sup>22</sup> Indeed, the updated CDC guidance recommended the use of 3HP in patients, infected with HIV, taking antiretroviral medications with acceptable drug-drug interactions with rifapentine. There are no data to guide use of once-weekly INH-and-rifapentine in children infected with HIV.
- Pregnancy: CDC recommends that LTBI treatment should be delayed until two to three months after pregnancy if no risk factor for TB progression is present (e.g. HIV infection, recent contact to an infectious TB case).<sup>23</sup> Among pregnant women with risk factors for TB progression, CDC continues to: recommend INH as the preferred regimen, recommends against the use of rifapentine, and does not reference the use of rifampin. However, given rifampin's excellent safety record in the context of treatment for active TB during pregnancy, its lower risk of drug-induced liver injury, and recent findings of a higher rate of adverse pregnancy outcomes among women infected with HIV and treated for LTBI with INH *during pregnancy* (vs. those treated with INH *after pregnancy*),<sup>24</sup> some experts feel that rifampin may in fact be the better option for treatment of LTBI in pregnancy.

## Daily ISONIAZID

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Completion rates of INH daily for 6 – 9 months are reported to be significantly lower than 4 months of daily rifampin or 3HP.<sup>3-20</sup> Furthermore, the incidence of drug-induced hepatitis is higher with INH compared to 4 months of daily rifampin or the 12 dose regimen.

- INH remains the first choice for children under 2 years old due to paucity of the data on rifampin or 3HP.

## Suggested Dosages for Each Regimen

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### A. Rifampin (RIF) daily

**Preparation: 150mg or 300mg capsules.**

Adult dosage: 10 mg/kg once daily (600 mg maximum).

Consider 450 mg once daily for adults who weigh less than 50 kg.

Pediatric dosage: 15-20mg/kg once daily (600 mg maximum).

### B. INH-and-Rifapentine once weekly

INH once weekly dosage

**Preparation of INH: 100 mg or 300 mg tablets.**

1. Adults and Children 12 years of age and older:

INH 15 mg/kg per dose once weekly, rounded up to the nearest 50 or 100 mg (max 900 mg).

2. Children age 2-11 years:

INH 25 mg/kg per dose once weekly, rounded up to the nearest 50 or 100 mg (900 mg maximum).

**Rifapentine once weekly dosage (both adults and children)**

**Preparation of Rifapentine: 150 mg tablets**

Kg	Lbs	Dosage
10.0–14.0 kg	22-31	300mg
14.1–25.0 kg	32-55	450mg

<b>Kg</b>	<b>Lbs</b>	<b>Dosage</b>
25.1–32.0 kg	56-71	600mg
32.1–49.9 kg	72-110	750mg
≥50.0 kg	111 or more	900mg max

### **C. Isoniazid (INH)**

Preparation: 100mg or 300mg tablets.

#### **Dosage for daily therapy**

1. Adults: 5 mg/kg once daily → Generally 300 mg once daily.  
Consider 200 mg once daily for 40 kg or less.
2. Children: 10-15 mg/kg once daily (300 mg/d maximum)

#### **Dosage for twice-weekly therapy:**

1. Adults: 15 mg/kg twice weekly (900mg/dose maximum).
2. Children: 20-30mg/kg twice weekly (900mg/dose maximum)

When INH is used in a patient with diabetes, HIV, renal failure, heavy alcohol use, poor nutrition and/or who is pregnant or breast-feeding, pyridoxine (vitamin B6) 25-50 mg should be given with each dose of INH to prevent peripheral neuropathy.

In any patient who develops symptoms of new or worsening peripheral neuropathy (e.g. paresthesia) on INH, pyridoxine should be added or increased (note: maximum dose is 100mg/d). If neuropathy fails to improve or progresses, strong consideration should be given to discontinuing INH in order to reduce the risk of permanent neuropathy.

## Clinical Evaluation Before Initiation of LTBI Treatment

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### **Medical History and Clinical Evaluation**

Obtain the following information:

- ✓ Age

- ✓ Weight
- ✓ Review and assessment of adequacy of previous treatment for active TB disease and/or LTBI
- ✓ A history of side effects due to INH or rifamycins (e.g. severe hepatitis, rash)
- ✓ If the patient is HIV-positive, current use of antiretroviral therapy, or a plan to start antiretroviral therapy in the next 4 months.
- ✓ List all medications that the patient is taking. Pay special attention to the current or planned future use of other medications that may be adversely affected by concurrent use of INH or rifamycin (e.g. warfarin, tacrolimus, anti-seizure medications)
- ✓ Current breastfeeding or pregnancy
- ✓ If taking oral contraceptives, **advise the patient to use additional barrier protection methods** because a rifamycin increases the metabolism of oral contraceptives.
- ✓ Evaluation for underlying liver disease.
  - history of alcohol abuse
  - injection drug use
  - viral hepatitis (B or C) or cirrhosis
  - women  $\leq$  3 months post-partum

### **Chest X-ray (CXR)**

Everyone considered for LTBI treatment should undergo a CXR to rule out pulmonary TB disease. It is recommended that CXR be no older than 3 months prior to LTBI treatment initiation. Children younger than 5 years of age (i.e. up to their fifth birthday) should have both a posterior-anterior (PA) and a lateral view of CXR.

All others should undergo at least a PA view. Additional follow up X-rays should be done at the physician's discretion.

## Patient Monitoring and Education During LTBI Treatment

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Patient education and regular assessments by health care professionals are essential for identifying adverse effects related to LTBI treatment.

When LTBI treatment is initiated, all patients should be educated about potential adverse effects and should be told to stop taking LTBI treatment and contact the medical provider if adverse effects develop. Patients should be advised regarding the following potential adverse effects:

- ✓ Fatigue, weakness
- ✓ Anorexia, nausea, vomiting, abdominal pain
- ✓ Dark urine, yellow eyes
- ✓ Rash

If using 3HP:

- ✓ Light headedness, fainting, flu-like symptoms

If using INH-containing regimen:

- ✓ Numbness or tingling in the hands and/or feet

It is recommended that appropriate educational materials be provided, in the patient's preferred language and reading level, with appropriate individualized needs considered.

In addition, rifamycins (including rifampin and rifapentine) typically cause orange discoloration of urine, sweat and tears for several hours to a day after ingestion.



Occasionally, patients on rifampin will also describe maroon-colored bowel movements. This is no cause for alarm and is not harmful.

Patients on self-administered treatment should generally receive a 1-month supply of medications and be seen by a health care professional to evaluate for adverse effects prior to providing another month of medications. At these monthly visits, education regarding adverse effects should be reiterated. If there is a concern about drug interactions, monitor clinically and with additional laboratory testing, if indicated.

Laboratory testing should be used as needed to evaluate specific adverse events that may occur during treatment.

## Laboratory Tests

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Baseline and monthly liver function tests (LFTs; AST/SGOT, ALT/SGPT, alkaline phosphatase, and total bilirubin) should be obtained for those who:

- ✓ Are HIV-positive
- ✓ Have a history of heavy alcohol ingestion, liver disease or chronic hepatitis
- ✓ Are pregnant or are postpartum (up to three months after delivery)
- ✓ Have a history of drug injection
- ✓ Are already taking potential hepatotoxic drugs for other medical conditions (e.g. statins, frequent use of acetaminophen)
- ✓ Had a recent abnormal liver function test
- ✓ Develop symptoms or signs of liver injury during treatment (e.g. fatigue, anorexia, nausea, abdominal pain, jaundice).

Criteria for treatment interruption based on abnormal liver function testing results:

- ✓ transaminase elevations >3 times the upper limit of normal IF symptoms of liver injury are present, OR

- ✓ transaminase elevations >5 times the upper limit of normal under any circumstances, OR
- ✓ total bilirubin >2.5mg/dL (regardless of transaminase results).

Baseline and monthly CBC including platelets may be considered for selected LTBI patients with hematologic issues (e.g. anemia, neutropenia, thrombocytopenia) when a rifamycin is prescribed.

## Expert Consultation

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Clinicians with questions about patients with adverse effects due to LTBI treatment, or with other challenging scenarios involving treatment of LTBI, may seek expert consultation through TB ECHO® ([www.doh.wa.gov/TBECHO](http://www.doh.wa.gov/TBECHO))

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