



Latent tuberculosis infection (LTBI) treatment guidance in Washington State

Promoting rifamycin-based, shorter-course regimens

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Background

Historically, based on the U.S. Centers for Disease Control and Prevention (CDC) recommendations published in 2000, nine months of daily isoniazid (INH) used to be the most widely used regimen for treatment of latent TB infection (LTBI). The initial LTBI treatment guidance in Washington state was published in 2018 to promote rifamycin-based, shorter-course regimens. In 2020, CDC and National TB Controllers Association (NTCA) revised the guidelines on LTBI treatment and they also recommended rifamycin-based, shorter-course regimens.¹ The aims of this revised guidance on LTBI treatment in Washington state are to incorporate the changes that were made in the national guidelines and to offer practical recommendations to clinicians in the state of Washington.

Daily RIFAMPIN, Once-Weekly ISONIAZID+RIFAPENTINE, and Daily ISONIAZID+RIFAMPIN

Three shorter LTBI regimens (daily rifampin for 4 months [4R], once-weekly isoniazid plus rifapentine for 12 weeks [3HP], and daily isoniazid plus rifampin for 3 months [3HR]) have higher rates of treatment completion compared to daily INH for 6 – 9 months. 4R and 3HP have lower rates of drug-induced liver injury. 4R has a lower rate of treatment discontinuation due to side effects. 4R, 3HP, and 3HR can be self-administered. The choice among 4R vs. 3HP vs. 3HR depends on the patient's and medical provider's preference. Patients may prefer one regimen over the other based on the frequency of dosing and/or the number of pills. See the following comparison table.

	Frequency	The typical number of pills each time (adults > 50 kg)	Completion rate (compared to INH)	Risk of drug-induced hepatitis (compared to INH)	Rate of treatment discontinuation due to adverse effects (compared to INH)	Drug-drug interactions (compared to INH)
4R	Once daily	2 pills	Higher	Lower	Lower	Higher
3HP	Once weekly	9 pills	Higher	Lower	Higher	High, but lower than 4R or 3HR
3HR	Once daily	3 pills	Higher	Similar	Higher	Higher
6 – 9 months of daily INH	Once daily	1 pill				

Notes

- Children: The American Academy of Pediatrics considers any of the regimen options adequate, depending on the circumstances for individual patients. 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.
- HIV infection: National guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV cite INH as the preferred regimen for LTBI in the context of HIV infection,² 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. There are no data to guide use of once-weekly INH + rifapentine in HIV-infected children.
- Pregnancy: CDC recommends that LTBI treatment should be delayed until two to three months after pregnancy unless there is a risk factor for TB progression (e.g., HIV infection, recent contact to an infectious TB case). INH and rifampin can be used to treat LTBI during pregnancy. 3HP has not been studied in pregnant women and should not be prescribed for women who are pregnant or expect to be pregnant in the next 3 months. Some experts feel that 4R may be the better option for treatment of LTBI in pregnancy, because of its lower risk of drug-induced liver injury and recent findings of a higher rate of adverse pregnancy outcomes among HIV infected women treated for LTBI with INH *during pregnancy* compared to those treated with INH *after pregnancy*.³

Daily ISONIAZID

Completion rates of daily INH for 6 – 9 months are significantly lower than 4 months of daily rifampin, 3HP or 3HR.

Furthermore, the incidence of drug-induced hepatitis is higher with INH compared to 4 months of daily rifampin, or 3HP.

Suggested Dosages for Each Regimen

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. Isoniazid (INH) + 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

Kg	Lbs	Dosage
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) daily

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.

D. INH + Rifampin daily

Rifampin: the same as “Rifampin (RIF) daily” dosage

INH: the same as “Isoniazid (INH) daily” dosage. Consider adding pyridoxine as described above.

Clinical Evaluation Before Initiation of LTBI Treatment

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

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

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

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)

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Reference List

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