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). In 2020, CDC and National TB Coalition of America (formerly the National TB Controllers Association or NTCA) revised the guidelines on LTBI treatment and recommended rifamycin-based shorter-course regimens. 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.

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
- History of contact to a person with TB disease. If yes, obtain detailed info including whether it was drug-resistant TB or not.
- A history of side effects due to INH or a rifamycin (e.g. severe hepatitis, rash).
- HIV status and anti-retroviral regimen plan HIV positive
- List all the medications the patient is taking. **Pay special attention to the current or planned future use of medications that may be adversely affected by concurrent use of INH or rifamycins** (e.g. current or planned antiretroviral therapy, anti-coagulation therapy, steroids, tacrolimus, anti-seizure medications, etc.)
- Current breastfeeding or pregnancy
- If taking oral contraceptives and a rifamycin-based regimen is planned, **advise the patient to use additional barrier protection methods** until the first normal menstrual period after completion of therapy because rifamycins increase the metabolism of oral contraceptives and may reduce their effectiveness.
- Evaluation for underlying liver disease.
  - history of alcohol abuse
  - injection drug use
  - viral hepatitis (B or C) or cirrhosis
  - people who are pregnant or $\leq$ 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 clinician's discretion but generally are not necessary if the initial X-ray is normal.

Treatment Regimens

There are several treatment regimens recommended in the United States for latent TB infection. The medications used to treat latent TB infection include the following:

- Isoniazid (INH)
- Rifapentine (RPT)
- Rifampin (RIF)

These medications are used on their own or in combination, as shown in the table. below. CDC and the National Tuberculosis Coalition of America (NTCA) preferentially recommend short-course, rifamycin-based, 3- or 4-month latent TB infection treatment regimens over 6- or 9-month isoniazid monotherapy. Short course regimens include:

- Four months of daily rifampin (4R)
- Three months of once-weekly isoniazid plus rifapentine (3HP)
- Three months of daily isoniazid plus rifampin (3HR)

Short-course treatment regimens, like 3HP and 4R, are effective, safe, and have higher completion rates than longer 6 to 9 months of isoniazid monotherapy (6H/9H). Shorter, rifamycin-based treatment regimens generally have a lower risk of hepatotoxicity than 6H and 9H.

In addition, a study among HIV-positive patients showed a 1-month regimen of daily rifapentine plus isoniazid (1HP 7/7) was noninferior to 9 months of daily isoniazid (9H 7/7) and was shown to have comparable safety and efficacy in those patients. However, this regimen has not been endorsed by CDC or NTCA for use. some experts have concerns about the study's methodology (e.g., not all subjects had confirmed TB infection), and local experience with this regimen is limited at the time of this writing.

- DHHS HIV OI guidelines support 1HP 7/7 as an alternative to 3HP, 3HR, 4R, or 9H in HIV infected patients whose anti-retroviral regimens would not have interactions with the rifapentine. (See: Mycobacterium tuberculosis: Adult and Adolescent OIs | NIH)
- Not recommended for use in other situations until/unless supported by clinical trial results.
- Coordinate with HIV care provider and seek TB expert consultation if considering use of this regimen.

If short-course treatment regimens are not a feasible or an available option, 6H and 9H are alternative, effective latent TB infection treatment regimens. Although effective, 6H and 9H have higher toxicity risk and lower treatment completion rates than most short-course treatment regimens.

All treatment must be modified if the patient is a contact of an individual with drug-resistant TB disease. Clinicians should choose the appropriate treatment regimen based on drug susceptibility results of the presumed source case (if known), coexisting medical conditions (e.g., HIV), and potential for drug-drug interactions. Consultation with a TB expert is advised if the known source of TB infection has drug-resistant TB.

Comparison of LTBI Treatment Regimens

Regimen	Frequency	Typical number of pills each time (adults > 50 kg)	Completion rate (compared to INH monotherapy)	Risk of drug-induced hepatitis (compared to INH monotherapy)	Rate of treatment discontinuation due to adverse effects (compared to INH monotherapy)	Drug-drug interactions (compared to INH monotherapy)
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				

Note: Pyridoxine 25 or 50 mg is usually added to any regimen containing isoniazid, increasing the pill burden by one.

Preferred Regimens

Four Months of Daily Rifampin

A regimen of 4 months of daily rifampin is a preferred treatment that is strongly recommended for HIV-negative adults and children of all ages. (No evidence is available for effectiveness in HIV-positive persons.) The effectiveness of this regimen was clinically equivalent to, and less toxic than, the standard regimen of 9 months of daily isoniazid in adults and children.

The potential disadvantages of the rifamycin-based regimens are:

- the many drug interactions, including warfarin, oral contraceptives, azole antifungals, and HIV antiretroviral therapy. Although there are no randomized control trials on the effectiveness of rifabutin in treating LTBI, it has been shown to have fewer or less pronounced drug interactions and NTCA LTBI treatment guidelines suggest that it can be considered for use in place of rifampin when rifampin is contraindicated due to drug-drug interactions and when isoniazid can also not be used. Drug interactions with weekly rifapentine are fewer than with rifampin and appear to be fewer than with rifabutin; therefore, weekly isoniazid and rifapentine could be considered when rifampin is contraindicated due to drug-drug interactions, although clinical data are limited.
- Drug-drug interactions between rifamycins and antiretroviral therapy are regularly updated by the U.S. Department of Health and Human Services (https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/0). In HIV-positive persons with low CD4+ lymphocyte counts, the risk for asymptomatic or subclinical TB disease increases, possibly facilitating rifampin resistance if TB disease is inadvertently treated with rifampin monotherapy. However, a meta-analysis and systematic review looking at six studies including both HIV infected and uninfected patients found no statistically significant increased risk of rifamycin resistance after LTBI treatment with rifamycin-containing regimens compared to non-rifamycin-containing regimens.

Three Months of Weekly Isoniazid Plus Rifapentine

A regimen of 3 months of once-weekly isoniazid plus rifapentine is a preferred regimen that is strongly recommended for adults and children aged >2 years, including HIV-positive persons (as drug interactions allow). This regimen, administered through directly observed therapy, had equivalent effectiveness and was not more toxic than the standard regimen of 9 months of daily isoniazid in adults and children aged >2 years. Treatment completion rates were higher with the 3-month regimen.

Potential disadvantages of this regimen include:

- cost of medications that are greater than most alternatives and the potential added costs if provided by directly observed therapy (DOT). Treatment completion was highest with DOT, although self-administered therapy (SAT) is an approved option.
- the need to take numerous pills simultaneously (10 pills once weekly compared with two or three pills daily for other regimens for most adults),
- the association with a systemic drug reaction or influenza-like syndrome that can include syncope and hypotension. Severe events sometimes—albeit rarely--require urgent medical attention or even hospitalization. The systemic drug reaction is self-limited and usually mild; no deaths have been reported.
- Potential drug interactions and acquired drug resistance if TB disease is not adequately excluded also are important considerations for all treatment regimens.

Three Months of Daily Isoniazid Plus Rifampin

A regimen of 3 months of daily isoniazid plus rifampin is a preferred treatment that is conditionally recommended for adults and children of all ages and for HIV-positive persons as drug interactions allow. HIV-negative adults and children with a positive tuberculin skin test (TST) who received 3 months of daily isoniazid plus rifampin appeared to have a similar risk for TB disease, hepatotoxicity, and adverse effects requiring discontinuation of therapy as those who received ≥6 months of isoniazid.

Among children aged <15 years specifically, a 3-month course of daily isoniazid plus rifampin appeared as effective as a 6-month or longer course of isoniazid, because direct comparisons found no difference in TB disease and no differences in adverse effects requiring discontinuation of therapy or hepatotoxicity.

In HIV-positive persons, no difference was found in the incidence of TB disease among those who received 3 months of daily isoniazid plus rifampin compared with those who received ≥6 months of isoniazid monotherapy, regardless of whether they were TST positive, TST negative, or anergic. Hepatotoxicity was less frequent among those receiving the shorter course of therapy, although discontinuation of therapy because of adverse effects was more frequent.

Potential drug interactions with rifampin and acquired drug resistance if TB disease is not adequately excluded also are important considerations (see previous section on 4 months of daily rifampin). In addition, hepatotoxicity risk might be greater with the two drugs given together than with either drug given alone.

Alternate Regimens

Six Months or Nine Months of 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.

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 100 mg/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.

Preparation is in 100 mg or 300 mg tablets.

Latent TB Infection Treatment Regimens (Dosing/Duration/Frequency)

Drug(s)	Duration	Dose	Frequency	Total Doses
Isoniazid (INH)* and Rifapentine (RPT)†	3 months	Adults and Children aged 12 years and older: INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum RPT: 10–14.0 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 Children aged 2–11 years: INH*: 25 mg/kg; 900 mg maximum RPT†: as above	Once weekly	12
Rifampin (RIF)§	4 months	Adults: 10 mg/kg Children: 15–20 mg/kg‖ Maximum dose: 600 mg	Daily	120
Isoniazid (INH)* and Rifampin)§	3 months	Adults: INH*: 5 mg/kg; 300 mg maximum RIF§: 10 mg/kg; 600 mg maximum Children: INH*: 10-20 mg/kg; 300 mg maximum RIF§: 15-20 mg/kg; 600 mg maximum	Daily	90
Isoniazid (INH)	6 months	Adults: 5 mg/kg Children: 10–20 mg/kg¶ Maximum dose: 300 mg	Daily	180
		Adults:15 mg/kg Children: 20–40 mg/kg¶ Maximum dose: 900 mg	Twice weekly‡	52
	9 months	Adults: 5 mg/kg Children: 10–20 mg/kg¶ Maximum dose: 300 mg	Daily	270
		Adults: 15 mg/kg Children: 20–40 mg/kg¶ Maximum dose: 900 mg	Twice weekly‡	76

- *Isoniazid (INH) is formulated as 100 mg and 300 mg tablets.
- †Rifapentine (RPT) is formulated as 150 mg tablets in blister packs that should be kept sealed until use.
- ‡Intermittent regimens must be provided via directly observed therapy (DOT), a HCW observes medication ingestion.
- §Rifampin (rifampicin; RIF) is formulated as 150 mg and 300 mg capsules.
- ‖The American Academy of Pediatrics (AAP) acknowledges that some experts use RIF at 20–30 mg/kg for the daily regimen when prescribing for infants and toddlers (Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:829–853).
- ¶The AAP recommends an INH dosage of 10–15 mg/kg for the daily regimen and 20–30 mg/kg for the twice weekly regimen.

Pregnancy and Breastfeeding

For most pregnant people, treatment for latent TB infection can be delayed until 2–3 months post-partum because of high risk of peripartum severe drug induced liver injury, though its risk due to rifamycin has not been well studied.

For people who are at high risk for progression from latent TB infection to TB disease, especially those who are a recent contact of someone with infectious TB disease, treatment for latent TB infection should not be delayed on the basis of pregnancy alone, even during the first trimester.

Breastfeeding should not be discouraged for people being treated with the first-line antituberculosis drugs because the concentrations of these drugs in breast milk are too small to produce toxicity in the nursing newborn. For the same reason, drugs in breast milk are not an effective treatment for TB disease or latent TB infection in a nursing infant.

Breastfeeding people taking INH should also take pyridoxine (vitamin B6) supplementation.

RIF can cause orange discoloration of body fluids, including breast milk. Orange discoloration of body fluids is expected and harmless.

There currently is not enough data to indicate whether the 3HP regimen is safe for people to take while breastfeeding.

TB Treatment Regimens for Pregnant People include:

- 4-month daily regimen of rifampin (RIF) (4R)
- 3-month daily regimen of isoniazid (INH) and RIF (3HR)
- 6- or 9-month daily regimen of INH (6H or 9H), with pyridoxine (vitamin B6) supplementation

Note: The 3-month weekly INH and rifapentine (3HP) regimen is not recommended for pregnant people or those expecting to become pregnant during the treatment period because its safety during pregnancy has not been studied.

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

If using a Rifamycin (including rifampin and rifapentine):

- These 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.

Appropriate educational materials should be provided, in the patient's preferred language and reading level, with appropriate individualized needs considered.

Patients on self-administered treatment (SAT) 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 (for both SAT and DOT patients), 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 Tests

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

- TB ECHO® (www.doh.wa.gov/TBECHO)
- WA State TB Nurse Consultants at TBServices@DOH.WA.GOV
- Curry International TB Center Warmline: https://www.currytbcenter.ucsf.edu/consultation

Reference List

For Health Care Providers

- CDC website: Treatment Regimens for Latent TB Infection
- CDC website: Treatment for TB During Pregnancy
- HIV.gov website: Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020
- Gupta A, Montepiedra G, Aaron L, et al. Isoniazid Preventive Therapy in HIV-Infected Pregnant and Postpartum Women. New England journal of medicine. 2019;381(14):1333-1346.
- Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV
- Latent TB Infection Treatment Regimens – Treatment Table
- Latent Tuberculosis Infection: A Guide for Primary Health Care Providers
- Treatment Guidelines
- National Tuberculosis Controllers Association (NTCA) Testing and Treatment of Latent Tuberculosis Infection in the United States: Clinical Recommendations
- Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2024 Report of the Committee on Infectious Diseases. 33rd ed. Itasca, IL: American Academy of Pediatrics; 2024.
- Update on Recommendations for Use of Once-weekly Isoniazid-Rifapentine Regimen to Treat Latent Mycobacterium Tuberculosis Infection
- Rifamycin Drug-Drug Interactions: A Guide for Primary Care Providers Treating Latent Tuberculosis Infection | Curry International Tuberculosis Center

For Patients

- Questions and Answers About TB
- Staying on track with TB medicine (Pamphlet)
- 12-Dose Regimen for Latent TB Infection-Medication Tracker and Symptom Checklist [PDF – 156 KB]
- TB and Pregnancy

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