Virginia Department of Health
Use of Isoniazid/Rifapentine for Treatment of Latent TB Infection in Health Department Settings

The identification and treatment of latent tuberculosis infection (LTBI) is a cornerstone of the U.S. strategy for the elimination of tuberculosis. In 2018, the Centers for Disease Control and Prevention (CDC) updated recommendations for the treatment of LTBI using a once-weekly regimen of isoniazid (INH) and rifapentine (RPT)[1]. This regimen offers practical advantages with clients who are unlikely to complete 9 months of daily INH or in settings such as correctional facilities, homeless shelters and clinics for recent immigrants.

These recommendations are an adjunct to guidelines on the diagnosis and treatment of latent tuberculosis that were published in 2000[3] and the 2011 recommendations.[2] Recommendations for regimens detailed in the previous guidelines for treating LTBI are unchanged and remain treatment options for any client. The recommendation of two months of rifampin/pyrazinamide recommended in the 2000 guidelines was later withdrawn due to increased risk of hepatotoxicity and death.[4]

Recommendations

1. INH-RPT can be considered for the treatment of LTBI in healthy patients ≥ 2 years of age after active disease has been adequately ruled out.
    a. This includes those with recent exposure, recent conversion from negative to positive on a test for LTBI, and those with radiographic findings of healed TB if active disease has been adequately ruled out.

2. The regimen can be considered for HIV-infected patients who are not taking anti-retroviral medications as well as those taking antiretroviral medications with acceptable drug-drug interactions with rifapentine.

3. INH-RPT regimen is **NOT** recommended for:
    a. Children < 2 years of age
    b. HIV-infected clients receiving antiretrovirals that have drug-drug interactions with rifapentine
    c. Pregnant women or those likely to become pregnant while undergoing treatment
    d. Clients with LTBI presumed to be INH or rifampin resistant

4. The regimen consists of a once weekly dose of both medications given for twelve weeks. Clinical teams have the option to give this regimen by Directly Observed Therapy (DOT) or by Self-Administered Therapy (SAT).
    a. Treatment completion rates are higher when the regimen is delivered by DOT[1], however DOT is costly and a burden for the patient. Healthcare providers should make decisions about whether or not DOT is needed with individual patients.
        i. VDH does not recommend SAT for those 18 years and under.
    b. Completion of this regimen is defined as 12 doses within 16 weeks.
        i. 11 doses within 16 weeks is acceptable if 12 doses cannot be completed.
    c. Doses should be separated by >72 hours to be countable.
    d. Dosing information is provided in Table 1.

5. Other Considerations
    a. Rifapentine, like rifampin and rifabutin, has the potential to cause many drug-drug interactions due to its effects of inducing a variety of metabolic pathways, particularly

those involving the cytochrome P450 system. This results in a decrease in the serum concentrations of many drugs, sometimes to sub-therapeutic levels. However, serum drug level monitoring is not recommended for clients being treated for LTBI.

b. Rifapentine is considered an intermediate enzyme inducer while rifampin is a potent inducer and rifabutin is the least potent inducer.
c. Before recommending the INH/rifapentine regimen for any given client, a careful review of all current medications, both prescription and over the counter (OTC) with a reference search for potential drug-drug interactions should be conducted.
d. Clients should be questioned during each monthly visit concerning new prescription and OTC medication additions since the last visit.

6. Monitoring
    a. Clinical Monitoring
        i. Clients should be taught the symptoms of adverse reactions to the medications and to seek medical attention should symptoms occur.
        ii. If clients report symptoms of adverse reactions, they should receive an immediate clinical assessment and monitoring.
        iii. Clients should be questioned at each monthly or DOT visit regarding symptoms of adverse reactions. Maintain vigilance for hypersensitivity reactions, especially hypotension or thrombocytopenia.
        iv. Conduct a monthly clinical assessment for side effects including brief physical examination for hypotension, jaundice, tenderness of liver, or rashes.
        v. Baseline liver function tests (ALT, AST, TBili, Alk phos) should be ordered for the following clients:
            - HIV-infected clients
            - Clients with active or a history of liver disorders
            - Clients in the immediate postpartum i.e., $\leq$ 3 months after delivery
            - Clients with regular alcohol usage or injection drug use
            - Baseline testing for older clients, especially those on other hepatotoxic medications, should be considered.
    b. Monthly monitoring of LFTs is not necessary unless baseline testing is abnormal, or the client is at risk for liver disease.
    c. Discontinue medication if the AST is $\geq$ 5 times upper limit of normal in the absence of symptoms or $\geq$ 3 times the upper limit of normal in the presence of hepatotoxic symptoms.
    d. Adverse reactions leading to hospital admission or death should be reported to VDH TB Program at 804-864-7906 for further reporting to appropriate federal medical safety monitoring programs.
    e. Pediatric Specific Monitoring
        i. Routine laboratory monitoring (baseline serum transaminases) and periodic (e.g., monthly) laboratory monitoring is warranted for children with:
            - malnutrition,
            - preexisting liver disease, and
            - additional risk factors for hepatotoxicity (such as receipt of other potentially hepatotoxic medications)
    f. Pregnancy Status Monitoring
        i. Documentation of last normal menstrual period should be documented in

the medical record.

ii. Routine pregnancy testing of females of child-bearing age is not recommended unless otherwise indicated.

iii. RPT can reduce the effectiveness of hormonal contraceptives; therefore, women who use hormonal birth control should be advised to add or switch to a barrier method when taking 3HP.

7. Adherence Monitoring for Self-Administered Therapy
    a. The first dose should be completed through DOT and include education about adherence strategies.
        i. Ask patients about their adherence to therapy and strategies they are using to ensure adherence. (This demonstrates you are not only interested in them adhering to their medication schedule, but also willing to help them continue to adhere to their medication schedule.)
            - Document these responses in the client's medical record.
        ii. Provide the patient with this handout (English version included below) in their preferred language (if possible) and instruct them to check off SAT doses. Add case manager's information to the form.
            - Provide instructions that if clients miss a dose, they should call their TB nurse case manager as soon as possible.
        iii. Discuss any identified barriers and propose joint solutions using motivational interviewing techniques to improve adherence.
        iv. Provide clear expectations that SAT adherence should be followed, or treatment completion will be conducted through DOT.
    b. Establish a monitoring system to identify any client who misses a medication visit or other scheduled appointment. Develop and implement a follow up process that includes a phone call to the client within three business days of missing a monthly clinic visit for treatment. On this call, the following should be discussed:
        i. Ask about side effects/TB symptoms/pregnancy
        ii. Advise on taking medication if appropriate (patient still has meds/no side effects or TB symptoms)
        iii. Reschedule clinic appointment as soon as possible if patient is agreeable
        iv. If patient wishes to discontinue treatment, record as "discontinued at patient's request" (with reason if possible).

Table 1 – Dosing

Drug	Dosage	Maximum dose
INH	15 mg/kg rounded to nearest 50/100 mg in patients ≥ 12 years	900 mg
	25 mg/kg rounded[5] to the nearest 50/100 mg in patients 2-11 years	
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 max	
Rifapentine tablets can be crushed and administered with semi-solid food for children unable to swallow pills		

Evidence base:

[1]Centers for Disease Control and Prevention. Update of Recommendations for Use of Once-Weekly Isoniazid-Rifapentine Regimen Treat latent *Mycobacterium tuberculosis* Infection. MMWR 2018;67(25):723-726. https://www.cdc.gov/mmwr/volumes/67/wr/mm6725a5.htm

[2]Centers for Disease Control and Prevention. Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat latent *Mycobacterium tuberculosis* Infection. MMWR 2011;60:1650-1653. http://www.cdc.gov/mmwr/pdf/wk/mm6048.pdf

[3]Centers for Disease Control and Prevention. Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. MMWR 2000;49 (No. RR-6) http://www.cdc.gov/mmwr/PDF/rr/rr4906.pdf

[4]Centers for Disease Control and Prevention. Update: Adverse Event Data and Revised American Thoracic Society/CDC Recommendations Against the Use of Rifampin and Pyrazinamide for Treatment of Latent Tuberculosis Infection – United States, 2003. MMWR 2003; 52:735-739. http://www.cdc.gov/mmwr/PDF/wk/mm5231.pdf

[5]Cruz AT and Starke JR. Completion Rate and Safety of Tuberculosis Infection Treatment With Shorter Regimens. *Pediatrics.* 2018;141(2):e20172838

Haas MK, Aiona K, Erlandson KM, Belknap RW. Higher Completion Rates With Self-administered Once-weekly Isoniazid-rifapentine Versus Daily Rifampin in Adults With Latent Tuberculosis. Clin Infect Dis. 2021 Nov 2;73(9):e3459-e3467. doi: 10.1093/cid/ciaa1364. PMID: 32915203.

Belknap R, Holland D, Feng PJ, Millet JP, Caylà JA, Martinson NA, Wright A, Chen MP, Moro RN, Scott NA, Arevalo B, Miró JM, Villarino ME, Weiner M, Borisov AS; TB Trials Consortium iAdhere Study Team. Self-administered Versus Directly Observed Once-Weekly Isoniazid and Rifapentine Treatment of Latent Tuberculosis Infection: A Randomized Trial. Ann Intern Med. 2017 Nov 21;167(10):689-697. doi: 10.7326/M17-1150. Epub 2017 Nov 7. PMID: 29114781; PMCID: PMC5766341.

MEDICATION TRACKER

The 12-Dose Regimen for Latent Tuberculosis (TB) Infection

Your Medication Schedule

(Providers: Indicate the appropriate number of pills and day)

Medicine	Number of pills per week	Frequency	Day
Isoniazid: ____ mg Rifapentine: ____ mg	TOTAL: _____ (Isoniazid: _____, Rifapentine: _____)	Once a week for 12 weeks (3 months)	M T W Th F S Sun

Your doctor may also add Vitamin B6 to your treatment plan.

Keeping Track of Your Treatment

On the table below, check the box and write the date to show when you took your medicine.

WEEK	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
EXAMPLE 5/7 - 5/13	☐ _____	☒ 5/8	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____
Week 1	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____
Week 2	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____
Week 3	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____
Week 4	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____
Week 5	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____
Week 6	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____
Week 7	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____
Week 8	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____
Week 9	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____
Week 10	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____
Week 11	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____
Week 12	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____	☐ _____

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www.cdc.gov/tb

CS292653B

SYMPTOM CHECKLIST

The 12-Dose Regimen for Latent Tuberculosis (TB) Infection

Patient Name: _____

Normal Side Effects

Most people can take their TB medicines without any problems. The rifapentine medicine may cause your urine (pee), saliva, tears, or sweat to appear an orange-red color. This is normal and the color may fade over time.

STOP taking your medicine and CALL your TB doctor or nurse right away if you have any of the problems below:

- ☐ Dizzy or lightheaded when sitting or standing
- ☐ Less appetite, or no appetite for food
- ☐ Stomach upset, nausea, or vomiting
- ☐ Stomach pain or stomach cramps
- ☐ Pain in your lower chest or heartburn
- ☐ Flu-like symptoms with or without fever
- ☐ Severe tiredness or weakness
- ☐ Fevers or chills
- ☐ Severe diarrhea or light colored stools (poop)
- ☐ Brown, tea-colored, or cola-colored urine
- ☐ Skin or whites of your eyes appear yellow
- ☐ Skin rash or itching
- ☐ Bruises, or red or purple spots on your skin that you cannot explain
- ☐ Nosebleeds, or bleeding from your gums or around your teeth
- ☐ Shortness of breath
- ☐ Pain or tingling in your hands, arms, or legs
- ☐ Feelings of sadness or depression

Please talk to your doctor or nurse if you have any questions or concerns about treatment for latent TB infection.

Doctor/Clinic Contact Information

Name of the staff caring for you: _____

Phone number: _____

Address: _____

Hours: _____

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