

12-dose Isoniazid (INH)/Rifapentine Regimen (3HP) for Treatment of Latent TB Infection (LTBI)

IMPORTANT NOTE: Rule out active disease in all persons prior to initiating treatment for LTBI.

What is the 12-dose INH/rifapentine regimen (3HP)?

It is 12 once-weekly doses of INH and rifapentine for the treatment of LTBI. The regimen is referred to as “3HP.”

Is the regimen effective? (1,2,3)

In 2017, a Centers for Disease Control and Prevention (CDC) Work Group conducted a systematic review and meta-analysis of the 3HP regimen. 19 articles representing 15 unique studies were included in the meta-analysis which determined that 3HP is as safe and effective as other recommended LTBI regimens and achieves substantially higher treatment completion rates.

What are the advantages of 3HP?

- The 12-dose regimen reduces treatment time by two-thirds (9 months to 3 months).
- Weekly dosing offers convenience for some groups.
- Treatment is completed at higher rates.
- There are lower rates of hepatotoxicity.

Does CDC recommend 3HP? (4)

CDC recommends 3HP. For current recommendation please see: Update of Recommendations for Use of Once-Weekly Isoniazid-Rifapentine Regimen to Treat Latent *Mycobacterium tuberculosis* Infection (<https://www.cdc.gov/mmwr/volumes/67/wr/mm6725a5.htm>).

Who is NOT recommended for treatment with the 12-dose regimen? (2,4,5)

- Children under 2 years of age;
- Patients with potential for severe or unmanageable drug interactions.
- Persons presumed infected with *M. tuberculosis* resistant to INH or rifampin;
- Pregnant women or women planning to become pregnant during treatment;
- Individuals who had prior adverse events or hypersensitivity to INH or rifampin.

What are the doses?

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

What is completion of therapy? (4)

Completion of therapy is defined in the study as completing at least 11 weekly doses of treatment within 16 weeks. Doses should be given at least 72 hours apart.

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Does this regimen have to be administered via directly observed therapy (DOT)?

Treatment completion rates are higher when the regimen is delivered by DOT (4), however DOT is costly and a burden for the patient. Health care providers should make decisions about whether or not DOT is needed with individual patients. Although DOT is not required, the TB Program, OHA recommends DOT for children.

How frequently were toxicities observed in the 12-dose regimen in the clinical trial participants? (1,4)

- Possible hypersensitivity (3.8%)
- Rash (0.8%)
- Hepatotoxicity (0.4%)
- Thrombocytopenia (infrequent)
- Other toxicities (3.2%)

Note: Please refer to product insert for full list of side effects.

What can a hypersensitivity reaction include and how should I respond? (6)

Hypersensitivity reactions may include a flu-like syndrome (e.g., fever, chills, headaches, dizziness, musculoskeletal pain), thrombocytopenia, shortness of breath or other signs and symptoms including wheezing, acute bronchospasm, urticaria, petechiae, purpura, pruritus, conjunctivitis, angioedema, hypotension or shock.

- **If moderate to severe reaction** (e.g., thrombocytopenia, hypotension), hospitalization or life-threatening event:

 **discontinue treatment.**

- **If mild reaction** (e.g., rash, dizziness, fever)

 **continue to monitor patient closely with a low threshold for discontinuing treatment.**

How do I report an adverse event regarding the 12-dose regimen?

- Report all adverse events to FDA MedWatch at www.fda.gov/Safety/MedWatch/default.htm.
- Report adverse events leading to death or hospitalization to Oregon Health Authority Public Health Division's TB Program at 971-673-0169 for reporting to the CDC.

Are there drug-drug interactions?

- INH increases blood levels of phenytoin and disulfiram.
- Rifapentine decreases blood levels of oral contraceptives, warfarin, sulfonylureas, methadone, steroids, some cardiac medications and some antibiotics including fluoroquinolones.

Note: Please refer to product insert for full list of drug-drug interactions.

What type of monitoring do I need to do? (4)

- Evaluate the patient monthly to identify adverse events and to assess treatment adherence;
- Baseline hepatic chemistry is recommended for patients with these specific conditions:
 - ◆ HIV infection;
 - ◆ Liver disorders;
 - ◆ In the postpartum period (≤ 3 months after delivery);
 - ◆ Regular alcohol or injecting drug use.
 - ◆ Consider also for older persons and those taking medications for chronic medical conditions.
- If baseline hepatic chemistry testing is abnormal, determine risk vs. benefit of treatment. If decision is made to treat, continue with subsequent hepatic chemistry testing.

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Resources

TB Program
Oregon Health Authority
Public Health Division
<http://healthoregon.org/tb>
971-673-0169

Centers for Disease Control and Prevention
Division of Tuberculosis Elimination
www.cdc.gov/tb
1-800-232-4636

Curry International Tuberculosis Center
www.currytbcenter.ucsf.edu
1-877-390-6682 or 415-502-4700

FDA MedWatch
www.fda.gov/Safety/MedWatch/default.htm
1-888-463-6332

References

1. Sterling, T., Villarino, M., Borisov, A., et al. (2011). Three months of rifapentine and isoniazid for latent tuberculosis infection. *The New England Journal of Medicine*, 365(23). 2155–2166.
2. Villarino, M., Scott N., Weis, S., et al. (2015). Treatment for Preventing Tuberculosis in Children and Adolescents. *JAMA Pediatrics*, 169(3): 247–255.
3. Belknap, R., Holland, D., Feng, P.J., et al. (2017). Self-administered Versus Directly Observed Once-Weekly Isoniazid and Rifapentine Treatment of Latent Tuberculosis Infection: A Randomized Trial. *Annals of Internal Medicine*, 167(10). 689–697.
4. Centers for Disease Control and Prevention. (2018). Update of Recommendations for Use of Once-Weekly Isoniazid-Rifapentine Regimen to Treat Latent Mycobacterium tuberculosis Infection. *MMWR* 67(25). 723–726.
5. Martinson, N., Barnes, G., Moulton, L., et al. (2011). New regimens to prevent tuberculosis in adults with HIV infection. *New England Journal of Medicine*, 365. 11–20.
6. Sterling, TR., Moro, RN., Borisov, AS., et al. (2015). Flulike and other systemic drug reactions among persons receiving weekly rifapentine plus isoniazid or daily isoniazid for treatment of latent tuberculosis infection in the PREVENT tuberculosis study. *Clinical Infectious Diseases*, 61 (4). 527–535.



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