

12-dose Isoniazid + Rifapentine Regimen (3HP) for the Treatment of TB Infection

NOTE: It is imperative to rule out active disease in all persons prior to initiating treatment for TB infection

What is the 12-dose INH + rifapentine regimen?

It consists of 12 once-weekly doses of isoniazid (INH) and rifapentine administered by directly observed therapy (DOT) or self-administered therapy (SAT) for the treatment of TB infection.

Is the regimen effective?

Randomized controlled trials in adults and children showed that the 12-dose regimen administered by DOT is as effective as 9 months of daily INH SAT for TB infection treatment, which is estimated to be about 90% effective. The 12-dose regimen was more likely to be completed when compared to 9 months of daily INH. Completion rates for the 12-dose regimen are similar in US populations whether given as DOT or SAT.

What are the advantages of the 12-dose regimen?

- The 12-dose regimen reduces treatment time by two-thirds (from 9 months to 3 months)
- Weekly dosing offers convenience
- Higher rates of treatment completion
- Substantially lower rates of hepatotoxicity

Who should be considered for treatment with the 12-dose regimen?

- The 12-dose regimen is recommended as an equal alternative to 9 months of daily INH by SAT for treating TB infection
- Short course regimens are preferred, whenever possible, to enhance the likelihood of TB infection treatment completion

Who is NOT recommended for treatment with the 12-dose regimen?

- Children under 2 years of age
- HIV-infected persons with unacceptable drug-drug interactions
- Individuals taking medications that may have drug interactions that are difficult to manage with the 12-dose regimen
- Persons presumed infected with *M. tuberculosis* resistant to INH or rifampin
- Pregnant women or women planning to become pregnant during treatment.

- Individuals who have had prior adverse events or hypersensitivity to INH or rifamycins

What are the doses?

Drug	Dosage	Maximum dose
INH	15 mg/kg rounded to nearest 50/100 mg 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	
	≥ 50.0 kg = 900 mg	
Rifapentine tablets can be crushed and administered with semi-solid food for children unable to swallow pills		

Does this regimen have to be administered via DOT?

- As of 2018, the CDC has approved this regimen for DOT or SAT
- A CDC-sponsored trial investigated SAT of 3HP and found that SAT is non-inferior in the United States³
- **The Los Angeles County Tuberculosis Control Program recommends that the 12-dose regimen be administered via DOT until the clinician becomes experienced with its potential side-effects and the patient is familiar with the dosing before administering this regimen via SAT. Initial DOT is strongly recommended in younger children**

What are the possible side effects?

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

NOTE: Refer to product insert for full list of side effects.

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

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

- If moderate to severe reaction (e.g., thrombocytopenia, hypotension, syncope), 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?

All adverse events should be reported to FDA MedWatch, <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>. Report adverse events leading to death or hospitalization to the local health department, who will then report to the CDPH TB Control Branch (TBCB). TBCB then reports these events to the CDC.

Are there drug-drug interactions?

- INH increases blood levels of phenytoin, carbamazepine and valproic acid
- Rifapentine decreases blood levels of numerous drugs (e.g., transplantation drugs, oral contraceptives, warfarin, sulfonyleureas, opioids, steroids, antihypertensives, etc.)
- Rifapentine has interactions similar to rifampin; it induces cytochromes P4503A4 & P4502C8/9

NOTE: refer to product insert and/or pharmacological reference for a full list of interactions.

What type of monitoring do I need to do?

- Monthly interviews and brief physical examinations to identify treatment-associated adverse events
- Baseline hepatic chemistry is recommended for patients with specific conditions:
 - HIV-positive
 - Liver disorders
 - Pregnancy and 3 – 6 months postpartum
 - Regular alcohol use
 - Consider also for older persons and those taking medications for chronic medical conditions

- If baseline hepatic chemistry testing is abnormal, continue with at least monthly testing as indicated

What is completion of therapy?

- Defined as completing at least 11 weekly doses of treatment within 16 weeks. Doses should be given at least 72 hours apart

What should be done when treatment is completed?

- Patients should receive written documentation of TST or IGRA testing results, CXR results, names and dosages of medications, and duration of treatment which can be presented anytime TB testing is requested
- Providers should re-educate patients about the signs and symptoms of TB disease and advise them to contact a medical provider if these symptoms develop
- Repeat CXR's are not indicated unless TB symptoms suggestive of active TB disease are present

What is the approximate public health (340B pricing) drug costs of the 12-dose regimen?

INH + rifapentine (entire treatment course)	\$96 + \$194
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How do I obtain Medi-Cal reimbursement?

- Use the ICD-10 codes for TB infection (LTBI)
- For public health providers, DOT is reimbursed at approximately \$19 per encounter

How do I get rifapentine for my program or clinic?

Rifapentine can be ordered directly from your distributor or wholesaler, or directly from the manufacturer, Sanofi-Aventis, at www.sanofi.us

Resources

Los Angeles County TB Control Program

<http://www.publichealth.lacounty.gov/tb> 213-745-0800

California Department of Public Health Tuberculosis Control Branch (TBCB)

<http://www.cdph.ca.gov/programs/tb/Pages/default.aspx>
510-620-3000

California TB Controllers Association <http://www.ctca.org/> 510-479-6139

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

Curry International Tuberculosis Center Warmline Consultation Service
<http://www.currytbcenter.ucsf.edu/> 877-390-6682 or 415-502-4700

FDA MedWatch <https://www.fda.gov/Safety/MedWatch/default.htm>