# Isoniazid and Rifampin (3HR) for the Treatment of TB Infection

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

## How is isoniazid and rifampin (3HR) prescribed to treat TB infection?

Isoniazid and rifampin are taken once daily for 3 months.

## Is the regimen effective?

Randomized controlled trials in HIV-negative adults and children with a positive tuberculin skin test (TST) who received a 3-month course of daily isoniazid and rifampin (3HR) appeared to have similar risk for TB disease, hepatotoxicity, and discontinuation of therapy due to adverse effects as those who received a 6-month course of isoniazid. Specifically, among children <15 years old, 3HR appeared as effective as a 6-month or longer course of isoniazid. Additionally, among HIV-positive persons regardless of whether they were TST-positive, -negative, or anergic, no difference was found in the incidence of TB disease among those who received 3HR compared with those who received 6 months or more of isoniazid.

## What are the advantages of 3HR?

- Reduces the treatment time by two-thirds (compared to 9 months of isoniazid)
- Higher rates of treatment completion which increases treatment effectiveness

## Who should be considered for treatment with 3HR for TB infection?

- 3HR is a preferred treatment that is conditionally recommended for adults and children of all ages and for HIV-positive persons as drug interactions allow

## Who is *NOT* recommended for treatment with 3HR?

- HIV-positive persons with unacceptable drug-drug interactions
- Individuals taking medications that may have drug interactions that are difficult to manage with isoniazid and/or rifampin
- Persons presumed infected with *M. tuberculosis* resistant to isoniazid and/or rifampin
- Individuals with known hypersensitivity reactions to isoniazid and/or rifampin

## What are the possible side effects?

- Rash
- Hypersensitivity reactions
- Mild CNS changes
- Hematologic abnormalities
- Orange discoloration of body fluids
- Peripheral neuropathy: Vitamin B6/pyridoxine supplementation can decrease risk of peripheral neuropathy in persons who are pregnant, breast feeding, those with DM, renal failure, HIV, & alcoholism. The usual dose of B6/pyridoxine is 25-50 mg daily for adults and 1-2 mg/kg daily for children
- Hepatotoxicity: clinically apparent hepatitis, liver failure, and jaundice occur very rarely in those < 20 years of age; risk increases with advancing age, during pregnancy and the early post-partum period, and preexisting liver disease. Fatal hepatitis has occurred with continued administration of isoniazid after onset of clinical hepatitis symptoms

## What is the dosage of 3HR for TB infection and how is it administered?

| Age group | Drug | Dosage | Maximum dose |
|---|---|---|---|
| Adults | Isoniazid | 5 mg/kg daily | 300 mg |
| | Rifampin | 10 mg/kg daily | 600 mg |
| Children | Isoniazid | 10-15 mg/kg daily | 300 mg |
| | Rifampin | 15-20 mg/kg daily | 600 mg |
| Rifampin capsules can be opened and the contents mixed with semi-solid food for patients who are unable to swallow pills. Isoniazid tablets can be split/crushed and mixed with semi-solid food for patients who are unable to swallow pills. B6/pyridoxine should be given with isoniazid to mitigate the risk of peripheral neuropathy. Please refer to the "Isoniazid (INH) for the Treatment of TB Infection" guideline for B6/pyridoxine dosing. | | | |

## Are there drug-drug interactions with 3HR?

- Isoniazid is a CYP3A4 C219 inhibitor and thus increases certain substrates (e.g., Dilantin (phenytoin), carbamazepine, among others). Closer monitoring may be considered for patients on such medications
- Rifampin induces cytochromes P4503A4 & P4502C8/9 and decreases blood levels of numerous medications (e.g. transplantation drugs, oral contraceptives, warfarin, sulfonylureas, opioids, steroids, etc.)
- Rifampin is contraindicated in HIV-positive persons being treated with certain combinations of antiretroviral drugs (ARVs). For more information on interactions with ARVs see: https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/whats-new

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

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## What type of monitoring is needed for 3HR treatment?

- 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 post-partum
  - 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, but more frequent testing, e.g. weekly or biweekly is appropriate until the patient's pattern for hepatic chemistry testing is established
- Therapy should be discontinued or held when ALT is ≥ 3 times the upper limit of normal if symptomatic of drug-induced hepatitis (e.g., anorexia and fatigue), and when ALT is ≥ 5 times the upper limit of normal without symptoms, or total bilirubin > 3.0. If planning to use INH + Rifampin regimen, please see guidelines "Rifampin for the Treatment of TB Infection" regarding additional considerations when using rifampin

## What is completion of therapy?

- Defined as completing 90 daily doses within a 4-month period

## 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 to present anytime TB testing is requested
- Providers should re-educate patients about the signs and symptoms of active TB disease and advise them to contact a medical provider if these symptoms develop
- Repeat CXRs are not indicated unless TB symptoms suggestive of active TB disease are present

## 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

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

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