More About Rifapentine (P) and using P with INH (H)

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Rifapentine Pharmacology

Egelund EF and Peloquin CA Expert Rev Clin Pharmacol. 2016 Aug [Epub ahead of print]
Alfarisi O et al. Expert Rev Clin Pharmacol.2017;10:1027

- Rifapentine is a semisynthetic cyclopentyl rifampin derivative
- The rifamycins bind to the β-subunit of MTB's DNA-dependent RNA polymerase, which inhibits messenger RNA elongation and are bactericidal against extracellular organisms
- Due to the shared mechanism of action between the rifamycins, cross-resistance occurs
- A similar spectrum of activity to rifampin
  - MIC against MTB is two to fourfold lower than rifampin's, ranging from 0.01 to 0.06 μg/mL

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- Rifapentine is hydrolyzed to its less active metabolite, 25-desacetyl rifapentine which are eliminated primarily via biliary excretion.
- Rifapentine's half-life is approximately 14–16 hours while 25-desacetyl rifapentine is approximately 17 hours.
- Food significantly impacts rifapentine's bioavailability,
  - meals can increase rifapentine's exposure from 33% to 86%, depending on meal composition, with high-fat meals having the greatest impact on bioavailability.
- Rifapentine's increase in bioavailability when administered with food is the opposite of rifampin's, which decreases with food administration.

Dosing for 3 HP

Rifapentine is available only as a 150 mg tablet for oral administration. It can be crushed for pediatric dosing

Adults and children > 45 kg

- 900 mg INH once weekly
- 900 mg Rifapentine once weekly
- Vitamin B 6 50 mg once weekly

- **Completion** - 11 to 12 doses in 16 weeks

Children 2 – 12 years*

- INH 15 mg/kg (round to nearest 50 or 100 mg tablet)
- Rifapentine
  - 10-14 kg: 300 mg
  - 14.1-25 kg: 450 mg
  - 25.1-32 kg: 600 mg
  - 32.1-49.9 kg: 750 mg
  - ≥ 50 kg: 900 mg

* Especially when short course is desirable; pill burden may be a problem

Pill Burden With 3HP is Currently a Problem for Some

- Current: 10 pills (6 rifapentine, 3 INH, 1 Vit B6)
- Future: 4 pills (3 RPT/INH + 1 B6)

2xPriftin® 150mg

+

Isoniazid®

=

PH 300/300

Rifapentine dosing

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Alfarisi O et al. Expert Rev Clin Pharmacol.2017;10:1027
Weiner M et al. Am J Respir Crit Care Med, 2004; 169: 1191

- Rifapentine safe at doses higher than 900 mg/dose given daily or weekly
- Rifapentine plasma concentration versus dose curve does not increase proportionally; doubling the dose does not result in twice the concentration: either AUC or Cmax.
- Dose modification by weight not necessary for 3HP

Rifapentine for TBI

Egelund EF and Peloquin CA Expert Rev Clin Pharmacol. 2016 Aug [Epub ahead of print]

- Factors that enhance rifapentine's suitability for LTBI
- Rifapentine binds to MTB's DNA-dependent RNA even with low enzyme activity, as seen with dormant mycobacteria.
- Rifapentine accumulates in human granulomas with intracellular/extracellular ratios of 24:1
- This ratio of intracellular/extracellular penetration of rifapentine is about four to fivefold higher than that of rifampin

Comparing features of rifampin versus rifapentine

Alfarisi O et al. Expert Rev Clin Pharmacol.2017;10:1027

	Rifampin	Rifapentine
• MIC	0.125–0.25 µg/mL	0.01–0.06 µg/mL
• Half-life	2 h	15 h
• Protein binding	80–85%	97–99%
• Food requirement	No	Yes
• Hepatic enzyme induction	3-fold	4.5-fold
• Cavitary penetration	Good	Poor
• Efficacy	Comparative efficacy at high doses to be determined	

Rifampin (rifamycin) Toxicity

- Cutaneous Reactions: 6%, generally self- limited
- Orange discoloration of body fluids
- Gastrointestinal symptoms: nausea, anorexia, abdominal pain
- Flulike symptoms: < 1% of patients on intermittent therapy.
- Severe immunologic reactions: thrombocytopenia, hemolytic anemia, acute renal failure and thrombotic thrombocytopenic purpura (each < 0.1% of patients)
- Severe Hepatotoxicity: nearly 0% as monotherapy, may appear cholestatic

Rifampin (rifamycin) Drug Interactions

- Interactions due to induction of hepatic microsomal enzymes (cytochrome P-450, CYP, enzyme system) that accelerate metabolism of multiple drugs
- Major concern is reduction in serum concentrations of common drugs (BCP's, warfarin, etc.) to ineffective levels
- Bidirectional interactions between rifamycins, INH and antiretroviral agents

Common Rifampin (Rifamycin) Drug Interactions

- HMG-CoA reductase inhibitors
- Oral anticoagulants
- Oral contraceptives
- Cyclosporine/Tacrolimus
- Digoxin
- Glucocorticoids
- Itraconazole/ketoconazole
- Methadone
- Phenytoin
- Theophylline
- Verapamil/diltiazem
- Amiodarone
- Midazolam
- Thyroid hormone

Percentage Reduction in AUC of PI's and NNRTI's by Rifampin

(Baciewicz Am J Med Sci 2008; 335: 126)

• Indinavir	89%
• Ritonavir	35%
• Nelfinavir	82%
• Atazanavir	72%
• Fosamprenavir	82%
• Saquinavir	84%
• Delavirdine	96%
• Nevirapine	20-58%
• Efavirenz	25%

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Panel's Recommendations

Only efavirenz (EFV)- or raltegravir (RAL)-based regimens (in combination with either abacavir/lamivudine [ABC/3TC] or tenofovir disoproxil fumarate/emtricitabine [TDF/FTC]) can be used with once-weekly isoniazid plus rifapentine (AIII).

https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/0

Mycobacterium Tuberculosis Disease with HIV Coinfection

(Last updated: Sept 22, 2017; last reviewed: September 22, 2017)

Three months of weekly rifapentine plus isoniazid is less hepatotoxic than nine months of daily isoniazid for LTBI.

Bliven-Sizemore E et al. Int J Tuberc Lung Dis. 2015;19:1039-44

- 6862 participants,
- 77 (1.1%) developed hepatotoxicity;
  - 52 (0.8%) were symptomatic;
  - 1.8% (61/3317) were on 9H and
  - 0.4% (15/3545) were on 3HP ($P < 0.0001$).
- Risk factors for hepatotoxicity were age, female sex, white race, non-Hispanic ethnicity, decreased body mass index, elevated baseline AST, and 9H.
- For persons with these risk factors, 3HP may be preferred to INH.

Flu-like 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

Sterling TR et al. Clin Infect Dis. 2015, 61; 52-535

- Among 7552 persons who received ≥1 dose of study drug,
- 153 had a systemic drug reaction (SDR):
  - 3.5% with 3HP vs 0.4% with 9H ($P < .001$).
- In the 3HP arm,
  - 63% had flu-like syndrome
  - 17% had cutaneous reactions
  - 0.3% had severe reactions (6 were hypotensive)
  - 6 reported syncope.
- Symptoms occurred after a median of 3 doses, and 4 hours after the dose; median time to resolution was 24 hours.

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Sterling TR et al. Clin Infect Dis. 2015, 61; 52-535

- No deaths or permanent sequelae from SDR;
- No instances of Stevens-Johnson syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms
- There was 1 episode each of thrombocytopenia (without evidence of bleeding), anemia (not hemolytic), and neutropenia.
- There were no reports of renal failure.
- The underlying mechanism for SDR is unclear.

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- Decisions regarding re-challenge in participants with SDR were made by the site investigator.
- About half of participants with an SDR, including the severe events, were not re-challenged.
- Difficult to ascertain whether isoniazid, rifapentine, or their combination was the cause of SDR.
- No early clinical predictors of subsequent SDR since the median time to onset in the 3HP arm was before the first monthly visit (week 3).

INH Hepatotoxicity

- Asymptomatic elevation of aminotransferases: 20% of patients
- Clinical hepatitis: 0.6% of patients
- Fulminant hepatitis (hepatic failure)
  - Approximately 4/100,000 persons completing therapy (continued INH with symptoms of hepatitis, prior INH hepatotoxicity, malnutrition).

Severe INH Liver Injuries Among Persons Being Treated for LTBI, U.S., 2004-2008

MMWR 3/5/10/ 59(08); 224-229

- CDC project to monitor SAEs with treatment of LTBI 2004-2008
- 10 patients with CDC on-site investigation
- All patients had:
  - indications for LTBI treatment,
  - were prescribed INH within recommended dosage range,
  - took the medication as prescribed
- Prescribers followed guidelines for monthly clinical monitoring
- Symptoms 1-7 months after INH started
- 2 patients INH discontinued within 3 days of symptoms, 8 stopped at least one week after symptom onset

Severe INH Liver Injuries Among Persons Being Treated for LTBI, U.S., 2004-2008

MMWR 3/5/10/ 59(08); 224-229

"Medical providers should emphasize to patients that *INH treatment should be stopped immediately upon the earliest onset of symptoms* (e.g. excess fatigue, nausea, vomiting, abdominal pain, or jaundice), even before a clinical evaluation has been conducted, and that initial symptoms might be subtle and might not include jaundice."

Treatment of Latent Tuberculosis Infection: An Updated Network Meta-analysis of 8 new and 53 previously included studies.

Zenner D et al. AIM;167:248-255

Table 2. ORs and Treatment Rankings for Hepatotoxicity, Derived From the Network Meta-analysis

Regimen	OR vs. Placebo (95% CrI)	OR vs. No Treatment (95% CrI)	Rank (95% CrI)
No treatment	0.24 (0.06-0.75)	1.00 (reference)	4 (2-7)
Placebo	1.00 (reference)	4.12 (1.33-15.88)	9 (7-10)
INH 6 mo	0.27 (0.10-0.60)	1.10 (0.40-3.17)	5 (3-7)
INH 9 mo	0.41 (0.08-1.62)	1.70 (0.35-8.05)	6 (3-10)
INH 12-72 mo	0.66 (0.26-1.32)	2.72 (0.96-7.44)	8 (6-10)
RPT-INH	0.13 (0.03-0.42)	0.52 (0.13-2.15)	2 (1-5)
RMP	0.03 (<0.02-0.16)	0.14 (0.02-0.81)	1 (1-2)
RMP-INH 3-4 mo	0.17 (0.05-0.46)	0.72 (0.21-2.37)	3 (2-6)
RMP-INH-PZA	0.58 (0.07-3.72)	2.41 (0.25-20.02)	7 (2-10)
RMP-PZA	0.80 (0.25-2.17)	3.32 (0.99-11.23)	9 (6-10)

CrI = credible interval; INH = isoniazid; OR = odds ratio; PZA = pyrazinamide; RMP = rifampicin; RPT = rifapentine.

Update of Recommendations for Use of Once-Weekly Isoniazid-Rifapentine Regimen to Treat Latent Mycobacterium tuberculosis Infection.

Borisov AS et al. MMWR Morb Mortal Wkly Rep. 2018 Jun 29;67(25):723-726

- Inform the patient or parents or legal guardians about possible adverse particularly drug hypersensitivity reactions, rash, hypotension, or thrombocytopenia.
- Conduct monthly evaluations to assess adverse effects.
- Order baseline hepatic chemistry blood tests (at least aspartate aminotransferase [AST]) for patients with the following specific conditions:
  - human immunodeficiency virus infection,
  - liver disorders,
  - postpartum period (≤3 months after delivery),
  - regular alcohol use,
  - injection drug use,
  - use of medications with known possible interactions.

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- Conduct blood tests at subsequent clinical encounters for patients whose baseline testing is abnormal and for others at risk for liver disease.
- Discontinue 3HP if a serum AST concentration is ≥5 times the upper limit of normal in the absence of symptoms or ≥3 times the upper limit of normal in the presence of symptoms.
- In case of a possible severe adverse reaction, discontinue 3HP and provide supportive medical care.
  - Conservative management and continuation of 3HP under observation can be considered in the presence of mild to moderate adverse events as determined by health care provider.

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- For patients coinfected with HIV, information about interactions between rifamycins (e.g., rifampin, rifabutin, and rifapentine) and antiretroviral agents, is available in the U.S. Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.
- These frequently updated guidelines address LTBI management in persons with HIV coinfection with tables on drug interactions.* https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/367/overview
- ***Use of concomitant LTBI treatment and antiretroviral agents should be guided by clinicians experienced in the management of both conditions.***

Update of Recommendations for Use of Once-Weekly Isoniazid-Rifapentine Regimen to Treat Latent Mycobacterium tuberculosis Infection.

Borisov AS et al. MMWR Morb Mortal Wkly Rep. 2018 Jun 29;67(25):723-726

- Approximately 4% of all patients using 3HP experience flu-like or other systemic drug reactions, with fever, headache, dizziness, nausea, muscle and bone pain, rash, itching, red eyes, or other symptoms.
- Approximately 5% of persons discontinue 3HP because of adverse events, including systemic drug reactions; these reactions typically occur after the first 3–4 doses, and begin approximately 4 hours after ingestion of medication.
- Hypotension and syncope have been reported rarely (two cases per 1,000 persons treated).
- If symptoms suggestive of a systemic drug reaction occur, patients should stop 3HP while the cause is determined. Symptoms usually resolve without treatment within 24 hours.
- Neutropenia and elevation of liver enzymes occur uncommonly

3HP Questions

a. What to do about common drug-drug interactions such as anti-hypertensives, hypoglycemic agents, lipid lowering drugs?
b. Are there adverse events unique to 3HP?
c. When a patient has classic flu-like reaction with Rifapentine, should therapy be stopped or should the patient be pre-medicated and treatment continued?
d. Can I use 3HP in patients with liver problems?
e. When is it safe to restart 3HP after an interruption for adverse events?

Retail cost at UTHSCT pharmacy for Rifapentine, INH and Rifampin

• Rifapentine 150 mg #6 (one week)	$18.25
• Rifapentine 150 mg #72 (12 weeks)	$218.97
• Isoniazid 300 mg #3 (one week)	$1.28
• Isoniazid 300 mg #36 (12 weeks)	$46.08
• Rifampin 300 mg #14 (one week)	$8.25
• Rifampin 300 mg #56 (4 weeks)	$33.00

HEARTLAND
NATIONAL TB CENTER
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The Menu of LTBI Treatment Options in 2018

Me, again

Treatment Options for LTBI

- INH +RPT once weekly
- Rifampin daily
- INH 9 daily
- INH 6 daily
- Moxifloxacin
- Rifabutin

- 12 weeks (12 doses)
- 4 months (120 doses)
- 9 months (270 doses)
- 6 months (180 doses)
- 6 months (180 doses)
- ?4 months (120 doses)

The longer the duration/more doses, the less likely your patient is to complete treatment

Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults.

Menzies et al, N Engl J Med. 2018 Aug 2;379(5):440-453.

- Open label trial in 9 countries comparing 4 months rifampin vs 9 months INH:
  - study endpoint: prevalence of TB 28 months after randomization
- Rmp: 3443 patients:
  - 4 active TB, 4 clinical TB
- INH: 3416 patients:
  - 4 active TB, 5 clinical TB

Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults.

Menzies et al, N Engl J Med. 2018 Aug 2;379(5):440-453.

- Treatment completion:
  - Rmp 79%,
  - INH 63% ($p < 0.001$)
- Clinically significant (drug stopped) hepatotoxic events:
  - rmp 0.3%,
  - INH 1.7% ($p < 0.001$)
- 4 months of rifampin was not inferior to 9 months INH for preventing development of active TB but with significantly higher completion rates and greater safety than INH.

Rifampin Treatment of TB Infection

- Pros vs INH:
  - Higher Completion Rates
  - Equally effective
  - Fewer Side Effects
  - Less Hepatotoxicity
  - Cost effective
  - Rifampin resistance uncommon
    - Globally 3%

- Cons vs INH:
  - Drug Interactions
    - Hormone Contraceptives
    - Warfarin
    - Prednisone
    - **HIV Antiretroviral agents**
    - And many more…must look up all drugs for interactions
    - Orange Body Fluids
  - Other Potential Side Effects (rare):
    - Rash
    - Thrombocytopenia
    - Anemia
    - Leukopenia
    - Allergic Interstitial Nephritis

Treatment for LTBI in contacts of MDR-TB patients, Federated States of Micronesia, 2009-2012.

Bamrah S. Int J Tuberc Lung Dis. 2014;18:912.

- 119 contacts of MDR-TB patients
- 12 mos daily FQ-based treatment of MDR TBI by DOT.
  - Moxi (45%), Levo (4%), Moxi + EMB, Levo + EMB, Levo + ETH
- 119 infected contacts, 104 began treatment, 15 refused
- Of the 104 who initiated treatment:
  - 93 (89%) completed treatment, 4 discontinued due to AE's.
  - None of the 104 contacts who undertook MDR LTBI treatment of any duration developed MDR-TB disease;
  - 3 of 15 contacts who refused and 15 unidentified contacts developed MDR-TB disease.

Questions: Alternative TBI Treatment

- What is the general practice for switching to a new regimen? If a patient has had 25% of the RPT/INH regimen (and is being switched to daily RIF), would you need 75% of the 4 month RIF regimen?

Future Studies for Rifapentine in TBI

- Assessment of the Safety, Tolerability, and Effectiveness of Rifapentine Given Daily for Latent Tuberculosis
  - • Drug: Rifapentine daily for 6 weeks
  - • Drug: Rifapentine and Isoniazid weekly for 12 weeks
  - • Drug: Rifampin and Isoniazid daily for 12 weeks
  - • Drug: Rifampin daily for 16 weeks
- Not yet recruiting

Pearls of Wisdom from Barbara Seaworth for Treating TBI

- Consider the shortest regimen possible to increase the odds of completion
- Be vigilant
- Be supportive…..and forgiving