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3HP DRUG-DRUG INTERACTIONS, INCLUDING ART

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Acronyms and Abbreviations

3HP	3 months of rifapentine and isoniazid, in 12 weekly doses
TPT	TB preventive therapy
DDI	Drug-drug interaction
INH or H	Isoniazid
RPT or P	Rifapentine
HIV	Human immunodeficiency virus
IPT	Isoniazid preventive treatment
NRTI	Nucleoside reverse transcriptase inhibitors
NNRTI	Non-nucleoside reverse transcriptase inhibitors
PLHIV	Person/people living with human immunodeficiency virus
PI	Protease inhibitors
CYP	Cytochrome P450 system
WHO	World health organisation
RIF	Rifampin
PK	Pharmacokinetics

1. What is 3HP?

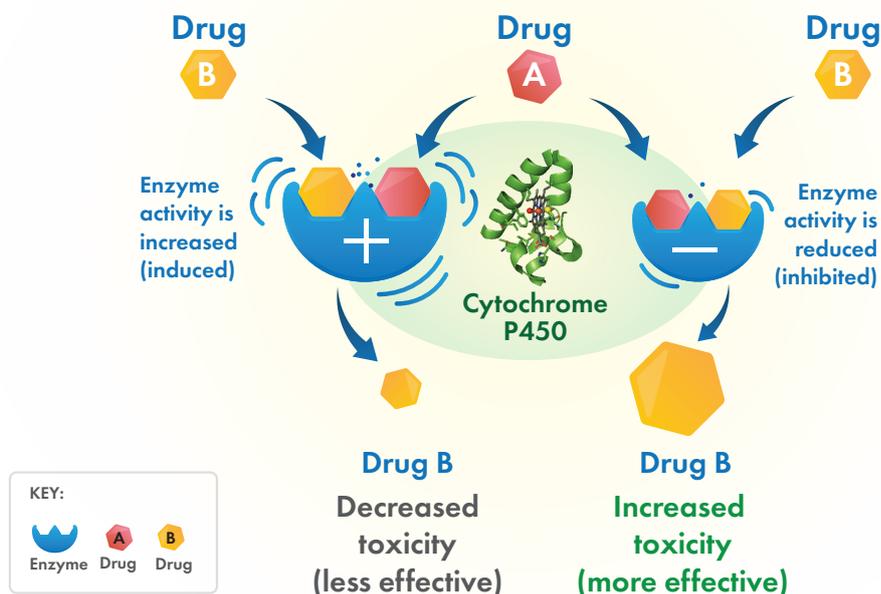
3HP is a short-course Tuberculosis Preventive Treatment (TPT) regimen which is taken once weekly for 12 weeks and endorsed by the WHO¹. It combines high dose isoniazid (H) and high dose rifapentine (P). Randomized controlled trials have shown that 3HP is at least as effective at preventing active TB as other recommended TPT regimens (including: 6-9 months of isoniazid alone, 3-4 months of rifampicin alone, and 3 months of daily rifampicin and isoniazid). 3HP is associated with significantly lower hepatotoxicity and higher rates of treatment completion than isoniazid preventive treatment^{2,3,4,5}.

2. What is a drug-drug interaction?

When two drugs are given together, there can be a change in either of the drug's effect on the body. A drug-drug interaction (DDI) can increase or decrease the action of either or both drugs, or can be the cause of adverse events. A DDI can therefore delay, enhance or decrease the absorption of either of the drugs taken together. Many DDI are caused by an enzyme system in the liver called the cytochrome P450. These enzymes can either be induced, and hence more active, or inhibited and hence less active. When more active, they increase the metabolism of other drugs that are passed through the same system and reduce the concentration of these drugs. This can render the second drug ineffective. When the enzyme complex is made less active, then the drugs administered will have a reduced metabolism, and their concentration will be increased in the body. They can then lead to more adverse events and side effects.

3. Drug-drug interactions with the 3HP regimen

Both daily rifapentine (RPT) and daily rifampicin (RIF) are known to strongly induce the cytochrome P450 enzyme system. Weekly RPT dosing also induces this system, although the duration of the induction is not clear when given weekly and caution is needed when prescribing RPT with some drugs. The induction and increase in activity of the enzyme means that the levels of these drugs are reduced, and can therefore be ineffective.



Isoniazid is also a known inhibitor of the cytochrome system, and therefore can slow the elimination of co-administered drugs. This can lead to an increase in side-effects. Some people are also slow acetylators of INH, meaning that they eliminate INH more slowly. This can lead to increased INH concentrations and can potentiate the effect on the cytochrome enzymes⁶.

As both drugs have opposing effects on the cytochrome system in some instances, the degree of inhibition or induction by each will determine the direction of the effect. Mostly, rifampentine is thought to be a more potent inducer than INH is an inhibitor if they are administered together.

Table 1: Common drug interactions with rifampentine and INH

Medication Class	RPT decreases blood levels of	INH increases blood levels of
Antiarrhythmics	Disopyramide/Mexiletine/ Quinidine/Tocainide	
Antibiotics	Chloramphenicol/Clarithromycin/ Dapsone/Doxycycline/ Fluoroquinolones	
Anticoagulants	Warfarin	Warfarin
Anticonvulsants	Phenytoin	Phenytoin, Carbamazepine
Antidepressants	Amitriptyline/Nortriptyline	Some SSRIs
Antimalarials	Quinine, Artemisin	Halofantrine
Antipsychotics	Haloperidol	Haloperidol, Pimozide
Antivirals	Antiretrovirals (Ritonavir)	
Azole Antifungals	Fluconazole, Itraconazole, Ketoconazole	Fluconazole, Itraconazole, Ketoconazole
Barbiturates	Phenobarbital	
Benzodiazepines	Diazepam	Diazepam, Triazolam
Beta-Blockers	Propranolol	
Calcium Channel Blockers	Diltiazem/Nifedipine/Verapamil	
Cardiac Glycoside Preparations	Digoxin	
Corticosteroids	Prednisone	
Fibrates	Clofibrate	
Oral hypoglycaemic agents	Sulfonylureas	
Hormonal Contraceptives	Ethinyl oestradiol/Levonorgestrel	
Immunosuppressants	Cyclosporine/Tacrolimus	
Methylxanthines	Theophylline	Theophylline
Narcotic analgesics	Methadone	Levomethyldate acetate
Phosphodiesterase-5 (PDE-5) Inhibitors	Sildenafil	
Thyroid Medications	Levothyroxine	

Likewise, a drug-drug interaction does not necessarily mean that the dosage needs to be adjusted or that concomitant administration needs to be completely avoided. Where available, pharmacokinetic studies can be referenced to understand the magnitude of the interaction and the effect, and whether dose adjustment is necessary. Country guidelines and international freely available resources should be consulted about drug-drug interactions and dose adjustments.

If in doubt about any drug interaction, please consult a pharmacologist.

4. Other considerations for co-administration of 3HP

Both INH and RPT can lead to side-effects. Notably INH can lead to liver damage especially when administered daily. Therefore, caution should be exercised when using with other drugs that have similar side effects, in order not to potentiate the occurrence of an adverse event. Common drugs where caution should be exercised are acetaminophen/paracetamol, alcohol, amoxicilline, terbinafine, phenothiazines, anabolic steroids should be avoided during treatment with 3HP. Likewise, unregulated supplements can lead to cytochrome activation or inhibition, which can potentiate liver damage or reduce efficacy of the regimen. Therefore, it is advised to avoid unregulated medicines and supplements when taking 3HP.

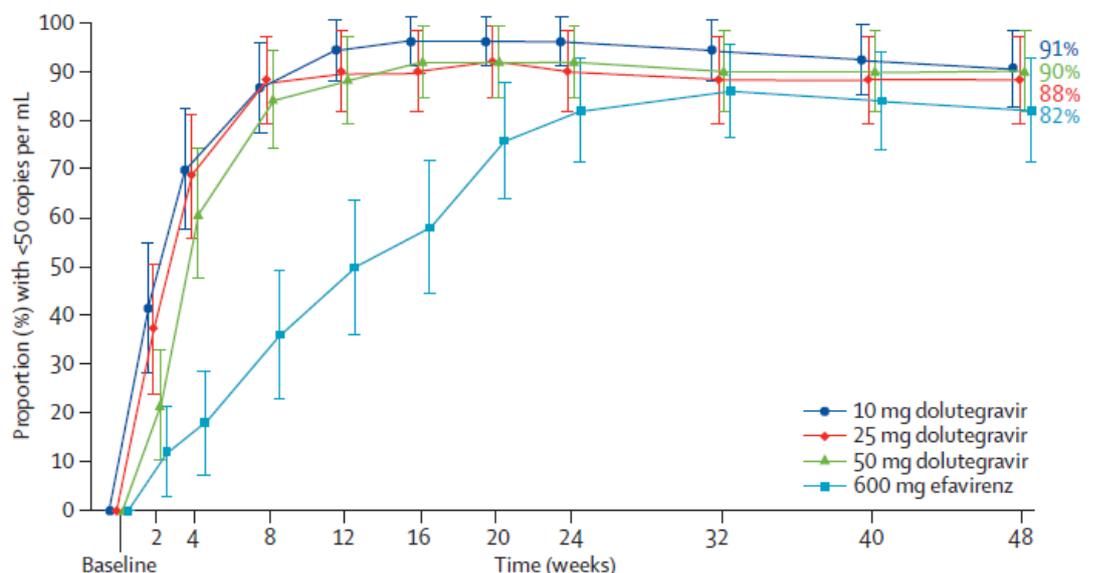
5. Antiretrovirals and 3HP

The 3HP regimen is intended to prevent TB in persons living with HIV. Therefore, special consideration needs to be taken to elaborate on the potential drug-drug interactions with this class of drugs.

5.1 Efavirenz and 3HP

3HP can be co-administered with efavirenz without clinically meaningful reductions in efavirenz mid-dosing concentrations or virologic suppression⁷ supporting the use of rifapentine with EFV, without dose adjustment⁸.

Figure 1: Effect of different doses of dolutegravir on viral suppression¹⁰



Information about drug-drug interactions between specific anti-mycobacterial agents including rifamycins (rifampin, rifabutin and rifapentine) and antiretroviral agents is available at Department of Health and Human Services, Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents External <https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0>. These frequently updated guidelines include a section addressing management of latent TB infection (LTBI) in persons co-infected with HIV, and tables with information on drug interactions. [Tables 18 and 19a-e](#) External provide up-to-date information concerning drug-drug interactions between specific antiretroviral agents and the several rifamycins, including rifapentine.

5.2 Dolutegravir and 3HP

The DOLPHIN study evaluated the safety and pharmacokinetics of 3HP co-administered with dolutegravir (DTG). 60 PLHIV in South Africa with undetectable viral loads on EFV-based regimens were switched to a DTG-based regimen for eight weeks. 3HP was co-administered with the DTG-based regimen after the first 8 weeks for 12 weeks, and then participants were followed up for four more weeks. 3HP decreased DTG bioavailability, and trough levels were decreased by approximately 50%. However, all trough levels but one was above the DTG IC90, and viral load remained suppressed in all patients. Overall, co-administration of DTG and 3HP was well-tolerated, safe and did not appear to require any dose-adjustment for DTG⁹.

The trough levels observed amongst patients with undetectable viral load in the DOLPHIN study were similar to trough levels observed amongst treatment naïve patients treated with 10mg of DTG in combination with dual-NRTI background regimen in the SPRING-1 study. These patients achieved viral suppression as rapidly as those receiving 50mg of DTG (Figure 1).

Therefore, DTG-based regimens (for example, the tenofovir, lamivudine and dolutegravir fixed dose combination) are recommended as safe and effective for patients newly initiating ART in co-administration with 3HP. This is currently being formally evaluated as a DOLPHIN sub-study. Given the pharmacokinetics of rifamycins in children, these data cannot be extrapolated to children under 15 years of age. Dolutegravir should not be co-administered with 3HP in children until more data is available.

5.3 Atripla and 3HP

Among 12 HIV-positive patients on a fixed dose combination antiretroviral treatment with emtricitabine, tenofovir disoproxil fumarate and efavirenz (Atripla), weekly RPT at a dose of 900mg resulted in minimal (C_{min}) reductions in efavirenz and tenofovir and did not modify HIV viral load or CD4 counts¹¹.

5.4 Raltegravir and 3HP

Administration of rifapentine with raltegravir (RAL) was found to be safe and well tolerated¹²; supporting the use of rifapentine with RAL¹³.

5.5 Antiretrovirals that cannot be used with 3HP

As potent enzyme inducers, the rifamycins can accelerate drug metabolism, resulting in significant reduction in ARV drug exposure. The common ARV drugs most affected by CYP induction include **all protease inhibitors (PIs) including kaletra (LPV/r)**, and some **non-nucleoside reverse transcriptase inhibitors (NNRTIs), including Nevirapine**¹⁴.

6. Contraception and 3HP

Most hormonal contraceptives are metabolized by the cytochrome system and will therefore be reduced when used at the same time as 3HP. In addition, there is insufficient data to show that 3HP is safe in pregnancy. Therefore, it is recommended to use non-hormonal methods of contraception or additional barrier methods for contraception while taking 3HP. Examples of these include male and female condoms, IUDs and diaphragms.

7. Antimalarials and 3HP

7.1 Background

Artemisinin-based combination therapies (ACTs) given for 3 days are recommended by WHO as the first-line treatment for uncomplicated *P. falciparum* malaria in all adults and children (with the exception of women in their first trimester of pregnancy). ACTs combine an artemisinin derivative with a partner drug. Artemisinin derivatives include dihydroartemisinin, artesunate and artemether.

5 ACTs are currently recommended by the World Health Organisation (WHO):

- artemether-lumefantrine (Coartem)
- artesunate-amodiaquine
- artesunate-mefloquine;
- artesunate + sulfadoxine - pyrimethamine;
- dihydroartemisinin-piperaquine.

The **latest WHO Malaria Guidelines**, published in 2015⁵ acknowledge the significant interactions between antimalarials and **rifampicin** in section 5.5 (pg. 56):

*“Concomitant administration of rifampicin during quinine treatment of adults with malaria was associated with a significant decrease in exposure to **quinine** and a **five-fold recrudescence rate**. Similarly, concomitant rifampicin with **mefloquine** in healthy adults was associated with **a three-fold decrease in exposure to mefloquine**”. In adults co-infected with HIV and TB who were being treated with Rifampicin, administration of **artemether+ lumefantrine** resulted in lower exposures to a 9 fold decrease in exposure to artemether, a 6 fold decrease in **dihydroartemesinin** and 3 fold decrease in **lumefantrine**”*

In 2015, the WHO concluded that “there is insufficient evidence at this time to change the current mg/kg body weight dosing recommendations; however, as these patients are at high risk of recrudescence infections, they should be monitored closely”

Referring to malaria treatment in special risk groups, the guidelines note that rates of treatment failure are higher with hyperparasitaemia and in areas with artemisinin-resistant *falciparum* malaria and malaria patients require greater exposure to antimalarial drugs (longer duration of therapeutic concentrations):

Options to manage this interaction include

- Increasing individual doses
- Increasing frequency
- Increasing duration
- Adding an additional antimalarial

However, it is also noted that increasing the dosage may not have the required effect (e.g. lumefantrine becomes saturated) or may cause toxicity. An additional advantage of lengthening treatment to 5 days (beyond the routine 3 days) is that it provides additional exposure of the asexual cycle to the artemisinin component as well as augmenting exposure to the partner drug. WHO recognises that the acceptability, tolerability, safety and effectiveness of augmented ACT regimens in special circumstances, including concomitant rifampicin therapy requires urgent evaluation¹⁶.

Induction of P450 cytochrome by intermittent doses of RPT is approximately 75-80% the magnitude of that caused by RIF. Daily dosing of RPT in the TBTC Study 29B resulted in greater induction of cytochromes than with RIF¹⁷, however, RPT is a less potent inducer when given weekly as in 3HP; this will likely wax and wane over the week and will be difficult to predict.

Other considerations:

There are important differences between using rifampicin (Rif) for TB treatment and rifapentine (RPT) for TB prevention. These include

- The risk/benefit calculation is necessarily different for co-administration of a preventative therapy (3HP) versus a curative one (TB treatment).
- Rifampicin forms a critical component of the Fixed Dose Combination (FDC) for TB treatment. There are no alternate options for TB treatment available for widespread use at this time. Rifapentine with INH (3HP) is one of the options available for TB prevention, alternatives are available
- TB preventive treatment may be interrupted, TB treatment should not be interrupted
- Health care workers and patients are likely to identify that a patient is taking TB treatment; they may miss that a patient is on a TB prevention regimen
- Treatment of severe malaria should not be compromised by 3HP at any stage
- 3HP could be a cause of malaria treatment failure, and where this is identified it must be addressed but it may not necessarily be identified in time for reasons including
- Patients often “self-medicate” for malaria without seeing a health care provider

In the case of malaria treatment failure, health care workers may not identify that the patient is on TB prevention/ the patient may not volunteer this information

7.2 Interim guidance for administration of 3HP in areas with high malaria prevalence

In the absence of information regarding 3HP and anti-malarials, the only guidance that can be offered currently is:

1. **If a patient is diagnosed with malaria but is not yet on TPT, decisions regarding 3HP initiation should be delayed until the episode of malaria has resolved.**

***Rationale:** if a patient is symptomatic/febrile due to malaria, then active TB cannot be effectively ruled out, and therefore a course of TPT should not be commenced*

2. **If a patient is diagnosed with malaria while on 3HP, the patient should be treated for malaria and clinically monitored according to national guidelines to ensure that the malaria is cured. At this stage, available evidence is insufficient to indicate that dosage of adjustment is required.**

***Rationale:** advice from WHO malaria section as stated in the WHO Malaria Treatment Guidelines that although there is a well understood DDI for TB treatment only (and not prevention and intermittent dosing), malaria treatment can proceed without dose adjustment.*

If a patient has malaria recrudescence while on 3HP, and the patient should be retreated for malaria according to national guidelines. The 3HP regimen should be withheld only if the new treatment also includes a drug with known interactions with rifamycins. In that case, 3HP should be recommenced once the episode of malaria is resolved.

***Rationale:** if a clinically significant DDI is already suspected in a particular patient due to malaria treatment failure, then retreatment should take that into consideration by withholding 3HP for the duration of malaria retreatment if using drugs that have a known interaction with rifamycins*

3. **If a patient meets diagnostic criteria for severe malaria (impaired consciousness, low blood glucose, high bilirubin/jaundice, bleeding, anemia, kidney failure and parasitemia >10%) while on 3HP, the 3HP regimen should be withheld and the patient should be urgently treated according to national guidelines. 3HP should be recommenced only once the episode of malaria is fully resolved.**

Rationale: severe malaria is associated with mortality approaching 100%, therefore all efforts should be made to ensure that treatment is successful, and 3HP should be withheld.

7.3 Other recommendations

- Malaria due to plasmodium vivax and ovale have a different treatment regimen. However, it is likely that drugs such as primaquine and tagenaquine, used for treatment in these subsets, would also have an interaction with RPT. Caution should therefore be exercised when co-administering these drugs. However, these forms of malaria are typically less severe and it would be unlikely to lead to more severe presentations if co-administered.

8. Key take home points

- Women who are using any hormonal contraceptives must be advised to use additional barrier methods to avoid pregnancy
- There is currently insufficient evidence to support the use of 3HP in pregnancy and it is therefore not recommended for pregnant women
- Caution should be exercised when co-administering any drug that could be decreased by RPT or increased by INH – advice from an expert should be obtained when in doubt
- Administration of most commonly used antiretrovirals is safe with 3HP (except Nevirapine and Protease inhibitors)
- Unregulated supplements should be avoided when taking 3HP as their effect on the regimen cannot be anticipated or measured

It is critical for patients to be counselled on the following:

- Inform other healthcare providers that they are taking 3HP
- Inform their 3HP providers if any other treatment is started
- Avoid other unregulated drugs or supplements or report their use to their healthcare worker

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