# **3HP Webinar Questions & Answers**

1. **In regards the Liver toxicity as we know the risk is higher in adults then in children. Dose the given number 1.8 % vs 0.4 % represents Adult patient risk or Pediatric patient?**

"The 3HP studies discussed in the webinar primarily discussed hepatotoxicity risks for adult patients, including the data quoted in the question. Safety data are available for childrnt and 3HP. In one study comparing 3HP and INH in 900 children (Villarino ME(1) et al. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. JAMA Pediatr. 2015 169:247-55), there was essentially no hepatotoxicity with either treatment arm. "

1. **Is anyone studying pregnancy rates in women on 4R or 3HP who are on hormonal forms of contraception? All of our information stating use a backup method with OCPs, mirena or skyla IUDs, depo-provera, etc., is based on little evidence.**

I am not aware of any ongoing data collection related to pregnancy as an AE with 3HP or rifampin.

1. **Did I miss Dr. Griffith answering the question about how to switch from one regimen to another w/ respect to dose calculating?**

My apologies. I think our consensus is that for patients who receive 3HP for several weeks it would be reasonable to count those weeks toward a total duration of TBI therapy. For instance, a patient who had 8 weeks of 3HP might be considered 2/3 of the way toward TBI treatment completion and could be given 3 months of INH or 6 weeks of rmp to complete a course of TBI therapy. My opinion is that for patients with only short 3HP exposure, arbitrarily one month or less, I would be in favor of restarting another regimen from the beginning. There is no guidance on this type of assessment either for 3HP or for other TBI therapy. I also think that the principle of “more is better" is operative here so that every effort is made to feel confident that patients have had adequate TBI therapy.

1. **What about patients who are awaiting transplants i.e. liver, or kidney?**

3HP may be especially useful for patients awaiting organ transplants because of the short duration of therapy which hopefully could be completed prior to the transplant and initiation of immune suppression. For kidney transplants 3HP should be no problem. For liver transplants it is trickier because of the potential for hepatotoxicity. I think it is reasonable to try in selected patients with close monitoring of liver enzymes and bilirubin, but other less hepatoxici regimens such as rifampin alone or fluoroquinolone may be preferable.

1. **About the RIPE regimen for TB treatment of a pediatric patient, I wanted to know if Rifampin 300 mg could be given twice a day as 1 tab every 12h?**

Once daily dosing of all TB drugs is optimal from PK/PD standpoint, but split dosing is permissible if required for patient drug tolerance.

1. **With the 3HP regimen how is the patient compliance to medication monitored when SAT is the option. Is there any lab (peak and trough) performed to trace presence of medication in the blood?**

Currently, there is no routine laboratory testing or mechanism for monitoring patient adherence. Drug levels could be useful for selected high risk patients.

1. **3HP recommended as "OK" for SAT rather than DOT by Tuberculosis Controllers Association. Waiting for CDC, ATS and/or IDSA to weigh in. Any idea when they will?**

Good question! 3HP SAT is now recommended in the 2018 CDC/ATS/IDSA guidance referenced in this presentation (June 2018)

1. **Is there potential for multiple drug resistance TB in LTBI patient who could tolerate only a few doses of 3hp?**

A few doses of 3HP is not a risk for developing drug resistance. For drug resistance to develop with 3HP, a patient would have to have active TB when 3HP is prescribed. Hopefully, that would be an extremely rare occurrence. Having said that if a patient with active INH resistant TB was started on 3HP, it would be possible for that patient to then develop rifapentine (rifamycin) resistance. The importance of excluding active TB prior to starting 3HP or any TBI therapy cannot be over-emphasized.

1. **How long after completion of Moxi was it determined that patients did not develop active disease?**

Subjects in that study were followed for 36 months.

1. **Special populations and suboxone and methadone use - do we attempt 3HP or just use 9H?**

Unfortunately, for patients on methadone, 3HP would be contraindicated and 9H would be preferred.

1. **We have lots of foreign-born college students with + IGRA: we hate to disrupt their studies and exams, is there a best time of day to dose with 3HP to minimize this?**

Because rifapentine bioavailability increases with food intake, any time of day would be acceptable, the closer to meals the better.

1. **For these college students, would potential side effects of 3HP be more than potential side effects of 4R?**

That is a tough question. In some of the large trials comparing 3HP and 9H, the total percentage of patients with AE's was actually higher in the 3HP group, although the percentages with severe events including hepatotoxicity was lower with 3HP. 3HP has not been compared directly with 4R. My impression is that, overall, l AE's are less with 4R than 3HP but that is an anecdotal impression.

1. **How important is increased use of IGRA over TST, thought to play?**

We are talking mostly about LTBI treatment with 3HP today, but please see recent 2017 CDC Diagnostic Guidelines <https://www.cdc.gov/tb/publications/guidelines/list_date.htm>

1. **Is Rifampin contraindicated for somone on Lovastatin?**

Not contraindicated although there is a moderate interaction. Rifampin has been reported to significantly increase the plasma clearance and decrease the serum concentrations of atorvastatin, simvastatin and fluvastatin, with the potential for reduced antilipemic efficacy. Although not studied, a similar interaction can be expected between other rifamycins (e.g., rifabutin, rifapentine) and other HMG-CoA reductase inhibitors (Statins). To evaluate this interaction, one option is to monitor serum lipid concentrations during co administration of rifamycins with HMG-CoA reductase inhibitors, although realistically, that type of monitoring is rarely done because of the short duration of the rifamycin exposure.

1. **If someone is 65 years of age and on Lovastatin would 3 HP be a better alternative than 9 months INH, provided there are no preexisting hepatic considerations?**

Probably yes from the standpoint of potential hepatoxicity but please see discussion about about interaction between rifamycins and statins.

1. **What is the risk of the HIV patient developing IRIS when starting 3HP with the antiretrovirals?**

There should be essentially no risk of developing an IRIS reaction in the absence of active TB disease.

1. **To clarify the LTBI tx for MDR contacts is 12 months FQ not 6?**

This is a tough question because there are very little data and no one knows the "right answer". The study from Micronesia utilized 12 months of flouroquinolone but many TB experts use 6 months rather than 12 months fluroquinolone therapy. I don't think there is enough data to definitively choose one duration over the other. Hopefully, CDC will provide some guidance in the near future. In the meantime I would follow the advice of the experts in your Regional TB COE.

1. **Can you clarify: Is it 12 or 6 months of moxi for contacts to MDR?**

See above.

1. **Speaking from a longer-term perspective, 3HP is a far newer regimen than the use of 6H or 9H. Moreover, rifapentine, like rifampin, has the potential for substantial drug-drug interactions. Moreover, 3HP has not been declared safe in pregnancy. I realize that 3HP has some advantages over 9H, but I question the safety profile given that it is simply far newer with nowhere near the clinical experience of INH.**

I certainly agree with your comments about the relative newness of 3HP (and rifapentine specifically) vs INH for TBI therapy. It is interesting that there is more safety information about rifapentine for TBI that there is for rifampin. I think the safety profile for rifapentine in TBI is solid. In the accumulation of that data, it has come to light that 3HP can be associated with hypotension and syncope, problems that I don't think were anticipated. Investigators have pointed out that it is not clear if these problems are associated with rifapentine, INH or the combination. Overall, the safety profile for rifapentine appears well established. There are, of course, always surprises such as the severe toxicity of rifampin and PZA.

1. **I would appreciate it if someone could respond to my question about the safety of 3HP vs. INH.**

We will get to it towards the end of the presentations.

1. **A second question: Are there any depot formulations of anti-TB meds in development? For example, there is depot Haldol, depo Provera. This would increase compliance and ensure pts received treatment.**

There are investigators looking into depot long-acting Bedaquiline for LTBI - data from animal models has been published.

1. **Can you watch the patient take meds via Facetime or Skype?**

Great question. electronic directly observed therapy (eDOT) is being utilized in various ways by US TB programs across the country. Check out CDC's eDOT toolkit at: <https://www.cdc.gov/tb/publications/guidestoolkits/tbedottoolkit.htm>

1. **How does 3HP completion rate compare to 4R? (As opposed to 66% to alternative regimens, which include both 9H and 4R).**

The 4R completion rate in the recent Menzies NEJM was 79% c/w 63% for 9H. In two TBTC studies from Tim Sterling et al, 3HP completion rates were 83% and 89%.

1. **How does rate of flu-like syndrome compare between 3HP and 4R?**

In the recent report by Menzies et al in the NEJM comparing 4R with 9H, there is not mention of flu-like illness in either arm.

1. **Can you reiterate the comments on food bioavailability with 3HP? I was under the impression that eating with each weekly dosage was advised.**

Food administration, especially fatty food, increases rifapentine bioavailability significantly (33% to 86%). Eating with each dose would be advantageous but not mandatory.

1. **What would be a contraindication to starting 3HP treatment for a patient who has been determined to have LTBI?**

INH or rifamycin hypersensitivity, severe hepatic disease, pregnancy, age < 2yrs, medications contraindicated with rifamycins (or INH), most antiretroviral agents (with the exception of some efavarenz and raltegravir based regimens), INH and/or rmp resistant TB exposure

1. **I would advocate for DOT practice with 3HP, I had to call and remind a few of my patients to come in, so I feel that if they were not being reminded weekly, they would have failed to do it at home with self-administered therapy. My thoughts is that could be why the 9mo daily treatment compliance was lower.**

Agree. While self-administration for 3HP is permitted, for adherence, completion, safety and efficacy reasons we strongly encourage DOT with 3HP.

1. **RIF and RPT and birth control interaction: Do these meds only affect oral contraception? IE: do not affect IUDs, Depo-Provera injections?**

They do not affect IUD's. For depo-provera, "Coadministration of medroxyprogesterone, a CYP3A substrate with rifamycins, strong CYP3A inducers should be avoided since it is expected to decrease concentrations of medroxyprogesterone acetate".