

**3HP is a combination of 2 drugs, rifapentine and isoniazid, which are taken once weekly for 3 months to get rid of latent TB infection**

**PREVENTING TB**



THE AURUM  
INSTITUTE

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THE AURUM  
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IMPAACT4TB  
PREVENTING TB TO END TB

## Clinicians Guidelines



# 3HP

Rifapentine & Isoniazid  
Tuberculosis Prevention

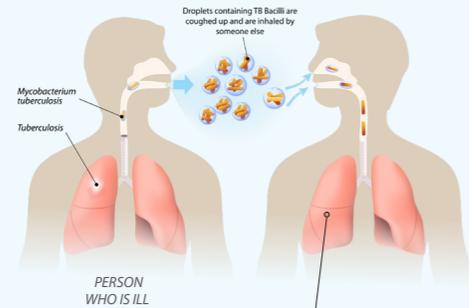


Overview of TB transmission

**STAGE 1:**

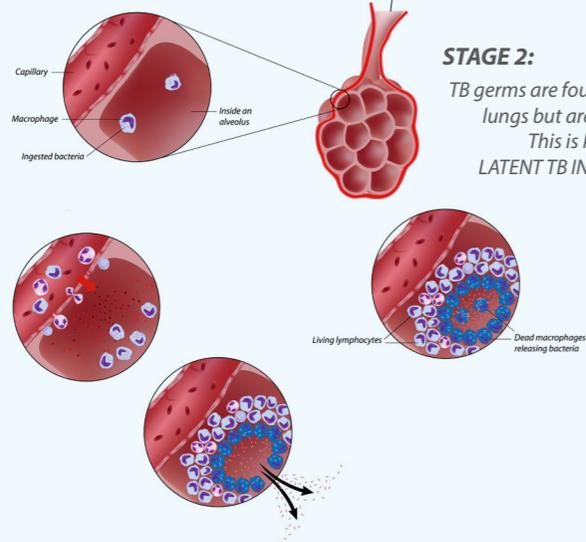
*Exposure*

*TB Bacilli are inhaled into the lungs of a healthy person via droplets sneezed, coughed or spat by another person who is ill with TB*



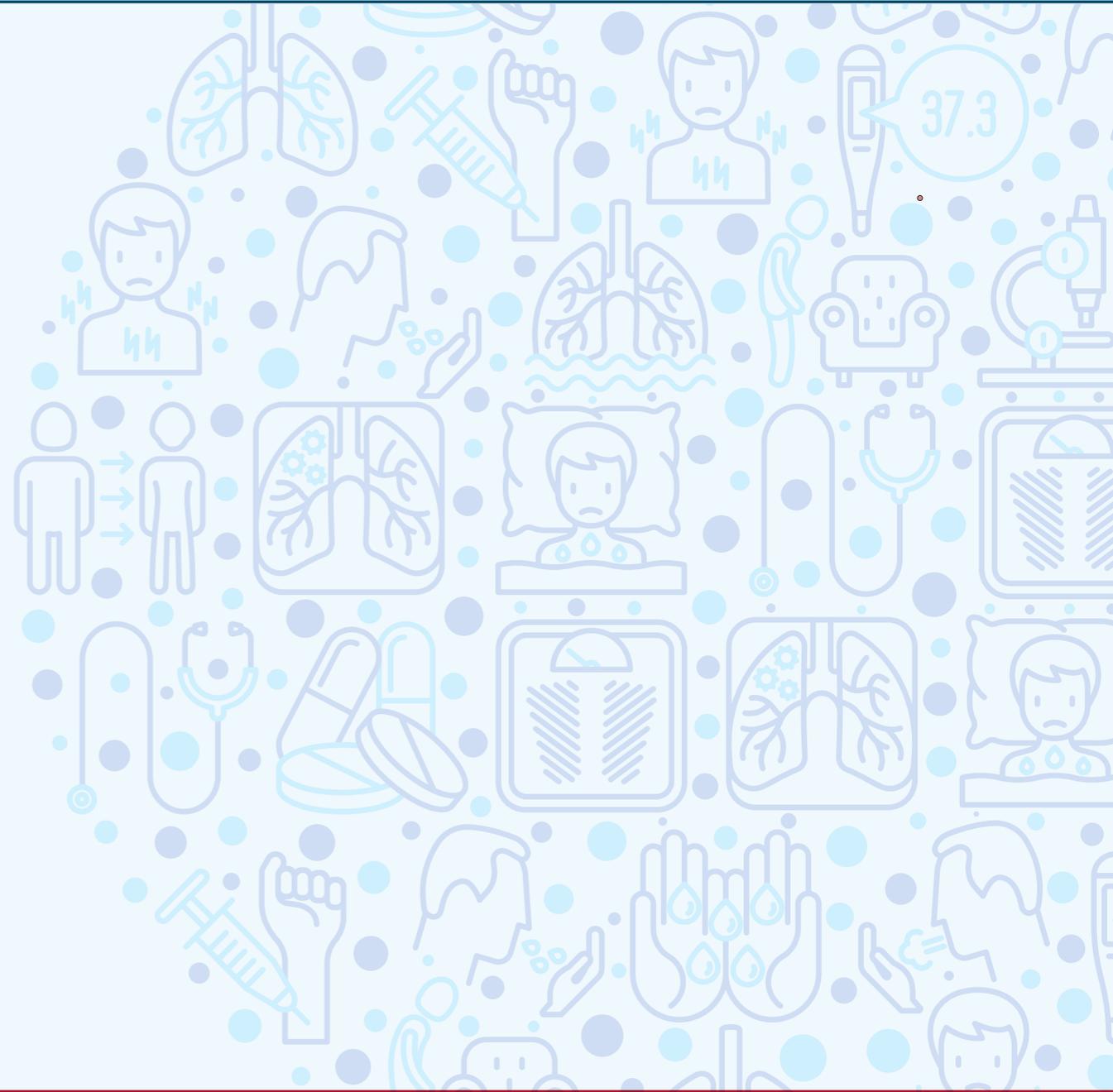
**STAGE 2:**

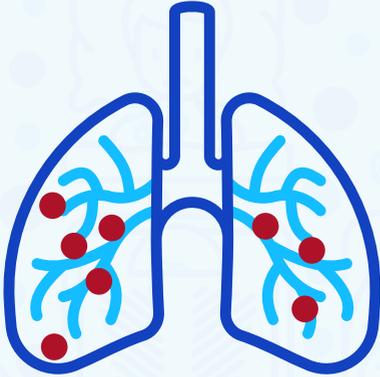
*TB germs are found in the lungs but are inactive  
This is known as LATENT TB INFECTION*



**STAGE 3:**

*Immune system unable to contain the TB BACILLI which escapes into the rest of the lungs - and possibly other parts of the body causing disease.  
This is known as ACTIVE TB.*





## What is Latent TB infection?

**Not everyone who is infected with Tuberculosis (TB) immediately develops TB disease. Some people go on to have a dormant form of TB that can be reactivated over time or when the immune system is suppressed. This form is called latent TB infection (LTBI), and treating it will prevent the person from getting active TB**

### Is treating latent TB infection effective?

Strong evidence shows that the treatment of TB infection (with isoniazid or rifampicin monotherapy, or in combination with other drugs) is effective in preventing progression to active disease in adults and children. There were an estimated 10 Million new cases of tuberculosis (TB) and around 1.6 million deaths attributable to TB in 2017. The World Health Organization (WHO) has set ambitious targets for reducing TB incidence and mortality in the next 10–20 years, with an aim to eliminating TB by 2035. Elimination of TB, however, cannot be considered without discussion of latent TB infection (LTBI), its diagnosis and treatment. 1.7 billion people are estimated to have LTBI and are at risk of developing TB in their lifetime.

## Is treatment of latent TB infection necessary?

Yes, it is **extremely important** to treat latent TB infection, particularly in those at high risk of progression to active TB disease, as it can **avert** the suffering and catastrophic economic costs associated with developing **active TB**

## Does TB preventive treatment (TPT) promote resistant TB?

No! The fact that TPT might promote resistance is a **myth that has prevented programs and individuals from accessing life-saving TB preventive treatment.**

There are a few reasons why the **development of resistance is extremely unlikely:**

- TPT is used for patients who do not currently have active TB
- Active TB can be quickly and easily excluded using simple screening algorithms
- Individuals with latent TB infection have a small number of slowly replicating bacteria in complexes in the lung. These “hidden” bacteria are at low risk of selecting for drug-resistance
- Most resistance arises from suboptimal treatment of active disease, hence preventing active disease may be beneficial for resistance overall
- Multiple trials have failed to find scientific evidence of a significant association between TB drug-resistance and the use of isoniazid or rifamycins for TPT

## What is 3HP?

3HP is a short-course **Tuberculosis Preventive Treatment (TPT)** regimen which is endorsed by the WHO. It combines high dose Isoniazid (H) and high dose rifapentine (P) once weekly for three months. 3HP is associated with significantly lower hepatotoxicity and higher rates of treatment completion than isoniazid preventive treatment.



## Is 3HP superior to IPT?

There is no evidence that 3HP is more effective than IPT, but studies have shown 3HP to be **equivalent** effective as IPT and other shorter regimens such as rifampicin alone or rifampicin/isoniazid in preventing progression to active disease. There is evidence, however, to show that 3HP is **less toxic** to the liver than IPT regimens, although the risk of systemic drug reactions is increased among those taking 3HP.

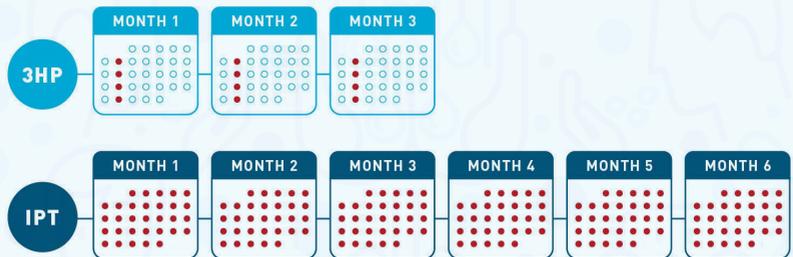
There is strong evidence to show that people taking shorter regimens such as 3HP are much **more likely to complete their course of treatment** than people taking IPT.

## Is 3HP cost-effective?

While 3HP is expensive in the short-term, the **shorter duration of treatment and higher rates of treatment completion** make it more cost-effective in the long-term.

## Could (and should) 3HP be used for a wider population?

Evidence to support rollout to a wider population such as health care workers and prisoners is very limited at present. The **superiority of 3HP (and other shortened regimens) with regard to treatment completion makes it a very attractive option**, particularly for use in correctional facilities and other dynamic or unpredictable environments.



**12 days of 3HP over three months vs 180 days (six months) of TPT**  
**Fewer doses, shorter duration, better adherence**



### **What about children?**

Children age 2 and up can take 3HP. However, there is no child friendly formula available on the market currently. Children who can swallow pills should be able to take 3HP. Children usually tolerate 3HP very well and have much lower rates of drug reactions. For more information on how to manage adherence in children, please refer to the technical brief on adherence found at <https://www.impaact4tb.org/library/>



### **What about pregnant women?**

Few studies have examined the safety of 3HP in pregnant women. More data will be available in 2020 but until then, it is not recommended to use 3HP in pregnancy. Caution should also be used in prescribing 3HP for women who are unwilling or unable to use barrier contraceptives, as 3HP can interact with hormonal contraceptives and put them at risk for unintended pregnancy.



**SAME DAY  
ONCE A WEEK  
FOR 12 WEEKS**

## How is 3HP used?

The 12-dose regimen called 3HP is the shortest of several available regimens recommended for treating latent TB infection.

**It consists of a once weekly dose of rifapentine and isoniazid, taken at the same time for 12 weeks.**

### Dosing of rifapentine and isoniazid for treatment of latent TB infection (3HP)

Medicine	Formulation	Weight bands for patients 2-14 years					Comments
		10-15 kg	16-23 kg	24-30 kg	31-34 kg	>34 kg	
Isoniazid	100 mg	3	5	6	7	7	adult 300 mg tab. can reduce pill burden
Rifapentine	150 mg	2	3	4	5	5	
Isoniazid+ Rifapentine	150 mg / 150 mg	2	3	4	5	5	FDC being developed

Medicine	Formulation	Weight bands for patients >14 years					Comments
		30-35 k	36-45 kg	46-55 kg	56-70 kg	>70 kg	
Isoniazid	300 mg	3	3	3	3	3	
Rifapentine	150 mg	6	6	6	6	6	
Isoniazid+ Rifapentine	300 mg / 300 mg	3	3	3	3	3	FDC being developed

## Who can take 3HP?

Persons with **no active TB** disease and **none of the following** contra-indications, can be started on 3HP:

- Age < 2 years
- Active Hepatitis (acute or chronic)
- Regular & heavy alcohol use
- Peripheral Neuropathy
- Women of child-bearing age who are wishing to conceive or not able to use barrier methods for contraception
- Pregnancy or breastfeeding
- Protease Inhibitor based antiretroviral therapy

Individuals at higher risk of peripheral neuropathy should be offered vitamin B6 (pyridoxine) supplementation with 3HP; if B6 is not available this should not delay starting a course of 3HP.

## How should 3HP be administered?

Clinicians should choose the mode of administration (directly observed therapy or self-administered therapy) based on local practice, individual patient attributes and preferences, and other considerations including risk of progression to severe forms of TB disease. Directly observed therapy is however not required for 3HP administration.

## How to handle a missed dose



Sunday



Sunday



Same Day

- Encourage a weekly routine of taking medications i.e. Sunday. If a patient misses Sunday, they can take 3HP within 3 days and go back to their normal Sunday routine
  - If they miss a dose for more than 3 days there are two options:
    - They can skip this dose and go back to their original chosen day i.e Sunday and continue until all 12 doses have been taken
- Or**
- Start the new schedule on the day they remembered to take the dose i.e. Schedule was a Sunday and only remembered Thursday, they now start a once weekly Thursday routine and forget about Sundays
- The 12 dose course should be finished by 16 weeks which provides some leeway for missed doses
  - 11 doses in 16 weeks can also be counted as sufficient, although not ideal

## Monitoring

Patients taking 3HP should be **monitored at monthly** visits to assess tolerability and adherence.

### Essential components of the visit are:

- Screen for active TB
- Screen for pregnancy
- Screen for AEs and assess tolerability
- Assess adherence and provide support as appropriate
- Assess for new medications that can interfere with 3HP

## Adverse Events



Clinicians should educate patients about possible adverse events, and instruct patients to use a symptom checklist (see below) and medication intake log.

- Patients should be evaluated monthly to assess adherence and treatment-associated adverse events.
- It is important that AEs are recorded and reported wherever possible.
- Minor adverse events are likely to occur in small proportion of individuals. Serious adverse events rarely occur and hence both the health care provider and patient should be vigilant and manage such events proactively.
- Because 3HP is a preventive treatment used to cure persons with no active disease, the risk of AEs should be especially minimized. Important AEs associated with 3HP are mostly drug reactions but some may be due to drug interactions with other medicines.
- In addition, active TB and pregnancy during 3HP treatment require special attention.

## Counselling for Adverse Events



- **Red/orange discoloration of urine and other body fluids such as sweat and tears while taking 3HP is normal and completely harmless. Individuals should be alert to the following symptoms:**
  - Weakness, fatigue, loss of appetite, persistent nausea (early symptoms of liver injury)
  - Flu-like, or other acute symptoms appearing shortly after taking a dose of 3HP
  - Symptoms of active TB (weight loss, night sweats, fever, cough)

## Management of Adverse Events

If an AE occurs while a patient is taking 3HP, **they should be advised not to take any further doses** until an assessment is made of the severity and nature of the AE.

### Assessment should include:

- Screen for active TB
- Past history
- History of the AE: type, onset and duration, severity
- Relevant physical examination

Management of the AE should always be guided by the clinical judgement. Suggested management:

- Severe drug reactions: seek urgent supportive care
- Mild/moderate drug reactions: reassurance, symptomatic relief, further assessment

## Pregnancy or active TB while on 3HP requires discontinuation of the drug.

- Pregnancy: discontinue 3HP
- Active TB: discontinue 3HP and start TB treatment



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

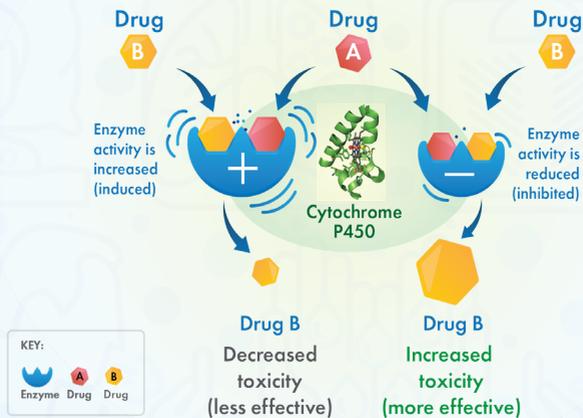
- If a patient is diagnosed with malaria but is not yet on TPT, decisions regarding 3HP initiation should be delayed until the episode of malaria has resolved.
- If a patient is diagnosed with malaria while on 3HP, the patient should be treated for malaria and clinically monitored according to national guidelines to ensure that the malaria is cured. At this stage, there is insufficient evidence to indicate that doses need to be adjusted.
- 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 can be restarted once the episode of malaria is resolved.
- 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.

## **Recording and Reporting**

- Routine pharmacovigilance procedures should be used for AEs associated with 3HP, where possible and according to national guidelines.
- At sentinel sites, AEs should additionally be reported according to the evaluation protocol.

## Drug-drug Interactions with 3HP

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. Drug reactions are usually mild and self-limiting, but occasionally they can be severe.



Rifampentine can cause a decrease in the activity of many drugs that pass through the cytochrome enzyme system. Caution should be exercised when co-administering 3HP with hormonal contraceptives, ART that includes protease inhibitors, some anti-seizure medicines as well as anti-malarials.

**Note the following:**



- Alternate forms of contraception should be used (barrier methods) when taking 3HP
- If malaria is diagnosed during 3HP treatment, the malaria treatment might be less effective. If malaria does not resolve, patients should be re-treated according to country guidelines. If a patient is receiving malaria treatment, they should hold off on taking their 3HP dose for that week and resume once the malaria course is completed.
- Patients taking a protease inhibitor for HIV should not receive 3HP. An alternate regimen containing efavirenz, dolutegravir, or raltegravir can be safely used instead
- Please consult the brief "drug-drug interactions" available at <https://www.impact4tb.org/library/> for further information on potential interactions, or consult a pharmacist.

