3HP ADVERSE EVENTS AND MONITORING SCHEDULE

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Acronyms and Abbreviations

AE  Adverse event
AST  Aspartate aminotransferase
BMI  Body mass index
H    Isoniazid
HIV  Human immunodeficiency virus
IPT  Isoniazid preventive treatment
LMIC Low and/or middle income country(ies)
P    Rifapentine
PLHIV Person/people living with human immunodeficiency virus
TB   Tuberculosis
TPT  Tuberculosis preventive treatment
ULN  Upper limit of normal
3HP  3 month regimen of weekly isoniazid and rifapentine
6H / 9H 6 or 9 months of daily isoniazid
3RH / 4RH 3 or 4 months of daily rifampicin and isoniazid

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1. What is 3HP?

3HP is a short-course TB preventive treatment (TPT) regimen taken once weekly for 12 weeks which is endorsed by the WHO. 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. What is an adverse event (AE)?

An unexpected medical problem that happens during treatment with a drug or other therapy. AEs may be mild, moderate, or severe, and may be caused by something other than the drug or therapy being given.

3. Drug reactions in adults and children

Overall, 3HP is a safe and effective treatment for latent TB infection. Clinically significant drug reactions are rarely experienced by patients taking 3HP, and even less commonly require discontinuation of treatment. Overall, drug reactions are similar in nature between adults and children, but are even less common in children than in adults. Children tolerate TPT very well.

3.1 Hepatotoxicity or drug induced liver injury (DILI)

Liver injury, also known as hepatotoxicity, rarely occurs in patients taking 3HP. When it occurs, it is more commonly due to isoniazid than rifapentine. Hepatotoxicity occurred most commonly after 3-4 doses of 3HP.

Table 1 Symptoms of liver damage in adults and children

<table>
<thead>
<tr>
<th>Early symptoms</th>
<th>Later symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Fatigue and/or somnolence</td>
<td>Jaundice (yellow skin and/or eyes)</td>
</tr>
<tr>
<td>Anorexia/loss of appetite</td>
<td>Itchy skin</td>
</tr>
<tr>
<td>Fever</td>
<td>Dark, brown or tan colored urine (darker</td>
</tr>
<tr>
<td></td>
<td>or additional discoloration than due to rifamycins)</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>Pale stools</td>
</tr>
<tr>
<td></td>
<td>Easy bruising or bleeding</td>
</tr>
</tbody>
</table>

3.2 Flu-like syndrome and other systemic hypersensitivity reactions

A flu-like syndrome and other hypersensitivity reactions are usually mild, self-limiting within 24 hours and do not reliably recur on re-challenge with 3HP. Most patients will be able to continue 3HP and complete the preventive treatment. Most patients will be able to continue 3HP and complete the preventive treatment.
### Table 2: Symptoms of flu-like or hypersensitivity reactions

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu-like</td>
<td>Fevers or chills AND Weakness, fatigue, muscle or bone aches, tachycardia or palpitations, flushing, syncope, dizziness, headaches, conjunctivitis, sweats, other similar symptoms.</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>Rash, itching, swelling of face or lips (angioedema), anaphylaxis.</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, abdominal pain.</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Shortness of breath, bronchospasm.</td>
</tr>
<tr>
<td>Severe hypersensitivity</td>
<td>Hypotension, tachycardia, syncope, bronchospasm, anaphylaxis.</td>
</tr>
</tbody>
</table>

### 3.3 Peripheral Neuropathy

Although neuropathy is associated with use of daily isoniazid, it has not been reported as a specific AE in studies of 3HP. Pyridoxine (B6), if available, can be administered with the weekly dose of 3HP to minimize the risk of peripheral neuropathy amongst those at higher risk.

### 3.4 Other Drug Reactions

Aside from the AEs described above, isolated instances of other rare drug reactions have been reported in patients taking 3HP. These include rash and/or pruritis, fever, nausea and/or vomiting, neutropenia, thrombocytopenia, seizures, and psychosis.

### 3.5 Comparison of Adverse Events with 3HP and Other TPT Regimens

When reviewing adverse events that occur in different settings, the overall reported rate of adverse events is in favour of 3HP when compared to regimens containing only INH or INH with daily Rifampicin.

### Table 3: Comparative rates of adverse events for different TPT regimens

<table>
<thead>
<tr>
<th></th>
<th>3HP</th>
<th>3-4HR</th>
<th>6H</th>
<th>9H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE (treatment related or not)</td>
<td>11.5%</td>
<td>29.7%</td>
<td>36.1%</td>
<td>17.6%</td>
</tr>
<tr>
<td>Withdrawals due to AEs</td>
<td>1.7%</td>
<td>2.2%</td>
<td>3.8%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Flu-like and/or systemic hypersensitivity reactions</td>
<td>3.8%</td>
<td>n/a</td>
<td>n/a</td>
<td>0.5%</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>1%</td>
<td>6.8%</td>
<td>2.7%</td>
<td>5.6%</td>
</tr>
</tbody>
</table>

### 4. Special Considerations for Drug Reactions in Children

AEs on all TPT regimens are typically less frequent and less severe in children than in adults. This has also been observed for children taking 3HP, for whom the treatment is safe.
5. Hepatotoxicity

Hepatotoxicity is rarely reported amongst children on TPT, occurring in about 1% of children taking isoniazid preventive therapy. In one randomized study comparing children treated with 3HP and a limited number of programmatic studies of 3HP in children, there were no cases of hepatotoxicity.

Up to 10% of children taking isoniazid alone can have liver enzyme elevations that do not result in clinically significant disease. Routine laboratory monitoring for hepatotoxicity in children is not recommended. Clinically significant disease is by definition symptomatic. Children with hepatotoxicity most commonly present subacutely with development of poor appetite, nausea, vomiting and/or abdominal pain (Table 1) that persist and worsen over time. Later, liver tenderness, hepatomegaly and jaundice develop. If identified early and medications are stopped, there are typically not permanent sequelae from the drug-induced hepatotoxicity.

5.1 Flu-Like Syndrome and Other Systemic Hypersensitivity Reactions

Flu-like and other systemic hypersensitivity reactions were similarly rare amongst children. Symptoms consistent with a flu-like syndrome were reported in approximately 0.6% of patients taking 3HP in one randomized study. Other systemic hypersensitivity syndromes were reported in approximately 1-2% of patients in this study, including cutaneous (rash, itching or oral blisters) or gastrointestinal symptoms (Table 2). In small programmatic studies of 3HP in children, no such hypersensitivity reactions were reported.

As in adults, hypersensitivity reactions are usually mild, self-limiting (<24 hours duration), and do not reliably recur with re-challenge of 3HP. More serious reactions are thought to be rare, no hospitalizations, life-threatening events, disability or permanent damage was seen in the pediatric 3HP trial.

5.2 Peripheral Neuropathy

Children and adolescents living with HIV and those with malnutrition may be at elevated risk of peripheral neuropathy. When available, vitamin B6 should be used to lower this risk. Initiation of 3HP should not be delayed if vitamin B6 is not available.

5.3 Comparison of 3HP and Other TPT Regimens In Children

Comparative rates of adverse events in children are presented in Table 4.

<table>
<thead>
<tr>
<th>Table 4 Comparative rates of adverse events in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>3HP</td>
</tr>
<tr>
<td>Any AE (treatment related or not)</td>
</tr>
<tr>
<td>Withdrawals due to AEs</td>
</tr>
<tr>
<td>Flu-like and/or systemic hypersensitivity reactions</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
</tr>
</tbody>
</table>
6. Other important medical events that can occur while taking 3HP

6.1 Active TB in Adults

Diagnosis with active TB is an important occurrence for patients taking 3HP. Because the regimen is demonstrated to be effective for treatment of latent TB infection but not for active TB, there is a risk that a patient who develops active TB will receive ineffective treatment. In turn, this may result in the development of drug resistance to either Isoniazid or rifapentine.

Active TB should be ruled out prior to commencing treatment with 3HP, and symptom screening for PLHIV and child contacts has been shown to be an effective way of doing so. Therefore, this event is rare. Nonetheless, no preventive treatment is 100% effective. Patients and providers should be prepared to recognise the symptoms of active TB so that 3HP can be withheld and further investigations conducted immediately.

6.2 Active TB in children

In children, identifying early symptoms of active TB disease can be challenging and progression to TB disease can occur despite preventive therapy or due to non-adherence to preventive therapy. Prior programmatic studies show this occurs in less than 1% of household child contacts receiving 6H. Symptom screening should occur at each follow-up visit. Should symptoms of active TB disease develop, TPT should be withheld and further investigation, including gastric aspirate, chest X-ray and physician evaluation, should be conducted immediately. The risk of developing resistance is highly unlikely given the paucibacillary nature of paediatric TB disease.

6.3 Other Medical Conditions in Adults and Children

Patients may develop other medical conditions while taking 3HP. There are two important considerations for patients who are diagnosed with other medical conditions while taking 3HP:

- Because the signs and symptoms of common acute illnesses overlap with those of active TB, providers should take care to include active TB in the differential diagnosis until symptoms have resolved (for example, lower respiratory tract infections).
- 3HP may interact with medicines used to treat other medical conditions, and so in most cases 3HP should be withheld until the new medical condition has been effectively treated (for example, potential interaction with artemisinin combination therapy for malaria or with fluconazole treatment for cryptococcal disease). For a more detailed discussion of this topic, see IMPAACT4TB Technical Brief on Drug-drug Interactions.

6.4 Pregnancy, Breastfeeding and Contraception

There is insufficient data to recommend 3HP in pregnant or breastfeeding women. If a patient becomes pregnant while taking 3HP, 3HP should be discontinued and the pregnancy should be recorded and reported.

Due to the interaction between rifapentine and hormonal contraceptives and because pregnancy is a contraindication, female patients of childbearing age should be counselled about risk and encouraged to use a barrier form of contraception while taking 3HP.

Although 3HP is not recommended in pregnant or breastfeeding women, analysis of small numbers of patients from clinical trials who became pregnant while taking 3HP found that rates of fetal loss and congenital abnormality were similar to rates in the general population. INH can be used in pregnancy although studies show conflicting results and country guidelines differ on their inclusion of pregnant women for TPT. Sound clinical judgement should be exercised when recommending TPT in pregnancy.
7. Baseline Assessment, Counselling and Monitoring for AEs

Individuals receiving TPT do not have active disease and therefore their risk for AEs during treatment must be minimized. This can be achieved by careful assessment of the patient prior to commencing 3HP, and routine monitoring during treatment.

7.1 Baseline assessment and monthly monitoring

<table>
<thead>
<tr>
<th>Result</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and eligibility</td>
<td>1. Use the algorithm to select the correct TPT regimen</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1. <strong>Must</strong> be ruled out before commencing any TPT using a symptom screening algorithm</td>
</tr>
<tr>
<td>Hepatotoxicity risk assessment</td>
<td>1. TPT is contraindicated in patients with likely severe liver disorders</td>
</tr>
<tr>
<td></td>
<td>a. Active hepatitis or</td>
</tr>
<tr>
<td></td>
<td>b. Cirrhosis (due to any cause)</td>
</tr>
<tr>
<td></td>
<td>2. TPT may be given with caution if higher risk (3HP is preferred)</td>
</tr>
<tr>
<td></td>
<td>a. Daily alcohol consumption</td>
</tr>
<tr>
<td></td>
<td>b. Liver disorders including viral hepatitis (without cirrhosis)</td>
</tr>
<tr>
<td></td>
<td>c. Postpartum period (≤3 months after delivery)</td>
</tr>
<tr>
<td></td>
<td>d. Concomitant use of other hepatotoxic substances</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>1. TPT is contraindicated in patients with existing peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td>2. Individuals at higher risk of peripheral neuropathy should be offered vitamin B6 (pyridoxine) supplementation with TPT:</td>
</tr>
<tr>
<td></td>
<td>a. PLHIV</td>
</tr>
<tr>
<td></td>
<td>b. Breastfeeding mothers</td>
</tr>
<tr>
<td></td>
<td>c. Diabetes</td>
</tr>
<tr>
<td></td>
<td>d. Renal failure</td>
</tr>
<tr>
<td></td>
<td>e. Daily alcohol consumption</td>
</tr>
<tr>
<td></td>
<td>f. Malnutrition</td>
</tr>
</tbody>
</table>
7.1.1 Monthly monitoring
Patients taking 3HP should be monitored monthly to assess tolerability and adherence. Essential components of the visit are:

• Screen for signs and symptoms of active TB
• Screen for symptoms of AEs (hepatotoxicity, flu-like/hypersensitivity reactions, peripheral neuropathy and assess tolerability
• Counsel about pregnancy, breastfeeding and barrier contraception
• Assess adherence and provide support as appropriate
• Assess for new medications that can interfere with 3HP
• Repeat AST for patients who had a raised baseline test

7.2 Counselling patients about early detection of AEs
Although monthly monitoring visits (as below) provide an opportunity to screen for signs and symptoms of AEs, rapid detection of AEs depends on a patient being counselled and empowered to recognize and act on symptoms as soon as they arise.

Guidance on counselling about the rationale for TPT, dosing and administration of 3HP, and suggestions to support adherence, are provided in a separate IMPAACT4TB Technical Briefs.

Patients with any 3HP related concern or symptom should contact a healthcare provider before taking another dose of 3HP

Because 3HP is a preventive treatment given to healthy patients, any evidence of an AE, or any change in the patient’s medical or social situation should prompt review. This is to ensure that any additional risk to patients from taking TPT can be avoided if at all possible. This key advice is summarized in Table 6 below:

Table 6  Counselling points for patients taking 3HP

<table>
<thead>
<tr>
<th>If you have symptoms concerning for liver damage or severe hypersensitivity:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Do not take any further doses of 3HP</td>
</tr>
<tr>
<td>• Contact a healthcare provider for advice as soon as possible</td>
</tr>
<tr>
<td>• Only continue taking 3HP once you have been advised to by your healthcare provider AST within normal limits</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>These are some of the situations in which you should also take the above steps:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Any persistent or concerning symptoms</td>
</tr>
<tr>
<td>• Any change in your health or medical situation (new medicine, new diseases)</td>
</tr>
<tr>
<td>• Any change in your social situation (moving away, change in job, not enough food)</td>
</tr>
</tbody>
</table>

7.2.1 Orange discoloration of urine, tears, sweat and other body fluids
Rifapentine (and other rifamycins) cause body fluids to develop an orange/red color. This is a normal result of excretion of the medicine and is harmless. Patients should be counseled to expect this harmless side effect and not be alarmed if they experience it.
7.2.2 Counselling about symptoms of hepatotoxicity
Patients should be counselled to seek advice from a healthcare provider at the earliest indication of hepatotoxicity, and not to take another weekly dose of 3HP until they have been advised to continue. Symptoms of hepatotoxicity are described in table 1.

To facilitate early identification of hepatotoxicity, patients should be strongly counselled on the early, mild but insidious symptoms (for example, persistent fatigue, weakness, loss of appetite). Patients should be counselled to seek advice immediately if any of these symptoms develop, and not to wait for increasing severity or the development of any further symptoms.

7.2.3 Counselling about alcohol use
Alcohol consumption may increase the risk of developing hepatotoxicity while taking 3HP. Patients should be counselled to minimise alcohol consumption while taking 3HP, and to avoid it entirely if possible.

7.2.4 Counselling about herbal supplements
Herbal supplements can cause liver damage. Patients should be counselled to avoid taking unregulated herbal supplements or those that are known to cause liver damage during treatment with 3HP.

7.2.5 Counselling about symptoms of flu-like or systemic hypersensitivity reactions
In the uncommon event that they occur, flu-like or systemic hypersensitivity reactions typically appear approximately 4 hours after taking a dose of 3HP. Patients should be counselled to seek advice from a healthcare provider at the earliest indication of this AE, and not to take another weekly dose of 3HP until they have been advised to continue.

Amongst these uncommon reactions, the most frequent is described as ‘flu-like’, and patients should be counselled about this recognizable syndrome. However, they should also be counselled that any concerning or acute symptom that develops after taking 3HP should prompt them to seek advice from a healthcare provider. Symptoms of flu-like and other hypersensitivity reactions are described in Table 2 above.

7.2.6 Counselling about active TB
Patients should be counselled about the difference between latent TB infection and active TB, and to recognize the symptoms of active TB. If symptoms of active TB develop while on 3HP, patients should be encouraged to contact a healthcare provider for further assessment. 3HP should be withheld until this has been done and active TB has been excluded.

7.2.7 Counselling about pregnancy, breastfeeding and barrier contraception
As described in section 6.3.3, there is insufficient data to recommend 3HP in pregnancy and breastfeeding women, and there is an interaction between rifapentine and hormonal contraceptives. Women of childbearing age should be counselled about these contraindications, and offered a pregnancy test if available. Women should be advised to choose a barrier form of contraception (if applicable, in addition to hormonal contraceptives) while taking 3HP.

7.2.8 Counselling about other diseases and medicines
While taking 3HP over a three-month period, patients may experience a change in their health. For example:

• Being diagnosed with malaria or any other acute illness
• Becoming pregnant
• Changing the type or dose of long-term medicines or supplements
• Active TB

Many different medicines can interact with 3HP – these interactions may reduce the effectiveness of the
3HP or the other medicine or expose the patient to AEs. Patients should be counseled that if they experience any change in their health situation, they should inform their healthcare providers that they are currently taking 3HP. They should not take any further doses of 3HP until they have been advised to continue by a healthcare provider.

Even if active TB has been ruled out prior to commencing treatment with 3HP, a patient may develop active TB during treatment with 3HP. In this rare situation, the patient may be at risk of developing drug resistant TB. Therefore, patients should be counseled on the symptoms of active TB and should be advised to seek advice from their healthcare provider if these develop.

7.2.9 Counselling for parents, guardians and caregivers of children taking 3HP
In general, children tolerate 3HP better than adults. Nonetheless, caregivers should be counseled about the common AEs that may arise, in addition to counselling about dosage and administration of 3HP. This should include:

• Red/orange discoloration of the urine and diaper which is harmless but may cause consternation
• Drug reactions (hypersensitivity reactions, flu-like syndromes and hepatotoxicity)
• Signs and symptoms of active TB in children (appendix 1)
• Pregnancy, breast feeding and barrier contraception for adolescents
• Other diseases including malaria, other medications including antiepileptic medications, or other acute illnesses

If caregivers suspect that a child taking 3HP is experiencing an AE, they should withhold 3HP and seek advice from a healthcare provider.

7.3 Routine monitoring on 3HP for adults and children
Patients taking 3HP should be monitored at monthly visits. The purpose of monthly visits is to screen for AEs, assess adherence and provide support as appropriate to safely retain the patient in care until treatment completion. Components of routine monthly monitoring visits are described below, with an emphasis on AEs.

7.3.1 Screen for active TB
Even if active TB has been ruled out prior to commencing treatment with 3HP, a patient may develop active TB during treatment with 3HP. Therefore, patients should be screened for the signs and symptoms of active TB at each monthly visit.

7.3.2 Counsel about pregnancy, breastfeeding and barrier contraception
At each visit, women of childbearing age should be counselled that they should not take 3HP if they are pregnant or breastfeeding, and that they should use barrier contraception while taking the treatment. Women should be offered a pregnancy test if available.

7.3.3 Screen for symptoms of AEs
Patients should be systematically evaluated for symptoms of the AEs frequently associated with 3HP:

• Hepatotoxicity (table 1, with an emphasis on early symptoms)
• Flu-like or systemic hypersensitivity reactions (table 2 above)
• Peripheral neuropathy (burning, stinging or numbness in hands or feet)

7.3.4 Routine monitoring of liver enzymes
For most patients, routine liver function testing is not recommended. Patients at higher risk for hepatotoxicity (as described above) should receive a baseline AST. If this test is within normal limits, no further routine monitoring is needed.
Patients with raised baseline AST (if this test was conducted, see baseline testing above) should have a repeat AST at each monthly visit.

Additional monitoring tests can be conducted for patients at higher risk of hepatotoxicity but with normal baseline AST on an individual basis and at the discretion of the treating clinician.

7.3.5 Assess adherence
Adherence should be assessed at every monthly monitoring visit. If appropriate, further support should be offered to assist the patient to remain safely in care until the end of treatment. Detailed guidance on this topic is provided in the technical brief on adherence.

8. Management of AEs in adults and children

Individuals receiving TPT do not have active disease and therefore their risk for AEs during treatment must be minimized. This can be achieved by careful assessment of the patient prior to commencing 3HP, and routine monitoring during treatment, see page on baseline assessment and monitoring.

Therefore, in general:

If an AE occurs while a patient is taking 3HP, they should be advised not to take any further doses and contact their healthcare center.

8.1 Assessment of possible AEs

Patients with a possible AE should be reviewed by a healthcare provider. The first step is to gather information about the nature and severity of the AE, and to determine if symptoms are consistent with any of the drug reactions associated with 3HP.

The evaluation should include:
- Past history
- Complete medical history
- Concomitant medication history, including supplements or unregulated medicines
- Dosage and administration history for 3HP
- Any previous reported or unreported symptoms associated with 3HP
- Onset, duration and course of the AE
- Type of AE (drug reaction / other medical condition / pregnancy / others)
- Severity of the AE (mild / moderate / severe)
- Relevant physical examination
- Screen for active TB

8.2 Immediate management of drug reactions

Drug reactions associated with 3HP usually are mild or moderate, and self-limiting. Rarely, drug reactions can be severe. Healthcare providers should respond with immediate management considering the nature and severity of symptoms and being alert to the possibility of a severe AE.

Signs and symptoms of severe drug reactions that may occur while taking 3HP are:
- Circulatory impairment (hypotension, tachycardia, syncope)
- Respiratory impairment (bronchospasm, wheeze, chest pain, tachypnea, syncope)
- Type I hypersensitivity (anaphylaxis, angioedema)
- Severe cutaneous reactions (rash with blistering, vesicles, or mucosal involvement)
### Table 7. Suggested management of selected AEs

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatotoxicity</strong></td>
<td></td>
</tr>
<tr>
<td>Any symptoms of hepatitis develop while taking 3HP</td>
<td>• Withhold 3HP&lt;br&gt;• Assess for other causes of symptoms (gastroenteritis, etc)&lt;br&gt;• Test AST (other liver function tests at provider discretion)</td>
</tr>
<tr>
<td>AST &lt;3x ULN (Test may have been conducted in a patient with symptoms or with raised baseline AST)</td>
<td>• Continue 3HP&lt;br&gt;• Monitor symptoms&lt;br&gt;• Reassess risk factors&lt;br&gt;• Check AST again if symptoms do not resolve</td>
</tr>
<tr>
<td>AST ≥3x ULN with any symptoms of hepatitis&lt;br&gt;OR&lt;br&gt;AST ≥5x ULN</td>
<td>• Withhold 3HP&lt;br&gt;• Monitor AST and symptoms&lt;br&gt;• Reassess risk factors&lt;br&gt;• Re-challenge 3HP once symptoms resolved and AST &lt;3x ULN</td>
</tr>
<tr>
<td>AST ≥10x ULN OR Symptoms of severe hepatitis: Jaundice, dark urine, abdominal pain</td>
<td>• Discontinue 3HP&lt;br&gt;• Supportive care including referral to higher level of care&lt;br&gt;• Monitor liver function tests</td>
</tr>
<tr>
<td><strong>Flu-like or systemic hypersensitivity reactions</strong></td>
<td></td>
</tr>
<tr>
<td>Severe hypersensitivity or cutaneous reactions, including angioedema and anaphylaxis</td>
<td>• Discontinue 3HP&lt;br&gt;• Provide urgent supportive care&lt;br&gt;• Refer for further assessment and management as appropriate</td>
</tr>
<tr>
<td>Flu-like syndrome (mild/moderate) OR&lt;br&gt;Mild cutaneous reactions (rash, itching) OR&lt;br&gt;Gastrointestinal reactions OR&lt;br&gt;Respiratory reactions</td>
<td>• Withhold 3HP&lt;br&gt;• Offer ancillary treatments for symptomatic management as appropriate&lt;br&gt;– Antihistamines (diphenhydramine, loratadine etc.)&lt;br&gt;– Antiemetics, antidiarrheals or ORS&lt;br&gt;– Bronchodilators, Steroids&lt;br&gt;• Monitor symptoms&lt;br&gt;• Re-challenge 3HP at next dose if symptoms resolve</td>
</tr>
</tbody>
</table>
8.2.1 Suggested management of specific AEs
Suggested management of selected specific AEs is described in Table 7.

9. Recording and reporting of AEs

9.1 Routine pharmacovigilance and reporting of AEs
3HP will replace daily IPT regimens in most cases. Patients taking IPT have at least as many AEs as those taking 3HP, therefore it is anticipated that recording and reporting of AEs associated with 3HP will align with existing processes for IPT where they exist.

However, in many LMIC settings, pharmacovigilance processes are not well resourced or established. Although 3HP has been shown to be safe and effective in clinical trials, experience with this regimen outside of research settings in LMIC is limited. To establish the safety profile of 3HP in routine practice, it is important that AEs are recorded and reported wherever possible. Refer to national guidelines about pharmacovigilance reporting and recording.

9.2 Specific activities in the IMPAACT4TB project
In the IMPAACT4TB project, sentinel sites in each country will record additional AE data above that required in routine service delivery. At target sites where 3HP will be implemented according to national guidelines, the project will support the delivery of routine pharmacovigilance in line with existing national processes.

Any severe AE which leads to hospital admission or death, should be reported to the project management unit and relevant country authorities.

### Other AEs

<table>
<thead>
<tr>
<th>Other AEs</th>
<th>Management</th>
</tr>
</thead>
</table>
| Active TB signs or symptoms OR Malaria diagnosis and treatment OR Diagnosis and treatment of other acute illness | - Withhold 3HP  
- Investigate and treat for active TB, malaria or other acute illness  
- Continue 3HP only after treatment of the acute illness is completed and symptoms have resolved |
| Pregnancy                                                               | - Discontinue 3HP  
- Discuss timing and options for completing a course of TPT               |
| Changed type or dose of long-term medicines                            | - Document the type and dose of concomitant medicines  
- Refer to technical brief on drug-drug interactions for more information  
- Continue 3HP only if safe to do so                                     |
10. Take home points

- Overall 3HP is safe.
- Minor adverse events are likely to occur in a small proportion of individuals/patients.
- Rarely serious adverse events may occur, and hence both the health care provider and patient should be vigilant and manage such events rapidly.

### 3HP and AEs

Because 3HP is a preventive treatment used to cure persons with no active disease, the risk of AEs should be especially minimized.

### Drug reactions

The most common drug reactions with 3HP are:
- Liver toxicity (less common than for IPT)
- Flu-like reactions (more common than for IPT)

Drug reactions are usually mild and self-limiting, but occasionally they can be severe.
Children usually tolerate 3HP very well and have much lower rates of drug reactions.

### Baseline assessment

Active TB must be ruled out before commencing 3HP.
3HP is currently not recommended in:
- Pregnancy
- Age <2 years

Information on baseline liver function is important in the following:
- HIV+ (done as part of ART assessment)
- Daily alcohol consumption
- Liver disorders including viral hepatitis
- Postpartum period (≤3 months after delivery)
- Concomitant use of other hepatotoxic substances

All HIV infected individuals should be offered vitamin B6 (pyridoxine) supplementation with 3HP.

### Counselling for AEs

Red/orange discoloration of urine and other body fluids while taking 3HP is normal and completely harmless.

If patients experience any symptoms concerning for an AE:
- Do not take any further doses of 3HP
- Contact a healthcare provider for advice
- Only continue taking 3HP if advised to do so by a healthcare provider

Individuals should be alert to the following symptoms:
- Weakness, fatigue, loss of appetite, persistent nausea (early symptoms of hepatotoxicity)
- Flu-like, or other acute symptoms appearing shortly after taking a dose of 3HP
- Symptoms of active TB
### TPT in children
- TPT in children
- Children (especially aged under 5) are at high risk of developing TB, and they tolerate TPT very well
- For older children and adolescents, include them in counselling wherever possible
- For 3HP, give crushed rifapentine with a small amount of tasty fatty foods (avoid fruits)
- If the child vomits the dose within 30 minutes, you should give another dose
- A small incentive can be useful to encourage children to take the medicine

### Routine monitoring
Patients taking 3HP should be monitored monthly to assess tolerability and adherence.

**Essential components of the visit are:**
- Screen for active TB
- Screen for AEs and assess tolerability
- Assess adherence and provide support as appropriate
- Assess for new medications that can interfere with 3HP

Repeat AST for patients who had a raised baseline test

### Management of AEs
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 of the healthcare provider. Suggested management:
- Severe drug reactions: seek urgent supportive care
- Mild/moderate drug reactions: reassurance, symptomatic relief, further assessment
- Pregnancy: discontinue 3HP

### Recording and reporting
Routine pharmacovigilance procedures should be used for AEs associated with 3HP, where possible and according to national guidelines.

At IMPAACT4TB sentinel sites, AEs should also be reported according to the evaluation protocol.
References


