



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 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 an adverse event (AE)?

According to the US National Institutes of Health National Cancer Institute, an AE is defined as:

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 given⁶.

This technical brief will address AEs associated with 3HP. These are mostly drug reactions, but other conditions such as pregnancy, development of active TB and malaria can be considered adverse events in the setting of 3HP treatment, if this is done under study conditions.

3. Drug reactions in adults

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. Severe reactions are particularly rare. Nonetheless, healthcare workers should be familiar with the important drug reactions so that they can recognise rare occurrences and manage them appropriately.

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.

10-20% of adult patients taking daily isoniazid either alone or in combination develop an asymptomatic rise in hepatic enzymes followed by a return to normal levels despite continuation of treatment. This is sometimes known as hepatic adaptation. It is a normal physiological response and is not dangerous.

Clinically significant hepatotoxicity, defined as a rise in liver enzymes (AST and ALT) to > 3x the upper limit of normal (ULN) with symptoms, or > 5x without symptoms, occurred in 0.4% (4 in 1000) of patients taking 3HP and 1.8% (18 in 1000) of patients taking 9H in one study⁷. A systematic review of randomized trials of TPT regimens reported that rates of hepatotoxicity were lower amongst patients taking 3HP than for any other recommended TPT regimen⁸.

Hepatotoxicity occurred most commonly after 3-4 doses of 3HP⁶. Risk factors for TPT-related hepatotoxicity include⁹:

- older age
- raised liver enzymes at baseline
- HIV infection
- pregnancy
- daily alcohol consumption
- comorbid liver disease
- concurrent use of other hepatotoxic substances including unregulated herbal supplements/medicines.

Hepatitis usually develops over a period of days to weeks. The first symptoms to develop are mild, persistent, insidious and somewhat non-specific. Later, symptoms more typically associated with hepatitis develop as a result of liver injury and cholestasis¹⁰. Early and later symptoms are compared in Table 1. Comparative rates of drug reactions are presented in Table 3.

Table 1 Symptoms of liver damage in adults and children

Early symptoms	Later symptoms
<ul style="list-style-type: none"> Weakness Fatigue and/or somnolence Anorexia/loss of appetite Fever Nausea or vomiting 	<ul style="list-style-type: none"> Abdominal pain Jaundice (yellow skin and/or eyes) Itchy skin Dark, brown or tan colored urine (darker or additional discoloration than due to rifamycins) Pale stools Easy bruising or bleeding

3.2 Flu-like syndrome and other systemic hypersensitivity reactions

Overall, 3HP is a safe and effective treatment for latent TB infection. A flu-like syndrome consisting of fever or chills, in combination with weakness, fatigue, muscle or bone aches, tachycardia or palpitations, flushing, syncope, dizziness, headaches, conjunctivitis, sweats or other similar symptoms, has been associated with intermittent rifamycin administration^{11, 12, 13}. **This is a rare drug reaction, is usually mild and self-resolving, and most patients will be able to continue 3HP to complete the preventive treatment.**

Symptoms consistent with this flu-like syndrome were reported in approximately 3-4% of patients taking 3HP in randomized and non-randomized studies¹⁴. Other systemic hypersensitivity syndromes were reported in approximately 1% of patients in one study, including cutaneous (rash, itching or swelling of lips or face – the most common), respiratory (cough, chest pain), gastrointestinal or other miscellaneous symptoms. In other studies of 3HP, no such reactions were reported. Flu-like and other hypersensitivity reactions are usually mild, self-limiting within 24 hours and do not reliably recur on re-challenge with 3HP. These reactions occurred most commonly after 3-4 doses of 3HP, and are associated with white race, female sex, age > 35 and lower BMI¹⁵.

Rarely, these reactions can be more severe, involving hypotension or syncope, and in very rare cases requiring hospitalization. In one study including patients taking 3HP, severe reactions were reported for 0.3% of participants (3 in 1000)³. Symptoms of flu-like or other hypersensitivity reactions are presented in Table 2. Comparative rates of drug reactions are presented in Table 3.

Table 2 Symptoms of flu-like or hypersensitivity reactions

Syndrome	Features	Frequency
Flu-like	Fevers or chills AND Weakness, fatigue, muscle or bone aches, tachycardia or palpitations, flushing, syncope, dizziness, headaches, conjunctivitis, sweats, other similar symptoms.	3-4%
Cutaneous	Rash, itching, swelling of face or lips (angioedema), anaphylaxis.	<1%

Gastrointestinal	Nausea, vomiting, abdominal pain.	Rare
Respiratory	Shortness of breath, bronchospasm.	Rare
Severe hypersensitivity	Hypotension, tachycardia, syncope, bronchospasm, anaphylaxis.	Very rare (<0.3%)

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 Rifampicin⁷.

Table 3 Comparative rates of adverse events for different TPT regimens

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

4. Special Considerations for Drug Reactions in Children

AEs on all TPT regimens are typically less frequent and less severe in children than in adults⁴. 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 hepatotoxicity⁴.

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 study⁴. 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 4 Comparative rates of adverse events in children^{4,15}

	Villarino et al		Spyridis, et al		Diallo, et al	
	3HP	9H	3-4HR	9H	4R	9H
Any AE (treatment related or not)	8%	10.1%	n/a	n/a	4.7%	12.8%
Withdrawals due to AEs	1.7%	0.5%	0%	0%	0%	0%
Flu-like and/or systemic hypersensitivity reactions	0.6%	0.2%	n/a	n/a	n/a	n/a
Hepatotoxicity	0%	0%	1.2%	6%	0%	0%

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^{16, 17}. 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 shows 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 population¹⁸. 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

7.1.1 Rule out active TB

All patients should first be evaluated for signs and symptoms of active TB (before commencing a course of TPT. Once active TB has been ruled out, eligible patients should be evaluated to assess their risk of AEs.

7.1.2 Assess contra-indications to 3HP

- 3HP is not recommended in the following patients and they should be offered an alternative to 3HP:
 - Persons living with HIV on Nevirapine and Ritonavir-based regimens (lopinavir, atazanavir)
 - Age under 2 years old
- Insufficient data to recommend 3HP in:
 - Women who are pregnant or contemplating pregnancy
 - Breastfeeding women

7.1.3 Baseline liver function testing

Although it is uncommon, specific attention should be paid to preventing hepatotoxicity because the risk factors for this AE can be easily identified and baseline testing can be conducted.

Clinicians should consider at least baseline AST (aspartate aminotransferase), and other liver function tests according to their national guidelines for implementing TPT, in the following patient groups:

- HIV infection (these are typically obtained when starting ART)
- Daily alcohol consumption
- Liver disorders including viral hepatitis
- Postpartum period (≤ 3 months after delivery)
- Concomitant use of other hepatotoxic substances including unregulated herbal supplements

For individuals with abnormal baseline test results, sound clinical judgement is required to ensure that the benefit of TB preventive treatment outweighs the risks and that regular monitoring can be ensured. Additional baseline tests can be considered on an individual basis (for example for elderly patients) at the discretion of the treating clinician. Suggested actions based on baseline liver testing are shown in Table 5.

Table 5 Suggested actions resulting from baseline liver function testing in specific groups

Result	Action
AST within normal limits	Commence 3HP and repeat AST only if symptomatic
AST \geq upper limit of normal	Repeat AST prior to 4 th dose of 3HP
AST $\geq 3x$ upper limit of normal	Do not start 3HP, further evaluation for liver disease

7.1.4 Baseline liver function testing in children

Otherwise healthy household child contacts do not require baseline liver function testing. Clinicians can consider using baseline liver function tests obtained for ART in children and adolescents living with HIV, having other liver disorders or taking other hepatotoxic medications. For children and adolescents with abnormal baseline liver function tests, risks and benefits of 3HP should be weighed. A standard approach to 3HP initiation based on baseline liver function tests as per adults (Table 5).

7.1.5 Patients at risk of peripheral neuropathy

Although peripheral neuropathy has rarely been recorded as an AE of 3HP⁷, the following patient groups at higher risk should take vitamin B6 (pyridoxine) supplements with each dose of 3HP:

- Breastfeeding mothers
- HIV infection
- Diabetes
- Renal failure
- Chronic alcohol dependence
- Malnutrition

Even among these patient groups, the risk of peripheral neuropathy associated with 3HP is low. Therefore, vitamin B6 supplementation is not a requirement for 3HP; treatment should not be delayed if vitamin B6 is not available in either children or PLHIV.

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

If you have symptoms concerning for liver damage or severe hypersensitivity:
<ul style="list-style-type: none"> • Do not take any further doses of 3HP • Contact a healthcare provider for advice as soon as possible • Only continue taking 3HP once you have been advised to by your healthcare provider AST within normal limits
These are some of the situations in which you should also take the above steps:
<ul style="list-style-type: none"> • Any persistent or concerning symptoms • Any change in your health or medical situation (new medicine, new diseases) • Any change in your social situation (moving away, change in job, not enough food)

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 counseled 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 counseled 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 counseled 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 counseled 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. Moreover, treatment completion for 3HP can be recorded if a patient takes 11 doses in 16 weeks – so 3HP can be withheld while an AE is assessed, and there is time for the regimen to be recommenced and completed if safe to do so.

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)

8.2.1 Suggested management of specific AEs

Suggested management of selected specific AEs is described in Table 7.

Table 7. Suggested management of selected AEs^{3,14}

Adverse event	Management
Flu-like or systemic hypersensitivity reactions	
Severe hypersensitivity or cutaneous reactions, including angioedema and anaphylaxis	<ul style="list-style-type: none"> Discontinue 3HP Provide urgent supportive care Refer for further assessment and management as appropriate
Flu-like syndrome (mild/moderate) OR Mild cutaneous reactions (rash, itching) OR Gastrointestinal reactions OR Respiratory reactions	<ul style="list-style-type: none"> Withhold 3HP Offer ancillary treatments for symptomatic management as appropriate <ul style="list-style-type: none"> Antihistamines (diphenhydramine, loratadine etc.) Antiemetics, antidiarrheals or ORS Bronchodilators Steroids Monitor symptoms Re-challenge 3HP at next dose if symptoms resolve
Hepatotoxicity	
Any symptoms of hepatitis develop while taking 3HP	<ul style="list-style-type: none"> Withhold 3HP Assess for other causes of symptoms (gastroenteritis, etc) Test AST (other liver function tests at provider discretion)
AST <3x ULN (Test may have been conducted in a patient with symptoms or with raised baseline AST)	<ul style="list-style-type: none"> Continue 3HP Monitor symptoms Reassess risk factors Check AST again if symptoms do not resolve
AST ≥3x ULN with any symptoms of hepatitis OR AST ≥5x ULN	<ul style="list-style-type: none"> Withhold 3HP Monitor AST and symptoms Reassess risk factors Re-challenge 3HP once symptoms resolved and AST <3x ULN
AST ≥10x ULN OR Symptoms of severe hepatitis Jaundice Dark urine Abdominal pain	<ul style="list-style-type: none"> Discontinue 3HP Supportive care including referral to higher level of care Monitor liver function tests

Other AEs	
Active TB signs or symptoms OR Malaria diagnosis and treatment OR Diagnosis and treatment of other acute illness	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Discontinue 3HP • Discuss timing and options for completing a course of TPT
Changed type or dose of long-term medicines	<ul style="list-style-type: none"> • 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

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.

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.

<p>3HP and AEs</p>	<p>Because 3HP is a preventive treatment used to cure persons with no active disease, the risk of AEs should be especially minimized.</p>
<p>Drug reactions</p>	<p>The most common drug reactions with 3HP are:</p> <ul style="list-style-type: none"> • Liver toxicity (less common than for IPT) • Flu-like reactions (more common than for IPT) <p>Drug reactions are usually mild and self-limiting, but occasionally they can be severe.</p> <p>Children usually tolerate 3HP very well and have much lower rates of drug reactions.</p>
<p>Baseline assessment</p>	<p>Active TB must be ruled out before commencing 3HP.</p> <p>3HP is currently not recommended in:</p> <ul style="list-style-type: none"> • Pregnancy • Age <2 years <p>Information on baseline liver function is important in the following:</p> <ul style="list-style-type: none"> • 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 <p>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.</p>
<p>Counselling for AEs</p>	<p>Red/orange discoloration of urine and other body fluids while taking 3HP is normal and completely harmless.</p> <p>If patients experience any symptoms concerning for an AE:</p> <ul style="list-style-type: none"> • 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 <p>Individuals should be alert to the following symptoms:</p> <ul style="list-style-type: none"> • 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 (appendix 1)

Routine monitoring	<p>Patients taking 3HP should be monitored monthly to assess tolerability and adherence. Essential components of the visit are:</p> <ul style="list-style-type: none"> • 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	<p>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:</p> <ul style="list-style-type: none"> • Screen for active TB • Past history • History of the AE: type, onset and duration, severity • Relevant physical examination <p>Management of the AE should always be guided by the clinical judgement of the healthcare provider. Suggested management:</p> <ul style="list-style-type: none"> • Severe drug reactions: seek urgent supportive care • Mild/moderate drug reactions: reassurance, symptomatic relief, further assessment • Pregnancy: discontinue 3HP
Recording and reporting	<p>Routine pharmacovigilance procedures should be used for AEs associated with 3HP, where possible and according to national guidelines.</p> <p>At IMPAACT4TB sentinel sites, AEs should also be reported according to the evaluation protocol.</p>

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