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.

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.

Specific drug reactions
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.

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>
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<tr>
<td>Fever</td>
<td>Dark, brown or tan colored urine (darker or additional discoloration than due to rifamycins)</td>
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<tr>
<td>Nausea or vomiting</td>
<td>Pale stools</td>
</tr>
<tr>
<td></td>
<td>Easy bruising or bleeding</td>
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</tbody>
</table>
2. Flu-like syndrome and other systemic hypersensitivity reactions
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. Most patients will be able to continue 3HP and complete the preventive treatment.

Symptoms of liver damage in adults and children

<table>
<thead>
<tr>
<th>SYNDROME/HYPERSENSITIVITY REACTION</th>
<th>SYMPTOMS</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>
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<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>
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</tbody>
</table>

3. Peripheral Neuropathy
Although neuropathy is associated with use of daily isoniazid, it has not been reported as a specific AE in use of 3HP. Pyridoxine (B6), should be administered with the weekly dose of 3HP to minimize the risk of peripheral neuropathy.

Management of selected 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.

Management of selected AEs

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>MANAGEMENT</th>
</tr>
</thead>
</table>
| Hepatotoxicity| • Withhold 3HP  
• Assess for other causes of symptoms  
• (gastroenteritis, etc)  
• Test AST (other liver function tests at provider discretion) |
<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatotoxicity (cont)</strong></td>
<td></td>
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</tbody>
</table>

- **AST <3x ULN**  
  (Test may have been conducted in a patient with symptoms or with raised baseline AST)  
  - 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**  
  - 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  
  - Discontinue 3HP  
  - Supportive care including referral to higher level of care  
  - Monitor liver function tests

| **Flu-like or systemic hypersensitivity reactions** | | |
|-------------------------------------------------|------------|

- **Severe hypersensitivity or cutaneous reactions, including angioedema and anaphylaxis**  
  - 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**  
  - Withhold 3HP  
  - Offer ancillary treatments for symptomatic management as appropriate  
    - Antihistamines (diphenhydramine, loratadine etc.)  
    - Antiemetics, antiarrheals or ORS  
    - Bronchodilators, Steroids  
  - Monitor symptoms  
  - Re-challenge 3HP at next dose if symptoms resolve
### Other AEs

| Active TB signs or symptoms | Withhold 3HP  
| OR Malaria diagnosis and treatment | Investigate and treat for active TB, malaria or other acute illness  
| OR Diagnosis and treatment of 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  

For updated information on IMPAACT4TB and to download a copy of this document and other materials related to TB preventive therapy, please visit: www.impaact4tb.org/library