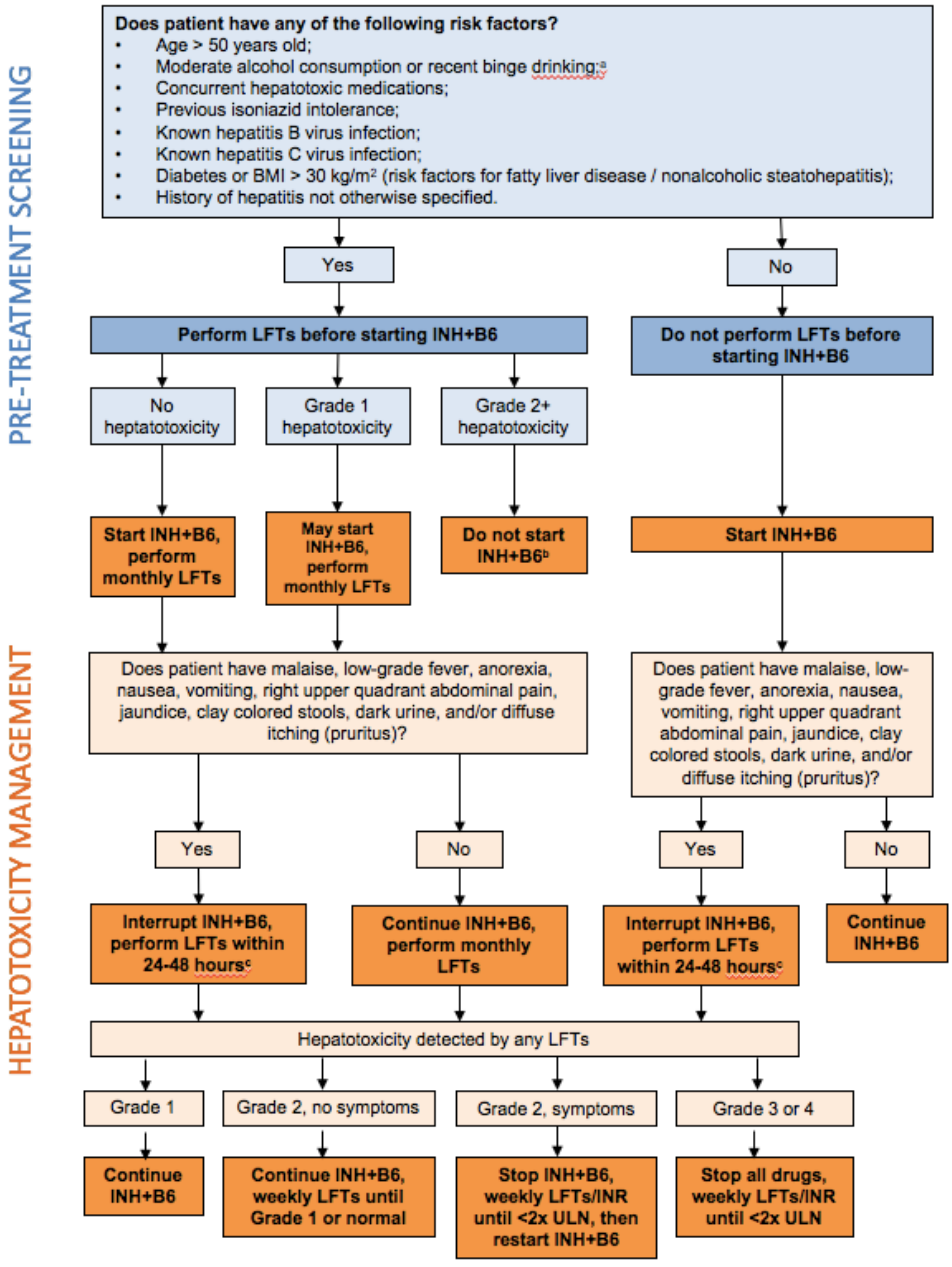
# HALT-TB Toxicity Management Guide for Adults Taking Isoniazid for Latent Tuberculosis Infection

Version 0.1, Date 17-Oct-2019

## A. Hepatotoxicity

**Figure A1.** Flow diagram of hepatotoxicity testing and management for patients receiving treatment for latent tuberculosis infection.




*Abbreviations*: B6, pyridoxine; BMI, body mass index; INH, isoniazid; INR, international normalized ratio; LFTs, liver function tests; ULN, upper limit of normal (defined by local laboratory).

[a] Moderate alcohol consumption is defined as up to 1 drink per day or 7 drinks per week for females, and up to 2 drinks per day or 14 drinks per week for males. Recent binge drinking is defined as 4 or more drinks for females or 5 or more drinks for males on the same occasion on at least 1 day in the past month.
[b] Evaluate for possible causes of hepatotoxicity. Consider rechecking LFTs one week later. If hepatotoxicity resolves to Grade 1 or lower, consider starting INH+B6 on a case-by-case basis after expert consultation.
[c] INH+B6 should be *temporarily interrupted* while awaiting LFT results in patients with suspected hepatotoxicity. If LFT results are normal, restart INH+B6.

1. Prevention: Prior to starting isoniazid, patients should be counseled to avoid hepatotoxic medications such as acetaminophen. Patients should also be advised to abstain from alcohol if possible. The "safe" number of alcoholic drinks while on isoniazid is not known. Patients with hepatic steatosis and nonalcoholic steatohepatitis should be advised to lose weight while on isoniazid treatment.

2. Diagnosis: Isoniazid is a common cause of hepatotoxicity. For patients who experience confirmed hepatotoxicity while taking isoniazid, the isoniazid is the most likely culprit. Hepatotoxicity is most commonly asymptomatic, but can be symptomatic. Symptoms that should raise suspicion for hepatotoxicity include malaise, low-grade fever, anorexia, nausea, vomiting, right upper quadrant abdominal pain, jaundice, clay colored stools, dark urine, and diffuse itching (pruritus). Patients may present with one or more of these symptoms. The diagnosis of hepatotoxicity is established, and its severity grade assigned, by liver function test (LFT) results as shown in Table A1.

Table A1. Hepatotoxicity severity grading index.

| Condition term | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Alanine Aminotransferase (ALT or SGPT) Increased | >ULN – 3.0 x ULN | >3.0 – 5.0 x ULN | >5.0 – 20.0 x ULN | >20.0 x ULN |
| Aspartate Aminotransferase (AST or SGOT) Increased | >ULN – 3.0 x ULN | >3.0 – 5.0 x ULN | >5.0 – 20.0 x ULN | >20.0 x ULN |
| Hyperbilirubinemia | >ULN – 1.5 x ULN | >1.5 – 3.0 x ULN | >3.0 – 10.0 x ULN | >10.0 x ULN |
| Hepatic failure | N/A | N/A | Asterixis; mild encephalopathy; limiting self-care activities of daily living | Moderate to severe encephalopathy; coma; life-threatening consequences |

*Abbreviation*: ULN, upper limit of normal (defined by local laboratory).

If a patient experiences hepatotoxicity, consider evaluating for other possible causes contributing to hepatotoxicity, such as viral hepatitis and potentially hepatotoxic medications, herbs, supplements, or toxic ingestions (e.g., alcohol). Any concomitant condition or medication increases the risk of hepatotoxicity while on isoniazid.

3. Monitoring: *Before* starting isoniazid, checking LFTs is indicated for some patients as shown in Table A2. *After* patients have started isoniazid, indications to perform LFTs during treatment are shown in Table A3. These recommendations are also summarized as a flow diagram in Figure A1.

For both Tables A2 and A3, baseline risk factors for hepatotoxicity include:

- Age > 50 years old;
- Moderate alcohol consumption or recent binge drinking;
    - Moderate alcohol consumption is defined as up to 1 drink per day or 7 drinks per week for females, and up to 2 drinks per day or 14 drinks per week for males.

    - Recent binge drinking is defined as 4 or more drinks for females or 5 or more drinks for males on the same occasion on at least 1 day in the past month.
    - Source: https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking
- Concurrent hepatotoxic medications;
- Previous isoniazid intolerance;
- Known hepatitis B virus infection;
- Known hepatitis C virus infection;
- Diabetes or body mass index >30 kg/m$^2$ (risk factors for fatty liver disease / nonalcoholic steatohepatitis);
- History of hepatitis not otherwise specified.

**Table A2.** Indications to perform LFTs at baseline (before starting isoniazid).

| Characteristic | Indication |
|---|---|
| Patients without baseline risk factors | Baseline LFTs not indicated before starting isoniazid |
| Patients with baseline risk factors | Baseline LFTs indicated before starting treatment<br>• If LFTs do not show hepatotoxicity, start isoniazid and check LFTs once monthly<br>• If LFTs show Grade 1 hepatotoxicity, consider starting isoniazid and check LFTs once monthly<br>• If LFTs show Grade 2 or higher hepatotoxicity, do not start isoniazid. Consider starting isoniazid if hepatotoxicity resolves to Grade 1 or lower on a case-by-case basis after expert consultation |

**Table A3.** Indications to perform LFTs for patients taking isoniazid.

| Characteristic | Signs/symptoms | Indication |
|---|---|---|
| Patients without baseline risk factors | Asymptomatic | Checking LFTs is not indicated |
| | Suspected hepatotoxicity[a] | Check LFTs within 24-48 hours[b] |
| Patients with baseline risk factors | Asymptomatic | Check LFTs once monthly |
| | Suspected hepatotoxicity[a] | Check LFTs within 24-48 hours[b] |

[a] Symptoms that should raise suspicion for hepatotoxicity include malaise, low-grade fever, anorexia, nausea, vomiting, right upper quadrant abdominal pain, jaundice, clay colored stools, dark urine, and diffuse itching (pruritus). Patients may present with one or more of these symptoms.
[b] Urgent testing (within 24-48 hours) should be performed in any patient with concern for hepatotoxicity. Isoniazid should be *temporarily interrupted* while awaiting LFT results in patients with suspected hepatotoxicity.

4. Management: Once confirmed by LFTs, hepatotoxicity is managed according to its severity grade (**Table A1**), guided by clinical presentation (symptoms) and LFT results (AST, ALT and bilirubin).

- Grade 1: Continue isoniazid.
- Grade 2:
    - Without symptoms: Continue isoniazid with once weekly monitoring of LFTs until resolution (return to baseline) or stabilization to Grade 1 or lower.
    - With symptoms: Discontinue isoniazid and monitor LFTs and international normalized ratio (INR) once weekly. Reintroduce isoniazid once LFTs return to baseline, or are at least lower than 2x ULN.

- Grade 3 and 4: Stop all drugs, including isoniazid; measure LFTs and INR once weekly (or more frequently, if clinically indicated). Re-challenge may be possible for patients only after expert consultation, mainly for patients who were receiving concomitant hepatotoxic drugs.

In all patients experiencing hepatotoxicity, review the concomitant treatment the patient is receiving and stop or replace any other potentially hepatotoxic non-tuberculosis drugs. Many medications, herbs, and supplements can cause hepatotoxicity. The most common medications are acetaminophen, allopurinol, antidepressants (bupropion, fluoxetine, paroxetine, sertraline, trazodone), antihypertensives (lisinopril, losartan, methyldopa), antimicrobials (ketoconazole, fluoroquinolones, tetracycline, valacyclovir), antipsychotics (risperidone), antiretrovirals (nevirapine, ritonavir), nonsteroidal anti-inflammatory drugs (aspirin, bromfenac, diclofenac), statins, and thiazolidinediones. An exhaustive list is available here: https://www.livertox.nih.gov/

For patients with Grade 2 or higher hepatotoxicity, systematically look for another cause of hepatotoxicity, such as viral hepatitis, biliary or hepatic disease. This can also be considered for patients with Grade 1 hepatotoxicity if they have concerning signs, symptoms, or exposure history that suggest another cause. If viral hepatitis is suspected, the following tests should be used:

- Hepatitis A virus (HAV): Check HAV IgG (positive if prior exposure) and HAV IgM (positive if recent exposure).
- Hepatitis B virus (HBV): Check HBV core antibody total (positive if prior exposure), HBV surface antigen (positive if active hepatitis), and HBV surface antibody (positive if immune).
- Hepatitis C virus (HCV): Check HCV antibody (positive if prior exposure).

Additional procedures that can be used to assess for cholestasis or mixed hepatotoxic and cholestatic injury include alkaline phosphatase tests and abdominal ultrasound, especially in patients with increased bilirubin or AST. For patients with Grade 4 heptatoxicity, all of the above should be done.

## B. Gastrointestinal Disorders

1. Diagnosis: Nausea/vomiting can be caused by isoniazid. Symptoms usually diminish over time while on the medication. If vomiting is persistent or is accompanied by jaundice or abdominal pain, this may be a sign of hepatotoxicity (see Section A above). Persistent vomiting could also be a sign of increased intracranial pressure. TB meningitis should be ruled out as a cause of vomiting in these cases. Diarrhea is associated with liquid formulations of isoniazid. *C. difficile* colitis is a possible complication of isoniazid or any other antibiotic.

**Table B1.** Gastrointestinal disorder severity grading index.

| Condition term | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Nausea | Mild or transient; maintains reasonable food intake | Moderate discomfort; intake decreased significantly; some activity limited | No significant intake; requires intravenous fluids | Hospitalization required |
| Vomiting | 1 episode in 24 hours | 2-5 episodes in 24 hours | >6 episodes in 24 hours or needing intravenous fluids | Physiologic consequences requiring hospitalization or requiring parenteral nutrition |
| Diarrhea | Mild or transient; 3-4 loose stools/day or mild diarrhea lasting <1 week | Moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week | >7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L intravenous fluids required | Hypotensive shock or physiologic consequences requiring hospitalization |

2. Management: Gastrointestinal disorders are managed according to their severity grade (Table B1).

- Grade 1: Continue isoniazid. Give medications with food.
- Grade 2: Increase oral fluid intake. If hepatotoxicity is suspected, stop isoniazid and refer for urgent assessment, including LFTs (see Section A above).
- Grade 3 and 4: Stop all drugs, including isoniazid. Hospitalize for administration of intravenous fluids and urgent assessment, including LFTs.

## C. Peripheral Neuropathy

1. Prevention: All patients taking isoniazid should receive 50 mg of pyridoxine (vitamin B6) daily even without symptoms of peripheral neuropathy. This is because isoniazid is a pyridoxine congener (molecular mimicker) and can therefore cause peripheral neuropathy in any patient. Since peripheral neuropathy can be irreversible, the risk/benefit calculation favors providing 50 mg of pyridoxine daily to all patients receiving isoniazid, as it is low cost and has minimal to no adverse effects.

2. Diagnosis: Peripheral neuropathy can be caused by isoniazid, even in those receiving pyridoxine. Comorbid conditions such as diabetes mellitus, HIV infection, prior trauma, nerve impingement, and concomitant medications such as ARVs or metronidazole may also cause neuropathy. The diagnosis of peripheral neuropathy is established by symptoms of paresthesia (burning or electric pain, numbness, or tingling) and examination findings. The Brief Peripheral Neuropathy Screen (BPNS) is a tool that integrates symptoms and examination findings to facilitate the diagnosis and severity grading of peripheral neuropathy.

**Table C1.** Peripheral neuropathy severity grading index.

| Condition term | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Paresthesia (Burning, Tingling, etc.) | Moderate discomfort; non-narcotic analgesia required; and/or BPNS subjective sensory neuropathy score 4-6 on any side. | Severe discomfort; or narcotic analgesia required with symptomatic improvement; and/or BPNS subjective sensory neuropathy score 7-10 on any side. | Severe impairment (decreased or loss of sensation to knees or wrists); and/or vibration perception score 3 (severe loss) and/or deep tendon reflex score 1. | Incapacitating; or not responsive to narcotic analgesia. |

*Abbreviation*: BPNS, Brief Peripheral Neuropathy Screen.

3. Management:

- Grade 1: Continue isoniazid and see the patient back in a week. If the adverse event is resolved, continue isoniazid. If the adverse event is still present, stop isoniazid. If symptoms resolve, consider restarting isoniazid.
- Grade 2: If currently administered, stop isoniazid. If symptoms resolve, consider restarting isoniazid.
- Grade 3: If currently administered, stop isoniazid. If symptoms resolve, consider restarting isoniazid.
- Grade 4: If currently administered, permanently stop isoniazid.

In all patients experiencing peripheral neuropathy:

- Increase the dose of pyridoxine to 100 or 200 mg/day until symptoms resolve;
- Check if the patient receives other drugs that may increase the risk of peripheral neuropathy (e.g., stavudine, didanosine, or metronidazole) and, if it is the case, stop the drug(s) if possible;
- Provide symptomatic relief if needed: non-steroidal anti-inflammatory drugs, acetaminophen, tricyclic antidepressants, and carbamazepine may be used according to efficacy and drug-drug interactions at the discretion of the clinician.

## D. Dermatologic Disorders

1. Diagnosis: Isoniazid can cause dermatologic complications including urticaria and skin rashes. Other concurrent medications may also cause dermatologic side effects and should be considered as culprits in the event of symptoms. Itchy skin (pruritus) may be a sign of hepatotoxicity if it is persistent or accompanied by jaundice or abdominal pain (see Section A above).

**Table D1.** Dermatologic disorder severity grading index.

| Condition term | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Rash | Small areas of redness/rash | Dry peeling or widespread rash | Wet peeling, ulcers or urticaria | Severe, widespread rash, necrosis requiring hospitalization |
| Itchy skin | Slight itching in localized areas | Severe itching in localized areas | Widespread itching over entire body | Uncontrollable scratching requiring hospitalization |

2. Management:

- Grade 1: Continue isoniazid. Administer antihistamine to control symptoms.
- Grade 2: Stop isoniazid. Administer antihistamine to control symptoms. If hepatotoxicity is suspected, stop all drugs and refer for urgent assessment including LFTs.
- Grade 3 and 4: Stop all drugs, including isoniazid. Hospitalize for further management.

## E. Headache

1. Diagnosis: Headache is a disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve. It can be caused by multiple medications, including isoniazid, and multiple conditions, including migraine and hypoglycemia. If headaches are severe and associated with vomiting, TB meningitis should be ruled out as an underlying cause.

**Table E1.** Headache severity grading index.

| Condition term | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Headache | Mild, no treatment required | Transient, moderate; treatment required | Severe; responds to initial narcotic therapy | Intractable; requires repeated narcotic therapy |

2. Management:

- Grade 1: Continue isoniazid.
- Grade 2: Continue isoniazid. Administer anti-inflammatory medications to control symptoms.
- Grade 3 and 4: Stop all drugs, including isoniazid. Consider narcotic medications to control symptoms.