

# Adverse events associated with use of Isoniazid preventive therapy among people living with HIV

## BACKGROUND

Isoniazid Preventive Therapy (IPT) is an important intervention recommended by WHO for preventing and reducing tuberculosis (TB) in people living with HIV.

- Because of their weakened immune system, people living with HIV are less able to fight TB infection and are more likely to develop active TB which can be deadly and can spread to others.
- Taking medicine containing the anti-TB drug isoniazid is a simple and cost-effective measure that prevents the TB bacteria from becoming active if it is present. Isoniazid has been a standard drug for tuberculosis treatment and preventive therapy due to high potency, infrequent toxicity, small bulk, and low cost.
- Treatment of latent TB infection (LTBI) also referred to as TB preventive therapy or chemoprophylaxis, helps to prevent progression of LTBI to active disease, both in HIV negative populations and those infected with HIV.
- TB preventive therapy using Isoniazid in people living with HIV reduces the risk by 33% (relative effect 0.67; CI 0.51– 0.87) and to a greater extent (64%) in tuberculin skin test positive persons. (1)

## ADVERSE EVENTS

**Isoniazid chemotherapy is generally safe.**

A Cochrane systematic review conducted in 2010 found adverse events leading to discontinuation of treatment to be more common when multiple drug combination therapy are used compared to Isoniazid alone. It also found that with Isoniazid alone, 56 events occurred among 2026 individuals in compared to 33 out of 1873 with placebo, a risk ratio of 1.66 [ 1.09, 2.51 ](1). However majority of the events subside with time and reassurance, and when severe are reversible if the drug is stopped early. The adverse events linked with IPT are listed below:

### Peripheral neuropathy

The most common adverse event associated with isoniazid treatment is peripheral neuropathy. The earliest symptom is paraesthesia, followed by pricking pain and burning sensation in the feet and later in the hands. If untreated, the symptoms worsen and cause distress to the patient. The frequency of neuropathy increases with the dose of Isoniazid. This condition is more common in patients with diabetes or uraemia, malnourished patients, and daily users of alcohol. It can be prevented by providing pyridoxine (vitamin B6) (10 mg/day).

### Hepatotoxicity

Rarely Isoniazid can also cause hepatotoxicity. It is more frequent with other potentially hepatotoxic agent's particularly active alcohol abuse. Hepatotoxicity induced by Isoniazid is reversible if the drug is stopped early.

## WHO RECOMMENDATION ON IPT

WHO recommends the use of Isoniazid 300mg daily for six months (and conditionally for 36 months) among adults and adolescents living with HIV and unlikely to have active TB, as a part of a comprehensive package of HIV care. (2)

## EVIDENCE: SAFETY OF ISONIAZID USE

The following evidence demonstrates the relative safety of isoniazid use in the treatment of latent TB infection in large populations

- A meta-analysis involving 38,257 subjects treated with isoniazid, estimated risk of clinical hepatitis at 6 per 1000 treated individuals, with a range of 0.0–2.9% (3) among different studies.
- A large clinical trial with 24,221 HIV infected persons receiving isoniazid preventive therapy in South Africa reported 132 study-defined adverse events in total 130 (0.54%) individuals with just 17 (0.07%) cases of clinical hepatotoxicity. (4) The clinical hepatotoxicity was significantly associated with consumption of alcohol
- In the BOTUSA clinical trial of 1762 PLHIV in Botswana only 1.1% of PLHIV who adhered to at least 4 months of treatment developed hepatitis including one death, presumed due to hepatotoxicity at month six. However further investigation into this case revealed that patient did not stop Isoniazid for several days after advice and also received paracetamol for cough prior to development of encephalopathy and death. In the same trial, 1.9% (19 of 1,006) patients who received 36 months of isoniazid developed severe hepatitis, including three with jaundice and two with hepatic encephalopathy. Another 3.1% (31 of 1,006) experienced moderate hepatitis. **No death was reported.** This and other trial also pointed out that concurrent use of antiretroviral therapy is not statistically associated with isoniazid-induced hepatitis and that more events occur with Nevirapine than with Efavirenz. (5)(6)(7)

## REFERENCES

1. Akolo C et al. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database of Systematic Reviews*, 2010, 1:CD000171
2. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings, 2011, World Health Organization, Geneva (available at [http://whqlibdoc.who.int/publications/2011/9789241500708\\_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241500708_eng.pdf))
3. Steele MA, Burk RF, DesPrez RM; Toxic hepatitis with isoniazid and rifampin. A meta-analysis; *Chest* 1991; 99: 465–471.
4. Grant AD, et.al; Adverse events with isoniazid preventive therapy: experience from a large trial; *AIDS* 2010, 24 (suppl 5):S29–S36
5. Tedla Z et.al; Isoniazid-associated Hepatitis in adults infected with HIV receiving 36 months of Isoniazid Prophylaxis in Botswana; *Chest*. 2015 May 1;147(5):1376–84
6. The TEMPRANO ANRS 12136 Study Group-A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa; *N Engl J Med* 2015; 373:808–822 August 27, 2015 DOI: 10.1056/NEJMoa1507198
7. Rangaka MX, Wilkinson RJ, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind placebo-controlled trial. *Lancet*. 2014;384(9944):682–690. doi:10.1016/S0140-6736(14)60162-8.
8. Getahun H, Matteelli A, Chaisson R, Raviglione M; Latent Mycobacterium tuberculosis Infection; *N Engl J Med* 2015; 2015;372:2127–35. DOI: 10.1056/NEJMra1405427

## MANAGEMENT OF ADVERSE EVENTS

**Close clinical monitoring:** As with any treatment, health care providers must weigh risks and benefits of isoniazid therapy in each individual. The risk of severe isoniazid induced hepatotoxicity can be minimized with close clinical monitoring. Obtaining a detailed and accurate medical history, and updating information at frequent intervals, will identify persons who require close monitoring. Asymptomatic elevation of serum liver enzyme concentrations occurs in 10%–20% of people taking INH and the concentrations usually returns to normal even when treatment is continued. It is generally recommended that isoniazid be withheld if a patient’s transaminase level exceeds three times the upper limit of normal if associated with symptoms or five times the upper limit of normal if the patient is asymptomatic. If hepatitis occurs it is also important to rule out other possible causes of injury (such as recrudescence of viral hepatitis). Patients should be instructed, at the start of treatment and at each monthly visit, to stop taking treatment and seek medical attention immediately if symptoms suggestive of hepatitis develop.

**Laboratory Testing:** WHO does not recommend routine baseline liver function testing for isoniazid preventive therapy given the paucity of data on its role, rarity of adverse events and absence of evidence on any real predictor for future toxicity. Laboratory testing should therefore be based on clinical indications and capacity of clinical services. (8) However, at any time during the treatment, laboratory testing is recommended for patients who have symptoms suggestive of hepatitis (e.g., fatigue, weakness, malaise, anorexia, nausea, vomiting, abdominal pain, pale stools, dark urine, chills) or who have developed jaundice.