# Is isoniazid so safe to use in tuberculosis preventive therapy?

Tuberculosis (TB) has emerged as a major warning to global public health as thirty three percent of the world population is considered to be infected with *Mycobacterium tuberculosis* (MTB) infection. Further, multi-drug-resistant strains of MTB in association with HIV, have created a fearsome aspect to the TB problem. Most drug-resistant clinical strains of MTB, are resistant to isoniazid (INH), one of the effective anti-TB drugs used for tuberculosis treatment. World Health Organization has recommended Isoniazid preventive therapy (IPT) for HIV-infected persons as part of the core services. While, two recent studies have shown that there was more than 60% reduction in TB in HIV-infected adults after isoniazid preventive therapy (IPT), one study reported that INH prophylactic therapy was not so much effective among the youngest children and that there was little evidence of mortality benefit in children of any age. Another systematic review on isoniazid preventive therapy and risk for resistant tuberculosis, reported that IPT therapy would decrease the number TB cases caused by isoniazid-susceptible strains but would have less effect on resistant strains, which would increase the proportion of resistant strains among subsequent cases of active TB. Further, it was suggested that the presence of active TB should be excluded before IPT and continued surveillance for isoniazid resistance is essential. As per TB drug resistance mutation database, 22 genes/proteins of MTB were reported to associate with INH resistance. Out of 22 genes/proteins, 11 genes were reported to be induced by INH. The detailed mechanism of resistance & induction in number of proteins is yet to be thoroughly understood.

Isoniazid is also not a safe drug and without toxicity, and side effects. Adverse effects of isoniazid have been reported by different researchers based on their clinical studies such as renal failure, liver injury and liver failure, development of agranulocytosis, isoniazid-induced tenosynovitis etc. Furthermore, isoniazid and/or its metabolites (e.g. hydrazine) may be associated with causing mitochondrial injury, which may lead to oxidant stress in mitochondria and destruction of energy homeostasis. In 2015, one study on the follow-up results of isoniazid chemoprophylaxis during biological therapy in Colombia, reported that 3.2 % patients developed active tuberculosis, and 17.2 % patients developed intolerance or toxicity related to INH. Based on their observation they suggested that chemoprophylaxis with INH seems to be effective and safe for the prevention of most TB reactivation in individuals with latent tuberculosis infection, but toxicity must be monitored during follow-up. However, disquiets have been raised about the wide use of INH due to its toxicity, predominantly hepatotoxicity; as biochemical monitoring is not routinely carried out during INH therapy.

Though, isoniazid preventive therapy (IPT) is increasingly recommended for preventing TB in normal children and treating latent tuberculosis infection in HIV patients, concerns about the risk for development of isoniazid-resistant tuberculosis with extensive use of INH should be considered before its widespread use in HIV infection, latent infection and in particular in children. There is need for detailed study to understand the role and mechanism of action of INH inside the host as

well as in tuberculosis bacilli to use the drug widely in preventive therapy of tuberculosis for the fear that one day it may not become ineffective in TB therapy.

***L. Jena*** *and* ***B. C. Harinath***
*Bioinformatics Centre, JBTDRC, MGIMS, Sevagram, Maharashtra, India*

## Publication

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