The 3 HP regimen for tuberculosis preventive treatment: safety, dosage and related concerns during its large-scale implementation in countries like India

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Summary

The 3-month once-weekly isoniazid-rifapentine (3 HP) regimen for tuberculosis preventive treatment recommended by WHO is being rolled in countries including India. It has higher completion rates and lower risk of hepatotoxicity than isoniazid preventive treatment, but trials also showed higher frequency of systemic drug reactions (SDRs) including flu-like syndromes and dizziness, and also uncommon Grade 3 or 4 adverse events like hypotension, syncope, bronchospasm. Low BMI is a risk factor for SDRs. Available data on safety of 3 HP in the Asian region is limited, heterogeneous, but points to a higher frequency of SDRs suggesting a need for caution in its large-scale implementation. 19% (118/614) of household contacts initiated on 3 HP in Delhi reported dizziness. Multiple lines of evidence including pharmacokinetic data suggest that the SDRs may be related to isoniazid and its plasma concentration. WHO and national guidelines for the 3 HP regimen currently recommend a fixed dose of once-weekly 900 mg isoniazid in adults regardless of body weight that poses a risk of SDRs for lower weight adults, amplified by the acetylator status and the lack of co-administration of pyridoxine. Weight based dosing, co-administration of pyridoxine and pharmacovigilance studies should accompany the roll out of 3 HP to ensure its safe and successful implementation.

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Introduction

Tuberculosis preventive treatment (TPT) is an important component of the global END TB strategy. Recently, the WHO recommended shorter rifamycin based regimens; 3 months of once-weekly isoniazid and rifapentine (3 HP), 4 months of daily rifampicin (4 R), 3 months of daily isoniazid and rifampicin (3HR), 1 month of daily isoniazid and rifapentine (1 HP) in contrast to the 6–9 month isoniazid containing regimens (6 H, 9 H) used earlier in view of evidence from randomised controlled trials (RCTs) on these shorter regimens.[1] The WHO also made a conditional recommendation on expanding the priority population to include to household contacts of patients with pulmonary tuberculosis of all ages, in addition to household contacts <5 years and those with HIV infection.[1] The RCTs of the 3 HP regimen in HIV negative individuals were conducted mainly in low TB burden countries like USA and Canada,[2] while those in HIV positive individuals were conducted also in countries like South Africa.[3,4] The 3 HP regimen is in the process of roll-out in programmatic management of tuberculosis preventive treatment in higher TB burden countries like India, that were not represented in these trials.[5] There are some concerns about the 3 HP regimen in this process related to its safety profile, dosing, and need for co-administration of pyridoxine. The WHO has announced that it will be updating its guidance for tuberculosis preventive treatment soon and it is hoped that this viewpoint will be taken into consideration in this process.[6]

The issue of systemic drug reactions with the 3 HP regimen

The PREVENT trial compared 3 HP (given in a weekly dose of isoniazid of 15–25 mg/kg rounded off to the nearest 50 mg to a maximum of 900 mg, rifapentine in a maximum dose of 900 mg and with incremental adjustment in subjects ≤50 kg) with 9 H (isoniazid 5–15 mg/kg to a maximum of 300 mg). The results showed that 3 HP was non-inferior to 9 H in prevention of TB disease, with lower rates of hepatotoxicity (0.4% vs. 2.7%, $p < 0.001$), and higher rates of treatment completion (82.1% vs. 69%, $p < 0.001$).[2] These advantages were also confirmed in later studies.[7] There was however a higher proportion of subjects in the 3 HP

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arm with adverse events attributed to the study drug (8.2% vs. 5.5%, p < 0.001). Some of these adverse events in the 3 HP arm were initially termed possible hypersensitivity reactions,[2] and the frequency of permanent discontinuation due to these was also higher in the 3 HP compared to 9 H arm (3.8% vs. 0.5%).[2] Later, as these did not appear immunologically mediated, these were termed systemic drug reactions (SDRs).[8] These were classified into mutually exclusive categories–cutaneous reactions (angioedema, rash, itching, anaphylaxis), flu-like syndrome (fever or chills, weakness, fatigue, dizziness, muscle aches, syncope, palpitations, red eyes, or sweats), gastrointestinal (vomiting, abdominal pain), respiratory (bronchospasm, cough and undefined[8]; and their risk factors were analysed.[8] Systemic drug reactions were strongly associated with the 3 HP arm (adjusted OR of 9.4 for SDR), while female sex, white race, and low BMI also emerged as risk factors.[8] Some of the SDRs were of high concern like hypotension, syncope, hives, angioedema, acute bronchospasm, while the more frequent SDRs comprised of flu-like syndrome (fever or chills, fatigue, weakness or muscle pain, dizziness, rash).[9] These systemic drug reactions were recorded only in the PREVENT trial when the patient reported these as a cause of discontinuation, which is a limitation.[9] The iAdhere trial that compared directly observed administration of 3 HP with self-administered therapy, addressed this issue by recording and grading the adverse effects prospectively.[9] In this trial, the frequency of SDRs was higher (11%) than seen in the PREVENT trial, and serious adverse events were seen in 0.5% of participants.[9] These systemic drug reactions occurred mostly in the first month, were usually mild, and nearly half of the participants with SDRs completed the therapy. A systematic review noted that 3 HP regimens was associated with higher rates of adverse events leading to permanent discontinuation of drug (8.2%) and higher rates of grade 3 and 4 events (3.6%; 95% CI: 2.2–6%), which was the lowest with the 4 R regimen.[10] An individual patient data meta-analysis that compared the completion, safety, and efficacy of 3 HP and 4 R compared to longer regimens, noted that while the treatment completion of 3 HP was 5% better than 4 months of rifampicin (4 R), the risk of serious adverse events (grade 3 or grade 4) was increased significantly (adjusted risk ratio of 3.46).[11] In fact the investigators of the PREVENT trial concluded in an analysis of the adverse events "As 3 HP is introduced into clinical practice, including populations that differ from our study population, clinical monitoring and continued vigilance for SDR are warranted."[8]

The data on safety of 3 HP regimen in Asians, who contribute the maximum to the global burden of TB is limited but expanding with experience of implementation in cohorts in India,[12] Bangladesh,[13] Pakistan,[14,15] South Korea,[16] Hong Kong,[17] and some trials in Taiwan[18] and China.[19,20] Table 1 shows the accepted terminology for classifying the frequency,[21] and severity of adverse drug reactions[22] that might be useful in putting this data in context. In India, six hundred and fourteen household contacts above 14 years were initiated on 3 HP (self-administered) in an observational study in TB Clinics in the national capital.[12] Of these 195 (32%) had adverse effects, of which 55% (107/195) had to seek medical attention. The most frequent adverse effects were dizziness/fainting in 19.2% (118/614) which constituted 62% of all adverse effects. The study noted discontinuation in 20 participants (3.2% of the total) due to adverse effects.[12]

In Dhaka community-based TPT with 3 HP was initiated in 1216 recipients of all ages, in a collaborative effort between the national programme and a non-governmental organisation.[13] The treatment completion rate was 97% in a setting where 73% of contacts eligible for 3 HP started treatment, and where multiple approaches (reminder phone calls, treatment counselling, home visits) were used to ensure treatment completion.[13] 65 (5.3%) developed adverse events, although in this calculation, any recipient with more than 1 adverse event was counted only once.[13] 42 (3.4%) discontinued therapy with 3 HP and in 32 of these the cause was side effects or fear of side effects and in 3 the therapy was discontinued by the physician.[13] Female sex, higher schooling and income, living in non-slum setting and absence of adverse events were predictors of treatment completion.[13]

	Very common	Common	Uncommon	Rare	Very rare
Frequency of adverse events[21]	≥1 in 10 Or ≥ 10%	≥1 in 100 to <1 in 10 Or ≥1% to <10%	≥1 in 1000 to <1 in 100 Or ≥0.1% to <1%	≥1 in 10,000 to <1 in 1000 Or ≥0.01% to <0.1%	<1 in 10,000 Or < 0.01%
Severity of adverse event[22]	**Grade 1** **Mild;** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	**Grade 2** **Moderate**; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL[a]	**Grade 3** **Severe or medically significant**, but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL[b]	**Grade 4** **Life threatening consequences; urgent intervention indicated**	**Grade 5** **Death indicated to ADR**

[a]Instrumental activities of daily living (ADL) refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money etc. [b]Self-care activities of daily living (ADL) refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Table 1: **Accepted terminology for interpretation of frequency and severity of adverse events.**

There are two reports related to 3 HP from Pakistan. The first is a comparison of treatment uptake and completion of 3 HP and 6 H regimens in contacts >2 years of age in a programmatic setting in Karachi in 2 different periods in 2016–17.[14] The second is the experience of scale up of 3 HP preventive treatment in 13,811 household contacts of patients with TB in the two cities Karachi and Peshawar.[15] In the earlier comparative study, the treatment uptake was similar in 6 H and 3 HP but treatment completion was 46% in the 6 H group vs. 67% in the 3 HP.[14] Adverse events occurred in 8 recipients (1%) in the 3 HP group with only GI symptoms (nausea, vomiting), shortness of breath and rash, and the treatment was discontinued on advice of the physician in 7 of these 8 recipients.[14] The low frequency of adverse events could have been an underestimation as the reasons for non-completion in the rest (32%) were not mentioned.[14] In the 3 HP scale up study in Karachi and Peshawar, the uptake as well as treatment completion was higher in Peshawar compared to Karachi (uptake of 65% vs. 59%, treatment completion of 93% vs. 69%).[15] 734 adverse events (5.3%) were documented in 461 patients, none of them were considered serious.[15] The common side effects were dizziness in 108 (0.8%), nausea and vomiting in 0.7%, and rash in 56 (0.3%). Again, a limitation is a report is absence of information on the reasons for non-completion in the rest of the subjects (31% in Karachi and 7% in Peshawar).[15]

In a study in South Korean healthcare workers, 1.8% (4/226) developed anaphylaxis with symptomatic bronchospasm in three and hypotension in one, while the SDR of flu-like syndrome was also more frequent (19%) than in the PREVENT TB trial (2.2%).[16] In light of the frequency of these serious adverse events the investigators considered it prudent not to recommend it for use in the general population in Korea, except in some particular risk groups.[16] In a Hong Kong cohort, 23.5% (44/187) participants administered 3 HP developed SDR and termination of 3 HP occurred in 13 (7.0%), mainly due to SDR or flu like symptoms.[17] In this cohort the presence of flu-like symptoms was associated with an adjusted OR of 4.9 (2.1–11.6) for termination of therapy.[17]

The results of a randomised controlled trial in elderly persons in China,[20] is relevant in view of the WHO recommendations to expand eligibility of TPT to all age groups.[1] The trial was terminated early because of high frequency of adverse effects in 19.1% and 17.1% respectively for 3 HP regimen and twice weekly isoniazid-rifapentine regimen.[20] Another study on 3 HP from Taiwan with 579 subjects that included the elderly noted an overall treatment completion rate of 83.1%, which was 73.9% in the elderly.[23] A high proportion of subjects (62.5%) experienced ≥1 ADRs.[23] SDR included hypotension in 10 (1.7%) subjects, adverse events ≥ Grade 3 were seen in 2.3%; and dizziness was seen in 31.8% of subjects.[23] An important adverse event was the occurrence of a hypertensive event in 1 in 9 elderly subjects, especially those with underlying hypertension; possibly due to the interactions between rifapentine and their antihypertensive drugs.[23] In another study in patients with silicosis in China initiated on 3 HP, a completion rate of only 54% was achieved due to high rates of adverse events; these included fatigue (53%), fever (24%) dizziness (23%), and Grade 3 or 4 ADRs (8%).[19]

In a trial comparing treatment completion and adverse events in 3 HP vs. 9 H in Taiwan, treatment completion was better in the 3 HP arm.[18] The frequency of hepatotoxicity was higher in the 9 H arm, but systemic drug reactions were more common in the 3 HP arm (3.8% vs. 0%, p = 0.06). The frequency of flu-like symptoms was similar to the PREVENT trial, but ADRs other than hepatoxicity were seen in 49.2% in the 3 HP arm and the frequency of any flu-like symptoms (including dizziness) was higher, occurring in 40.2%.[18] Of the 10.6% who discontinued therapy with 3 HP, 9.2% did this owing to ADRs. The incidence of Grade 3 events was 2.3% and there was no grade 4 event, and most ADRs were well tolerated.[18]

A systematic review of adverse events of isoniazid-rifapentine noted that given the inconsistent event reporting and heterogeneity of populations, there was a need for caution in interpreting safety data with 3 HP.[24] The evidence suggests that systemic drug reactions and flu-like symptoms including dizziness have been observed in diverse population and risk groups in Asia in frequencies that would qualify as common or very common, with common to uncommon occurrence of serious ADRs including hypotension. Dizziness appears to be a very common adverse event documented in India, Hong Kong Taiwan, China. Although completion rates in some trials in the region were better than 9 H, ADRs were a predominant cause of termination in subjects.

The possible association of 3 HP related systemic drug reactions with isoniazid

The mechanism underlying the pattern and severity of adverse effects of the 3 HP is not clear.[8] In the context of the 3 HP regimen, these ADRs could be dose related, non-dose related (idiosyncratic or immunological reactions), time-related (related to cumulative dose) to the two drugs, alone or in combination.[25] Most ADRs with 3 HP occur after the first 3–4 doses and in the 4 h after ingestion.[8] Rifapentine could be a possible culprit drug as another rifamycin, high dose intermittent rifampicin is associated with production of antibodies and a flu like syndrome.[26] However, the frequent lack of symptoms on re-challenge with rifapentine in the PREVENT trial,[8] and its association with age, sex, BMI and use of concomitant medications that has been noted suggest that these SDRs are unlikely to be immunologically mediated.[8] Also, weekly rifapentine used in a TB treatment trial

was not associated with these kind of SDRs or flu-like symptoms,[27] and in a recent pharmacokinetic study there was no association between maximal plasma concentration, or area under curve (AUC) levels of rifapentine and these symptoms.[28] With regard to the role of isoniazid in causing these ADRs, the use of INH has also been associated with flu-like symptoms to the tune of 1–9.8%.[29,30] In a recent population based pharmacokinetic study, a higher maximum (or peak) serum concentration of isoniazid was associated with higher risk of any adverse drug reaction and flu-like symptoms with adjusted odds ratios of 3.04 and 2.76 respectively.[28] This association with concentration of isoniazid is evidence that some of the SDRs may be related a dose-related effect of isoniazid.[28] In a large study, adverse events due to isoniazid were dose related- 2.5% in the high dose group (average dose 16 mg/kg) compared to 0.2% in a dose of 300 mg day.[31] Another study also reported an association between NAT2 gene polymorphisms which are linked to isoniazid metabolism and SDR.[32] The association with low BMI, and the lower rates of tolerating isoniazid rechallenge (15% vs. 71% for rifapentine in those with systemic drug reactions) also suggest that the isoniazid component and the doses of isoniazid in the trial may be relevant.[8] The high frequency of dizziness reported in the Indian study could be thus be possibly attributable to INH and its dose.[12] Flu-like syndromes as well as episodes of anaphylaxis have been described with INH.[33,34]

In the absence of any formal RCT of the 3 HP regimen in India or a comparable setting, and the paucity of data on safety from India, there are 3 key issues related to the safety of the regimen in India. First, the dose of INH in this WHO recommended and NTEP endorsed 3 HP regimen is inappropriate for the weights in Indian subjects, that will result in exceeding the maximum recommended dose in a significant proportion of subjects. Second, the acetylator status of the Indian population needs to be taken into consideration. Finally, there is a lack of availability or even a recommendation for requirement for use of pyridoxine as an adjunct to the administration of this regimen.

1. Dosing of isoniazid in the 3 HP regimen and its implications.

In this viewpoint article I limit the discussion to the doses of INH in 3 HP to adults as in children the doses are weight-appropriate and there are other alternatives like 3 HR that are being used. In the current WHO guidelines for TPT with 3 HP, in subjects >14 years and in the weight range of ≥30 kg to >70 kg a uniform weekly dose of 900 mg (as 3 tablets of 300 mg each) isoniazid has been recommended, based on the dose in the PREVENT trial.[1] This recommendation goes against the principle of weight-based dosing of anti-tubercular drugs that has been used in guidelines for treatment of tuberculosis.[26,35,36]

The recommended standard daily dose of isoniazid for INH-susceptible tuberculosis or the daily isoniazid preventive treatment is 5 mg/kg in adults and 10–15 mg/kg in children. In case of the once-weekly isoniazid for either indication the maximum recommended dose is 15 mg/kg.[26] In the case of drug-resistant tuberculosis where high dose-isoniazid (designated as Hh) was used earlier as a companion drug, the recommended doses were 10–15 mg/kg in adults and 15–20 mg/kg in children.[35] So the highest recommended dose of INH recommended for either daily dosing in drug-resistant TB or weekly dosing in drug-susceptible TB or TB infection is 15 mg/kg. This translates into maximum doses of 450–600 mg across the lowest or the highest weight bands.[37]

Table 2 shows doses of isoniazid in different indications and in extremes of weight bands (30–35 kg in lower range and >70 kg in higher range). These range from 225 to 375 mg daily for drug-susceptible treatment, 450–600 mg daily in high-dose isoniazid treatment for drug-resistant TB, and a fixed dose of 900 mg weekly isoniazid recommended by WHO in the 3 HP regimen. age >14 years. This dose of 900 mg is higher than the maximum recommended weight-based dose (15 mg/kg) for any subject weighing <60 kg. In the weight band of 30–45 kg subjects, this fixed dose would translate into a weight-based dose of 20–30 mg/kg, approaching the toxic dose of 30 kg.[38] There are reports of isoniazid causing neurological syndromes as a part of toxicity that varies with doses 2% at the dose of 5 mg/kg to about 15% at 10 mg/kg, which is dose related with toxicity that may include peripheral neuropathy, dizziness, dysarthria, confusion and even seizures.[39] Seizures

Indication	Dosing schedule	Weight based dose	Dose of isoniazid in adults in lower range of weight band of 30–35 kg	Dose of isoniazid in adults in upper range of weight band (>70 kg)
Isoniazid in treatment of drug-susceptible tuberculosis[58]	Daily	4–6 mg/kg	225 mg if administered as FDC, 300 mg if administered as loose	375 mg if administered as FDC or loose.
High-dose Isoniazid for treatment of drug resistant TB[35]	Daily	10–15 mg/kg in adults[a]	450 mg	600 mg
Isoniazid dose in 3 HP regimen for TB preventive treatment (as per WHO guideline)[1]	Once weekly	Fixed dose in WHO guideline[b]	900 mg	900 mg

FDC: Fixed-dose combination. [a]Dose of 15–20 mg/kg recommended in children. [b]Maximum dose recommended is 15 mg/kg in American Thoracic Society guidelines.[26]

Table 2: **Isoniazid doses for different indications in adults.**

have been documented in a recipient of the 3 HP, who was an immunocompetent adult without malnutrition, and was attributed to the INH component.[40]

Adult weights in India are lower than in other populations, and extrapolation of fixed doses should be avoided. In the PREVENT trial the median (interquartile range) BMI was 27 (23–31) kg/m^2, the median weight was 67 kg, and the dose of 900 mg was appropriate to the weight in this population.[2] In contrast the mean BMI in Indian adult men and women according to recent data was 22.8 (4.1) kg/m^2 and 22.61 (4.5) kg/m^2.[41] In the RATIONS trial the weights of the adult household contacts who were men and women were 51.1 kg and 42.6 kg respectively.[42] A cautionary note on the higher frequency of adverse events in Indian patients due to use of these fixed doses that were inappropriate in an Indian context was sounded in a 1986 paper.[43] "There is a tendency for Indian patients to receive high drug dosages in terms of body weight, as fixed doses which have been established for heavier Western patients are transferred without adjustment to light-weight Indian patients."[43] However, the technical guideline for the national tuberculosis programme in India in 1997 mentioned with regard to drug doses for adults "For adults, drugs will be given in the recommended number of pills/capsules irrespective of body weight."[44] The dose of isoniazid recommended was 600 mg three times a week,[44] at a time when the WHO recommendations for isoniazid dosing was 10 mg/kg (8–12 mg/kg) three times a week.[45] In an article in 2008, we drew attention to the low weights seen in Indian patients that we had documented and pointed that a single uniform dose regardless of weight in adults was resulting in potentially toxic doses for adults in the lower weight ranges.[46] A detailed evaluation across 4 states of India showed that adverse effects of medicines including weakness and dizziness were identified as the most frequent cause of interruption of treatment.[47] Over the last few decades the programme did establish weight-based dosing for patients with tuberculosis where underweight patients got weight-appropriate doses.[36] This past experience with tailoring anti-tuberculosis drug doses to weights in India should inform current recommendations and practice.

2. The acetylator status of Indians and the risk for adverse events.

Isoniazid is metabolised by the N-Acetyltransferase 2 gene (NAT2).[38] In case of persons who are slow acetylators, the potential for adverse effects, including hepatotoxicity, are higher.[38] In a study from India, 55% of individuals were found to be slow acetylators, and their plasma isoniazid levels were found to be higher.[48] In a recent study on patients, 58% were slow acetylators and 35% were intermediate acetylators and their median 2-h concentrations were 2–2.5 times that of the 7% who were fast acetylators.[49] The potential for adverse events may be higher in slow acetylators in India who will have even higher INH levels with this high dose isoniazid in the 3 HP regimen. In fact, the WHO recommends a lowering of the isoniazid dosage if the population has a high prevalence of slow acetylators.[1]

3. Isoniazid therapy and the necessity for co-administration of pyridoxine.

Isoniazid therapy can have both acute and chronic toxicity. The common forms of chronic toxicity–peripheral neuropathy (due to pyridoxine deficiency caused by isoniazid) and hepatotoxicity, have been less common with the 12 dose 3 HP regimen. On the other hand, the profile of ADRs reflect acute toxicity of isoniazid with neurological symptoms like dizziness, drowsiness, and general and cardiovascular symptoms like flu-like symptoms, hypotension, with or without features of anaphylaxis.[34] Isoniazid also causes varied neurological manifestations as a result of the functional pyridoxine deficiency, like acute psychosis, seizures, obtundation and even coma, all of which have been show to reverse with pyridoxine in adequate doses.[40,50,51] Dizziness has been noted as a prodrome of psychosis.[52]

The pathophysiology of adverse drug reactions with isoniazid partially involve its effect on pyridoxine which is involved in functioning of over 60 enzymes involved in amino acid, carbohydrate, lipid metabolism, including synthesis of neurotransmitters like GABA and glutamate.[53] Isoniazid leads to pyridoxine depletion directly and by inhibiting the phosphokinase enzyme that results in its biologically active form.[53] This has an effect on the metabolic cycle of neurotransmitters, like GABA and glutamate.[38] Isoniazid is also a weak monoamine oxidase inhibitor and can cause serotonin syndrome in the presence of other antidepressants.[54]

The necessity of co-administration of pyridoxine with the 3 HP regimen needs to take into account the dose of isoniazid involved. In persons administered standard dose isoniazid (5 mg/kg daily), pyridoxine supplementation (25–50 mg daily) is co-administered to prevent peripheral neuropathy, in individuals at risk such as those with malnutrition, chronic alcohol dependence, HIV infection, renal failure or diabetes, or who are pregnant or breastfeeding, who can develop neuropathy even with the standard dose. Individuals who are slow acetylators may also be at higher risk.[26] The 3 HP regimen is a high dose isoniazid regimen,[1] as it involves administration of a 3-fold dose of isoniazid (900 mg instead of a maximum of 300 mg), although once weekly. In such a regimen, pyridoxine has been considered necessary in the context of daily use in drug-resistant tuberculosis.[37] The current therapy for drug-susceptible tuberculosis does not provide universal access to pyridoxine in India, although a significant proportion of Indian patients are at risk of INH induced

neurotoxicity due to prevalent undernutrition, diabetes and alcohol use.[55] The current WHO guidelines acknowledge that subjects at risk should be given pyridoxine, but also states that the nonavailability of pyridoxine should not be a reason to withhold TPT.[1] The status of pyridoxine deficiency in Indians has not been adequately assessed, but a recent study conducted in apparently healthy adults (less than 5% had low BMI) revealed multiple micronutrient deficiencies of which pyridoxine deficiency in 46% (30% in mild form and 16% in severe form) was the second most common.[56] We would argue that given the population at risk and the higher doses of INH that will be administered it would be prudent to consider pyridoxine as an essential rather than optional adjunct to isoniazid used in the 3 HP regimen.

The RCTs of 3 HP regimen did not administer pyridoxine as a routine and therefore it is not known if some of these adverse events could have been mitigated with co-administration of pyridoxine. A recent randomised clinical trial showed significant reduction of some of the CNS (e.g. dizziness) and GI related adverse drug reactions of quadruple therapy for *Helicobacter pylori* when pyridoxine was used as an adjunct.[57]

The way forward

There is paucity of data around safety profile of 3 HP in high TB burden countries but the available evidence suggests that adverse events are frequent, mostly well-tolerated, but may be severe and could lead to discontinuation of therapy. It is critical to minimise the possibility of adverse effects as their occurrence can not only cause individual harm but also undermine public confidence in this preventive intervention. The uniform dose of 900 mg isoniazid across adult weights of 30–70 kg is inappropriate for a lower weight Indian population and the program should consider weight-based dosing with narrower bands that are already used in treatment of patients with tuberculosis. A representative profile of the population with regard to acetylator status is needed. Pyridoxine should be available for co-administration with higher dose isoniazid in light of prevalent pyridoxine deficiency and undernutrition, diabetes, alcohol use. The NTEP could implement the 3 HP with weight-appropriate doses and co-administration of pyridoxine, with appropriate monitoring of persons and collection of data on adverse events. The NTEP may also consider alternative regimens of TPT recommended by WHO (1 HP and 4 R) that have not been associated with systemic drug reactions and flu like syndromes.[1] There is a need also to generate pharmacological and clinical evidence to tailor TPT interventions like 3 HP to different populations.

Contributors

AB formulated the concept, conducted the literature search, interpreted the findings and drafted the manuscript.

Declaration of interests

None.

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References

1 *WHO consolidated guidelines on tuberculosis. Module 1: prevention-tuberculosis preventive treatment*. Geneva: World Health Organization; 2020.
2 Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*. 2011;365(23):2155–2166.
3 Sterling TR, Scott NA, Miro JM, et al. Three months of weekly rifapentine and isoniazid for treatment of Mycobacterium tuberculosis infection in HIV-coinfected persons. *AIDS*. 2016;30(10):1607–1615.
4 Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med*. 2011;365(1):11–20.
5 Guidelines for Programmatic Management of Tuberculosis Preventive Treatment in India. *National TB elimination programme. Central TB division*. New Delhi: Ministry of Health and Family Welfare, Government of India; 2021.
6 *Tuberculosis preventive treatment: rapid communication*. Geneva: World Health Organization; 2024.
7 Njie GJ, Morris SB, Woodruff RY, Moro RN, Vernon AA, Borisov AS. Isoniazid-rifapentine for latent tuberculosis infection: a systematic review and meta-analysis. *Am J Prev Med*. 2018;55(2):244–252.
8 Sterling TR, Moro RN, Borisov AS, et al. Flu-like and other systemic drug reactions among persons receiving weekly rifapentine plus isoniazid or daily isoniazid for treatment of latent tuberculosis infection in the PREVENT tuberculosis study. *Clin Infect Dis*. 2015;61(4):527–535.
9 Sadowski C, Belknap R, Holland DP, et al. Symptoms and systemic drug reactions in persons receiving weekly rifapentine plus isoniazid (3HP) treatment for latent tuberculosis infection. *Clin Infect Dis*. 2023;76(12):2090–2097.
10 Melnychuk L, Perlman-Arrow S, Lisboa Bastos M, Menzies D. A systematic review and meta-analysis of tuberculous preventative therapy adverse events. *Clin Infect Dis*. 2023;77(2):287–294.
11 Winters N, Belknap R, Benedetti A, et al. Completion, safety, and efficacy of tuberculosis preventive treatment regimens containing rifampicin or rifapentine: an individual patient data network meta-analysis. *Lancet Respir Med*. 2023;11(9):782–790.
12 Sharma N, Bakshi R, Basu S, Zode M, Arora R, Khanna A. Implementation of tuberculosis preventive therapy with INH-Rifapentine (3HP) for latent tuberculosis infection management in household tuberculosis contacts in India: a prospective study. *Trop Med Int Health*. 2023;28(12):890–900.
13 Rahman MT, Hossain F, Banu RS, et al. Uptake and completion of tuberculosis preventive treatment using 12-dose, weekly isoniazid-rifapentine regimen in Bangladesh: a community-based implementation study. *Trop Med Infect Dis*. 2023;9(1).
14 Jaswal M, Farooq S, Madhani F, et al. Implementing 3HP vs. IPT as TB preventive treatment in Pakistan. *Int J Tubercul Lung Dis*. 2022;26(8):741–746.
15 Hussain H, Jaswal M, Farooq S, et al. Scale-up of rifapentine and isoniazid for tuberculosis prevention among household contacts in 2 urban centers: an effectiveness assessment. *Clin Infect Dis*. 2023;77(4):638–644.
16 Jo KW, Kim JS, Kwon HS, et al. Adverse event and treatment completion rates of a 12-dose weekly isoniazid and rifapentine course for South Korean healthcare workers. *Respir Med*. 2019;158:42–48.
17 Chang K-C, Huang S-S. How flu-like syndromes contribute to termination of weekly rifapentine-based TB preventive therapy is still poorly predictable. *Clin Infect Dis*. 2022;75(10):1865–1866.
18 Sun HY, Huang YW, Huang WC, et al. Twelve-dose weekly rifapentine plus isoniazid for latent tuberculosis infection: a multicentre randomised controlled trial in Taiwan. *Tuberculosis*. 2018;111:121–126.

19 Ruan QL, Huang XT, Yang QL, et al. Efficacy and safety of weekly rifapentine and isoniazid for tuberculosis prevention in Chinese silicosis patients: a randomized controlled trial. *Clin Microbiol Infection*. 2021;27(4):576–582.
20 Gao L, Zhang H, Xin H, et al. Short-course regimens of rifapentine plus isoniazid to treat latent tuberculosis infection in older Chinese patients: a randomised controlled study. *Eur Respir J*. 2018;52(6).
21 European Commission. Guideline on summary product characteristics revision 2. https://healtheceuropaeu/medicinal-products/eudralex/eudralex-volume-2_en2009.
22 US Department of Health and Human Services. *Common terminology criteria for adverse events (CTCAE) version 5*. 2017.
23 Huang HL, Lee MR, Cheng MH, et al. Impact of age on outcome of rifapentine-based weekly therapy for latent tuberculosis infection. *Clin Infect Dis*. 2021;73(5):e1064–e1071.
24 Pease C, Hutton B, Yazdi F, et al. A systematic review of adverse events of rifapentine and isoniazid compared to other treatments for latent tuberculosis infection. *Pharmacoepidemiol Drug Saf*. 2018;27(6):557–566.
25 Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet*. 2000;356(9237):1255–1259.
26 Nahid P, Dorman SE, Alipanah N, et al. Official American thoracic society/centers for disease control and prevention/infectious diseases society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis*. 2016;63(7):e147–e195.
27 Jindani A, Harrison TS, Nunn AJ, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N Engl J Med*. 2014;371(17):1599–1608.
28 Lee MC, Fujita Y, Muraki S, et al. Isoniazid level and flu-like symptoms during rifapentine-based tuberculosis preventive therapy: a population pharmacokinetic analysis. *Br J Clin Pharmacol*. 2023;89(2):714–726.
29 Eule H, Werner E, Winsel K, Iwainsky H. Intermittent chemotherapy of pulmonary tuberculosis using rifampicin and isoniazid for primary treatment: the influence of various factors on the frequency of side-effects. *Tubercle*. 1974;55(1):81–89.
30 Dutt AK, Moers D, Stead WW. Undesirable side effects of isoniazid and rifampin in largely twice-weekly short-course chemotherapy for tuberculosis. *Am Rev Respir Dis*. 1983;128(3):419–424.
31 Berte SJ, Dimase JD, Christianson CS. Isoniazid, Para-aminosalicylic acid and Streptomycin intolerance in 1744 patients. An analysis of reactions to single drugs and drug groups plus data on multiple reactions, type and time of reactions and desensititation. *Am Rev Respir Dis*. 1964;90:598–606.
32 Lee M-R, Huang H-L, Lin S-W, et al. Isoniazid concentration and NAT2 genotype predict risk of systemic drug reactions during 3HP for LTBI. *J Clin Med*. 2019;8(6):812.
33 Motion S, Humphries MJ, Gabriel M. Severe 'flu'-like symptoms due to isoniazid—a report of three cases. *Tubercle*. 1989;70(1):57–60.
34 Crook MJ. Isoniazid-induced anaphylaxis. *J Clin Pharmacol*. 2003;43(5):545–546.
35 *WHO operational handbook on tuberculosis Module 4: treatment- drug-resistant tuberculosis treatment*. Geneva: World Health Organization; 2020.
36 Revised National TB Control Programme. *Technical and operational guidelines for tuberculosis control in India*. New Delhi: Central TB Division,Ministry of Health and Family Welfare; 2016.
37 World Health Organization. *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis*. 2014.
38 Ignatius EH, Dooley KE. Chemotherapy of tuberculosis and non-tuberculous mycobacteria, including leprosy. In: Brunton LL, Knollmann BC, Goodman Gilman's, eds. *The pharmacological basis of therapeutics*. 14th ed. New York, NY: McGraw-Hill Education; 2023.
39 Goldman AL, Braman SS. Isoniazid: a review with emphasis on adverse effects. *Chest*. 1972;62(1):71–77.
40 Navalkele B, Bueno Rios MX, Wofford JD, Kumar V, Webb RM. Seizures in an immunocompetent adult from treatment of latent tuberculosis infection: is isoniazid to blame? *Open Forum Infect Dis*. 2020;7(5):ofaa144.
41 Verma M, Esht V, Alshehri MM, et al. Factors contributing to the change in overweight/obesity prevalence among Indian adults: a multivariate decomposition analysis of data from the national family health surveys. *Adv Ther*. 2023;40(12):5222–5242.
42 Bhargava A, Bhargava M, Meher A, et al. Nutritional supplementation to prevent tuberculosis incidence in household contacts of patients with pulmonary tuberculosis in India (RATIONS): a field-based, open-label, cluster-randomised, controlled trial. *Lancet*. 2023;402:627.
43 Parthasarthy RSG, Janardhanam B, Ramachandran P, Santha T, Sivasubramanian S ea. Hepatic toxicity in south Indian patients during treatment of tuberculosis with short course regimens containing isoniazid, rifampicin and pyrazinamide. *Tubercle*. 1986;67:99–108.
44 Revised National Tuberculosis Control Programme. *Technical guidelines for tuberculosis control in: central TB division*. New Delhi: Ministry of Health and Family Welfare; 2000.
45 World Health Organisation. *Treatment of tuberculosis: guidelines for national programmes*. World Health Organization; 1997.
46 Bhargava A, Jain Y. The Revised National Tuberculosis Control Programme in India: time for revision of treatment regimens and rapid upscaling of DOTS-plus initiative. *Natl Med J India*. 2008;21(4):187–191.
47 Dandona R, Dandona L, Mishra A, Dhingra S, Venkatagopalakrishna K, Chauhan LS. Utilization of and barriers to public sector tuberculosis services in India. *Natl Med J India*. 2004;17(6):292–299.
48 Singh N, Dubey S, Chinnaraj S, Golani A, Maitra A. Study of NAT2 gene polymorphisms in an Indian population: association with plasma isoniazid concentration in a cohort of tuberculosis patients. *Mol Diagn Ther*. 2009;13(1):49–58.
49 Hemanth Kumar AK, Ramesh K, Kannan T, et al. N-acetyltransferase gene polymorphisms & plasma isoniazid concentrations in patients with tuberculosis. *Indian J Med Res*. 2017;145(1):118–123.
50 Yadav R, Kumar M, Kumar N, Chacham S. Pyridoxine in isoniazid-induced psychosis. *Sudan J Paediatr*. 2022;22(2):190–192.
51 Brent J, Vo N, Kulig K, Rumack BH. Reversal of prolonged isoniazid-induced coma by pyridoxine. *Arch Intern Med*. 1990;150(8):1751–1753.
52 Kass JS, Shandera WX. Nervous system effects of antituberculosis therapy. *CNS Drugs*. 2010;24(8):655–667.
53 Lheureux P, Penaloza A, Gris M. Pyridoxine in clinical toxicology: a review. *Eur J Emerg Med*. 2005;12(2):78–85.
54 O'Brien ME, Gandhi RG, Kotton CN, Adamsick ML. Risk of serotonin syndrome with isoniazid. *Antimicrob Agents Chemother*. 2020;65(1).
55 Bhargava M, Bhargava A. Pyridoxine for patients suffering from drug-susceptible tuberculosis in India. *Public Health Action*. 2018;8(2):97.
56 Sivaprasad M, Shalini T, Reddy PY, et al. Prevalence of vitamin deficiencies in an apparently healthy urban adult population: assessed by subclinical status and dietary intakes. *Nutrition*. 2019;63-64:106–113.
57 Cui M-Y, Zhang M-J, Jiang Q-L, et al. Can vitamin B6 alleviate the adverse reactions of quadruple anti-Helicobacter pylori regimen?: randomized controlled trial. *BMC Infect Dis*. 2023;23(1):590.
58 *WHO operational handbook on tuberculosis. Module 4: treatment-drug-susceptible tuberculosis treatment*. Geneva: World Health Organization; 2022.