MINIREVIEWS

Debunking the myths perpetuating low implementation of isoniazid preventive therapy amongst human immunodeficiency virus-infected persons

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Abstract

Isoniazid preventive therapy (IPT) is the administration of isoniazid (INH) to people with latent tuberculosis (TB) infection (LTBI) to prevent progression to active TB disease. Despite being life-saving for human immunodeficiency virus (HIV)-infected persons who do not have active TB, IPT is poorly implemented globally due to misconceptions shared by healthcare providers and policy makers. However, amongst HIV-infected patients especially those living in resource-limited settings with a high burden of TB, available evidence speaks for IPT: Among HIV-infected persons, active TB- the major contraindication to IPT, can be excluded with symptom screening; chest X-ray and tuberculin skin testing are unreliable and often lead to logistic delays resulting in increased numbers of people with LTBI progressing to active TB; the use of IPT has not been found to increase the risk of the development of INH mono-resistance; IPT is cost-effective and cheaper than the cost of treating cases of active TB that would develop without IPT; ART and IPT have an additive effect on the prevention of TB, and both are safe and beneficial even in children. In order to sustain the recorded gains from ART scale-up and to further reduce TB-related morbidity and mortality, more efforts are needed to scale-up IPT implementation globally.

Key words: Human immunodeficiency virus; Isoniazid preventive therapy; Tuberculosis; Chemoprophylaxis

Core tip: To better inform healthcare providers, policy makers and human immunodeficiency virus-infected persons about isoniazid preventive therapy (IPT), this article summarizes the existing evidence in support

of IPT including recommendations for scale-up of implementation globally.

INTRODUCTION

The human immunodeficiency virus (HIV) infection and tuberculosis (TB) have both remained significant global health challenges claiming millions of lives every year. Despite improved access to antiretroviral therapy (ART), the burden of TB among HIV-infected individuals has remained high. In 2012, the World Health Organization (WHO), reported an estimated 8.6 million TB cases and 1.3 million deaths from the disease (including 320000 deaths among HIV-positive people)[1]. Majority of these deaths are preventable with the use of available evidence-based strategies.

Active TB disease can be prevented among HIV-infected individuals either by protecting them from being exposed to *Mycobacterium tuberculosis* (*M. tuberculosis*), the organism responsible for the disease or by preventing those already infected from progressing from latent infection to active disease. This is important because HIV-infected persons who are co-infected with latent TB are not likely to transmit TB to others nor develop drug resistant TB. Therefore, treatment of latent TB infection (LTBI) has the added benefit of reducing the incidence of resistant TB and thus contributing to the control of multi-drug resistant TB and extensively drug resistant TB.

A Cochrane review that included 12 trials with a total of 8578 randomized participants showed that preventive therapy with any anti-TB drug *vs* placebo was associated with a 32% lower incidence of active TB [Risk ratio (RR) 0.68, 95%CI: 0.54 to 0.85], although this benefit was found to be more pronounced in individuals who were tuberculin skin test (TST) positive (RR 0.38, 95%CI: 0.25 to 0.57) than in those who had a negative test (RR 0.89, 95%CI: 0.64 to 1.24) and efficacy was similar for all regimens (regardless of drug type, frequency or duration of treatment)[2]. However, among the available regimens for treatment of LTBI, isoniazid (INH) preventive therapy (IPT) is the one commonly recommended and has been shown to be very effective and safe among people living with HIV[2]. IPT is the administration of INH to people with latent tuberculosis (TB) infection (LTBI) to prevent progression to active TB disease. Its use is a component of the TB/HIV collaborative activities recommended by the WHO

to decrease the burden of TB in people living with HIV[3].

The use of IPT for at least six months has been recommended by the WHO for HIV-infected children and adults without active TB including pregnant women, those receiving ART, and those who have successfully completed TB treatment[4]. Furthermore, the guidelines also emphasize that a TST is no longer required for the initiation of IPT in people living with HIV. However, despite available evidence regarding the efficacy of IPT, and the recommendation from WHO that IPT be included in the minimum care package for people living with HIV, this life saving and cost-effective intervention is still not being widely implemented.

In 2008, WHO reported that the provision of IPT remains at very low levels, with the number of people who received IPT reaching only 27056 in 2006 – equivalent to less than 0.1% of the 33.0 million people estimated to be infected with HIV globally and Botswana alone accounted for 70% of the total number of people reported globally[5]. In a cross-sectional survey conducted *via* email by the WHO amongst HIV programme officers in 69 selected countries having a high burden of HIV and HIV/TB co-infection, 21 of 41 countries (51.0%) that responded had a national policy but only 6 (28.0%) had achieved nationwide IPT implementation[6]. This picture seems to have improved but is still far below what is generally expected. According to the WHO, an estimated 50.0% of those newly enrolled in HIV care globally meet the eligibility criteria for IPT[4]. However, of the reported 1.6 million people newly enrolled in HIV care in 2012, only 0.5 million (31.0%) were provided with IPT with South Africa accounting for 71.0% of the global total with 370000 people[1]. In contrast, of the 0.14 million HIV-infected people screened for TB in Nigeria in 2012, only 2300 (1.6%) of them received IPT while of the 69000 HIV-infected persons screened for TB in Swaziland in 2012, only 1900 (2.8%) of them were prescribed IPT[1].

The low level of implementation can be attributed to several reasons given by healthcare providers and policy makers. Most of these excuses or challenges can be termed myths because there is enough evidence in support of full scale implementation of IPT globally. These myths include the following: (1) it is difficult to exclude active TB among people living with HIV; (2) chest X-ray is necessary before initiating IPT; (3) use of IPT will increase the risk of the development of INH mono-resistance; (4) ART alone is sufficient for preventing TB among people living with HIV; (5) it is difficult for those on ART to adhere to treatment with IPT; (6) the use of IPT is associated with increased side effects of INH and therefore not safe; (7) use of IPT is not cost effective; (8) IPT cannot be used in children; and (9) TST is needed before prescribing IPT.

We hereby discuss the range of evidence available in support of IPT implementation even in the face of the above challenges or myths.

AVAILABLE EVIDENCE

Active TB can be excluded using symptom screening

Excluding active TB disease before the initiation of preventive therapy is required to minimize the risk of drug resistance as a result of inadvertent treatment of active TB with an inadequate regimen[7]. Within all HIV care and treatment centers, TB screening should be considered as one of the first services to be offered to all patients irrespective of their treatment status. Among asymptomatic HIV-positive patients, it is possible to use symptom screening to exclude active TB. Interestingly, reports from Botswana and Zambia suggest that the rate of TB is very low among asymptomatic HIV-positive individuals[8,9]. In a study conducted in South Africa, it was reported that symptoms alone were adequate to exclude TB in 129 Cape Town patients, all of whom were in WHO stage 3 or 4[10].

A good screening rule was developed using results from a meta-analysis of 12 observational studies that involved over 8000 HIV-infected persons[11]. The analysis showed that individuals exhibiting none of 4 symptoms namely current cough, night sweats, fever or weight loss have a very low probability of having TB disease (negative predictive value of 97.7% at 5.0% TB prevalence among people living with HIV). Therefore, those who do not have current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT[4] while those with symptoms should have further work-up for TB and those found positive should be offered a full treatment course for TB. There is the need to avoid a situation where HIV-infected persons are not placed on anti-TB medications and are also not offered the benefits of IPT. Therefore, the algorithm for TB screening in adults and adolescents living with HIV in HIV-prevalent and resource-constrained settings developed by the WHO should be adequately followed[4].

Chest X-ray is not mandatory before prescribing IPT

The data on the utility of chest X-ray on IPT programmes is still not very clear[8,9]. Though chest X-ray is helpful in the diagnosis of active TB, it must be noted that HIV-infected patients with active TB may have normal chest X-rays. In one study, about 8.0% of HIV-infected patients with pulmonary TB had normal chest X-rays[12] and chest X-rays were normal or not consistent with TB in 23.0% of patients in another study[13]. One study that evaluated the impact of HIV co-infection on the chest radiographic pattern and extent of pulmonary TB in Ethiopian out-patients showed that HIV-infected patients had chest X-rays classified as normal or with minimal involvement compared with HIV-negative individuals[14]. These findings may be partially due to the subjective components of reviewing X-rays which include correctly taking and interpreting the X-rays.

In view of the above, symptom screening alone is recommended currently for the exclusion of TB in resource limited settings[4]. This recommendation is based on the burden of evidence that currently exists. A study conducted in Cape Town, South Africa to validate screening instruments found that a combination of 2 or more of weight loss, cough, night sweats or fever had a sensitivity of 100.0% and specificity of 81.0% and had the best fit using logistic regression (Wald statistic 19.64, $P < 0.001$) and also that including Mantoux Testing and Chest X-ray did not improve the performance of the screening instruments[10]. This finding is in line with several other studies that have found that chest X-rays are not sensitive especially in patients with HIV.

A study by Samandari *et al*[15] comparing 3 screening policies namely symptom screening alone, symptom screening with Chest X-ray and Symptom screening with Chest X-ray and tracking showed that though the inclusion of Chest X-ray reduced the number of new cases of INH resistance (because additional cases of active TB were recognized and therefore IPT was given to fewer people with active TB), the inclusion of chest X-rays actually increased the number of TB cases by 15.8% and the number of deaths from TB by 13.0% because there was attrition of patients during the Chest X-ray screening process and less people benefitted from the protective benefits of IPT[15]. Thus according to the WHO, for IPT, chest X-ray can be done if available, but is not required to classify patients into TB and non-TB groups[4].

IPT does not increase the risk of the development of INH mono-resistance

One of the major reasons given for poor utilization of IPT to prevent active TB is the belief that IPT can result in subsequent resistance to INH in patients who later develop active TB[16,17]. Theoretically, if active TB is missed and the bacterial load is large enough, treatment with monotherapy or an inadequate regimen has the potential to generate drug resistance[18]. Though the impact of widespread use of IPT on drug resistance is not well known, a systematic review of data from studies published in English, French and Spanish between 1951 and October, 2003 that assessed the effect of primary IPT on the risk of INH-resistant TB in populations without HIV reported that the risk of resistance in those given IPT was not statistically different from those that received placebo[16]. The study authors support the expansion of IPT use in line with the recommendations from the HIV/TB working group of the Stop TB partnership[3].

Van Halsema *et al*[19] described a case series of miners derived from a cluster randomized trial in which clusters were randomized either to receive TB screening and IPT or routine TB control consisting of annual case finding by chest radiograph and targeted IPT offered to individuals with HIV or silicosis with results that do not suggest an increase in the proportion of INH resistance cases among those exposed to TB screening and IPT[19]. Randomized controlled trails (RCT) of the effect

of IPT in HIV-infected patients in Botswana, India and South Africa also did not show an increased risk of INH resistance amongst patients given IPT[20-22].

Furthermore, it has been reported that patients with INH-resistant TB respond to standard short course anti-TB therapy just as well as patients without INH-resistant TB, though those with INH-resistant TB do suffer a slightly increased risk of relapse[23]. Therefore, even though there is a possibility of INH-resistant TB following the use of IPT in HIV-infected people, the benefits in terms of its effectiveness and efficacy must be balanced against this risk.

IPT is useful in combination with ART
To reduce the burden of TB among HIV-infected persons, the WHO recommends intensified case finding (ICF), IPT, infection control, and early initiation of ART[4]. ART is the most potent and widely implemented TB preventive intervention among people living with HIV (PLHIV)[4]; its use profoundly reduces the incidence of TB in PLHIV and with continued use, the risk of TB progressively declines. Although treatment with ART has been estimated to result in more than 80.0% reduction in the risk of TB[24], some reports showed that even after ART initiation TB incidence remains very high[24-26]. This suggests that, even among those with adequate response to ART, other interventions are needed to control the TB epidemic in PLHIV[25].

Observational studies from Brazil and South Africa have shown that the combined effect of ART and IPT in preventing TB among PLHIV is significantly higher compared to ART alone[27,28]. Two retrospective analyses on assessing the advantages of using IPT with ART concluded that the benefit of combining INH and ART was additive[27,29]. In a study in Ethiopia it was found that using either IPT or ART alone among PLHIVs reduced the incidence of TB by 68.0% and 65.0% respectively while co administration of IPT and ART reduced the incidence by 80.0% to 82.0% when either initiated together or IPT was initiated before ART[30]. Concomitant use of IPT and ART also improves adherence to IPT, as shown in a study in Brazil where being on ART was associated with higher completion of IPT[31].

There is good treatment adherence with the use of IPT
Good treatment adherence with the use of IPT has been reported and has been found to be associated with several factors, including availability and access to quality health care, favorable economic, social and cultural environments[32]. A study conducted in Thailand to determine the level of and reasons associated with adherence to TB preventive therapy among asymptomatic HIV-infected individuals recorded 74.3% completion of a nine-month IPT regimen[33]. Swaminathan *et al*[22] in their RCT conducted in India to compare the efficacy of a 6 mo and 36 mo regimen for prevention of TB in HIV-infected patients also recorded high adherence, even with the 36-mo IPT regimen.

In addition to the existing evidence in support of good adherence to IPT are the results obtained from a cross-sectional study conducted in Ethiopia to assess adherence to IPT and associated factors among PLHIV[34]. In this study, the level of self-reported adherence of IPT was found to be 89.5% (CI 86.1 to 92.3). Another important finding in this study was the fact that patients who were on ART were more likely to be adherent [95%CI, COR = 1.97 (1.01–3.84)] than patients who were on Pre-ART[34].

Good adherence to IPT has also been recorded among children. In a cohort study conducted in Cape Town, South Africa to investigate the combined effect of IPT and ART on TB risk amongst HIV-infected children, INH was well tolerated with excellent adherence[35]. Similar results were also obtained in another RCT conducted in the same city but compared daily to three times a week dosing of INH among HIV-infected children[36]. The overall adherence to INH was excellent, with a mean adherence of 94.7%[36]. From these studies, it is clear that good adherence with the use of IPT can be achieved even with concurrent treatment with ART.

IPT is safe and is not associated with increased risk of INH side-effects
Like most other medications, anti-TB medications are primarily metabolized by the liver and potentially can lead to drug-induced hepatitis and other adverse events (*e.g.*, nausea, vomiting, gastritis, peripheral neuropathy, and rashes)[22]. This understanding has retarded the implementation of INH as a prophylaxis for TB among many care givers despite WHO recommendations. The side effect of major concern with regards to IPT is hepato-toxicity, which has been found to occur in a very small proportion of individuals receiving treatment[37,38]. The hepato-toxic effect of INH could be mild (subclinical) with good prognosis or fatal which is less common. Fatal INH-induced hepatitis occurs in 0.001% to 0.06% depending on several other factors such as increasing age (*i.e.*, over 35 years) and frequent alcohol ingestion[39,40]. Clinical monitoring and good patient education can help in reducing the risk of toxicity[41]. In a study in Seattle, without laboratory monitoring, only 11 cases of hepatitis were reported after about seven years of monitoring over 11000 patients on INH and only one case needed hospitalization[41]. The authors concluded that the rate of INH hepato-toxicity during clinically monitored preventive therapy was lower than has been reported previously suggesting that clinicians should have greater confidence in the safety of IPT.

A report from a RCT conducted in Botswana showed no difference in adverse events between participants on placebo *vs* those on INH for 30 mo (1.0% *vs* 1.3% respectively; *P* = 0.36). A similar trial conducted in India reported only 3.0% (22/683) of participants in both study arms (*i.e.*, Ethambutol *vs* INH) with side effects related to study drugs[22]. This risk of side effects was marginally higher in another trial reported by

Rangaka *et al*[42] with 1.5% of participants on placebo *vs* 2.9% of participants on INH developing side effects (*i.e.*, grade 3 or above raised alanine transaminase level; clinical hepatitis; grade 2 or above rash or peripheral neuropathy), but the use of INH by participants on ART had no additive toxic effect[42]. The experience from Brazil indicated that expanded use of IPT in HIV-infected persons is achievable with high adherence and low adverse events[31]. Therefore, the fear of INH side effects should not prevent the implementation of IPT.

IPT use is cost-effective
Cost-effectiveness analytical studies conducted in the United States and South Africa found that compared with no prophylaxis, short and long course IPT use amongst PLHIV saved an average of $5 in medical care, for every $1 spent on prophylaxis[43,44]. In addition, the 6-mo regimen reduced the incidence of TB by an average of 23.0% to 47.5% and increased life expectancy by an average of 7.2 mo[43,45]. The cost-utility analysis of an IPT program in Uganda showed that the provision of IPT for HIV-infected persons was cost-effective[46].

In the pre-ART era, Bell *et al*[47] found that in sub-Saharan Africa, when IPT was given daily for 6 mo, there was a savings of $24.16 per person on medical care, social costs and costs associated with treating secondary infections. In resource-limited settings, where ART was not always available, the savings made and demonstrated reduction of TB and HIV-associated morbidity and mortality using IPT is desirable[47]. Even as recent as 2012, with expanded access to ART, an analysis in Southern India found that the ART-induced increases in CD4 counts attenuated the absolute IPT efficacy of reducing the risk of TB infection and related mortality, thus increasing the cost-effectiveness of IPT and making it good value for money[48].

IPT is recommended for use in children
TB is a leading cause of death in adults and more so in children due to their increased vulnerability to infection[49]. This vulnerability is even more pronounced in children living with HIV as TB is the leading cause of death among children with HIV in TB endemic areas[50]. HIV-infected children are also more likely to have severe respiratory disease and extra pulmonary TB and acquire TB at all ages compared with HIV negative children who are more at risk only during infancy[35,51]. Therefore, the need to protect HIV-infected children from acquiring TB cannot be over emphasized. Over the years the efficacy of INH as prophylaxis for TB in children has given rise to a lot of controversy due to inadequate data and trials revealing conflicting results[35,49].

A study by Madhi *et al*[51] showed no significant effect when INH is used for prophylaxis in children with or without HIV. This study was included in a recent meta-analysis by Ayieko *et al*[50] and the authors explained that the reason for the null results could be due to the fact that TB was over-diagnosed in the study since few cases were confirmed microbiologically and many of the TB cases met only minimal criteria[49,50]. Another explanation given was that the initial study involved mostly infants (median age 96 d, range 90-120 d) while the studies with a positive effect included older children suggesting that age may be an effect modifier of TB development in children receiving IPT.

On the other hand more recent studies have shown promising results making the body of evidence available stronger. The safety of the use of INH in children has also been reported by several studies[49,52]. In 2006 a randomized control trial found a 72.0% risk reduction in TB in children receiving INH compared to placebo. This study also found a 54.0% risk reduction in mortality[53]. A cohort analysis of another RCT conducted by Frigati *et al*[35] found a reduction in TB incidence in HIV-infected children randomized to receive IPT compared with placebo[35]. Further reduction in the risk of TB was found when comparing children receiving ART and IPT to those receiving ART and placebo[35]. The meta-analysis by Ayieko *et al*[50] found a strong positive effect against TB in HIV negative children although, the results for the effect on HIV-infected children was inconclusive because the analysis included only 2 studies.

Based on this moderate quality of evidence, the WHO strongly recommends IPT for use amongst HIV-infected children above 12 mo of age who are unlikely to have active TB or have not had any contact with a person infected with TB and for those less than 12 mo of age, prophylaxis is strongly recommended for those who have had contact with an infected person and in whom active TB has been ruled out[4].

TST is not necessarily required for the implementation of IPT
TST is the administration of purified protein derivative (PPD) in individuals with exposure risk to TB in order to identify those who may have acquired latent infection and for whom prevention would be beneficial[54]. The previous WHO policy statement on preventive therapy against TB in people living with HIV recommended TST as a condition for IPT implementation in developing countries[55]. Additionally, results of a meta-analysis of RCT showed that TB preventive therapy was more effective amongst HIV-infected person who are TST positive than those who are TST negative[2]. However, while TST was successfully implemented as a screening tool in developed countries[56,57], it has not been so well received in resource-poor nations where TB burden is greatest. Apart from limitations of low sensitivity and specificity (51.0% in HIV-infected persons *vs* 94.0% in HIV negative persons with active pulmonary TB)[56,58], it requires a lot of resources including adequately trained manpower to administer and read the test, need for repeat visits by patients, difficult logistics of cold chain maintenance and cost of tuberculin procurement which may be prohibitive for a large scale prevention program[4,54].

TST status of an individual is influenced largely by the degree of immunodeficiency[59]. An RCT conducted in India assessed two cohorts of HIV-infected patients; one with active pulmonary TB and the other without evidence of active TB. The cohort without active TB was found to have a lower TST-positive rate of 27.6% at CD4 < 100 cells/μL against 42.0%-48.0% of those with CD4 > 100 cells/μL in the same group[58]. The authors concluded that TST is a poor predictor of both latent and active TB in HIV-infected individuals in TB endemic countries and that programmes offering treatment for LTBI should consider including all HIV-infected individuals regardless of TST status, or use other indicators, such as CD4 count[58]. Thus a negative TST in an HIV-infected person may be due to anergy leading to missed opportunity for those who should have been offered chemoprophylaxis[4].

Botswana, one of the few African countries that have implemented a successful national IPT program since 2001 uses the WHO symptom checklist alone without the need for a TST or chest X-ray as this was found to increase loss to follow up[21]. After its pilot in 2005, Brazil made a similar recommendation to WHO that TST not be used as a screening tool to reduce waiting time between diagnosis and those who are TST positive would likely benefit more from implementation of IPT in patients[31].

In its 2011 revised guidelines, WHO makes a strong recommendation for the provision of IPT to all HIV-infected patients in TB-endemic countries (prevalence of latent TB > 30%) irrespective of TST status[4]. However, since TST positive individuals derive greater benefits from treatment of LTBI, TST could still be requested where feasible[4].

CONCLUSION

With the available evidence discussed above, the benefits of IPT are far more than the perceived risks. Therefore, to scale up implementation of IPT at both global and country levels, more efforts are needed in order to fully implement the recommendations contained in the WHO Policy Guidelines for IPT (2008)[45]. HIV programs should own IPT services and provision of IPT must be fully included as part of the basic care package for all PLHIV. Perhaps, the use of IPT should be included in the range of palliative care services provided to all PLHIV, like Cotrimoxazole, nutritional supplements and anti-malarial medication during visits to most ART clinics. Additionally, patients should be properly educated in order to know the importance of IPT and thus be able to demand prescription of IPT from their providers. Others measures include the inclusion of IPT as part of ART scale-up, integration of HIV and TB services, full development of national policies for IPT, continued promotion of the concept of the Three I's, improved and stronger advocacy at all levels, improved monitoring and evaluation of IPT programmes, and pursuing the

possibility of co-formulation of Cotrimoxazole and INH to further aid treatment adherence and improve access.

Furthermore, implementation studies to further understand the best models for IPT implementation and scale-up at country level are needed. Since the fear of INH mono-resistance is one of the barriers to full scale IPT implementation, reports on the risks and benefits associated with the administration of INH in error to undiagnosed people with active TB are also needed[4]. Although, a recent report showed that in HIV-infected persons, 36 mo IPT was more effective than the current 6 mo regimen[21], additional studies are needed to clarify this. With all these efforts, the gains achieved through ART scale-up globally would be better consolidated with further reduction in TB incidence, improved survival and lower mortality among PLHIV. Conclusively, more needs to be done by the policy makers and the experts to ensure effective and strategic implementation of IPT especially in high HIV burden resource-constraint settings.

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