ORIGINAL ARTICLE

Isoniazid Preventive Therapy in Persons Living with HIV attending an Anti-retroviral Clinic in North India

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Abstract

Background: The risk of developing tuberculosis (TB) is several times greater in people living with HIV (PLHIV) than those without it. The TB/HIV syndemic continues to be a global public health challenge. Isoniazid Preventive Therapy (IPT) was found to be effective in reducing incidence of TB by almost 50%, under programme conditions in India. However, data on efficacy, safety, and completion rates of IPT among PLHIV in India are limited. Thus, this study aimed at documenting outcomes of IPT in terms of completion rate, adverse events and incidence of active tuberculosis.

Materials and Methods: An outpatient antiretroviral therapy (ART) centre-based cohort of 101 PLHIV aged ≥18 years in whom IPT (300 mg isoniazid + 50 mg pyridoxine) had been initiated in the last 28 days, after ruling out active TB were recruited and followed up. Participants lost to follow-up or expired (due to causes not related to IPT) were excluded from the adverse events and TB occurrence analysis.

Results: About 92.1% participants completed IPT and 24.7% developed minor adverse events during IPT. None of the patients who received IPT developed active TB infection at the end of follow-up.

Conclusion: Co-administration of IPT with ART does not compromise safety or compliance.

Keywords: Antiretroviral, Isoniazid Preventive Therapy, Tuberculosis.

Introduction

Tuberculosis (TB) is the most common opportunistic infection amongst people living with human immunodeficiency virus (PLHIV) and accounts for 25% of deaths amongst them in India. The risk of developing TB is 21-34 times greater in PLHIV compared to those without HIV infection.[1] The TB/HIV syndemic is a global public health challenge which needs to be addressed on a war footing.

The widespread institution of antiretroviral therapy (ART) has been instrumental in lowering the risk of TB through immune reconstitution, but the risk remains high despite achievement of good CD4 cell recovery, thereby underlining the need to implement other preventive interventions such as Isoniazid Preventive Therapy (IPT). The World Health Organization (WHO) and Joint United Nations Programme on HIV/AIDS (UNAIDS) issued a statement in 1998 recognizing the effectiveness of IPT among PLHIV and recommended its use as part of an essential care package for these patients.[2] A systematic review found that IPT reduced the overall risk of TB by 33% and by 64% when targeted to PLHIV who had a positive tuberculin skin test.[3]

Despite strong recommendations globally, the uptake of IPT has been limited due to difficulties in excluding active TB, added pill burden for patients, side effects, poor adherence to IPT, and concerns about development of drug resistance. In a review done by the WHO Guidelines Group, adherence for IPT ranged from 34-98%.[4] A prospective multicentric study with phased implementation was conducted to assess the uptake and effectiveness of IPT in reducing TB incidence in a cohort of PLHIV enrolled into HIV care between 2013 and 2016 at seven ART centres in four states of India. IPT was found to be effective in reducing TB incidence by almost 50%, under programme conditions in India.[5] However, there is dearth of data regarding feasibility, efficacy, safety, and completion rates of IPT among PLHIV in India. There are specific concerns about adverse events of isoniazid in those with concurrent ART. Our study had a value addition as it addressed several aspects regarding IPT in the Indian population.

MATERIALS AND METHODS

A hospital-based prospective cohort study was conducted in an ART centre of a tertiary care teaching hospital of Delhi, India. The study population constituted all PLHIV aged ≥18 years, initiated on IPT (<28 days from recruitment to the study) from the ART centre. Participants lost to follow-up or expired (due to causes not related to IPT) were excluded from the adverse events and TB occurrence analysis. Information regarding socio-demographic profile (age, gender, religion, educational status), baseline characteristics (CD4 count, ART regimen, viral hepatitis co-infection, biochemical profile including serum alanine aminotransferase level) was collected. All participants were followed up at 2, 6 and 9 months after initiation of IPT.

The outcomes of interest in this study were the IPT completion rate, incidence of adverse events and occurrence of active TB infection during 9-month follow-up. Patients who were lost to follow-up or expired (due to causes not related to IPT) were excluded from the adverse events and TB occurrence analysis. Patients who were transferred to other hospitals were excluded from all outcome analysis.

Adherence was assessed using the pill count method at 2, 6 and 9 months (where applicable) of follow up. Adherence assessment for the remaining months of IPT not evaluated by participant interaction were supplemented by monthly adherence records of the ART Clinic. The reasons for interruptions in IPT intake were noted from records and it was ensured that the participant underwent counselling to improve adherence for ensuing months. Assessment for adverse events was guided by appearance of symptoms and signs in the participant. The participant was enquired regarding the appearance of the various commonly reported adverse effects of isoniazid. Occurrence of TB was considered if the participant was removed from IPT and initiated on antitubercular therapy at any point of time within 9 months of start of IPT.

Statistical analysis: The data collected as a part of this study were entered in a computer based spreadsheet and analysed using SPSS version 20.0. The continuous variables were reported as mean (± standard deviation, SD). The categorical variables were reported as number (percentage).

RESULTS

A total of 101 PLHIV aged ≥18 years in whom IPT (300 mg isoniazid + 50 mg pyridoxine) had been initiated from the ART centre in the last 28 days, after ruling out active TB were enrolled for study. The mean (± SD) age of the study population was 39.9 (± 10.9) years. There were 58.4% (*n*=60) male participants and 40.6% (*n*=41) female participants. The most commonly reported mode of HIV transmission was heterosexual (*n*=87; 86.1%). The majority of the participants (92.1%) in the study group belonged to WHO clinical stage I. The mean (± SD) CD4 count at the time of recruitment was 461 (± 240) cells/μL.

Out of 101 participants in the study, 68 (67.3%) participants received cotrimoxazole prophylaxis therapy (CPT) in the past and 56 (55.4%) participants were on CPT at the time of recruitment. Past history of tuberculosis was present in 22 (21.8%) participants with 2 participants giving a prior history of tuberculosis on two occasions.

Out of 101 participants, 85 (84.2%) completed 6 months of IPT without any interruption. However, 8 (7.9%) participants completed IPT with some interruption while 8 (7.9%) subjects did not complete IPT. Thus, the cumulative IPT completion rate of the study population was 92.1%. The reasons for interrupted IPT uptake in 16 study participants are shown in ***Table I***.

Around 24.7% patients developed minor adverse events during IPT (***Table II***). The most common adverse events recorded were weakness or fatigue (44.0%) followed by nausea and vomiting (32.0%). Some of the participants experienced more than one adverse event. On clinical examination during follow up at 2nd, 6th and 9th months, none of the participants reported symptoms of hepatotoxicity and none had jaundice. One participant complained of paraesthesia but showed no signs of peripheral neuropathy and managed to continue IPT. None of the patients who were exposed to IPT (including those who stopped IPT prematurely) developed active TB infection at the end of follow-up.

TABLE I. Reasons For Interruption in Isoniazid Preventive Therapy (IPT) amongst Study Participants (*N*=16)

Reasons for interruption	*IPT completed with some interruption (n=8)*	*IPT not completed (n=8)*
Lack of conviction due to not having tuberculosis	8	8
Pill burden	0	3
Concerned about adverse reactions	1	2
Good CD4 count	1	2

Table II. Adverse Event Profile Amongst Study Participants While Receiving Isoniazid Preventive Therapy

Adverse event	*No of participants*
Weakness or fatigue	11
Nausea and vomiting	8
Skin rash	7
Allergic reaction with swelling of lips and face	2
Gastric discomfort	2
Paraesthesia	1
Fever	1

DISCUSSION

The present study was a hospital-based prospective cohort study that assessed the outcome of IPT in 101 PLHIV taking treatment and care from ART centre of tertiary care teaching hospital in Delhi. The overall completion rate of IPT in our study was high (92%) and comparable to previous studies.[6-8] Despite the increase in pill burden, IPT was well tolerated with concurrent ART. A previous study reported IPT completion rate as 77.1% which was even higher in subjects on ART (78.3%).[9] Another study by Takarinda, *et al* reported 80.6% IPT completion rate.[10] Such a high completion rate in our study could probably be due to the fact that all participants were on ART at the time of study and majority were in WHO clinical stage I with higher mean CD4 counts. This result is also a reflection of services provided at the centre through an effective national program like appropriate preparation with synchronized IPT and ART supplies; trained nursing staff and counsellors educating participants regarding IPT at every follow up visit, financial benefits to patients on ART etc. In our study the major reason for interruption of IPT was a lack of conviction to consume IPT in the absence of tuberculosis. Two participants did not complete IPT due to adverse events like nausea, vomiting and weakness in one and swelling of lips and face in the other. In the study by Takarinda, *et al* non-completion of IPT was attributed to loss to follow up in majority of participants; adverse effects of IPT and non-availability of IPT were reported as reasons in 7.2% and 4.5% of the participants for non-completion of ART.[10] Another study quoted that severe adverse drug reaction like skin rash and transaminitis were reasons behind stopping IPT in 6.5% (n=3) participants; other reasons were loss to follow up and stopping IPT on their own by participants.[8]

Although the benefit of IPT among PLHIV is well established, there have been concerns about adverse events of isoniazid, particularly when co-administered with ART. In our study all participants were clinically stable during the follow up period over 9 months. None of the study participants reported any major adverse event while minor adverse events were reported by 25 (24.7%) subjects. The most common adverse event noted was weakness or fatigue. Other studies from different parts reported hepatotoxicity as a common adverse effects.[7,8,10] The relatively low incidence of adverse events recorded in our study may be because of lower incidence of hepatitis B or C coinfection, higher mean CD4 counts, absence of advanced (stage III/IV) illnesses. It is also possible that some less severe adverse events may be understated as they were recorded on the basis of recall or from records maintained by staff at the centre.

It was seen that concomitant IPT with ART had significant protective effect on occurrence of TB compared to ART alone.[9] Zero incidence of TB in our study could not be attributed to IPT alone as our study was not a comparative study against IPT naïve participants. Other studies reported different incidence of TB in patients on IPT ranging from 2.2% to 3.1%.[7,8] It is also plausible that since majority of our study participants were in WHO clinical stage I, had good CD4 counts and the mean duration of consumption of ART had been for more than 4 years, which could have resulted in zero incidence of tuberculosis in our study.

Our study found that IPT is a feasible and relatively safe strategy in PLHIV. Coadministration of IPT and ART gives additive prophylaxis against reactivation of TB and has not been shown to compromise safety or compliance in our study. However, this was a single centre study with a small sample size and thus there are limitations in statistical power to detect small subgroup effects and generalizability. Due to a limited number of follow up visits, the majority of data was collected by recall leaving scope for inaccurate estimates. Multicentre studies with longer follow up of participants across all stages of HIV are needed to determine the outcomes of IPT in PLHIV. Future studies also need to address the risk of developing drug-resistant TB after exposure to IPT.

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