

Assessment of isoniazid preventive therapy in the reduction of tuberculosis among ART patients in Arba Minch Hospital, Ethiopia

Ashenafi Aboessie
Tsegaye Yohanes

Department of Medical Laboratory
Sciences, College of Medicine
and Health Sciences, Arba Minch
University, Arba Minch, Ethiopia

Background: Tuberculosis (TB) is the most frequent life-threatening opportunistic disease among people living with HIV and remains a leading cause of mortality, even among persons receiving antiretroviral therapy (ART). Isoniazid preventive therapy (IPT) and cotrimoxazole prophylaxis have been recommended for the benefit of HIV/AIDS-infected individuals to prevent opportunistic infections. The aim of this study was to assess IPT prophylaxis in the reduction of TB among ART patients.

Methods: The study was a hospital-based retrospective study. A total of 271 study participants' available information such as demographic data, the type of prophylaxis used, and TB/HIV coinfection status as well as other variables were collected from clinical laboratory and HIV care/ART follow-up clinic. Data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 20.0.

Results: TB-infected ART patients were higher among non-IPT group (37 [27.8%]) compared to IPT group (12 [8.7%]). The finding showed that IPT prophylaxis significantly reduces acquiring TB with the relative risk =0.31 (95% confidence interval =0.122, 0.49) in ART patients of this study site where the tuberculosis prevalence is prominent. ART had significant contribution for CD4⁺ T-cell lymphocyte count improvement in both IPT and non-IPT groups ($P<0.05$) in this study.

Conclusion: IPT had significant contributions to reduce the burden of TB in ART patients than non-IPT group. This result highlights the use of IPT for the prevention of TB, especially for all ART patients. Other longitudinal studies are needed to observe the benefits and side effects of IPT prophylaxis in tuberculin skin test-positive individuals.

Keywords: IPT prophylaxis, ART patients, tuberculosis, CD4⁺ T-cell count, opportunistic disease

Background

In 2015, there were 2.1 million (1.8–2.4 million) new HIV infections worldwide, adding to up to 36.7 million (34.0–39.8 million) people living with HIV. There were also 25.5 million (24.0–28.7 million) people living with HIV in sub-Saharan Africa, and sub-Saharan Africa accounts for almost 66% of the global total of new HIV infections.¹ HIV infection is a major public health problem. The progression of HIV infection is exacerbated with coinfections such as malaria, tuberculosis (TB), and other opportunistic diseases. The existence of these coinfections and the consequences of immune interaction events deteriorate the immunocompetent capability of coinfecting individuals.

TB remains the leading cause of death among people living with HIV, accounting for around one in three AIDS-related deaths. However, some progress had been made with a decline of 32% of TB-related deaths among people living with HIV

Correspondence: Tsegaye Yohanes
Department of Medical Laboratory
Sciences, College of Medicine and
Health Sciences, Arba Minch University,
PO Box: 21, Arba Minch, 1078, Ethiopia
Tel +251 91 209 8208
Email tsegaye.yohanes@yahoo.com

since 2004. In 2015, 10.4 million people fell ill with TB and 1.8 million died from the disease (including 0.4 million among people with HIV). Over 95% of TB, deaths also occur in low- and middle-income countries. TB patients are also the more likely to develop active TB. The risk of active TB is greater in persons with altered immune system.² TB is a life-threatening opportunistic disease in HIV/AIDS patients, with high mortality even among patients receiving antiretroviral therapy (ART).³

The World Health Organization (WHO) estimates that one-third of the world's population is latently infected with *Mycobacterium tuberculosis*. Latent TB infection results when individuals infected with *M. tuberculosis* carry the organism in a latent state, which is characterized by slowed or intermittent metabolism and replication below the level necessary to produce clinical illness.⁴ Whereas in the general population, the lifetime risk of progression from latent TB infection to active disease is about 10%, HIV-positive persons who are infected with *M. tuberculosis* have a 5%–8% annual risk and a 30% lifetime risk of developing active TB.⁵

TB transmission and control measure have faced challenges due to coinfection with HIV. HIV and TB service delivery is insufficiently integrated, and too many people are losing their lives because they are unable to either prevent TB or access life-saving medications for both diseases. The disease in HIV coinfecting individuals also leads to high progression to AIDS. In addition, the lack of case detection problem and early treatment of TB delay the curative and as well as survival rate of coinfecting individuals.⁵

Besides early initiation of ART, the main intervention to prevent TB in people living with HIV is isoniazid preventive therapy (IPT). Worldwide, significant progress has been made to minimize morbidity and mortality among people living with HIV/AIDS. The benefits of ART and IPT for preventing TB have been proven in adults and children in various settings. The clinical trials have shown that IPT dramatically reduces the incidence of TB among people living with HIV, including those on ART.^{3,6}

Although study of cotrimoxazole (CTX) prophylaxis in HIV-infected adults with active pulmonary TB found that TMP-SMX has significantly reduced morbidity and mortality, a study from South Africa has produced evidence showing that adjunctive CTX in HIV-positive TB patients improved survival rates by 53%.⁷ However, WHO reported that IPT taken for 6–12 months reduces the risk of TB disease by 33% among all people with HIV and by 64% in HIV-positive people who have a positive tuberculin skin test.³

Currently, the use of prophylaxis for this devastating disease is more advantageous to prevent earlier the development

of other opportunistic diseases, since TB is highly associated in the depletion of CD4⁺ T-cell count in coinfecting individuals. The maximum benefits from TB preventive therapy are achieved in HIV-infected persons with evidence of TB infection as demonstrated by a positive tuberculin skin test. However, benefit has been shown among HIV-infected persons in general, regardless of their tuberculin test result. This study aimed to determine to assess the outcome of IPT prophylaxis in the prevention of TB and improvement of the immune system as determined by the CD4⁺ T-cell count in ART patients.

Methods and materials

Study area

This study was carried out in Arba Minch hospital ART clinics. Arba Minch town is found in southern region of Ethiopia, which is 505 km far from Addis Ababa and 270 km from Hawassa, the regional capital city. Arba Minch hospital is serving a population of more than 1.7 million. Infectious diseases make up the major share of disease load in Arba Minch hospital, with malaria ranking first. The hospital provides services such as Outpatient department, Inpatient departments (medical, surgical, obstetrics, and gynecology), ophthalmology, maternal and child health, pharmacy, laboratory, and ART and TB clinics.

Study design and Period

This retrospective study included all ART patients who had been taking IPT prophylaxis from September 2010 to August 2011 in Arba Minch hospital in ART clinic. Study subjects were included by simple random sampling methods in non-IPT group and IPT group database sheets without considering the duration of ART treatment. However, selection bias was a challenge because of total number of patients who had been on IPT and fulfilled the criteria were not sufficient to be included by simple random sampling method. ART patients who were not volunteered to take IPT treatment were grouped as non-IPT group. However, those ART patients who discontinued IPT were excluded whether their TB status was positive or negative.

Sample size determination

The sample size was determined based on the prevalence of TB infection. The prevalence of TB infection is 68% in HIV coinfecting individuals and 38% in non-HIV infected individuals, 95% confidence interval, and 5% marginal error with 80% statistical power. Considering all the above prevalence and constants, 271 individuals were estimated to be included for this study.

Data collection

Data were collected from HIV care/ART follow-up form and registration book in ART clinic as well as laboratory data. Study subjects were included based on IPT status, and patients who had a registered baseline CD4⁺ T-cell count and full information in ART clinic were included. All ART users in the previous 1 year were assessed for coinfection, current situation, and other variables. All necessary demographic data were collected to get the whole information.

Data analysis

All raw data collected from the register were entered and analyzed using data analysis software Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM Corporation, Armonk, NY, USA). This data includes sociodemographic data, cotrimoxazole and TB prophylaxis, TB status, IPT duration, and CD4⁺ T-cell count value. Independent sample *t*-test and bivariate statistical analysis were used. Values were also considered to be statistically significant when *P*-values are less than or equal to 0.05.

Ethical issues

Leadership in Strategic Information Program Coordination Office (Ethiopia Public Health Association) approved the study. Arba Minch College of Health Sciences Research Affairs Ethical Committee also provided approval to collect the data and to conduct the study in Arba Minch Hospital. Written informed consent was deemed not required and waived by Arba Minch College of Health Sciences Research Affairs Ethical Committee, as all data were de-identified and kept strictly confidential. Permission was also

obtained from Arba Minch Hospital Medical Directorate Office to conduct the study in the ART clinic, where the data were also deidentified and kept strictly confidential.

Results

Description of the study participants

Two hundred seventy one study subjects were included from both groups: IPT group had 138 (50.9%) and non-IPT group had 133 (49.1%). One hundred twelve (41.3%) were male and 159 (58.7%) were female. Among these study participants, 48 (34.7%) and 90 (65.3%) were male and female, respectively, from IPT group. Among non-IPT, 64 (48.1%) and 69 (51.9%) were male and female, respectively. Among the total study participants, 112 (41.3%) were aged between 25–34 years. The mean (standard deviation [SD]) age of the participants was 31.27+12.0, and the median age was 30 (Table 1).

Orthodox Christians constituted 176 (64.9%) of the participants, followed by protestants 72 (26.6%). Ninety-three (34.3%) study participants were unable to read and write. Similarly, 95 (35.1%) participants were educated up to a primary level. Almost half of the study participants 150 (55.4%) were married, while 61 (22.5%) had never married (Table 1).

HIV/TB coinfection

Two hundred seventy one study participants were randomly selected based on IPT status from ART clinics. All study participants had been taking cotrimoxazole prophylaxis. However, only 138 (50.9%) of ART patients had been taking IPT prophylaxis for a minimum of 6 months and above. Among IPT group who have been taking the

Table 1 Sociodemographic characteristics of study participants on ART with prophylaxis status in Arba Minch hospital, 2010

Sociodemographic characteristics	Group	IPT group number (%)	Non-IPT group number (%)	Total number (%)
Age	0–14 yr	18 (13.0)	8 (6.0)	26 (9.6)
	15–24 yr	13 (9.4)	13 (9.8)	26 (9.6)
	25–34 yr	52 (37.6)	60 (45.1)	112 (41.3)
	≥35 yr	50 (36.2)	57 (42.8)	107 (39.5)
Sex	Male	48 (34.7)	64 (48.1)	112 (41.3)
	Female	90 (65.3)	69 (51.9)	159 (58.7)
Religion	Orthodox	83 (60.1)	93 (70.0)	176 (64.9)
	Protestant	37 (26.8)	35 (26.3)	72 (26.6)
	Others	13 (9.4)	10 (7.5)	23 (8.4)
Educational status	Illiterate	53 (38.4)	40 (30.0)	93 (34.3)
	Primary	48 (34.7)	47 (35.3)	95 (35.1)
	Secondary and above	32 (23.1)	51 (38.3)	83 (25.8)
Marital status	Single	31 (21.7)	30 (23.3)	61 (22.5)
	Married	76 (53.6)	74 (57.1)	150 (55.4)
	Others	31 (22.4)	29 (21.8)	60 (22.1)
Total		138 (50.9)	133 (49.1)	271 (100)

Abbreviations: ART, antiretroviral therapy; IPT, isoniazid prevention therapy; yr, year.

Table 2 Association of sociodemographic characteristics with TB status in IPT group in Arba Minch hospital, 2010

Sociodemographic characteristics	Groups	IPT group (n=138)		RR (95% CI)
		TB positive number (%)	TB negative number (%)	
Sex	Male	5 (10.4)	43 (89.6)	1.00
	Female	7 (7.8)	83 (92.2)	0.75 (0.25, 2.23)
Age	0–14 yr	1 (12.5)	7 (87.75)	1.00
	15–24 yr	1 (7.7)	12 (92.3)	0.62 (0.04, 8.52)
	25–34 yr	3 (5.0)	57 (95.0)	0.40 (0.05, 3.4)
	≥35 yr	7 (12.3)	50 (87.7)	0.98 (0.14, 6.98)
Marital status	Single	3 (9.7)	28 (90.3)	1.00
	Married	5 (6.6)	71 (93.4)	0.68 (0.17, 2.67)
	Others	4 (12.9)	27 (87.1)	1.33 (0.32, 5.47)
Educational status	Illiterate	3 (7.5)	37 (92.5)	1.00
	Primary	7 (14.9)	40 (85.1)	2.15 (0.51, 8.96)
	Secondary and above	2 (3.9)	49 (96.1)	0.52 (0.09, 2.98)
Religion	Orthodox	9 (9.7)	84 (90.3)	1.00
	Protestant	2 (5.7)	33 (94.3)	0.59 (0.13, 2.60)
	Others	1 (10.0)	49 (90.0)	1.03 (0.15, 7.34)
Total		12 (8.7)	126 (91.3)	

Abbreviations: CI, confidence interval; TB, tuberculosis; IPT, isoniazid prevention therapy; RR, relative risk; yr, year.

prophylaxis, 12 (8.7%) of the study participants were infected by TB, whereas the remaining 126 (91.3%) study participants were TB negative after 6 months duration on IPT (Table 2).

As shown in Table 2, among IPT group in univariate analysis, primary educational level had higher possibility to acquire TB infection compared to the illiterate (relative risk [RR]=2.15; 95% confidence interval [CI]=0.51, 8.96). Out of the 133 participants also in the non-IPT group, 19 (14.2%) males and 18 (13.5%) females were coinfecting with TB. And about 37 (27.8%) participants had acquired TB infections.

In the non-IPT group, age, religion, and educational level played a more significant role in acquiring TB infection compared with their reference values, as shown in Table 3.

As Table 4 shows, IPT prophylaxis users were protected from TB infection with statistically significant difference compared with those who did not use IPT prophylaxis (RR =0.32; 95% CI =0.122, 0.49) in this study.

CD4⁺ T-cell count profile

Out of 138 cases of IPT group, 86 (62.3%) checked their CD4⁺ count status, and the remaining percentage of study

Table 3 Association of sociodemographic characteristics with TB status in non-IPT group in Arba Minch hospital, 2010

Sociodemographic characteristics	Groups	Non-IPT group (n=133)		RR (95% CI)
		TB positive number (%)	TB negative number (%)	
Sex	Male	19 (29.7)	45 (70.3)	1.00
	Female	18 (26.1)	51 (73.9)	0.88 (0.51, 1.52)
Age	0–14 yr	6 (33.3)	12 (66.7)	1.00
	15–24 yr	4 (30.8)	9 (69.2)	0.92 (0.32, 2.62)
	25–34 yr	13 (25.0)	39 (75.0)	0.75 (0.34, 1.68)
	≥35 yr	14 (28.0)	36 (72.0)	0.84 (0.38, 1.85)
Marital status	Single	9 (30.0)	21 (70.0)	1.00
	Married	17 (23.0)	57 (77.0)	0.77 (0.38, 1.52)
	Others	11 (37.9)	18 (62.1)	1.26 (0.62, 2.59)
Educational status	Illiterate	15 (28.3)	38 (71.7)	1.00
	Primary	14 (29.2)	34 (70.8)	1.03 (0.56, 1.96)
	Secondary and above	8 (25.0)	24 (75.0)	0.88 (0.42, 1.85)
Religion	Orthodox	21 (25.3)	62 (74.4)	1.00
	Protestant	9 (6.7)	28 (21.0)	0.96 (0.49, 1.89)
	Others	7 (53.8)	6 (46.2)	2.13 (1.14, 3.97)
Total		37 (27.8)	96 (72.2)	

Abbreviations: CI, confidence interval; TB, tuberculosis; IPT, isoniazid prevention therapy; RR, relative risk; yr, year.

Table 4 TB status with prophylaxis type used among patients on ART in Arba Minch hospital, 2010

Type of prophylaxis	AFB smear result		RR (95% CI)
	Positive number (%)	Negative number (%)	
IPT group	12 (8.7)	126 (91.3)	0.32 (0.122, 0.49)
Non-IPT group	37 (27.8)	96 (72.2)	
Total	49 (18.0)	222 (82.0)	

Abbreviations: ART, antiretroviral therapy; AFB, acid-fast bacillus; CI, confidence interval; TB, tuberculosis; IPT, isoniazid prevention therapy; RR, relative risk.

subjects did not get the opportunity to check CD4⁺ T-cell count because of the problem with the automated machine, shortage of reagents, etc. Among non-IPT group, only 54 (40.6%) study subjects' CD4⁺ count values were obtained with two intervals. With independent sample *t*-test statistical analysis, at the baseline, both groups' mean CD4⁺ T-cell count value was not significantly different. Therefore, it was comparable at baseline ($P=0.5$). The difference was not significantly different ($P=0.2$) after 6 months. However, the mean CD4⁺ count showed an improvement in IPT group and non-IPT group ART patients after 6 months. Both the IPT group and non-IPT group had significant CD4⁺ T-cell count improvement. This might be due to use of ART treatments for CD4⁺ T-cell count improvements (Table 5).

Discussion

In countries where TB is common, many people have been exposed to TB and have a latent infection. The WHO recommends the use of IPT in HIV-infected patients in countries with high prevalence of HIV infection. IPT can prevent latent TB infection from developing into active disease. A 6-month course of IPT reduces the risk of getting TB for people living with HIV by 33%.⁸ This study assessed the outcome of IPT prophylaxis in the reduction of TB among ART patients. Furthermore, the study also evaluated ART benefit to improve the immune status of ART patients.

Table 5 Mean CD4⁺ count change, with prophylaxis type, among ART users from Arba Minch hospital, Ethiopia, 2010

Period	IPT group (n=86)	Non-IPT group (n=54)	P-value
Mean CD4 ⁺ count (SD) At the baseline	267.66 (146.59)	252.41 (179.41)	0.5
Mean CD4 ⁺ count (SD) After 6 mo	389.55 (221.09)	346.04 (245.32)	0.2
P-value	0.00	0.01	

Abbreviations: ART, antiretroviral therapy; IPT, isoniazid preventive therapy; SD, standard deviation; mo, month.

In this study, about half of the study participants were aged between 25 and 34 years old. In agreement with the survey of Ethiopia Demographic and Health Survey 2005, higher magnitude of HIV was found in this age group. Furthermore, the majority of study participants were married, similar to the surveillance reports of Ethiopia.⁹

Consistent with this study, a study from Brazil found that IPT and ART were both effective in reducing TB risk in HIV-infected adults.¹⁰ This finding agreed with others that showed the benefit of IPT combined to ART to reduce TB risk in HIV-infected patients.¹¹ Overall, the combination of the two interventions was considerably more protective than either alone.

ART alone in non-IPT group had an effect on the improvement of CD4⁺ T-cell count with statistically significant difference in this study. Consistent with other studies, ART alone reduces the risk of TB.^{12,13} This could be due to the benefit ART in suppression of viral load and restoration of the immune status of the patients that prevent opportunistic diseases. However, the proportion of TB coinfecting participants was higher among non-IPT group than IPT group in this study.

Both IPT and ART are associated with reduced TB, and patients had higher CD4⁺ T-cell count in this study. Although *M. tuberculosis* can activate HIV-infected CD4⁺ lymphocytes and lead to progression from HIV infection to clinical AIDS, the wider use of IPT and combination with ART in patients with HIV can improve TB prevention in high-burden areas.¹⁴ Additionally, there is also a WHO recommendation that shows that IPT given for 6–12 months after TB treatment is effective in reducing the risk of recurrent TB disease.¹⁵

In addition, in agreement with Walker et al,¹⁶ evidence from the data has shown that CTX therapy reduces mortality among persons with HIV. Thus, this preventive therapy contribution to reduce TB infection by preventing the decline of CD4⁺ T-cell count in the study participants.

At baseline, CD4⁺ T-cell counts were lower in the cases of IPT/ART group and ART alone compared with 6 months later. The preventive therapy and ART drugs had an effect on increasing CD4⁺ T-cell lymphocyte count, and even patients on ART alone had much better immune restoration.¹⁷ In addition, since ART supports the participants mean CD4⁺ count improvement, this might have contributions to prevent active TB.

Limitations

This study has several limitations; the tuberculin skin test was not done on the study participants and there was a missing data, and WHO staging as well as ART duration was not evaluated since it was a retrospective study.

Conclusion

IPT in conjunction with ART had a significant contribution in reducing TB infection and CD4⁺ T-cell count improvements. Improvement of CD4⁺ T-cell count might be occurring due to ART in both IPT and non-IPT group. Therefore, IPT combined with ART is valuable to prevent reactivation/exogenous infection of TB in ART patients. Other long-term studies are recommended to assess the effect of IPT prophylaxis on ART patients.

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Author contributions

AA has contributed to conception of the study question, designed the study, collected data, analyzed data, interpreted data, and drafted the manuscript, and TY has involved in data collection, data analysis, data interpretation, and drafting of the manuscript. Both authors agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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