THE EFFECT OF RIFAPENTINE AND ISONIAZID THERAPY ON IGRA REVERSION AND CONVERSION AMONG HIV POSITIVE INDIVIDUALS IN ADDIS ABABA: A RETROSPECTIVE COHORT STUDY.

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Abstract

Interferon-γ release assays (IGRAs) such as QFT gold plus is one of the main tools for the diagnosis of latent TB infection (LTBI). The main objective this study was to assess the effect of Rifapentin and Isoniazid (3HP) on IGRA reversion and conversion.

IGRA reversion and conversion rates have generally been reported after preventive TB therapy, but rates vary widely depending on different settings and there was no study conducted in Ethiopia on IGRA reversion and conversion in post 3HP.

A retrospective cohort study of 519 human immunodeficiency virus (HIV) positive individuals who had follow up at Zewditu and Alert Hospitals in Addis Ababa, Ethiopia underwent testing with QuantiFERON (QFT) gold plus at enrolment and 12-month follow-up after taking Rifapentine and Isoniazid (3HP) prophylaxis therapy were included in the final analysis in this study to assess the reversion and conversion of IGRA.

The rate of IGRA reversion among LTBI positives and the rate of conversion among latent Tuberculosis infection (LTBI) negative at baseline was 67/169 (39.6 %) and 66/350 (18.9 %) respectively. The observed high IGRA conversion rates indicated a higher rate of Mycobacterium TB infection among LTBI negative patients despite taking 3HP. The prevalence of LTBI among HIV positive individuals was found to be 169/519 (32.6 %; 95% CI 28.5% to 36.5%). Having a history of tuberculosis is substantially associated with LTBI (AOR=1.7 [95% CI 1.15, 2.52]).

IGRA reversion rate after taking Rifapentin – INH prophylaxis therapy was fairly high and the rate of IGRA conversion was high despite taking the tuberculosis prophylaxis. Hence targeted screening approach for diagnosing latent tuberculosis infection in HIV/AIDS patients using appropriate methods before administration of TB preventive therapy is recommended.

List of abbreviations and acronyms

AIDS	Acquired immunodeficiency syndrome
BCG	Bacillus Calmette Guerin
CD	cluster of differentiation
CFP	cluster of differentiation
CXR	Chest X-ray
HIV	human immunodeficiency virus
HP	Rifapentine and Isoniazid
IGRA	Interferon-gamma release assay
INH	Isonicotinic acid hydrazide
IPT	Isoniazid preventive therapy
LTBI	latent tuberculosis infection
MTB	Mycobacteria tuberculosis
QFT	QuantiFERON test
QFT-GIT	QuantiFERON-Gold in Tube
QFT-Plus	QuantiFERON- Plus
HP	Rifapentine and
PLHIV	People living with HIV
TB	tuberculosis
MTBC	Mycobacterium tuberculosis complex
TST	Tuberculin skin test
WHO	World Health Organization

Definition of terms

Latent tuberculosis infection: (LTBI)	is defined as a state of a persistent immune response to stimulation by Mycobacterium tuberculosis antigens with no evidence of clinically manifest active TB
IGRA conversion:	Defined as QFT result at screening Negative and follow-up QFT at month 12 turned to be positive.
IGRA reversion	Defined as QFT result at screening positive and follow-up QFT at month 12 turned to be negative.
High TB burden countries:	Countries characterized by a high burden of TB (TB incidence >100/100 000 population)
Low TB burden countries:	Countries characterized by a low burden of TB (TB incidence <10/100 000 population).
Preventive treatment:	Treatment offered to individuals who are considered to be at risk for TB disease to reduce that risk.

Operational definitions

Treatment completed	Defined as taking at least 11 doses out of 12 doses.

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1.0 Statement of the problem

Globally, Tuberculosis (TB) is one of the old diseases that still causes serious public health problems (1). About 8.6 % of all reported cases of TB were people living with HIV (PLHIV) (1).

According to the 2018 WHO report, more than 1.7 billion people (23 % of the world 's population) have latent TB, which means that people have been infected with the Mycobacteria tuberculosis complex (MTBC) but are not (yet) ill and cannot transmit the disease (2). These latently infected individuals act as a huge reservoir for the development of active TB disease. Most infected people have no signs or symptoms of TB disease and are not infectious, but are at risk of developing active TB disease and will become infectious (2).

A relatively small proportion (5-10%) of the estimated 1.7 billion of LTBI positive will develop active TB disease during their lifetime with the majority developing TB disease within the first 2-5 years after the initial infection. The likely hood of developing active TB disease is much higher among HIV-infected people (5-15 % each year and ~50 % throughout their lifetime) (3). However, the likelihood of LTBI progression to active TB disease depends on bacterial, host, and environmental factors (4)

HIV infection is one of the most known risk factors for the progression of latent tuberculosis infection to active disease. People living with HIV are 21 times more likely to develop active TB than HIV-negative individuals (5). HIV and TB are known to have a strong effect on the immune system, as they may interfere with the host's immune response to pathogens.

Interferon-gamma release assays (IGRA) reactions may be reversion if the initial QFT positive test turned out to be negative in the subsequent test or conversion if the initial QFT negative result turned out to be positive. There is inconsistency in the

rate of IGRA reactions in high and low TB burden countries, as well as variations within the different types of TB preventive therapy. In a recent systematic review and meta-analysis report, the rate of reversion among those taking TB prophylaxis was 24.9% (6). Low rates of IGRA reversion and conversion after TB prophylaxis were reported in high TB burden countries (7,8).

Treatment of latent TB infection among high-risk populations, such as HIV / AIDS, can avert the progression of latent tuberculosis infection to active TB disease and is a key component of the end TB strategy to control and eliminate tuberculosis (5). TB preventive treatment lowered the overall TB risk by 33% for HIV positive patients whereas, for those who were LTBI positive, the reduction increased to 64% (5).

People living with HIV who have a positive LTBI test benefit more from preventive treatment than those who have a negative LTBI test (5). Many developing countries have not implemented LTBI screening as a pre-requisite for preventive TB therapy. The current Ethiopian Guideline recommends preventive TB treatment for HIV positive individuals irrespective of the status of latent tuberculosis infection (9).

To the best of our knowledge, in Ethiopia, IGRA reversion and conversion rates for post-3HP prophylaxis therapy have not been studied before and may, therefore, be used as a basis for further studies.

2.0 Literature review

2.1 The burden of TB-HIV co-infection

Globally, 37.9 million people were living with HIV / AIDS and about 770,000 died of HIV-related deaths in 2018 (10,11). More than two-thirds of all HIV-positive people live in the WHO African Region (25.7 million) (11). In the same year, 690,000 HIV-positive people were living in Ethiopia and 11,000 died of AIDS-related illness (12).

Ethiopia is one of the triple burdened countries with high prevalence of TB/HIV co-infection. The prevalence of TB-HIV co-infection in Ethiopia was reported to be 22% (13). The Prevalence of TB among HIV patients in the capital Addis Ababa was reported to be 10.4% (14).

HIV is the most recognized risk factor for reactivation of latent TB infection to active disease (15). People living with HIV are 20 to 30 times more likely to develop active TB disease than those without HIV (16). Patients with TB disease may have symptoms such as cough, fever, night sweating, or weight loss (16). People with active TB may infect 10–15 other people through close contact over a year (17). A person who has kept TB active untreated infects 10 to 15 other individuals a year (18). On average, 45 % of HIV-negative people with TB, and almost all HIV-positive people with TB will die without proper treatment (17).

Approximately 10 million new cases of active tuberculosis were identified worldwide in 2018, of which 8.6 % were HIV-positive people (72 % in Africa). Also, approximately 1.45 million TB-related deaths have been reported (1.2 million HIV-negative deaths and an additional 251,000 HIV-positive deaths) (1).

Geographically, the majority of TB reported cases were in WHO regions of Southeast Asia (44 %), Africa (24 %) and the Western Pacific (18 %), with lower percentages in the Eastern Mediterranean (8 %), the Americas (3 %) and Europe (3

%) (1). Eight countries accounted for two-thirds of the global total: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (6%), Nigeria (4%), Bangladesh (4%) and South Africa (3%). These and 22 other countries on the WHO list of 30 high TB burden countries accounted for 87% of the world's TB cases (1). Most of the 30 countries with the highest TB burden have 150–400 per 100,000 population (18,19) And more than 500 in a few countries, including Mozambique, the Philippines, and South Africa (20). The estimated incidence of tuberculosis in Africa as a whole is 2.489,000 per year, which is equivalent to 237 per 100,000 population (21).

Globally, Ethiopia is one of the 14 countries with triple TB burden, TB, TB / HIV co-infection, and multidrug-resistant tuberculosis (MDR-TB) (22). Ethiopia ranks 4th in Africa and 11th among the 22 countries burdened by high tuberculosis (21). The estimated incidence of tuberculosis in Ethiopia is 164,590 per year, which is equivalent to 151 per 100,000 population (1,21). The TB mortality rate in Ethiopia is estimated to be 29,000 per year (23).

2.2 Burden of latent TB infection

Approximately one-quarter of the world's population has latent TB, which means that people have been infected with TB but are not (yet) ill with the disease and cannot transmit the disease (22). A fairly low proportion (5-10%) of the approximate 1.7 billion people infected with M. Tuberculosis will develop TB disease over their lifetime, which means that there is a 170-fold difference between LTBI and active TB disease (2,24).

The prevalence of latent TB infection among HIV positive individuals in South Africa and Hong Kong was 32.9% and 32% respectively (25,26). In one study, the prevalence of LTBI was 39.8% among HIV-positive patients with blood donors at Gondar Hospital, Ethiopia (27). The prevalence of latent Tb among healthy individuals in Addis Ababa was found to be 44.9% using QFT-GIT assay test (28).

Most infected individuals have no signs or symptoms of TB disease and are not contagious, but are at risk of developing active TB disease and becoming contagious (29,30). The reactivation of TB can be averted by preventive treatment. The efficacy of Currently available regimens for the treatment of LTBI has a range from 60% to 90%, the protection of which can last for up to 5 years (5,24,31).

The likely hood of developing active TB disease is much higher among HIV infected people (9). This is greatly increased by human immunodeficiency virus co-infection (5 -15% per year and ~50 % over lifetime) (3); It is also higher among those affected by risk factors, such as malnutrition, diabetes, smoking and alcohol consumption (3).

However, the pathogen is completely eradicated in ~10% of people while others only succeed to contain infection as some bacilli escape killing and remain in non-replicating (dormant) state (latent tuberculosis infection) in old lesions (32). The dormant bacilli may resurrect and cause active disease if the immune response is impaired (33). While active transmission contributes significantly to cases of active disease in high tuberculosis burden countries, most cases of active disease in low tuberculosis incidence countries emerge from this pool of latently infected individuals (33).

2.3 Diagnosis, IGRA reaction, and treatment of LTBI

A positive tuberculin skin test or a more recent and reliable interferon-gamma release test in a person with no clear signs of active disease suggests a latent tuberculosis infection (34). In countries with a high tuberculosis burden, the WHO strongly recommends that TB prophylaxis be given to high-risk groups such as HIV positive individuals to reduce the risk of Mycobacterium tuberculosis infection and its progression to active tuberculosis (30,35). The number of HIV positive individuals who received TB preventive treatment in 2017 was 958,559 (30).

In the developed world, interferon-gamma release assays (IGRAs) are becoming the primary method for diagnosing latent TB infection (LTBI) (34). A new variant of the

QuantiFERON assay, QuantiFERON-TB Gold Plus (QFT-Plus), contains 4 test tubes. These are the nil, TB1, TB2 and mitogen. The two MTB antigen tubes; TB1 (containing ESAT-6 and CFP-10 peptides) and TB2 (containing ESAT-6 and CFP-10 peptides and shorter antigen peptides engineered specifically to activate CD8 + T-cells) and TB7.7 antigen (36). CD8 + T-cell stimulation could improve sensitivity in people recently infected with TB (37). Under the guidelines of the United States Center for Disease Control and Prevention, IGRA conversion was defined as baseline IFN-γ < 0.35 IU / mL and follow-up IFN-γ 0.35 IU / mL, whereas IGRA reversion was defined as baseline IFN-γ 0.35 IU / mL and IFN-γ < 0.35 IU / mL follow-up (38).

Several studies have shown MTBC bacillary load decrement and IGRA reversion during LTBI therapy, but the results were inconsistent depending on the different settings. (8,39–42). The observed rates of reversion were higher, especially in low TB burden countries. Two studies conducted in Korea (a country with a low TB burden) reported higher reversion rates of 52.6% and 41.3% (41,42). Another study conducted in Japan (low TB burden country) reported an IGRA reversion rate of 25% (39).

Countries with a high TB TB burden reported lower IGRA reversion compared to low TB burden countries. A 5% IGRA reversion reported in two studies in South Africa (8,43) And a 20.5% rate of IGRA reversion was reported in Uganda (44). A recent systematic review and meta-analysis study showed that the summary rate of reversion of IGRA was 24.9% among those taking TB prophylaxis (6)

Preventive TB therapy is an intervention that should be part of the HIV / AIDS care package (45,46). Recently, T-cell interferon-gamma release assays (IGRAs) have become useful in the diagnosis of Mycobacterium tuberculosis infection and could be useful biomarkers of response to treatment of latent TB infection (47).

The main aim of the treatment of latent tuberculosis infection is to prevent the progression of TB infection to active clinical disease (48). For many years, Isoniazid (INH) administered daily for 6 to 12 months has been the mainstay of treatment as prophylaxis for individuals at risk of developing active TB with efficacy ranging from 60 to 90 % (48). Other effective regimens include daily rifampin and IoniazideI for 3 or 4 months, daily isoniazid and rifampin for 3 months, and isoniazid (900 mg) and rifapentine (900 mg) once weekly for 12 weeks (5). Many studies have shown that the 3-month isoniazid-rifapentine regimen was as effective as the 9-month isoniazid regimen and associated with a higher completion rate of treatment (89% vs. 64%) (34,48,49).

Among the 15 high TB / HIV burden countries reporting data, TB preventive treatment coverage ranged from 1% in Eswatini to 53% in South Africa (5). In 2017, TB prevention therapy coverage among HIV positive individuals in Ethiopia was 45% (50). WHO estimates that at least 30 million people will be eligible for TB preventive treatment between 2018 and 2022 (30). In countries with a high incidence of TB, WHO guidance issued in 2018 includes a new recommendation to consider testing and treatment for people aged 5 years or more who are household contacts of bacteriological confirmed pulmonary TB cases (30).

Two of the RCTs involved HIV adults from South Africa, Peru and some countries with a low incidence of TB showed no significant difference in the incidence of active TB among participants with 3-month weekly rifapentine plus isoniazid regimen and 6-or 9-month isoniazid monotherapy regimen (RR 0.73, 95 % CI 0.23;2.30) (5). Besides, the risk of hepatotoxicity was substantially lower with the 3-month weekly rifapentine plus isoniazid regimen in adults with HIV (RR 0.26, 95 % CI 0.12; 0.55) and those without HIV (RR 0.16, 95 % CI 0.10;0.27) respectively (5). The weekly regimen was also associated with a higher completion rate in all subgroups (adults with HIV: RR 1.25, 95% CI 1.01; 1.55; adults without HIV: RR 1.19, 95% CI 1.16;1.22, children and adolescents: RR 1.09, 95% CI 1.03;1.15) (5). One random clinical trial comparing the incidence of TB between a 3-month weekly

regimen of rifapentine plus isoniazid and continuous isoniazid monotherapy in adults with HIV infection found that there was no substantial difference in TB incidence in intention-to-treat analysis; however, a per-protocol study showed a lower risk of TB infection or death among participants with continuous isoniazid (5).

2.4 Significance of the study

To the best of our knowledge, this is the first study in Ethiopia addressing, IGRA reversion and conversion rates for post-3HP prophylaxis therapy. and may, therefore, be used as a basis for further studies.

3.0 Objectives of the study

3.1 General objective

To assess the effect of Rifapentine and Isoniazid (3HP) therapy on IGRA reversion and conversion among HIV positive patients.

3.2 Specific objective

1. To assess the rate of IGRA reversion and IGRA conversion and determine risk factors.
2. To assess the prevalence of latent TB infections among HIV positive patients and associated risk factors.

4.0 Methods

4.1 Study area, design and period

We used secondary data from the first year follow-up of the WHIP3 TB clinical trial, which was a multi-country multi-site Phase III clinical trial, registered under NCT02980016.

The present study was a retrospective cohort study in Addis Ababa, the capital of the Federal Democratic Republic of Ethiopia. It was held in 2 government hospitals, namely Zewditu Memorial and Alert hospitals, from 1 June 2017 to 30 September 2018.

4.2 Source population

The source populations were those HIV positive individuals living in and around Addis Ababa**.**

4.3 Study population

The study populations were all HIV positive individuals who were having follow up at Zewditu Memorial and Alert Hospitals and received 3HP prophylaxis.

4.3.1 Inclusion criteria

- Male and female HIV positive individuals whose age is >18
- Participants who had QFT gold plus result available at screening and month 12
- Participants who took 3HP as TB prophylaxis for at least 11 weeks.

4.3.2 Exclusion criteria

- QFT results with an indeterminate result
- Confirmed or suspected TB disease during 12-month follow up

- Participants who are lost to follow up during the 12-month follow up
- Pregnancy or breastfeeding during a 12-month follow-up.

4.4. Sample size

This study was based on data extracted from a clinical trial of 3HP TB prophylaxis provided to HIV-positive patients with follow-up from 1 June 2017 to 30 September 2018 at Zewditu Memorial and Alert Hospitals. A total of 519 participants who meet the eligibility criteria were included in this study.

4.5 Data extraction

Two data collectors were recruited to extract data from the case report form (CRF) of the parent study using the data extraction tool for each participant (see Annex B).

The variables in the study were;

Independent Variables which were extracted includes

Age, sex, marital status, education status, ART started date, CD4count, type of TB preventive medication and amount of dose taken, viral load, concomitant disease, concomitant medication, previous history of TB with the date of treatment, previous history of TB preventive treatment with the date of treatment.

Dependent Variables were

- IGRA reversion,
- IGRA conversion
- Prevalence of LTBI

4.6 Statistical analysis

Data were extracted with the data extraction tool (Annex B). Data were checked for completeness, cleaned manually, and then variables were coded and entered to Epi-

data version 4.6.0.0, then exported into Stata version 14.2 and IBM SPSS statistics version 25 for analysis.

Descriptive statistics for the variables tested are presented in the tables as absolute numbers and percentages. In the case of numeric variables, the distribution normality was tested with the Shapiro Wilk test. Numeric data with asymmetrical distributions were summarized with median (interquartile range). The frequency with 95% CI and percentage were used to describe the categorical variable. For comparison of two proportions with the different sample sizes for reversion proportions, Minitab 19.2 statistical software was used.

Associations between independent variables and outcomes of interest have been estimated using both bivariate and multivariate logistic regression. The strength of the association was measured using the odds ratio and the 95 % confidence interval.

4.7 Ethical clearance

Ethical clearance and a waiver of informed consent was obtained from the scientific and ethics review committee of the center for innovative drug development and therapeutic trials for Africa (CDT Africa). Concerning confidentiality, every effort was made to keep the confidentiality of the study records, and information extracted was identified by a unique study number. The parent study, WHIP3TB clinical trial, had ethical clearance from the national ethics board, Addis Ababa University institutional review board and Ethiopian food and drug authority (EFDA).

4.8 Dissemination plan

The findings of this study will be submitted to Addis Ababa University, College of health science, and CDT-Africa as part of the Master of Science in a clinical trial. It will be presented during the final defense for partial fulfillment of a Master of Science in a clinical trial. It will be communicated through annual students and staff

research conferences, annual clinical trial day and will be sent to journals for publication.

5.0 Results

5.1 Socio-demographic characteristics

The socio-demographic and clinical characteristics of the participants in the study were shown in Table 5.1. A total of 519 participants who had QFT tests performed during enrolment and 12 months of follow-up to 3HP as tuberculosis prophylaxis for 3 months were included in the analysis of this study. More than half of the study participants were females 317 (61.1%). The age range was between 18 and 77 years with a median age of 46 (IQR: 40-52) years.

In assessing the educational level of the study participants, among the 519, participants with no formal education were 95 (18.3%), grade 1 to 7 were 149 (28.7%), Grade 8-12 were 219 (42.2%) and 56 (10.8%) of the study participants were above grade 12. Regarding marital status, 234 (45.1 %) of participants were married, 78 (15 %) were single, 90 (17.3 %) divorced / separate, and 117 (22.6 %) were widowed.

At enrollment, the clinical characteristics of QFT-positive (169/519) and QFT-negatives (350/519) were comparable. The median age and CD4 count among QFT positives at enrollment were 46 (IQR 40-51) and 516 (IQR 332-654) respectively. The median age and CD4 count among QFT negatives at enrollment were 46 (IQR 40-52) and 491 (IQR 326- 666) respectively.

Nearly half of the 256 participants (49.3%) had CD4 counts greater than or equal to 500, while 213 (41.1%) had CD4 counts of 200-500 and only 50 (9.6%) had CD4 counts below 200. Two third of the participants 350 (67.4%) had a history of treatment for tuberculosis one year before enrollment to the study. Most of the

participants 470 (90.6%) did not take IPT prophylaxis one year before enrollment to the study.

Table 5.1: The socio-demographic and clinical characteristics of HIV positive individuals who took 3HP preventive therapy at Zewditu Memorial and Alert Hospitals (June 2017- Sep 2018)

Characteristics		Number	Percent
Sex	Female	317	61.1
	Male	202	38.9
Age (years)	18-27	16	3.1
	28-37	78	15.0
	38-47	206	39.7
	48+	219	42.2
Education status	No school	95	18.3
	Grade 1-7	149	28.7
	Grade 8-12	219	42.2
	Diploma	37	7.1
	Bachelor and above	19	3.7
Marital status	Single	78	15.0
	Married	234	45.1
	Divorced/Separated	90	17.3
	Widowed	117	22.6
CD 4 count	$\leq$ 200	50	9.6
	200-500	213	41.0
	$\geq$ 500	256	49.3
History of TB treatment	No	350	67.4
	Yes	169	32.6
History of IPT	No	470	90.6

Yes	49	9.4

5.2 IGRA reversions after 3HP prophylaxis

IGRA reversion is a change in the QFT result that was positive at enrollment and turned negative at month 12 follow-up. Out of a total of 519 study participants, 169 were QFT positive at enrollment. The IGRA reversion rate among QFT positive patients after taking 3HP prophylaxis once a week was 67/169 (39.6 %; 95% CI 32.5 % to 47.3 %).

In bivariate and multivariate logistic regression analysis, there was no significant association between IGRA reversion and sex, age, CD4 count, history of tuberculosis treatment, and history of IPT prophylaxis (Table 5.2).

Table 5.2: Risk factors for IGRA reversions among HIV positive individuals who took 3HP preventive therapy at Zewditu Memorial and Alert Hospitals (June 2017- Sep 2018)

Characteristics	QFT positive at enrollment N (%)	IGRA reversions N (%)	COR (95% CI)	AOR (95% CI)
Sex				
Female	93 (55.0%)	37 (39.8%)	1	1
Male	76 (45.0%)	30 (39.6%)	0.99 (0.53, 1.83)	1.15 (0.67, 1.98)
Age group				
18-27	3 (1.8%)	0 (0%)	1	1
28-37	26 (15.4%)	6 (23.1%)	0.39 (0.14, 1.09)	0.51 (0.20, 1.28)
38-47	66 (39.1%)	29 (43.9%)	1.03 (0.53, 2.01)	1.85 (0.50, 6.79)
48+	74 (43.8%)	32 (43.2%)	1	
CD4 count				
≤ 200	17 (10.0%)	11 (64.7%)	1	1

200-500	64 (37.9%)	27 (42.2%)	0.40 (0.13, 1.21)	0.55 (0.25, 1.21)
≥ 500	88 (52.1%)	29 (32.9%)	**0.27 (0.09, 0.80)**	0.49 (0.22, 1.07)
History of TB treatment				
No	99 (58.6%)	42 (42.4%)	1	1
Yes	70 (41.4%)	25 (35.7%)	0.75 (0.40, 1.42)	1.18 (0.69, 2.04)
History of IPT				
No	155 (91.7%)	63 (40.7%)	1	1
Yes	14 (8.3%)	4 (28.6%)	0.58 (0.18, 1.95)	0.58 (0.20, 1.69)

COR = Crude Odds Ratio AOR= Adjusted Odds Ratio CI = Confidence Interval.
Bold numbers are statistically significant findings.

5.3 IGRA conversions after 3HP prophylaxis

IGRA conversion means a change in the QFT result that was negative at enrollment and turned positive at follow-up. Out of the total 519 study participants, 350 were QFT negative at enrollment. The proportions of IGRA conversions at 12 months after taking 3HP prophylaxis once a week for 3 months was 66/ 350 (18.9%; 95% CI 15.1% to 23.3%).

In bivariate and multivariate logistic regression analysis, there was no significant association between IGRA conversions and sex, age, CD4 count, history of tuberculosis treatment, and history of IPT prophylaxis (Table 5.3).

Table 5.3: Risk factors for IGRA conversion among HIV positive individuals who took 3HP preventive therapy at Zewditu Memorial and Alert Hospitals (June 2017- Sep 2018)

Characteristics	QFT Negative at enrollment N (%)	IGRA reversions N (%)	COR (95% CI)	AOR (95% CI)
Sex Female	224 (64.0%)	45 (20.1%)	1	1
Male	126 (36.0%)	21 (16.7%)	0.80 (0.45, 1.41)	0.88 (0.48, 1.59)
Age group				
18-27	13 (3.7%)	4 (30.8%)	1	1
28-37	52 (14.9%)	10 (19.2%)	0.54 (0.14, 2.10)	0.55 (0.14, 2.19)
38-47	140 (40.0%)	29 (20.7%)	0.59 (0.17, 2.05)	0.64 (0.18, 2.27)
48+	145 (41.4%)	23 (15.9%)	0.42 (0.12, 1.49)	0.46 (0.13, 1.64)
CD4 count				
≤ 200	33 (9.4%)	5 (15.2%)	1	1
200-500	149 (42.6%)	24 (16.1%)	1.08 (0.38, 3.06)	1.18 (0.41, 3.40)
≥ 500	168 (48.0%)	37 (22.0%)	1.58 (0.57, 4.38)	1.67 (0.59, 4.65)
History of TB treatment				
No	251 (71.7%)	46 (18.3%)	1	1
Yes	99 (28.3%)	20 (20.2%)	1.13 (0.63, 2.03)	1.11 (0.61, 2.02)
History of IPT				
No	315 (90.0%)	64 (20.3%)	1	1
Yes	35 (10.0%)	2 (5.7%)	0.24 (0.06, 1.02)	0.24 (0.05, 1.02)

5.4 Prevalence and associated risk factors for latent tuberculosis infection

The prevalence of latent TB infection among HIV positive individuals at enrollment was 169/519 (32.6%; 95% CI 28.5% to 36.5%). After adjusting for potential confounding variables, the prevalence of LTBI at enrollment was significantly associated with a history of previous tuberculosis treatment at least once before enrollment. Hence the chance of QFT test positivity at enrollment was 1.7 times higher among those HIV positive individuals who had a history of tuberculosis treatment (AOR= 1.7 [95% CI 1.15, 2.52]) compared to those who didn't have a history of tuberculosis treatment. Other factors like Sex, Age, CD4 count, and previous IPT prophylaxis were not significantly related to latent tuberculosis infection at enrollment (Table 5.4).

Table 5.4: Background characteristics and the prevalence of LTBI at enrollment among HIV positive individuals who took 3HP preventive therapy at Zewditu Memorial and Alert Hospitals (June 2017- Sep 2018).

Characteristics	Number of participants N (%)	Prevalence of LTBI N (%)	COR(95% CI)	AOR (95% CI)
Sex				
Female	317 (61.1%)	93 (29.3%)	1	1
Male	202 (38.9%)	76 (37.6%)	1.45 (1.00, 2.11)	1.41(0.95, 2.08)
Age group				
18-27	16 (3.1%)	3 (18.8%)	1	1
28-37	78 (15.0%)	26 (33.3%)	2.17 (0.57, 8.28)	2.14 (0.55, 8.27)
38-47	206 (39.7%)	66 (32.0%)	2.04 (0.56, 7.41)	1.85 (0.50, 6.79)
48+	219 (42.2%)	74 (33.8%)	2.21 (0.61, 8.00)	1.99 (0.54, 7.28)
CD4 count				
$\leq$ 200	50 (9.6%)	17 (34.0%)	1	
200-500	213 (41.1%)	64 (30.1%)	0.83 (0.43, 1.60)	0.86 (0.44, 1.68)
$\geq$ 500	256 (49.3%)	88 (34.4%)	1.02 (0.54, 1.93)	1.10 (0.57, 2.12)
History of TB treatment				
No	350 (67.4%)	99 (28.3%)	1	1
Yes	169 (32.6%)	70 (41.4%)	**1.79 (1.22, 2.63)**	**1.70 (1.15, 2.52)**
History of IPT				
No	470 (90.6%)	155 (33.0%)	1	1
Yes	49 (9.4%)	14 (28.6%)	0.81 (0.42, 1.56)	0.85 (0.43, 1.66)

COR = Crude Odds Ratio AOR= Adjusted Odds Ratio CI = Confidence Interval.

Bold numbers are statistically significant findings.

6.0 Discussion

Interferon-gamma release assays (IGRAs), such as QFT gold plus are becoming the main tools for the diagnosis of latent TB infection (LTBI) (34). IGRA reversion and conversion reactions have been reported for many years whether the patient has received TB preventive therapy or not (6,38).

IGRA reversion and conversion rates for post-prophylaxis treatment with 3HP have not been studied in Ethiopia before, and this finding may, therefore, be used as a basis for further studies. For this study, 519 HIV positive individuals who underwent QFT gold plus testing at enrollment and 12 months after 3HP as prophylaxis therapy were included in the final review. IGRA reversion among positive LTBI patients was higher than IGRA reversion among all study participants, regardless of LTBI status.

Several studies have shown IGRA reversion and conversion during LTBI therapy, but the results were inconsistent depending on the different settings (8,39–42). In a systematic review and meta-analysis of IGRA reversals, a summary reversion rate of 24.9% was reported among those taking TB prophylaxis (6). A comparable result was seen in the previous study in Korea, a low endemic tuberculosis country with a reversion rate of 41.3% (42).

In countries with high tuberculosis burdens such as South Africa and Uganda, IGRA reversion rates after IPT prophylaxis were only 5% and 20.5% respectively (7,8). In contrast to the reversion rates observed in high TB burden countries, a higher IGRA reversion rate of 67/169 (39.9 %) was observed in the current study. The discrepancy in IGRA reversion may be due to the efficacy of Rifapentin added to Isoniazid in the current study.

A previous study in Thailand on IGRA conversion after taking IPT for 9 months showed that the annualized conversion rate was 10% (40). The conversion rate for IGRA was 66/350 (18.9%) in the present study, which was much higher than that observed in Thailand. This difference may be due to the high rate of infection with

mycobacteria tuberculosis in countries with high tuberculosis burdens such as Ethiopia.

According to the recent WHO Guideline for the management of latent Tuberculosis infection, HIV-positive people who have a positive LTBI test benefit more from preventive treatment than those who have a negative LTBI and LTBI test, where possible, can be used to identify such individuals (5).

The prevalence of latent TB infection among HIV positive individuals in this study was 32.6% consistent with other studies in South Africa, where the prevalence of LTBI was 32.9% among HIV-positive patients (25). However, the prevalence of LTBI observed in this study was much lower than in other study conducted in Kampala, Uganda, 47.5% (51). This variation in prevalence may be explained by the fact that the study in Kampala , Uganda, was carried out using a TST test that is known to have been affected by the BCG vaccination status.

The previous history of tuberculosis infection has been significantly associated with latent tuberculosis infection (AOR 1.70 (95% CI 1.15, 2.52). A similar finding has been reported in Korea and Norway, where the occurrence of latent tuberculosis infection has been significantly associated with a history of tuberculosis infection (18,52). However, it was not clear that IGRA positivity in patients with a history of tuberculosis was due to persistent immune responses from previous TB infection (antigen-specific T-memory cells induced by previous TB disease may persist for a long time) or to the presence of living Mycobacterium tuberculosis in the body (52). Previous studies of IGRA positivity among individuals with a history of tuberculosis showed that QFT had a limited role in diagnosing LTBI in patients with a history of tuberculosis infection (52).

Other possible predictors such as sex, age, CD4 count, and history of latent tuberculosis infection was not significantly associated with IGRA reversion, IGRA conversion, or risk of latent tuberculosis infection in this study. Previous LTBI

prevalence studies in high TB burden settings reported that LTBI had a significant positive association with age and male gender (25,51).

7.0 Limitations of the study

This study was a secondary data analysis of a multi-country multi-site clinical trial initially designed to answer a different primary research question. Some of the limitations to be mentioned include that the analysis could only answer questions based on the available data, so some data such as the history of recent close contact with active TB infection have not been collected, even if it could be a predictive factor for IGRA reversion and IGRA conversion.

The other limitation was that the test used to diagnose latent TB was QFT gold plus, which does not differentiate between active TB or latent TB.

8.0 Conclusion

High rate of IGRA reversion for LTBI positives and high conversion rates for LTBI negatives were observed, indicating a higher rate of mycobacterium TB infection among LTBI negative patients despite taking 3HP and a higher reversal rate among LTBI positive patients. Moreover, the IGRA reversion and conversion rates were not significantly associated with sex, age, CD4 count, previous history of TB treatment, and prior history of IPT.

The observed prevalence of LTBI among HIV positive individuals was 32.6%. Which indicates that almost one-third of HIV positive individuals were positive for LTBI. It was noted that the prevalence of latent TB was significantly associated with the history of TB treatment.

9.0 Recommendation

IGRA reversion rate after taking Rifapentin – INH prophylaxis therapy was fairly high even in high tuberculosis burden countries like Ethiopia and the rate of IGRA conversion was high despite taking the tuberculosis prophylaxis. Hence targeted screening approach for diagnosing latent tuberculosis infection in HIV/AIDS patients using appropriate methods before administration of TB preventive therapy might be indicated. However since this study was not controlled study, prospective study with control may be needed to ascertain the true effect of Rifapentin – INH prophylaxis on QFT gold plus reversion and conversion.

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Annex

Annex A: WHO recommended dosages of drugs for the treatment of LTBI

Drug regimen	Dose per kg body weight	Maximum dose
Isoniazid alone, daily for 6 or 9 months	Adults, 5 mg Children, 10 mg (range, 7–15 mg)	300 mg
Daily rifampicin alone for 3–4 months	Adults, 10 mg Children, 15 mg (range, 10–20 mg)	600 mg
Daily isoniazid plus rifampicin for 3–4 months	Isoniazid: Adults, 5 mg Children, 10 mg (range, 7–15 mg) Rifampicin Adults, 10 mg Children, 15 mg (range, 10–20 mg)	Isoniazid, 300 mg Rifampicin, 600 mg
Weekly rifapentine plus isoniazid for 3 months (12 doses)	Individuals aged ≥ 12 years: Isoniazid: 15 mg Individuals aged 2–11 years: isoniazid: 25 mg Rifapentine: 10.0–14.0 kg = 300 mg 14.1–25.0 kg = 450 mg 25.1–32.0 kg = 600 mg 32.1–50.0 kg = 750 mg > 50 kg = 900 mg	Isoniazid, 900 mg Rifapentine, 900 mg

Annex B: Data extraction tool

Data item	Available Value	Missed	Additional notes
Data extraction date			
Participant ID			
Participant ARM			
Age			
Sex			
Marital status			
Education status			
Concomitant disease			
Concomitant medication			
ART start date			
CD4 count			
Viral load			
Previous History of TB			
Latent TB treatment			
Weeks of RIF – INH treatment			
QFT result at enrollment			
QFT result at month 12			