



# **St. Paul's Hospital Millennium Medical College (SPHMMC)**

## **Department of Public Health**

### **Ethiopian Field Epidemiology and Laboratory Training Program**

---

Effect of Isoniazid Preventive Therapy on TB Incidence and Mortality among HIV patients on Highly Active Antiretroviral Treatment in Addis Ababa Public Health Facilities

By  
Enyew Birru (MD)

Submitted to the Department of Public Health, St. Paul's Hospital Millennium Medical College  
in Partial Fulfillment for the degree of Master of Public Health in Field Epidemiology

October, 2019

Addis Ababa

**Aman Yesuf (Ass. Professor of Epidemiology)**

**Temesgen Geleta (BSC, MPH)**

**9<sup>th</sup> October 2019**

**Addis Ababa**

**DECLARATION**

I hereby declare that, this Field Epidemiology compiled body of work is my original work and has not presented for a degree another person in this or any other university and all source material used for this compiled body work have been duly acknowledged.

Name: Enyew Birru

Signature\_\_\_\_\_

Date\_\_\_\_\_

The MPH in Field Epidemiology compiled body work has been submitted for examination with my approval as a university academic advisor

Name:

Signature\_\_\_\_\_

Date\_\_\_\_\_

# **St. Paul's Hospital Millennium Medical College (SPHMMC)**

## **Department of Public Health**

---

**Effect of Isoniazid Preventive Therapy on TB Incidence and Mortality among HIV patients  
on Highly Active Antiretroviral Treatment in Addis Ababa Public Health Facilities**

**BY:**

**Enyew Birru (MD)**

**ETHIOPIA FIELD EPIDEMIOLOGY TRAINING PROGRAM**

**DEPARTMENT OF PUBLIC HEALTH, ST. PAUL'S HOSPITAL MILLENNIUM  
MEDICAL COLLEGE**

**APPROVAL BY EXAMINED BOARD**

\_\_\_\_\_  
Chair person, School Graduate Committee

\_\_\_\_\_  
Advisor

\_\_\_\_\_  
Examiner

\_\_\_\_\_  
Examine

## Acknowledgment

On behalf of my work, I am so grateful to my mentors, Mr. Aman Yesuf and Mr. Temesgen Geleta, who did their mentorship responsibility with courage and purpose on this thesis preparation. I owe my deepest gratitude to MOH, and SPHMMC who enabled me to have a knowledge and skill with their successful coordination and scientific management of the program and for financially sponsoring this thesis work.

I would also like to acknowledge SPHMMC Public health department for their kindly supports and coordination of the program. Finally, I must be thankful to all my families and friends who supported me throughout the preparation this thesis work on all fronts.

## Abstract

**Introduction:** *HIV* is the strongest risk factor for developing tuberculosis (TB) in those with latent or new *Mycobacterium tuberculosis* infection. In Ethiopia, timely initiation of Antiretroviral therapy (ART) and Isoniazid preventive therapy (INH) provision for *HIV* infected patients is recommended by the national TB/*HIV* collaborative activities guideline and its implementation has been started since 2007. However, there is no up to date information to quantify the number of incident TB cases and mortalities averted with proper implementation of this preventive strategy in Addis Ababa public health facilities.

**Objective:** To determine the effect of Isoniazid preventive therapy on incidence of tuberculosis and all-cause mortality among *HIV* infected patients who are on highly active anti-retroviral therapy (HAART) in Addis Ababa public health facilities from May-August 2019

**Methods:** Retrospective cohort study was conducted in selected public health facilities of Addis Ababa city administration among *HIV* patients on HAART enrolled in to the care from July 2012 to July 2017. The sources of data were the routine paper based national ART register, patient medical records and the computer data base. Data was entered on excel 2010, cleaned and exported to SPSS version 24 for analysis. Means, medians, frequencies, and interquartile ranges were employed as descriptive statistical analysis. Incidence rates in person-time are computed for 'incident TB' and all-cause mortality, and IRR is calculated to compare between groups. Multivariable cox-proportional hazards regression is employed to identify factors associated with incident TB cases and all-cause mortality.

**Results:** A total of 930 patients were included in the study of which 57% of the patients were females with a mean age of 42.87 (SD=10.2) years. Overall TB incidence rate was 15.3/1000 (95% CI=11.6-19.8) person-months and INH exposure was found to have marked protection against TB (aHR=0.18; 95% CI=0.09-0.34) and mortality (aHR=0.08; 95% CI=0.02-0.25) in INH exposed patients. INH exposure (aHR=0.21, 95% CI=0.10-0.43), working functional status (aHR=0.24, 95% CI=0.08-0.71) WHO clinical stage 1 (aHR=0.12; 95% CI=0.04-0.41) were factors associated with incident TB cases whereas, INH exposure (aHR=0.07; 95% CI=0.02-0.29), WHO clinical stage 1 (aHR=0.10; 95% CI=0.03-0.39), clinical stage 2 (aHR=0.36; 95% CI=0.13-0.99) and, weight below 50kg (aHR=9.67; 95% CI=1.22-76.80) and 50-59kg (aHR= 9.1; 95% CI=1.15-72.6) were the factors significantly associated with mortality.

**Conclusion:** INH is found very helpful in averting increased TB incidence and mortality among patients on HAART; therefore it is highly recommended to intensify its coverage and timely initiation among *HIV* patients. Earlier identification of *HIV* infected patients by maximizing the community awareness and targeted testing programs in public health facilities will be very helpful to provide the INH prophylaxis timely and curb the progress of the disease and development of TB.

## Table of Contents

|                                                                               |     |
|-------------------------------------------------------------------------------|-----|
| Acknowledgment .....                                                          | 1   |
| Abstract.....                                                                 | iii |
| List of Tables .....                                                          | vi  |
| List of Figures .....                                                         | vi  |
| List of Acronyms and Abbreviations .....                                      | vii |
| 1. Introduction .....                                                         | 1   |
| 1.1 Background .....                                                          | 1   |
| 1.2. Problem Statement.....                                                   | 2   |
| 1.3. Significance of the study .....                                          | 2   |
| 2. Literature Review .....                                                    | 4   |
| 2.1. Effect of Isoniazid Preventive Therapy on Incidence of TB:.....          | 4   |
| 2.2. Effect of Isoniazid Preventive Therapy on Mortality: .....               | 5   |
| 2.3. Determinants of Incident TB cases and mortality among HIV patients:..... | 6   |
| 3. Objective .....                                                            | 8   |
| 3.1. General Objective .....                                                  | 8   |
| 3.2. Specific Objectives .....                                                | 8   |
| 4. Methods.....                                                               | 9   |
| 4.1. Study area and Setting .....                                             | 9   |
| 4.2. Study design and period .....                                            | 9   |
| 4.3. Source population and study population.....                              | 9   |
| 4.4. Sampling procedure and sample size calculation .....                     | 10  |
| 4.5. Data source and data collection procedure:.....                          | 10  |
| 4.6. Variables.....                                                           | 11  |
| 4.7 Inclusion and Exclusion criteria.....                                     | 11  |
| 4.8 Data processing and analysis .....                                        | 12  |
| 4.9 Data quality checks .....                                                 | 13  |
| 4.10 Operational Definition: .....                                            | 13  |
| 4.11 Ethics .....                                                             | 13  |
| 5. Results .....                                                              | 14  |
| 5.1. Socio-demographic characteristics of study groups .....                  | 15  |

|                                                                               |    |
|-------------------------------------------------------------------------------|----|
| 5.2. Clinical characteristics of study groups.....                            | 16 |
| 5.3. TB Incidence rates between INH exposed and non-exposed groups: .....     | 17 |
| 5.4. Incidence of Mortality between INH exposed and non-exposed groups: ..... | 17 |
| 6. Discussion.....                                                            | 22 |
| 7. Conclusion .....                                                           | 25 |
| 8. Recommendations .....                                                      | 26 |
| 9. References .....                                                           | 27 |
| Annexes.....                                                                  | 29 |

## List of Tables

|                                                                                                                                                                                            |    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Table 1: Sample size calculation to assess the effect of INH provision on TB incidence and mortality in Addis Ababa city selected public health facilities, 2019 .....                     | 10 |
| Table 2: Socio-demographic characteristics of HIV patients on HAART at enrollment in Addis Ababa city selected public health facilities by IPT status, 2019 .....                          | 15 |
| Table 3: Baseline clinical characteristics of HIV patients on HAART at enrollment in Addis Ababa city selected public health facilities by IPT status, 2019 .....                          | 16 |
| Table 4: Comparison of TB incidence rates among patients on HAART in Addis Ababa city selected public health facilities based on INH exposure, 2019.....                                   | 17 |
| Table 5: Comparison of patient mortality among HIV patients on HAART in Addis Ababa city selected public health facilities by INH status, 2019.....                                        | 18 |
| Table 6: Cox proportional hazards analysis of factors associated with incident Tuberculosis cases among HIV patients on HAART in Addis Ababa selected public health facilities, 2019 ..... | 20 |
| Table 7: Cox proportional hazards analysis of factors associated with incident deaths among HIV patients on HAART in Addis Ababa selected public health facilities, 2019.....              | 21 |

## List of Figures

|                                                                                                                                                                                                      |    |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Figure 1: Flow diagram showing selection of study participants based on INH exposure status in Addis Ababa city selected public health facilities, 2019.....                                         | 14 |
| Figure 2: Kaplan-Meier probability of hazards function for TB Incidence among HIV patients on HAART in Addis Ababa selected public health facilities by IPT status, 2019; .....                      | 18 |
| Figure 3: Kaplan-Meier probability of hazards function for death Incidence among HIV patients on HAART in Addis Ababa selected public health facilities by IPT status, 2019; Log rank P= 0.000 ..... | 18 |

## List of Acronyms and Abbreviations

|        |                                                |
|--------|------------------------------------------------|
| aHR    | adjusted Hazard Ratio                          |
| BMI    | Body Mass Index                                |
| CI     | Confidence Interval                            |
| CPT    | Cotrimoxazole preventive therapy               |
| EDHS   | Ethiopian Demographic and Health Survey        |
| HAART  | Highly Active Antiretroviral Therapy           |
| INH    | Isoniazid                                      |
| IPT    | Isoniazid Preventive Therapy                   |
| IQR    | Interquartile Range                            |
| IRB    | Institutional Review Board                     |
| IRR    | Incidence Rate Ratio                           |
| LTFU   | Lost to Follow-up                              |
| MDR    | Multi-Drug Resistant                           |
| MUAC   | Mid-Upper Arm Circumference                    |
| NGO    | Non- Governmental Organization                 |
| OI     | Opportunistic Infection                        |
| PLWH   | People Living With HIV                         |
| PY     | Person-Year                                    |
| RVI    | Retroviral Infection                           |
| SPHMMC | Saint Paul Hospital Millennium Medical College |
| TB     | Tuberculosis                                   |
| TST    | Tuberculin Skin Test                           |
| WHO    | World Health organization                      |

# 1. Introduction

## 1.1 Background

Tuberculosis has existed for millennia and remains a major global health problem. In 2015, TB was one of the top 10 causes of death worldwide, ranking above *HIV/AIDS* as one of the leading causes of death from an infectious disease(1). *HIV* is the strongest risk factor for developing tuberculosis (TB) disease in those with latent or new *Mycobacterium tuberculosis* infection. The risk of developing TB is between 20 and 37 times greater in people living with HIV than among those who do not have *HIV* infection(2). For these reasons, regular screening of all *PLWHIV* for active TB disease and provision of either treatment for active disease or preventive therapy, and the provision of earlier ART are essential(3).

In 2004, WHO packaged IPT as one of the 12 collaborative *TB/HIV* activities(4) and repackaged as part of the Three 'I's for *HIV/TB* (Isoniazid preventive treatment, infection control for TB, and intensified case finding) in 2008(5). It also revised its policy on IPT in 2010 reiterating the importance of IPT as a core function of services provided to *PLHIV*. IPT given to *HIV* infected patients without TB disease including those receiving ART, and those who have successfully completed TB treatment for at least 6 months reduces the risk of developing TB by 33–67% for up to 48 months. Evidence also showed that, giving IPT for at least 36 months (as a surrogate for lifelong treatment for *PLHIV*) is beneficial in a setting with high prevalence of TB and a high likelihood of transmission(5).

In Ethiopia, IPT provision for *HIV* infected patients is recommended by the national *TB/HIV* collaborative activities guideline and its implementation has been started since 2007(6). Clinical practice in the country with regard to initiating IPT depends on results of symptom screening, WHO Clinical stage of the patient and whether there is contraindication for IPT or not. *PLHIV* who are completely without symptoms of TB (cough, fever, weight loss, etc.) could be given IPT.

In Addis Ababa, based on the 2016/17 *TB/HIV* sentinel facilities report 78% of the facilities had completed the full course of IPT regimen [10] and another cross-sectional study conducted in 10

facilities of the city reported a third (28.7%) of all interviewed PLWH self-reported that they had been treated with IPT(7).

## 1.2. Problem Statement

In 2017, Worldwide, TB caused an estimated 1.3 million deaths (range, 1.2–1.4 million, 95% CI) among *HIV*-negative people and there were an additional 300,000 deaths from TB (range, 266 000–335 000) among *HIV*-positive people. In total, 8% of the 1.5 million people who were reported to be newly enrolled in *HIV* care in 2017 were diagnosed with TB during the same year(8). On the other hand, Over 35% of *HIV* related deaths are attributed to TB co-infection making TB the leading killer amongst *HIV* infected people (9). Morbidity and mortality from drug-sensitive and drug-resistant TB among *PLHIV* are unacceptably high (10). In Ethiopia in 2018, a total of 172,000 all forms incident TB cases, 28600 deaths and 12,000 TB incident cases among *HIV* positive peoples were reported nationally(8).

A meta-analysis led by WHO found out that HAART reduces the individual risk of TB disease by 65%, irrespective of the CD4 cell count but recent evidence has shown that the combined use of IPT and HAART among *HIV* infected patients significantly reduces the incidence of TB by up to 97% (11). However, uptake of IPT has been relatively low in most developing countries including Ethiopia. Operational difficulties in making TST are sometimes perceived to be a barrier to the provision of IPT, however WHO strongly recommends that in resource constrained settings like Ethiopia, TST shouldn't be a requirement for initiating IPT and that PLWH should be started on IPT following negative symptom based screening(5).

In Ethiopia, there are few facility based studies done to show the effect of IPT on tuberculosis incidence alone or together with HAART by different scholars but there is limited recent data on the effect of this TB preventive strategy in Addis Ababa health facilities, the capital city of Ethiopia. Moreover, there is only a single study done to show the effect of IPT on mortality in Ethiopian setup even-though multiple studies have been done worldwide showing highly variable outcomes.

## 1.3. Significance of the study

This study will be a good source of up to date information for policy makers and implementers to understand the added effect of IPT provision for *HIV* patients on HAART in the prevention of

incident TB cases in Addis Ababa city. It also helps to upgrade the implementation of this preventive strategy by the city health bureau based on evidence. In addition, the study will help to quantify the reduction in all-cause mortality, if any, among HIV infected patients on HAART by providing IPT. Assessing factors related with patient outcomes (i.e. TB incidence and all-cause mortality) will help to identify factors that need to be addressed and direct programmatic activities to focus on the identified problems to decrease TB incidence and mortality in *HIV* patients.

## 2. Literature Review

### 2.1. Effect of Isoniazid Preventive Therapy on Incidence of TB:

A retrospective cohort study was conducted in Dares Salaam region, Tanzania from 2011 to 2014 using secondary data of *HIV* positive adults receiving care and treatment services with a median follow up time of 3.4 years for patients who ever received IPT and 1.3 years among those who never received IPT showed that, a total of 3124 TB cases occurred during 114,926 total person-years of follow up. The overall TB incidence rate was 2.7/100 person-years and patients on IPT had 48% (IRR = 0.52) lower TB incidence rate compared to patients who were not on IPT(12).

In a 4-year prospective comparative study at two *HIV* clinics in central Thailand among ART naïve *HIV*-infected patients aged  $\geq 15$  years conducted from January to December 2004 and followed for 4 years revealed no significant difference between the IPT exposed and non-exposed groups. The incidence of pulmonary TB over 4 years was not significantly different between the IPT and non-IPT groups (0.80 cases vs. 1.76 per 100 person-years [PY],  $P = 0.13$ ). However, the incidence of pulmonary TB in the non-IPT group was significantly higher during the first 6 months (8.60 vs. 0 cases/100 py,  $P = 0.01$ ) and among patients with initial CD4 < 200 (9.41 vs. 0 cases/100 py,  $P = 0.02$ ). The survival analyses demonstrated a protective effect of IPT ( $P = 0.04$ ) for early TB(13).

On the contrary a randomized, double-blind, placebo-controlled trial done in Nairobi, Kenya showed no statistically significant protective effect of daily isoniazid for 6 months. A total of 684 subjects were involved in the study with half of them received isoniazid and half received placebo. The incidence of TB in the isoniazid group was 4.29 per 100 PY of observation and 3.86 per 100 PY of observation in the placebo group, giving an adjusted rate ratio for isoniazid versus placebo of 0.92 (95% CI, 0.49-1.71)(14).

Another meta-analysis and systematic review study assessed ten randomized clinical trials that assigned 7619 *HIV* patients to IPT or placebo group. An overall 35% of TB risk reduction (RR = 0.65) was found in all participants, however, larger benefit of IPT was observed in Tuberculin Skin Test (TST) positive participants, with pooled relative risk reduction of 52%. There was no

statistically significant effect of IPT on TB occurrence in TST negative or unknown participants(15).

Another randomized, double-blind, controlled trial compared isoniazid (INH) with placebo among TST-negative adults with World Health Organization Stage 3 or 4 *HIV* disease. INH/placebo was administered for 12 months by patient-nominated supervisors. In the randomized arms, the incidence of TB was 18/100 person-years (py) in the INH arm and 11.6/100 py in the placebo arm. So the study did not find any association between INH preventive therapy and reductions in incident TB among TST-negative adults with advanced *HIV* disease, though the study had limited statistical power(16).

A retrospective cohort study was conducted from January, 2008 to February 31, 2012 in Jimma University Specialized Hospital (JUSH), Ethiopia. A total of 588 patients on pre-ART care (294 IPT and 294 non-IPT group) were followed retrospectively for a median duration of 24.1 months. During the follow up period, 49 individuals were diagnosed with tuberculosis, giving an overall incidence of 3.78 cases per 100 person year (PY). The incidence rate of TB was 5.06 per 100 PY in non-IPT group and 2.22 per 100 PY in IPT user group(17).

In a multi-centered retrospective cohort study conducted in 14 Addis Ababa public health facilities involving 2,524 patients' chart review between 2007 and 2010 with a mean age of 34.9 revealed that, among all HIV infected patients who were followed for 4106 Person-Years, a total of 277 incident Tuberculosis (TB) cases occurred. TB Incidence Rate was 0.21, 0.86 & 7.18 per 100-PY among IPT completed, in-completed and non-exposed patients, respectively. The adjusted Incidence Rate Ratio (aIRR) among IPT completed vs. non-exposed patients was 0.037(18).

## **2.2. Effect of Isoniazid Preventive Therapy on Mortality:**

Meta-analysis and systematic review study which assessed ten randomized clinical trials involving 7619 *HIV* patients showed that, IPT reduce the risk of all-cause mortality yet statistically non-significant RR = 0.90 although participants who had 12 months of IPT tend to have a reduced risk(15).

Another randomized, double-blind, placebo-controlled trial done in Nairobi, Kenya showed the adjusted rate ratio for tuberculosis for isoniazid versus placebo for tuberculin skin test (TST)

positive subjects were 0.6 and for the TST- negative subjects, 1.23. The adjusted mortality rate ratio for isoniazid versus placebo was 1.18 (95% CI, 0.79-1.75). Overall there was some reduction in mortality, although this was not statistically significant(14).

Another systematic review of 41 articles involving over 45,000 persons living with HIV was done to see the impact of IPT on all-cause mortality. There were a total of 18 studies (9 RCTs, 6 cohort/non-randomized studies, and 3 systematic reviews) that reported on mortality in adults receiving IPT as compared to no IPT (or placebo). Fourteen of these found no significant reduction in all-cause mortality. Of the 4 articles that found a significant mortality reduction with IPT, 2 were conducted exclusively among individuals who were TST positive(19).

Another double-blind placebo controlled RCT that compared 6 months of INH to 36 months of INH among 1,995 *PLHIV* in Botswana. In this setting, the researchers found that the overall benefit of IPT appeared to decline about 200 days after the regimen was completed, and continuing IPT for 36 months resulted in a significant decrease in mortality when compared to 6 months of IPT (aHR 0.32; 0.11–0.90). However, this was only true for participants who were TST positive(20). A similar RCT comparing 6 months of INH plus ethambutol to 36 months of INH alone in India found no significant difference in mortality, irrespective of TST status(21).

A retrospective cohort study was undertaken at Tikur Anbessa Specialized Hospital (TASH) and Zewditu Memorial Hospital (ZMH) on 185 patients receiving IPT (6 months) plus ART and 557 patients receiving ART alone; The mortality cases noted in patients treated by IPT plus ART versus ART alone were 18 (4.5 cases/100 PYs) and 116 (10 cases/100 PYs), respectively. In reference to the ART alone, the IPT plus ART reduced the likelihood of death significantly and median time to death was about 26 months(22).

### **2.3. Determinants of Incident TB cases and mortality among HIV patients:**

Factors associated with higher risk for incident TB included; being male, WHO stage III and IV, being underweight while overweight, obese, having baseline CD4 cell count between 200 and 350 cells/ $\mu$ l and CD4 count above 350 cells/ $\mu$ l were associated with lower risk of developing TB(12).

In other study Gender, residence area, employment status, baseline WHO stage of the disease (AIDS) and level of CD4 counts were identified as risk factors for TB incidence. The aIRR

among patients who took Highly Active Anti- Retroviral Therapy (HAART) with IPT compared to those who took HAART alone was 0.063 (95% CI 0.035-0.104). IPT significantly reduced occurrence of active TB for 3 years, so the study concludes that, its implementation should be further strengthened in the country(18).

Predictors of higher TB risk were: being on clinical WHO stage III/IV (adjusted hazard ratio (AHR = 3.05, 95% confidence interval (CI): 1.61, 5.81); non-IPT user (AHR = 2.02, 95% CI: 1.04, 3.92); having CD4+ cell count less than 350 cells/ $\mu$ l (AHR = 3.16, 95% CI: 1.04, 3.92) and between 350–499 cells/ $\mu$ l, (AHR = 2.87; 95% CI: 1.37 - 6.03) and having episode of opportunistic infection (OI) in the past (AHR = 2.41, 95% CI: 1.33-4.34)(17).

In the retrospective cohort study done in Addis Ababa, WHO stage IV (aHR 2.42: 95% CI 1.42–4.11), CD4 values 350cells/mm<sup>3</sup> (aHR 0.52; 95% CI 0.28–0.94), adherence to ART (aHR 0.12; 95% CI 0.08–0.20), primary levels of education (aHR 2.20; 95% CI 1.07–4.52); and alcohol consumption (aHR 1.71; 95% CI 1.04–2.81) were factors strongly associated with mortality(22).

### 3. Objective

#### 3.1. General Objective

- ❖ To determine the effect of Isoniazid preventive therapy on incidence of tuberculosis and all-cause mortality among *HIV* patients on HAART in Addis Ababa public health facilities from May-August 2019.

#### 3.2. Specific Objectives

- ❖ Primary Objectives
  - To determine the effect of Isoniazid preventive therapy on the incidence of tuberculosis among *HIV* patients on HAART in Addis Ababa city public health facilities from
  - To determine the effect of Isoniazid preventive therapy on all-cause mortality among *HIV* patients on HAART in Addis Ababa city public health facilities
- ❖ Secondary Objectives
  - To identify factors associated with increased incidence of Tuberculosis among *HIV* patients on HAART in Addis Ababa public health facilities
  - To identify factors associated with increased incidence of Mortality among *HIV* patients on HAART in Addis Ababa public health facilities

## 4. Methods

### 4.1. Study area and Setting

Addis Ababa, Ethiopia's sprawling capital in the highlands bordering the Great Rift Valley is the country's commercial and cultural hub. It was founded in 1886 and has a population of 2,739,551 according to the last census in 2007. It is where the African union headquarters, United Nations Economic commission for Africa as well as various other continental and international organizations are based. It has a subtropical highland climate with temperature differences of 10c and an elevation of 2,200 meters(23).

As of march 2019, the city administration is providing *HIV* care and treatment service to 93, 316 clients with its 79 health centers, 11 hospitals, 14 NGO ART sites and 25 private hospitals and medical centers(24).

### 4.2. Study design and period

Retrospective cohort study design was employed for this study and it includes clients who enrolled in to the treatment and care from 8<sup>th</sup> July 2012-7<sup>th</sup> July 2017 and their outcome was followed until the censoring date (7<sup>th</sup> July 2019). Data collection was done from July-August 2019.

### 4.3. Source population and study population

#### **Source Population:**

All clients enrolled into *HIV* care and treatment program and on HAART in three randomly selected public health facilities of Addis Ababa city, namely Zewditu memorial hospital, Minilik 2<sup>nd</sup> referral hospital and Semein health center.

#### **Study Population:**

Randomly selected HIV clients on HAART enrolled to the treatment and care program from 8<sup>th</sup> July 2012 to 7<sup>th</sup> July 2017 in the three selected public health facilities which includes Zewditu Memorial Hospital, Dagmawi Minilik Hospital and Semein Health center.

#### 4.4. Sampling procedure and sample size calculation

Sample size was determined using sample size determination formula for cohort studies using Statcalc, Epi-info version 7.2.1.0. Sample size was determined both for Tuberculosis incidence and incident mortality cases and the maximum of the two sample size was taken for this study. For sample size calculation the following conditions were considered;

$\alpha = 0.05$  (two tailed)      Power = 80%      Proportion of cases to controls = 1:1

**Table 1: Sample size calculation to assess the effect of INH provision on TB incidence and mortality in Addis Ababa city selected public health facilities, 2019**

| Variables           | Incidence for INH exposed | Incidence for INH non-exposed | n1  | n2  | Total n |
|---------------------|---------------------------|-------------------------------|-----|-----|---------|
| TB incidence        | 0.6/100 person-years (25) | 3.4/100 person-years (25)     | 460 | 460 | 920     |
| Mortality incidence | 4.5/100 person-years (21) | 10/100 person-years (21)      | 384 | 384 | 768     |

To date, 11 hospitals and 79 health centers are providing *HIV* care and treatment services in Addis Ababa city. From these public health facilities, two hospitals namely Zewditu Memorial hospital and Dagmawi Minilik hospital and one health center namely Semein health center were selected randomly for this study. All INH exposed patients who were on HAART during the specified period were included as exposure group, whereas randomly selected equal numbers of patients with no history of INH exposure during the specified period were included as the non-exposed group.

#### 4.5. Data source and data collection procedure:

The main sources of data were the ART register, which is the routine paper-based patient record system, the patient's medical record and the smart care or the computer ART data register. Data were collected from all clients enrolled into the care and treatment from 8<sup>th</sup> July 2012 – 7<sup>th</sup> July 2017 and date of censoring for the follow-up was 7<sup>th</sup> July 2019. Data collection was done by two trained nurses by using data abstraction checklist adopted from another similar study done elsewhere and it was supervised by the main researcher.

## 4.6. Variables

### Dependent Variables

- ❖ TB
- ❖ Death

### Independent variables

- Isoniazid Preventive Therapy (INH)- main exposure variable
- Socio-demographic variables (age, sex, religion, marital status, education)
- Clinical variables (Weight, Functional status, WHO clinical stage, CD4 count, viral load, drug regimen, follow-up status and adherence)

## 4.7 Inclusion and Exclusion criteria

### Inclusion criteria:

- ❖ **Exposed:** All randomly selected *HIV* clients on HAART in the selected health facilities enrolled into the care and treatment center from 8<sup>th</sup> July 2012 to 7<sup>th</sup> July 2017 and completed the 6 month INH prophylaxis
- ❖ **Not exposed:** All *HIV* clients on HAART in the selected health facilities enrolled into the care and treatment center from 8<sup>th</sup> July 2012 to 7<sup>th</sup> July 2017 and not exposed to a single dose of INH during the specified period

### Exclusion criteria:

- Patients not screened for TB, those who have active TB and on treatment at time of enrollment
- Patients with incomplete data on important variables
- All transfer-in cases
- All pediatric clients (Age below 18 years)

## 4.8 Data processing and analysis

Data were entered on excel 2010 worksheet, cleaned and exported to SPSS version 24 for analysis. Descriptive statistics such as means (SD) and medians (IQR) were used to summarize continuous variables. Frequency and proportion were used for categorical variables.

Mann-Whitney test was used to compare the median weight and CD4 count. Chi square test was used to compare the proportions in socio-demographic characteristics and clinical characteristics of the patients between exposed and non-exposed groups.

Overall tuberculosis incidence rate was calculated as the number of TB cases per 1000 person-months and incidence rate was calculated for IPT exposed group and non-exposed group independently. Person-time at risk of TB was accrued from the day of starting on HAART until death; transfer out to other facility; loss to follow-up (LTFU); develop Tuberculosis, last date of patient visit to clinic or 7<sup>th</sup> July 2019 (i.e. censoring date) whichever occurred first. Incidence rate ratio was computed to compare incidence rate between the exposed and non-exposed group. Mortality rates (MR) per 1000 person-months (PMs) of follow-up was employed to determine rates of all-cause mortality. Person-time at risk of death is accrued from the date of starting on HAART to the date of death, lost to follow-up or last date of patient visit whichever occurred first.

Kaplan-Meier hazards function plots was used to calculate the crude effect of exposed and non-exposed groups on hazards probabilities to acquire TB and is compared using the log rank test. Multivariable Cox proportional hazards regression model is used to obtain the factors (exposures) associated with incident TB cases. The model is constructed by adding one variable at a time. The decision to keep a variable in the model was done if P-value was below 0.15. Model fitness is checked with Proportional hazards model assumptions. Kaplan Meir hazards function plots was done to compare overall survival rates between the two groups. Cox regression was done to determine the association between different socio-demographic and clinical variables (age, sex, CD4 count, viral load, WHO clinical stage, baseline functional status, BMI, INH status and ART adherence) on all-cause mortality..

## 4.9 Data quality checks

Data were collected by trained health professionals. Half day on site training was given on the procedure of data collection to the data collectors. Piloting of the data collection tool was done in one health center after IRB approval was obtained for data collection. The data collection was supervised by the principal investigator and co-investigator daily and double data entry was done by data clerks for 10% of randomly selected data to cross-check for consistency and any errors on data entry.

## 4.10 Operational Definition:

**INH Exposed:** All clients included in the study and had completed the 6 month Isoniazid prophylaxis

**Incident TB cases:** All clients included in the study and are confirmed to develop tuberculosis and registered as positive for Tuberculosis on the registry/medical card before the date of censoring.

**All-cause mortality:** All clients included in the study and who died while on follow-up and registered as died on the ART register/medical card before the censoring date.

## 4.11 Ethics

The protocol had been submitted to SPHMMC IRB for approval. Once approval was obtained support letter was sought from Addis Ababa health bureau to the different health facilities included on the study. Oral consent was obtained from the hospital administration based on the support letter obtained from the health bureau before data collection was started. Oral consent was also taken from each department focal person's. Data collection was kept anonymous and patient identification was done only by their MRN and unique identifier numbers. Data was presented in aggregate form and no mention of information specific to the study personnel was included on this study.

## 5. Results

A total of 930 randomly selected HIV patient medical records that were enrolled and started on HAART in three public health facilities (two hospitals and one health center) of Addis Ababa city were revised. Among them half of the patients (i.e. 465 patients) had INH exposure and the remaining half didn't have INH exposure after started on HAART. Most of the patients were females (57%) and the mean age of the patients was 42.87 (SD =10.2). A larger group of the patients were in the age range of 35-44 years accompanying 40% of the cases whereas all the other entire age groups make up only 60% of the study population.

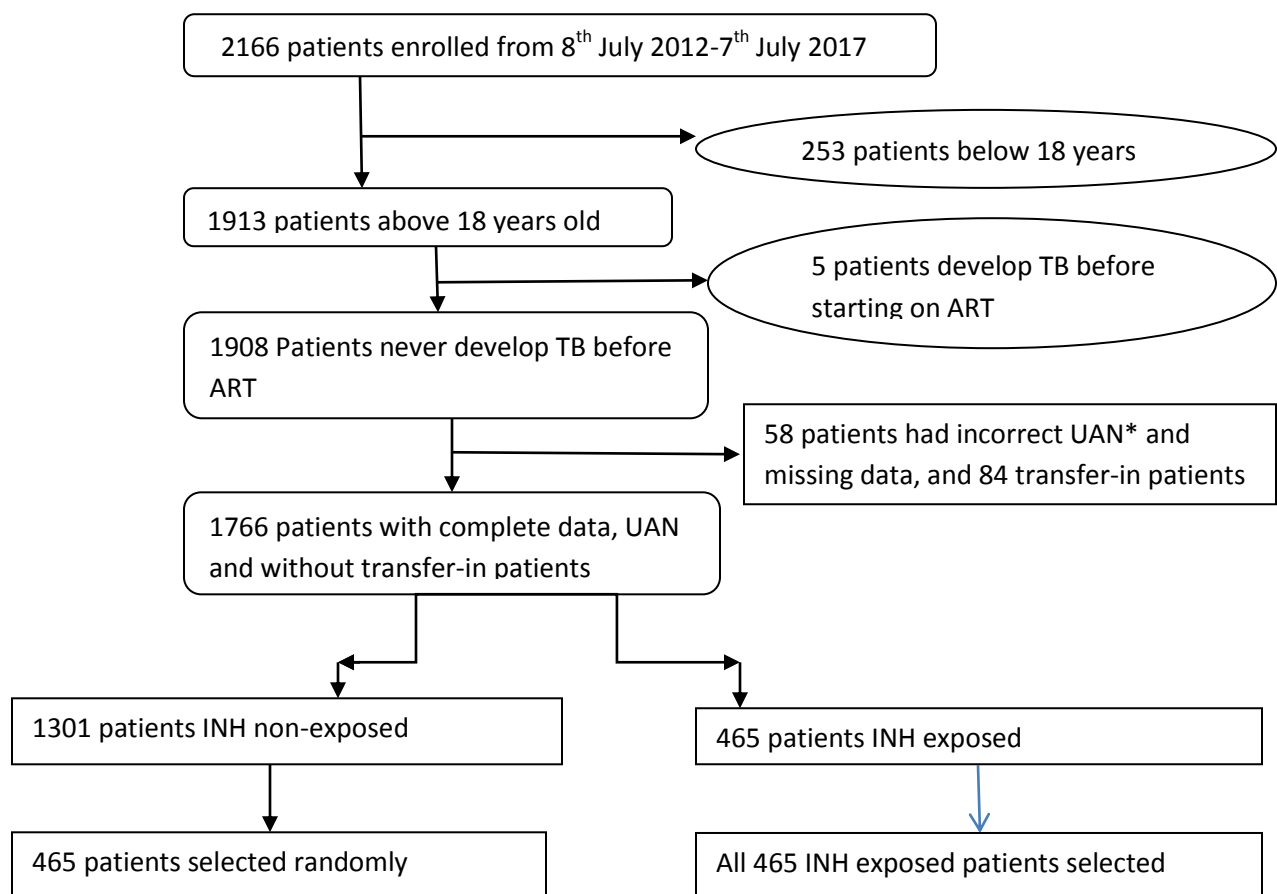


Figure 1: Flow diagram showing selection of study participants based on INH exposure status in Addis Ababa city selected public health facilities, 2019

## 5.1. Socio-demographic characteristics of study groups

Compared to the other sub-city's most of the patients came from Kirkose sub-city (30%) while 398 (66%) of the patients were from the other nine sub-cities of Addis Ababa but only 22 (3.7%) patients were from outside Addis Ababa. From a total of 665 medical records whose literacy level have been recorded, two-third (421) of the patients had completed secondary school and above with only 51 (7.7%) patients not attending any kind of formal school. Orthodox Christian followers constitute 642 (85%) of the patients with the other entire religions making up only 15% of the group. From 647 medical cards whose marital status has been obtained, 278 (43%) patients had married and 195 (30%) patients have never married. Comparison was made between INH exposed and a non-exposed group based on their socio-demographic status, and a significant difference between the INH exposed and non-exposed groups was seen on their religious group status, literacy level and marital status.

**Table 2: Socio-demographic characteristics of HIV patients on HAART at enrollment in Addis Ababa city selected public health facilities by IPT status, 2019**

| Variable             | Total<br>n (%) | INH exposed;<br>n=465 | INH not exposed;<br>n=465 | X <sup>2</sup> P-value |
|----------------------|----------------|-----------------------|---------------------------|------------------------|
| Mean age (SD)        | 42.87 (10.2)   | 42.37 (9.53)          | 43.38 (10.88)             |                        |
| Age category (years) |                |                       |                           | 0.068                  |
| 15-24                | 28 (3.0)       | 11                    | 17                        |                        |
| 25-34                | 194 (20.9)     | 97                    | 97                        |                        |
| 35-44                | 377 (40.5)     | 205                   | 172                       |                        |
| 45+                  | 329 (35.4)     | 150                   | 179                       | 0.14                   |
| Sex                  |                |                       |                           | 0.84                   |
| Male                 | 405 (43.5)     | 204                   | 201                       |                        |
| Female               | 525 (56.5)     | 261                   | 264                       |                        |
| Religion             |                |                       |                           | 0.000                  |
| Orthodox             | 642(69.0)      | 346                   | 296                       |                        |
| Muslim               | 62 (6.7)       | 32                    | 30                        |                        |
| Other                | 51 (5.5)       | 42                    | 9                         |                        |
| Marital status       |                |                       |                           | 0.000                  |
| Married              | 278 (29.9)     | 174                   | 104                       |                        |
| Never married        | 195 (20.9)     | 154                   | 41                        |                        |
| Other                | 174 (18.7)     | 104                   | 70                        |                        |
| Education            |                |                       |                           | 0.000                  |
| No formal education  | 51 (5.5)       | 22                    | 29                        |                        |
| primary              | 193 (20.8)     | 124                   | 69                        |                        |
| Secondary            | 305 (32.8)     | 174                   | 131                       |                        |
| Tertiary             | 116 (12.5)     | 63                    | 53                        |                        |
| Address              |                |                       |                           | 0.45                   |
| Kirkose              | 179            | 91                    | 88                        |                        |
| Other sub-city       | 398            | 180                   | 218                       |                        |
| Out of A.A.          | 22             | 10                    | 12                        |                        |

Some variables had missing records

## 5.2. Clinical characteristics of study groups

The clinical characteristics of the study groups shows that, the median CD4 count of the patients was 187 (IQR=92-316) and just more than half the patients (53%) had a CD4 count of less 200, however, only 168 (19%) patients had CD4 count above 350. Around two-third (602) of the patients have been either WHO stage 1 or stage 2 at time of enrollment. The baseline median weight of the patients was 60Kg (IQR=51-68Kg) with patients below 50Kg and above 70 Kg constitute quarter of the total study population each. Baseline BMI was computed for patients with complete medical records for height and was found out that 310 (55%) of them were in the normal range of BMI. About 131 (23%) of the patients were either under-weight or obese with a mean BMI of 22.54 (SD=4.5). Around 821 (90%) of the patients had a working functional status at time of enrollment with only 32 (3.5%) patients being bed-ridden.

By the end of the follow-up period on this study, about 699 (85%) of the study participants were still alive on ART with the remaining 15% patients being either dropped from follow-up, lost, transferred out to other facility or dead. It is also shown that, 91% of INH exposed patients were alive on ART at censoring date while only 61.5% of non-exposed study populations alive on ART. About 817 (89%) patients had started on 'TDF-3TC-EFV' regimen at enrollment with remaining patients started on other adult regimens. By the end of the study follow-up, about 55 patients have developed TB after started on HAART with or without INH exposure whereas a sum of 32 patients were dead. When INH exposed and non-exposed groups are compared based on their baseline clinical characteristics, there was a significant difference between the two groups based on all measures except on their weight ( $p=0.28$ ), regimen ( $p=0.076$ ) and Viral load status ( $p=0.84$ ).

**Table 3: Baseline clinical characteristics of HIV patients on HAART at enrollment in Addis Ababa city selected public health facilities by IPT status, 2019**

| Variable         | Total<br>n (%) | INH exposed;<br>n=465 | INH not exposed;<br>n=465 | X <sup>2</sup> P-value |
|------------------|----------------|-----------------------|---------------------------|------------------------|
| Function         |                |                       |                           | 0.000                  |
| Working          | 821 (88.3)     | 424                   | 397                       |                        |
| Ambulatory       | 63 (6.8)       | 26                    | 37                        |                        |
| Bedridden        | 32 (3.4)       | 5                     | 27                        |                        |
| Weight (Kg)      |                |                       |                           | 0.28                   |
| <50              | 214 (23.0)     | 103                   | 111                       |                        |
| 50-59            | 227 (24.4)     | 112                   | 115                       |                        |
| 60-69            | 239 (25.7)     | 141                   | 98                        |                        |
| 70+              | 201 (21.6)     | 104                   | 97                        |                        |
| Median Wt. (IQR) | 60 (51-68)     | 60 (52-68)            | 57 (50-68)                | 0.13                   |
| Regimen          |                |                       |                           | 0.076                  |
| 1e               | 817 (65.9)     | 399                   | 418                       |                        |
| Other            | 105 (10.5)     | 63                    | 42                        |                        |
| Follow-up status |                |                       |                           | 0.000                  |

|                  |                |              |               |              |       |
|------------------|----------------|--------------|---------------|--------------|-------|
|                  | Alive on ART   | 699 (75.2)   | 413           | 286          |       |
|                  | Dropped        | 126 (13.5)   | 19            | 107          |       |
|                  | Other          | 94 (10.1)    | 22            | 72           |       |
| VL               |                |              |               |              | 0.84  |
|                  | Not suppressed | 905 (97.3)   | 453           | 452          |       |
|                  | Suppressed     | 25 (2.7)     | 12            | 13           |       |
| Adherence        |                |              |               |              | 0.000 |
|                  | Not good       | 532 (57.2)   | 218           | 314          |       |
|                  | Good           | 398 (42.8)   | 247           | 151          |       |
| CD4              |                |              |               |              | 0.000 |
|                  | <200           | 467 (50.2)   | 224           | 243          |       |
|                  | 200-350        | 243 (26.1)   | 139           | 104          |       |
|                  | >350           | 168 (13.5)   | 91            | 77           |       |
| Median CD4 (IQR) |                | 187 (92-316) | 203 (106-325) | 166 (81-305) | 0.018 |
| WHO Stage        |                |              |               |              | 0.03  |
|                  | Stage 1        | 374 (40.2)   | 199           | 175          |       |
|                  | Stage 2        | 228 (24.5)   | 125           | 103          |       |
|                  | Stage 3        | 165 (17.7)   | 74            | 91           |       |
|                  | Stage 4        | 129 (13.9)   | 52            | 77           |       |

Some variables had missing records

### 5.3. TB Incidence rates between INH exposed and non-exposed groups:

The total follow-up time for TB incidence was 43,117 months with 24,958 months being contributed by INH exposed patients and the rest 18,159 months by the non-INH group. The median follow-up time for TB incidence among INH exposed and non-exposed group was 58 (IQR=43-69) months and 39 (IQR=22-63) months respectively. Overall TB incidence rate was 15.3/1000 person-months (95%CI= 11.6-19.8) and being INH exposed after started on HAART is 82% (95% CI =0.09-0.34) protective compared to non-exposed groups.

**Table 4: Comparison of TB incidence rates among patients on HAART in Addis Ababa city selected public health facilities based on INH exposure, 2019**

| INH status | No of TB cases | Total Person months (TPM) | Incidence rate per 1000 Pm (95%CI) | IRR (95%CI)      |
|------------|----------------|---------------------------|------------------------------------|------------------|
| No INH     | 44             | 18,159                    | 29.8 (21.9-39.6)                   | 1.0              |
| INH        | 11             | 24,958                    | 5.2 (2.7-9)                        | 0.18 (0.09-0.34) |
| Total      | 55             | 43,117                    | 15.3 (11.6-19.8)                   |                  |

### 5.4. Incidence of Mortality between INH exposed and non-exposed groups:

The total follow-up time for death incidence was 44,283 months with INH exposed patients constituting 25,197 months of the follow-up period. The median follow-up period for death among INH exposed and non-exposed group was 58 months (IQR=43-69) and 39 months (IQR=22-63) respectively. The overall

incidence of mortality was 8.5/1000 person-months (95% CI =5.97-11.97). INH exposure had 92% (p5% CI; 0.02-0.25) protection against death compared to patients who had no exposure for INH.

**Table 5: Comparison of patient mortality among HIV patients on HAART in Addis Ababa city selected public health facilities by INH status, 2019**

| IPT status | No of deaths | Total person months (TPM) | Incidence rate per 1000PM (95%CI) | IRR (95%CI)      |
|------------|--------------|---------------------------|-----------------------------------|------------------|
| No IPT     | 29           | 17,920                    | 18.2 (12.4-25.8)                  | 1.0              |
| IPT        | 3            | 25,197                    | 1.4 (0.36-3.83)                   | 0.08 (0.02-0.25) |
| Total      | 32           | 44,283                    | 8.5 (5.97-11.97)                  |                  |

Comparison of the hazards ratio of patients for incident TB cases at the end of the follow-up period between INH exposed and non-exposed group is depicted in figure 1 below. INH non-exposed patients had higher probability of acquiring TB at the end of the follow-up period compared to INH exposed patients (log rank P=0.000).

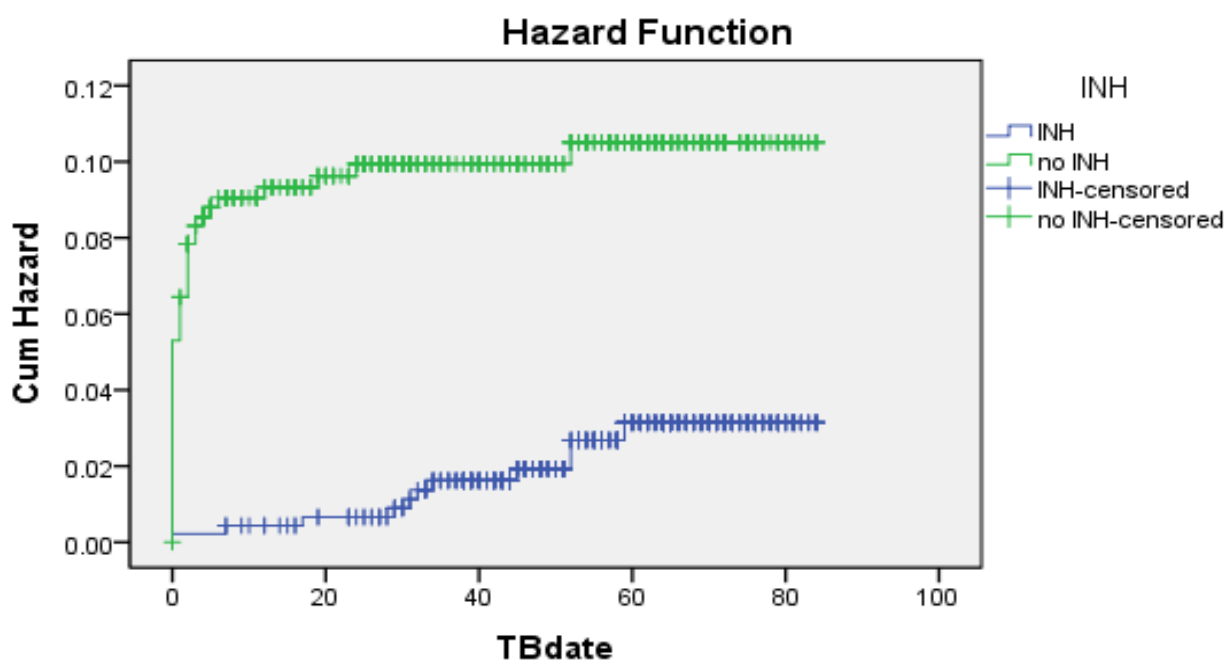


**Figure 2: Kaplan-Meir probability of hazards function for TB Incidence among HIV patients on HAART in Addis Ababa selected public health facilities by IPT status, 2019;**

**Log rank P= 0.000**

Kaplan-Meir probability of survival functions for patient mortality showed that, INH non-exposed patients had lesser survival at the end of the follow-up compared to INH exposed patients (Log rank P=0.000).

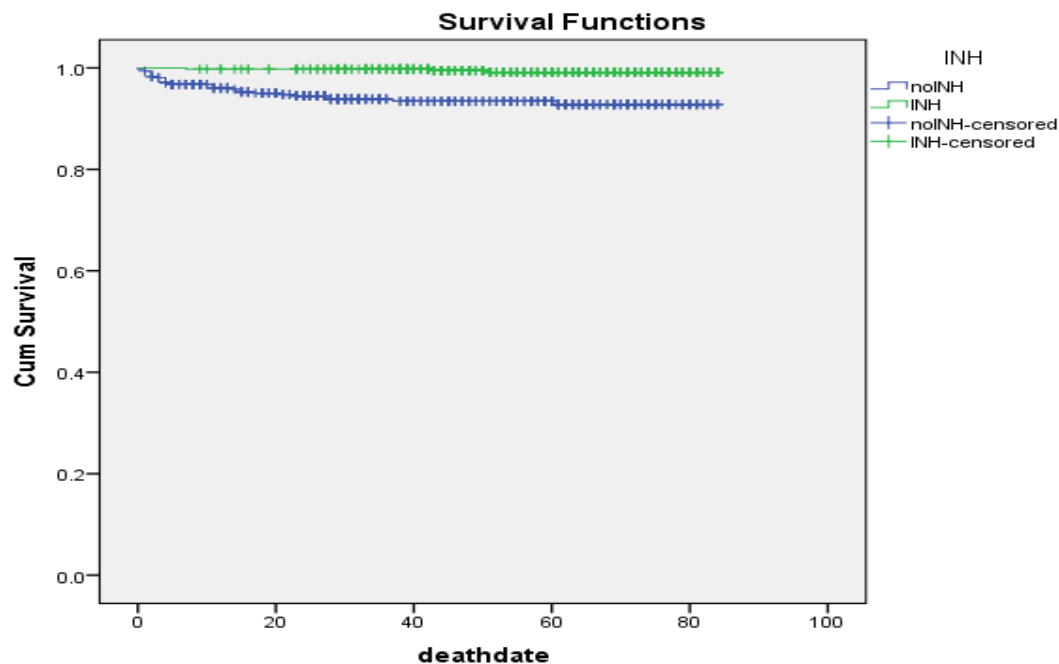


**Figure 3: Kaplan-Meier probability of survival functions for mortality among HIV patients on HAART in Addis Ababa selected public health facilities by IPT status, 2019**

**Log rank P= 0.000**

### **Cox Proportional hazards model**

A number of socio-demographic characteristics and clinical variables were entered into bivariate analysis and assessed for association with ‘time to TB incidence’ using cox-regression analysis. Clinical characteristics of the patients including CD4 level below 200, patient weight below 50kg and 50-59 kg and not having good adherence for HIV treatment were associated with increased risk of incident TB cases whereas having viral suppression, exposure for INH, being alive on ART at the end of the follow-up period, baseline WHO clinical staging of stage 1 and stage 2 and having a working or ambulatory status at enrollment were found to be protective for TB incidence. Other demographic and clinical variables including age, sex, marital status; education level and drug regimen were not associated with TB incidence.

On the multivariable analysis only few clinical variables were added significantly to the model. On this model INH exposed patients were found to be 79% (95% CI=0.10-0.43) protected against TB incidence compared to non-exposed patients after controlling for CD4 level, weight, VL status, adherence on HAART, follow-up status, WHO clinical stage and functional status of the patient. Similarly having a

baseline clinical profile of WHO clinical stage 1 and working functional status were found 88% (95% CI=0.04-0.41) and 76% (95% CI= 0.08-0.71) protective against TB incidence compared to WHO stage 4 and bed-ridden functional patient status respectively. But none of the patient's clinical characteristics was found having increased risk for TB incidence.

**Table 6: Cox proportional hazards analysis of factors associated with incident Tuberculosis cases among HIV patients on HAART in Addis Ababa selected public health facilities, 2019**

| Variable                | TB (%)    | No TB (%)  | Unadjusted |            | Adjusted |            |
|-------------------------|-----------|------------|------------|------------|----------|------------|
|                         |           |            | HR         | 95% CI     | HR       | 95% CI     |
| <b>INH</b>              |           |            |            |            |          |            |
| <b>No</b>               | 44 (9.5)  | 421 (90.5) | 1.0        |            | 1.0      |            |
| <b>Yes</b>              | 11 (2.4)  | 454 (97.6) | 0.22       | 0.11-0.43* | 0.21     | 0.10-0.43* |
| <b>CD4</b>              |           |            |            |            |          |            |
| <b>&lt;200</b>          | 36 (7.7)  | 431 (92.3) | 2.6        | 1.0-6.65*  | 0.9      | 0.33-2.49  |
| <b>200-350</b>          | 10 (4.1)  | 233 (95.9) | 1.3        | 0.46-3.9   | 1.0      | 0.36-3.20  |
| <b>&gt;350</b>          | 5 (2.9)   | 163 (97.1) | 1.0        |            | 1.0      |            |
| <b>Weight (Kg)</b>      |           |            |            |            |          |            |
| <b>&lt;50</b>           | 17 (7.8)  | 201 (92.2) | 3.26       | 1.2-8.85*  | 1.9      | 0.61-6.35  |
| <b>50-59</b>            | 17 (7.4)  | 214 (92.6) | 3.16       | 1.2-8.39*  | 2.2      | 0.79-6.12  |
| <b>60-69</b>            | 9 (3.7)   | 235 (96.3) | 1.0        |            | 1.0      |            |
| <b>70+</b>              | 7 (3.4)   | 200 (96.6) | 1.37       | 0.4-4.3    | 1.3      | 0.35-4.80  |
| <b>VL</b>               |           |            |            |            |          |            |
| <b>Unsuppressed</b>     | 51 (5.6)  | 854 (94.4) | 1.0        |            | 1.0      |            |
| <b>Suppressed</b>       | 4 (16)    | 21 (84)    | 0.6        | 0.36-0.99* | 0.80     | 0.26-2.51  |
| <b>Adherence</b>        |           |            |            |            |          |            |
| <b>Good</b>             | 15 (3.8)  | 383 (96.2) | 1.0        |            | 1.0      |            |
| <b>Not good</b>         | 40 (7.5)  | 491 (92.5) | 1.5        | 1.15-2.08* | 1.24     | 0.59-2.61  |
| <b>Follow-up status</b> |           |            |            |            |          |            |
| <b>Alive on ART</b>     | 34 (4.9)  | 665 (95.1) | 0.43       | 0.2-0.9*   | 0.26     | 0.03-2.11  |
| <b>Dropped</b>          | 13 (10.3) | 113 (89.7) | 1.18       | 0.49-2.85  | 1.34     | 0.51-3.50  |
| <b>Others</b>           | 8 (8.5)   | 86 (91.5)  | 1.0        |            | 1.0      |            |
| <b>WHO Stage</b>        |           |            |            |            |          |            |
| <b>Stage 1</b>          | 4 (1.1)   | 370 (98.9) | 0.06       | 0.02-0.18* | 0.12     | 0.04-0.41* |
| <b>Stage 2</b>          | 17 (7.5)  | 211 (92.5) | 0.43       | 0.22-0.83* | 0.93     | 0.40-2.15  |
| <b>Stage 3</b>          | 15 (9.1)  | 150 (90.9) | 0.56       | 0.28-1.1   | 0.77     | 0.35-1.71  |
| <b>Stage 4</b>          | 19 (14.7) | 110 (85.3) | 1.0        |            | 1.0      |            |
| <b>Function</b>         |           |            |            |            |          |            |
| <b>Working</b>          | 38 (4.6)  | 783 (95.4) | 0.11       | 0.06-0.22* | 0.24     | 0.08-0.71* |
| <b>Ambulatory</b>       | 6 (9.5)   | 57 (90.5)  | 0.26       | 0.09-0.71* | 0.31     | 0.09-1.08  |
| <b>Bed-ridden</b>       | 10 (31.3) | 22 (68.7)  | 1.0        |            | 1.0      |            |

\* Significant factors

Patient's demographic and clinical characteristics were also assessed against death incidence with a cox-regression. On the bivariate analysis, the entire patient's profile was analyzed but only few variables were associated with incident mortality cases. Here, INH exposure, age group between 35-44 years and WHO clinical stage 1 and 2 were protective whereas weight below 50 kg, 50-59kg and 70+ kg had increased risk for incident deaths during the follow-up period.

On the multivariable analysis it is observed that, Patient's exposure for INH was 93% (95% CI= 0.02-0.29) protective from death compared to non-exposed patients. Age group 25-34 years, baseline WHO

clinical staging of stage 1 and stage 2 were also 91% (95% CI=0.01-0.80), 90% (95% CI= 0.03-0.39) and 64% (95% CI= 0.13-0.99) protective from death compared to age group above 45 years and WHO clinical stage 4 respectively. On the other hand, patient weight below 50kg and 50-59kg is found to have 9.7 times (95% CI= 1.22-76.8) and 9.1 times (95% CI=1.15-72.6) increased risk for death incidence compared to patient weight 60-69kg.

**Table 7: Cox proportional hazards analysis of factors associated with incident deaths among HIV patients on HAART in Addis Ababa selected public health facilities, 2019**

| Variable           |                | Death (%) | No death (%) | Unadjusted |            | Adjusted |             |
|--------------------|----------------|-----------|--------------|------------|------------|----------|-------------|
|                    |                |           |              | HR         | 95% CI     | HR       | 95% CI      |
| <b>INH</b>         | <b>No</b>      | 29 (6.2)  | 436 (93.8)   | 1.0        |            | 1.0      |             |
|                    | <b>Yes</b>     | 3 (0.6)   | 462 (99.4)   | 0.09       | 0.03-0.29* | 0.07     | 0.02-0.29*  |
| <b>Age</b>         |                |           |              |            |            |          |             |
|                    | <b>15-24</b>   | 0         | 26 (100)     | 0.0        |            | 0.0      |             |
|                    | <b>25-34</b>   | 3 (1.7)   | 170 (98.3)   | 0.30       | 0.09-1.04  | 0.09     | 0.01-0.80*  |
|                    | <b>35-44</b>   | 9 (2.4)   | 365 (97.6)   | 0.43       | 0.19-0.96* | 0.58     | 0.25-1.32   |
|                    | <b>45+</b>     | 20 (5.5)  | 344 (94.5)   | 1.0        |            | 1.0      |             |
| <b>Weight (Kg)</b> |                |           |              |            |            |          |             |
|                    | <b>&lt;50</b>  | 11 (5)    | 207 (95)     | 10.65      | 1.38-82.5* | 9.67     | 1.22-76.80* |
|                    | <b>50-59</b>   | 9 (3.9)   | 222 (96.1)   | 10.07      | 1.28-79.5* | 9.15     | 1.15-72.58* |
|                    | <b>60-69</b>   | 1 (0.4)   | 243 (99.6)   | 1.0        |            | 1.0      |             |
|                    | <b>70+</b>     | 7 (3.4)   | 200 (96.6)   | 8.26       | 1.0-67.10* | 7.13     | 0.87-58.55  |
| <b>WHO Stage</b>   |                |           |              |            |            |          |             |
|                    | <b>Stage 1</b> | 4 (1)     | 370 (99)     | 0.09       | 0.03-0.27* | 0.10     | 0.03-0.39*  |
|                    | <b>Stage 2</b> | 7 (3.1)   | 221 (96.9)   | 0.25       | 0.10-0.62* | 0.36     | 0.13-0.99*  |
|                    | <b>Stage 3</b> | 8 (4.8)   | 157 (95.2)   | 0.42       | 0.18-1.02  | 0.54     | 0.20-1.43   |
|                    | <b>Stage 4</b> | 13 (10)   | 116 (90)     | 1.0        |            | 1.0      |             |

\*Significant factors

## 6. Discussion

Majority of the patients were females (57%) and mean age was 42.87 years (SD=10.2). The baseline median CD4 count of the patients was 187 (IQR= 92-316) with 19% of patients having a CD4 count above 350. The mean BMI of the study groups was 22.54 (SD=4.5) and 90% of them had a working functional status at enrollment into the care. Patients who are exposed to INH had 82% (95% CI: 0.09-0.34) and 92 % (95% CI: 0.02-0.25) protection level from developing TB and incident deaths compared to non-exposed patients respectively. The hazard function curve shows significant difference of probability (Log rank  $P=0.00002$ ) to incident TB cases or deaths between INH exposed and non-exposed groups of patients. The multivariable analysis of factors associated with incident TB cases shows that, INH exposure, WHO stage 1 and a working functional status were found to be protective against TB. INH exposure, WHO stage 1 and stage 2 were protective against incident deaths whereas weight below 50kg was associated with higher risk of death incidences.

Incidence of TB among INH exposed patients and the level of protection against TB added by using INH (82%) on this study is superior compared to a cohort study conducted in Tanzania where INH exposure has only 48 % protection(12). It is even much higher than another meta-analysis study where the protection level stated as only 35% but on that study the benefit was more pronounced in the TST positive patients with a risk reduction of 52%(15). On our study TST status was not assessed, however. Other studies conducted in Jimma town and in Addis Ababa city public health facilities also showed similar results even with a better level of TB incidence reduction in the Addis Ababa study compared to this study with an adjusted incidence rate ratio of 0.037(17, 18).

On the other hand, a prospective study conducted in Central Thailand among ART naïve HIV patients and a randomized controlled trial done in Nairobi, Kenya showed no significant difference in TB incidence between INH exposed and non-exposed patients however, the first study still demonstrates better protection of INH exposed patients in the first six months of therapy ( $P= 0.04$ ). Another RCT study conducted on WHO stage 3 or stage 4 patients also demonstrates no significant difference in TB incidence among TST negative patients though it shows significant protection among TST positive patients(13, 14, 16).

Findings from this study should be interpreted in a way that INH exposure was considered positive when patients complete the full 6 months course but in some of the other studies mentioned here, the exposure period is not clearly known which might decrease the protection level of the prophylaxis if the complete course is not achieved. In addition, this study has tried to delineate the line for incidence of TB between INH exposed and non-exposed patients in the face of HAART exposure for all patients and hence,

findings shown on this study may demonstrate the synergistic effect of the two drugs. The presence of synergy between the two drugs is also documented on a study conducted in five hospitals in south Ethiopia(24). On this study only those patients who started on INH after starting on HAART were compared to the other studies that investigate the difference in protection level of INH irrespective of the exposure period in relation to HAART and as a result could potentially underestimate its protection level. This was supported by another study which shows a better protection level by starting on INH after HAART compared to INH started anytime in relation to the HAART timeline(24).

On this study the effect of INH on preventing mortality (IRR=0.08) is more pronounced than its effect on reducing TB incidence but this is in contrary to other studies done world-wide. Randomized controlled trial done in Nairobi, Kenya showed some reduction in mortality with INH exposed groups but it was not a statistically significant difference with adjusted mortality rate ratio of 1.18 (95% CI: 0.79-1.75)(14). Similarly, A systematic review involving 41 articles and with over 45,000 study participants reported no significant difference in mortality between INH exposed and non-exposed groups except 4 articles who reported a significant difference especially in TST positive adults(20). But a study done in Addis Ababa in two public health facilities reported similar result to this study showing a significant difference in mortality between the two groups (4.5/100PY vs. 10/100 PY b/n IPT and non-IPT group respectively)(22). This difference could be emanating partly from lack of power on this study as only few deaths were recorded in general and also because, most of the INH non-exposed patients had poor clinical condition at enrollment.

Our study also showed that INH exposure, WHO clinical stage 1 and working functional status are the factors that are strongly related with decreased incidence of TB while controlling for all the other demographic and clinical factors. While many of the other studies also identified similar factors for increased incidence of TB regarding WHO clinical stage 4 and INH non-exposed patients indifferently, the level of protection added by having a working functional status at enrollment is a relatively new finding here. But this can also be explained by the fact that, patients in the earlier stages of WHO clinical stages will have a working functional status unless they had other co-morbidities. CD4 level below 200 is found to have increased risk of TB in most of the other studies, however, on this study even if it shows some degree of increased incidence of TB on the bivariate analysis, it has no more significantly increased risk of TB when the other co-founders are controlled(12, 17, 18, 22).

This study also demonstrates INH use and earlier WHO clinical stages (i.e. Stage 1 and stage 2) at baseline were found to be protective from mortality and it has consistency with other studies with regard to the protection of earlier WHO stages or increased risk of late WHO (stage 3 and 4) clinical stages(15,

22). But other studies didn't show any benefit of INH use on preventing mortality contradicting with our study of marked benefit of INH on decreasing mortality incidence. But this is due to the fact that, the mere survival and the good status of the patient at enrollment by itself opens the door for possible INH exposure. In this study, it is observed that patient's poor clinical status at enrollment will likely decrease their survival and their chance for INH exposure and hence will likely create a false analogy between INH non-exposure and high mortality. This could be evidenced by the lack of INH exposure in the 27 patients from an entire 32 bed-ridden patients at enrollment. Weight below 50 Kg has shown a marked increase in the risk of mortality on this study which could be due to the poor status of the patient's condition on the INH non-exposed patients but it's not identified as risk in other studies.

Demographic and clinical variables including being male, underweight, unemployment and having opportunistic OI were observed with increased risk of TB in other studies but it was not the case on this study(12, 18). CD4 values above 350 and adherence to ART were also identified as protective against mortality in previous researches but no association was found here(22).

**Limitation:** On this study a complete record of all the variables from all medical records was not obtained and hence, medical records which lacks the basic records for which the research has intended to cover are excluded from the outset but variables which will not affect the main aim of the study are kept for descriptive analysis despite the missing values. Therefore, interpretation of the socio-demographic data analysis should be viewed with this perspective. Secondly INH uptake was considered for inclusion from 08 July 2012 to 07 July 2017 for patients enrolled in ART care. But patients might still take INH during the pre-ART care and this will under-estimate the INH uptake history since they will be counted under non-exposed group and in return might have effect on decreasing TB incidence in non-exposed patients. On the other hand, Patients grouped under the non-exposed group but took INH after the 07 July 2017 until the censoring date (07 July 2019) during the follow-up period, are excluded from the study to avoid the added benefit of protection from TB incidence. As a result, this might introduce some bias by eliminating patients who are enrolled into the care and treatment in the later years of the follow-up.

Patients who are included in the study as control group (INH non-exposed) and developed TB are considered as non-exposed even if these patients took INH later after they are treated for TB. So history of INH exposure used for this analysis might not tell the whole picture of the patient's exposure and should be interpreted cautiously.

## 7. Conclusion

Most of the study groups included for this study were females (57%) and their mean age was 42.87 (SD=10.2) with age range 35-44 years constituting the major (40%) share from the entire age group. The median CD4 count of the study participants was 187 (IQR=224) and most of the patients (53%) have a CD4 count below 200. Most of the patients (64.7%) were either WHO stage 1 or stage 2 patients. The median weight and mean BMI of the patients was 60kg (IQR: Q1=51, Q3=68) and 22.54 (SD=5.4) respectively. About 88% of the patients had a working functional status at enrollment with the remaining few patients having either ambulatory or bed-ridden status. Around 85% of the patients were alive on ART at time of censoring with all the other entire remaining status including; dropped, lost to follow-up, transfer-out and dead constituting 15% of the patient's status.

INH exposed and non-exposed groups of patients had 24,958 and 18,159 person-months of follow-up for incident TB cases respectively. The overall TB incidence rate was 15.3 per 1000 person-months (95% CI=11.6-19.8) and INH exposure is found to have marked protection against TB (aHR= 0.18, 95%CI=0.09-0.34) compared to non-exposed patients. Overall patient mortality in the study groups is also determined to be 8.5 per 1000 person-months (95% CI=5.97-11.97) but INH exposure give patients significant protection against death (aHR=0.08, 95% CI=0.020-0.25) compared to non-exposed patients.

A number of patient demographic and clinical variables were entered and analyzed with cox-regression model to identify factors associated with incident TB cases and incident mortalities. INH exposure (aHR=0.21; 95% CI=0.10-0.43), baseline WHO clinical stage 1 (aHR=0.12; 95% CI=0.04-0.41) and working functional status (aHR= 0.24; 95% CI= 0.08-0.71) at enrollment were factors identified to have association with incident TB cases. On the other hand INH exposure, age group 25-34 years, baseline WHO clinical stage 1 and stage 2 were 93% (95% CI=0.02-0.29), 91% (95% CI=0.01-0.80), 90% (95% CI=0.03-0.39) and 64% (95% CI=0.13-0.99) protective from death/mortality respectively whereas weight below 50 kg and 50-59kg is found to have 9.7 times (95% CI=1.22-76.8) and 9.1 times (95% CI=1.15-72.6) increased risk for mortality respectively compared to patient weight 60-69kg.

## 8. Recommendations

On this research INH is found to be very helpful in minimizing TB incidence and mortality among HIV clients on HAART but INH coverage is minimal in Addis Ababa and in general in Ethiopia as evidenced by previous literatures and government reports. Therefore, intensifying INH coverage in the HIV care and treatment program by the health facilities is strongly recommended to decrease further the incidence of new TB cases and mortalities among HIV patients.

It is also noted on this study that, patients with poor medical condition (i.e. bedridden and ambulatory patients) at enrollment looks to have no access to get INH; this could be due to the fact that patients who had late presentation to the clinics will either die early or will be diagnosed with TB that, they will not get the chance to take INH. So, awareness creation and ad vocation by the city administration health bureau, public health facilities and all partners who are supporting the service regarding the comprehensive HIV care and treatment program should be strengthened to capture the patients early and provide the service.

On our study it is also observed that, INH exposure seems to have effect on patients' follow-up status to treatment as most of INH exposed patients were still alive on ART at time of censoring compared to non-exposed patients. But this association needs to be studied further by scholars with a better design and power to see the real association between the two.

Patients with low CD4 count and in the later part of WHO clinical stages (stage 3 & 4) are not getting INH prophylaxis compared to their counterparts. This usually occurs because clinicians will be reluctant to provide INH prophylaxis since they are not in a position to rule out TB with the routine simple screening methods at this stage of the disease where more complicated and extra-pulmonary TB cases ensue. Therefore, it is necessary to provide capacity building trainings to clinicians and improve the facility infrastructures for TB diagnosis among HIV patients by government and all stakeholders.

On the hazard function, it is noted that most of INH non-exposed population gets TB in the first one or two months of follow-up or at the time of enrollment to care but afterwards the rate of increment in TB incidence between exposed and non-exposed groups is comparable. This is usually due to patients' late presentation to the ART clinic after OI's ensue. Hence, it is important to curb the progress of the disease in this group of patients with early identification of HIV patients by intensifying awareness creation and targeted testing programs.

Patients' with poor functional status (bedridden) and WHO clinical stage 4 diseases are strongly associated with high risk of TB on this study. Therefore, special attention should be given in these groups of patients for early initiation of INH prophylaxis by clinicians in these health facilities.

## 9. References

1. Organization WH. Global Tuberculosis Report. Switzerland: 2016 ISBN 978 92 4 156539 4.
2. WHO. Global Tuberculosis control: a short update to the 2010 Report. December 2009. Geneva, Switzerland. Geneva, Switzerland: World Health Organization, 2010.
3. Organization WH. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach, 2010 revision. Austria: WHO, 2010 ISBN 978 92 4 159976 4.
4. Haileyesus Getahun JvG, Antony Harries, Mark Harrington, et al. Interim policy on collaborative TB/HIV activities. Geneva, Switzerland: World Health Organization, HIV/AIDS STDaDo; 2004.
5. Organization WH. WHO Three I's Meeting Report. Intensified case finding (ICF), isoniazid preventive therapy (IPT) and TB infection control (IC) for people living with HIV. 20, Avenue Appia CH-1211 Geneva 27, Switzerland: WHO Press, HIV/AIDS; 2008.
6. Ethiopia FMOHo. Impementation Guideline for TB/HIV Collaborative Activities in Ethiopia. In: Department DPaC, editor. Addis Ababa 2007.
7. Amenu Wesen Denegetu BLD. Tuberculosis case finding and isoniazid preventive therapy among people living with HIV at public health facilities of Addis Ababa, Ethiopia: a cross-sectional facility based study. *BioMed Central*. 2014;14:52.
8. Organization WH. Global Tuberculosis Report. Geneva, Switzerland: WHO, 2018.
9. WHO. Tuberculosis fact sheet. Geneva, Switzerland: 2016.
10. Charles D. Wells JPC, Lisa J. Nelson, Kayla F. Laserson, Timothy H. Holtz, Alyssa Finlay, Kenneth G. Castro, and Karin Weyer. HIV Infection and Multidrug-Resistant Tuberculosis-The Perfect Storm. Supplement article. 2007.
11. Organization WH. Programmatic Update: Antiretroviral Treatment As Prevention (TASP) of HIV and TB. Geneva, Switzerland: 2012.
12. Amon Sabasaba HM, Geoffrey Somi, Angella Ramadhani, Michael J. Mahande. Effect of isoniazid preventive on tuberculosis incidence and associated risk factors among HIV infected adults in Tanzania: a retrospective cohort study. *BMC Infectious Diseases*. 2019;19:8.
13. T. Khawcharoenporn AA, W. Manosuthi, S. SUNKANUPARPH, L. M. Mundy. Isoniazid preventive therapy and 4-year incidence of pulmonary tuberculosis among HIV-infected Thai patients. *The International Journal of Tuberculosis and Lung Disease*. 2012;16(3). Epub 341.
14. Mark H. HM, Lyn E., Jeremiah C., Joanne M., Willie G., Earnest J., Joseph O., Lawrence T., Joseph K., Elizabeth N., Joab B., Charles G., Francis P., John P., Paul N., Keith M.,. Isoniazid preventive therapy for tuberculosis in HIV-1-infected adults: results of a randomized controlled trial. *Medline*. 1997;11(7):875-82. Epub 11 June 1997.
15. Henok Tadesse Ayele MSMvM, Thomas P. A. Debray, Marc J. M. Bonten. Isoniazid Prophylactic Therapy for the Prevention of Tuberculosis in HIV Infected Adults: A Systematic Review and Meta-Analysis of Randomized Trials. *PLoS ONE*. 2015;10(11)(E0142290). Epub November 9, 2015.
16. A. Mohammed LM, R. Ehrlich, R. Wood, F. Cilliers, G Maartens. Randomised controlled trial of isoniazid preventive therapy in South African adults with advanced HIV disease *The International Journal of Tuberculosis and Lung Disease*. 2007;11(10):1114-20.
17. Lelisa Fekadu Assebe HLR, Alem Desta Wubeneh, Wondwossen Terefe Lerebo, Saba Maria Lambert. The effect of isoniazid preventive therapy on incidence of tuberculosis among HIV-infected clients under pre-ART care, Jimma, Ethiopia: a retrospepective cohort study *BioMed Central*. 2015;15:346.
18. Mahlet Semu TGF, Girmay Medhin, Dawit Assefa. Efectiveness of isoniazid preventive therapy in reducing incidence of active tuberculosis among people living with HIV/AIDS in public health facilities of Addis Ababa, Ethiopia: a historical cohort study. *BMC Infectious Diseases*. 2017;17:5.

19. Melissa A. Briggs CE, Surbhi Modi, Nicholas Kenji Taylor, Anand Date. Use of Isoniazid Preventive Therapy for Tuberculosis Prophylaxis Among People Living with HIV/AIDS: A Review of the Literature. *J Acquir Immune Defic Syndr*. 2015;68 (Suppl 3):S297-S305.
20. Samandari T AT, Nyirenda S, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2011;377(9777):1588-98. Epub May 7 2011.
21. Soumya Swaminathan PAM, Narendran Gopalan, Vemkatesan Perumal, Ramesh Kumar Santhanakrishnan, et al. Efficacy of a Six-Month versus a 36-Month Regimen for Prevention of Tuberculosis in HIV-Infected Persons in India: A Randomized Clinical Trial. *PLoS ONE*. 2012;7(12).
22. Dumessa Edessa JL. A Description of Mortality Associated with IPT plus ART Compared to ART Alone among HIV-Infected Individuals in Addis Ababa, Ethiopia: A Cohort Study. *PLoS ONE*. 2015;10(9).
23. Wikipedia. Addis Ababa. 2019 [updated 13 September 2019; cited 2019]; Available from: [https://en.m.wikipedia.org/wiki/Addis\\_Ababa](https://en.m.wikipedia.org/wiki/Addis_Ababa).
24. Bureau AAcAH. 2019.
25. Kesetebirhan Delele Yirdaw DJ, Zewdu Gashu, M. E. Edginton, et al. Beneficial Effect of Isoniazid Preventive Therapy and Antiretroviral Therapy on the Incidence of Tuberculosis in People Living with HIV in Ethiopia. *PLoS ONE*. 2014;9(8).
26. Health FDRoEMo. GUIDELINES FOR CLINICAL AND PROGRAMMATIC MANAGEMENT OF TB, LEPROSY AND TB/HIV IN ETHIOPIA. Fifth ed. Addis Ababa 2012.

## Annexes

## Annex 1: Data collection tool

[illegible]





## Annex 2: Consent Form

I.....will sign these letter of consent on behalf of.....hospital/health center by agreeing that for Dr. Enyew Birru to conduct this research in our institution after checking that he had an approval of the proposal from SPHMMC on .....date, .....number. With this I would like to ask all the departments to support him in his activity in our facility

Sign.....

Date.....