TUBERCULOSIS INCIDENCE, PREDICTORS AND TB FREE SURVIVAL AMONG HIV INFECTED ADULTS WHO COMPLETED ISONIAZID PREVENTIVE THERAPY IN HAWASSA COMPREHENSIVE SPECIALIZED HOSPITAL, SIDAMA REGIONAL STATE.

A RETROSPECTIVE COHORT STUDY

BY: AMANUEL FANTA

OCTOBER, 2020
ADDIS ABABA, ETHIOPIA.

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OCTOBER, 2020
ADDIS ABABA, ETHIOPIA.

APPROVAL SHEET BY THE BOARD OF EXAMINERS

I, the undersigned MSc student, declare that I have submitted my original work on the title "*tuberculosis incidence, predictors and TB free survival among HIV infected adults who completed isoniazid preventive therapy in hawassa comprehensive specialized hospital, sidama regional state, Hawassa Ethiopia, 2020"* for examination.

Submitted by:

Amanuel Fanta (BSc) _____ _____

Name of student Signature Date

This thesis by Amanuel Fanta is accepted in its present form by the board of examiners as satisfying thesis for degree of masters in pediatrics and child health nursing.

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STATEMENT OF DECLARATION

By my signature below, I declare and affirm that this thesis is my own work. I have followed all ethical principles of research in the preparation, data collection, data analysis and compilation of this thesis. Any scholarly matter that is included in the thesis has been given recognition through citation.

This thesis is submitted in partial fulfillment of the requirements for a master degree of pediatrics and child health nursing at the Addis Ababa University. The thesis will deposit in Addis Ababa University library and will made available to borrowers under the rules of the library. I solemnly declare that this thesis has not been submitted to any other institution anywhere for the award of any academic degree, diploma of certificate.

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ACRONYMS

AAU	Addis Ababa University
AFB	Acid-Fast Bacilli
AIDS	Acquired Immune Deficiency Syndrome
AHR	Adjusted Hazard Ratio
ART	Anti Retro Viral Therapy
ARV	Anti Retro Viral Drug
CPT	Cotrimoxazole Preventive Therapy
CHCT	Couple HIV Counseling and Testing
FMOH	Federal Ministry of Health
HAART	Highly Active Anti-Retroviral Therapy
HIV	Human Immunodeficiency Virus
HUCSH	Hawassa University Comprehensive specialized Hospital
IPT	Isoniazid Preventive Treatment
LTBI	Latent TB Infection
LDC	Least Developed Countries
MSC	Master of science
OI	Opportunistic Infection
PLWH	People Living With HIV
PICHT	Provider Initiated HIV Counseling and Testing
PYO	Person Year Observation
TB	Tuberculosis
VCT	Voluntary Counseling and Testing
WHO	World Health Organization

ABSTRACT

Background: Tuberculosis (TB) is the most frequent life threatening opportunistic disease and the leading cause of death in HIV-infected people. At the same time, antiretroviral therapy (ART) is the single most important way to reduce the incidence of TB in people living with the HIV infection. However, people with HIV on ART remain highly vulnerable to TB. Taking a six month course of Isoniazide Preventive Therapy (IPT) is known to reduce the risk of TB in people with HIV and latent TB by 32-64% for two to three years.

Objectives: The aim of the study was to assess the incidence, predictors and TB free survival among HIV/AIDS patients on ART who completed IPT in Hawassa Comprehensive Specialized Hospital.

Methods: Five years Health institution based retrospective cohort study design was Conducted using a checklist to gather data from 483 randomly selected Adult HIV patients charts. The data extraction tool was developed from the standardized ART entry and follow up form currently used by the ART clinics based on WHO model. Data was cleared and entered into Epi-data V-4.62 and exported to SPSS V-25 for further statistical analysis. Data was analyzed by bivariate and multivariable analysis using Cox regression proportional hazard model. Survival was calculated and compared with the Kaplan Meier and log rank test respectively.

Results: A total of 483 HIV positive adults were studied. The median follow up time was 54 months (IQR = 20–41.75). A total of 55 TB cases occurred in 1490 total PY of follow up. The overall TB incidence was 3.7/100 PYO (95%CI; 2.6–2.8). Factors associated with TB incidence include; being Female (AHR = 2.07, 95% CI; 0.78–5.26), WHO stage III and IV (AHR = 3.2, 95% CI; 1.15–8.95) and IV (AHR = 4.5, 95% CI; 0.19–1.094), Hgb <11 mg/dl were 3 times more likely to had TB than Hgb >11 mg/dl (AHR= 3.17; 95%CI, 0.15 to7.01). Bedridden at baseline were 3.28 times at higher risk of developing TB (AHR 3.28; 95%CI, 0.134 to 8.06). Individuals who completed IPT were 94% less likely to develop TB (AHR 0.60; 95%CI, 0.018 to 0.203). Viral load <1000copies/ml were 1.96 more likely to developed TB than >1000 copies/ml (AHR=1.96; 95%CI, 0.04 to 2.20).

Conclusion: Completion of IPT significantly reduced TB incidence by 94.0% and IPT had significantly protected occurrence of active TB for five years among HIV infected patients.

Keywords: Adults, HIV/AIDS, Incidence, Predictors, Survival, Tuberculosis, Hawassa, Ethiopia.

1. INTRODUCTION

1.1 Background

Tuberculosis (TB) is an infectious disease caused by the Mycobacterium tuberculosis that affects the lungs (pulmonary TB), but can also affect other sites (extra pulmonary TB), and has remained a major global health problem.(1). A relatively small proportion (5–10%) of the estimated 1.7 billion people infected with M. tuberculosis will develop TB disease during their lifetime(2) .In 2018, TB was one of the top 10 causes of death worldwide and the leading killer among HIV-positive people, ranking above HIV/AIDS as one of the leading cause of death from infectious diseases. Out of the 1.5 million TB-caused deaths reported in 2018, 251 000 (223 000—281 000) occurred in HIV-positive patients. Globally, it was estimated that there were 10.4 million TB cases, including 1.2 million among HIV-positive people(2).

In spite of the availability of antiretroviral therapy (ART), Tuberculosis (TB) is the most common presenting illness among people infected with Human Immunodeficiency syndrome Virus (HIV)(3). People living with HIV are at about thirty times at higher risk of developing TB compared to non-HIV infected individuals(3). HIV co-infection have been associated with unusual presentations of TB such as smear negative and abnormal chest radiographs thus causing a diagnostic challenge, poor treatment outcome and subsequent increased mortality(4).

As HIV affects immune control of TB, HIV-infected patients with latent TB infection (LTBI) have an increased risk of developing active TB, the most common opportunistic disease among HIV-infected patients, and the leading cause of death in patients with the Acquired Immune Deficiency syndrome (AIDS) in the developing world(5). The human immunodeficiency virus (HIV) pandemic presents a massive challenge to the control of tuberculosis (TB) at all levels. Tuberculosis is also one of the most common causes of morbidity and one of the leading causes of mortality in people living with HIV/AIDS (PLWH). In 2016, 10.4 million cases of TB were reported by World Health Organization (WHO) worldwide (6). From infectious diseases' statistics, Tuberculosis (TB) and Human Immunodeficiency Virus (HIV) are the leading causes of death globally. Despite many efforts have been made to control and prevent the dual occurrences of the diseases, yet TB is the leading cause of mortality and morbidity in People Living with HIV (PLWH)(7).

Globally, approximately one million of PLWH are co-infected with TB in 2017 and more than one third of the world population is infected with Tuberculosis (TB) of which 5–10% develops active TB. The reactivation of Latent TB infection (LTBI) to active TB diseases is pronounced among PLWH by approximately 20 times on average(7). A number of factors have contributed to the global TB crisis, among which Human Immune deficiency Virus (HIV) infection is the greatest known risk factor for the development of active tuberculosis (TB) in individuals with latent TB infection. The rapid increase in HIV epidemic in many developing countries has resulted in an equally dramatic rise in the estimated number of new TB cases in developing countries. (8). In this regard, WHO had proposed a framework of strategic actions for HIV care programs to optimally integrate TB into their service. The core activities of this framework include isoniazid preventive therapy (IPT) as a key component among other measures to control latent tuberculosis(9).

Ethiopia, which continues to be one of the least developed countries (LDC) in the world, is tenth in the world for TB with an estimated annual incidence of 163 per 100,000 for new smear positive pulmonary TB and 378 per 100,000 for all forms of TB cases. In addition, the TB/HIV co-infection rate in Ethiopia is estimated at 7.2% (10)(11). HIV infection, impairing the immune system, increases the susceptibility to infection by of mycobacterium tuberculosis and progression to active disease. The TB epidemic is further, aggravated by drug resistance, social inequalities, limited TB control efforts and limited access to health care services(12)

1.2 Statement of the problem

Tuberculosis (TB) is a communicable disease that is a major cause of ill health, one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent (ranking above HIV/AIDS)(2). Globally, approximately one million PLWH (Patient Living with HIV) co-infected with TB in 2017. The 2019 WHO report shows that in the year 2018, there were an estimated 10 million new (incident) TB cases worldwide, of which 5.7 million were men, 3.2 million were females and People living with HIV accounted about 9% of the total. There are Eight countries which are listed to account around 66% of the new TB cases they are: India, China, Indonesia, Philippines, Pakistan, Nigeria, Bangladesh, and South Africa(2). TB is the leading cause of death among PLWH attributable to 300,000 HIV-associated TB deaths in 2017 in which Africa accounted for the largest shares (84%). Moreover, PLWH faces the threat of drug-resistant TB. If diagnosis is delayed there is increased risk of mortality from multi-drug resistant and extensively drug-resistant TB(7).

In 2019 WHO reported that, 58, 000, 00 lives were saved between 2000 and 2018 by global efforts to end TB. There are also10,000,000 people fell ill with TB in, 1,500,000 people died of TB and 484,000 people fell ill with drug-resistant TB in 2018(2). Tuberculosis (TB) has been continuing to be the major threat to global health with a high burden of disease for which account about more than 10 million new cases per year which less than two thirds are reported(2) .Although the global number of TB deaths fell by 42% between 2000 and 2017, and the annual decline in the global TB incidence rate is currently 1.5% (1), much action is needed to accelerate progress towards achieving global milestones to end TB (2). TB can affect everyone, but specific population groups have a higher risk of acquiring TB infection and progressing to disease once infected; these groups include people living with HIV infection, health workers and others in settings with a high risk of transmission of M. tuberculosis(13).

Tuberculosis (TB) is a major global public health problem. In 2016, 10.4 million cases of TB were reported to World Health Organization (WHO) worldwide. India accounts for one fourth (2.8 million cases) of global TB burden. Approximately 0.5 million Indians die annually because of TB.(6) The risk of developing TB is between 20 to 37 times greater in HIV infected individuals when compared to immunocompetent individuals.

As a result, TB is the commonest infection and common cause of death among HIV-infected individuals(12). Tuberculosis incidence in South Africa was estimated at 948/100,000 in 2007 and is higher still among miners, partly due to high prevalence of HIV (estimated at 29%) and silicosis(14) In the African region, which has the highest TB/HIV burden, three out of four patients with TB knew their HIV status. In fact, 70% of patients with TB known to be living with HIV and from those in 2,013 were started on antiretroviral therapy (ART). Also Tanzania has a high HIV prevalence and a high TB incidence country(15).

According to the WHO report in 2019, Ethiopia ranks ninth amongst the world's30 high TB burden countries in the world and TB is the second leading cause of hospital death in the country(2). In Ethiopia, 79% of HIV infected individuals were screened for active TB, of whom 15% had TB/HIV co-infection. Only 19% of the HIV positive clients without active TB were provided with IPT in 2010. This dual epidemic of HIV/AIDS and TB is a growing concern that challenges the Ethiopian government's efforts towards prevention and control of both diseases(12). In 2018 the annual incidence of HIV among adults aged 15-64 years in urban Ethiopia was 0.06%, which corresponded to approximately 7,000 new cases of HIV annually while Prevalence of HIV among adults ages 15-64 years in urban Ethiopia is 3.0%: 4.1% among females and 1.9% among males(14). This corresponds to approximately 380,000 people living with HIV (PLWH) ages 15-64 years in urban Ethiopia as of April 2018. Prevalence of HIV among children ages 0-14 years in urban Ethiopia is 0.3%, and is the same among both females and males(16).

ART is the single most important way to reduce the incidence of TB in people living with HIV. However, people with HIV on ART remain highly vulnerable to TB. Urgent action is thus required to prevent, diagnose, and treat TB in people living with HIV. Their families and their communities must also be involved(17). In this regard WHO had proposed a frame work of strategic actions for HIV care programs to optimally integrate TB in to their service. The core activities of this framework includes isoniazid preventive therapy (IPT) as a key component among other measures to control latent tuberculosis(18) Cognizant of this fact the national TB/HIV collaboration in Ethiopia adopted the twelve, WHO recommended collaborative activities of which one is Isoniazid Preventive Therapy (IPT) (19).

IPT completion decreases the risk of progression to active disease in those with recent infection and decreases the risk of reactivation of latent disease. Yet, published data on IPT effectiveness integrated into routine health care services are limited. The risk of TB in HIV- infected patients who completed IPT and time to TB occurrence has not been studied enough especially in southern Ethiopia. Understanding of this issue provides information to optimize an effective implementation of IPT programs among HIV- infected patients(20). So far in Ethiopia no sufficient studies have been conducted to assess the incidence, Predictors and time to TB incidence. Therefore, the objective of this study is to determine TB incidence, predictors and TB free survival among HIV-positive patients who completed IPT in Hawassa University specialized hospital (21).

1.3. Significance of the study

Tuberculosis and HIV/AIDS fuels one another. TB contributes to immune impairment, making the body vulnerable to frequent illnesses and increasing demand for energy and nutrients, thereby accelerating disease progression. Therefore, tuberculosis incidences and TB free survival of HIV infected adult patients is not well known after initiation and completion of IPT. There are no studies done on incidence, predictors and TB free survival time of adult HIV patients in Hawassa Comprehensive specialized hospital and around the study area. The study will serve as the base line data to estimate the incidence of TB, its Predictors and TB free survival time among HIV patients in relation to INH exposure status; whether it was constant, ascending, or descending for the last five years in relation to efforts for TB control in the study area, and fulfilled the goals of the national and regional global stop target. The study also serve as a source for information and as a starter for other researchers who want to assess similar study based on primary data in the area and as a reference material for comparison with other similar works in the country.

2. LITERATURE REVIEW

2.1 Overview of HIV, TB and Isoniazid preventive therapy

According to the World Health Organization, a third of the world's population is infected with Mycobacterium tuberculosis. (17) Mycobacterium tuberculosis is the bacterial causative agent of a disease that has been a leading cause of death for much of earth's history and still is for many developing countries. Maarten and Wilkinson noted recent regional changes in the incidence of TB with improvements made in many regions while incidence in sub-Saharan Africa has increased. This increase is correlated with the HIV epidemic in Africa and presents complex challenges in the task of controlling TB. (17) Anti-Retroviral Therapy (ART) has improved the prognosis of HIV and reduced the risk of TB infected patients. Isoniazid Preventive Therapy (IPT) aims to reduce the development of active TB in patients with latent TB.(18) This research aims in to determine the TB incidence rate and predictors of TB incidence among HIV- infected adult patients who completed IPT(21).

2.2 Incidence of TB among PLWH

Studies indicated that HIV infections and TB were increasing worldwide.(22) Persons with HIV infection were at high risk of active TB as HIV attacks the immune system. In 2017, Ishani, Kainne and Ray (22) described that TB incidence weighted to the general population was 0.57 per 100 PY. Ninety-three percent of those with incident TB were estimated to be still on ART by the end of their follow-up period but none of the patients who were receiving IPT at baseline. Also TB cases were diagnosed during the follow-up period which yielded an incidence rate of 1.43 per 100 PYO (11)The TB incidence rate in a follow-up duration of 6-12 months and more than 12 months after IPT completion was 1.78 per 100 PYO and 2.99 per 100 PYO respectively(11). According to the research done by van Griensven, a total of 14 (3.1%) cases of tuberculosis were diagnosed during IPT, at a median of 7 seven weeks after IPT initiation(23). Out of 77/126 sputum samples cultured Mycobacterium tuberculosis; 42 were culture-negative and seven had no culture results available after IPT initiation. (24) Similar studies in Arbaminch Ethiopia indicate that TB-infected ART patients were higher among non-IPT group (37 [27.8%]) compared to IPT group (12 [8.7%]). The finding showed that IPT prophylaxis significantly reduces acquiring TB with the relative risk in ART patients of this study site where the tuberculosis prevalence is prominent. ART.(21) A trial of early antiretroviral and isoniazid preventive therapy in Africa indicates that the early initiation of

ART and 6 months of IPT independently resulted in a risk of severe HIV-related illness that was 44% lower and a risk of death from any cause that was 35% lower than the risks with deferred initiation of ART and no IPT(25).

2.3 Risk Factors for Tuberculosis Incident

About 5 to 10% of infected persons who do not receive treatment for latent TB infection will develop TB disease at some time in their lives. For persons whose immune systems are weak, especially those with HIV infection, the risk of developing TB disease is much higher than for persons with normal immune systems(26). According to the review article which was conducted on Risk Factors for Tuberculosis cite, there are two factors that contribute to the development (incidence) of active TB. These are endogenous and exogenous factors. In addition to the main risk factors for example human immunodeficiency virus (HIV), malnutrition, and young age), the new variables such as diabetes, indoor air pollution, alcohol, use of immunosuppressive drugs, and tobacco smoke play a significant role at both the individual and population level. Behavioral and socioeconomic factors are also shows increase in incidence of TB. Specific groups such as health care workers are also at an increased risk of TB infection and disease(27).

Advanced WHO clinical stage at ART initiation, hepatitis B virus infection, low BMI, high VL, anemia, and poor average percentage ART adherence were all associated with increased risk of incident TB(28) Another important finding associated with incident TB was CD4 count below 200 which was found to be a strong predictor of TB. Patients with CD4 count below 200 cells/µL have more risk of developing TB as compared to patients with CD4 count above 500 cells/µL. (29). An eight years follow up cohort study in south Africa shows that the crude analysis of updated CD4 cell count has strongest association with incident TB (30). TB incidence was 9 times greater during person-time accrued at CD4 cell counts below 100 cells/mm^3 compared person-time at CD4 cell counts above 700 cells/ml. Viral loads >1000 copies/ml were associated with over three times the risk of incident TB. Duration of ART was also associated with incident TB in crude analyses (31).

Other risk factors for developing TB are being male gender, age 15-49, use of recreational drugs and malnutrition(32). In meta-analysis study, smoking did not remain independently associated with incident TB in multivariate analysis in spite of the fact that remarkably high prevalence of reported

past (25.9%) and current (29.0%) smoking were found(33). Tuberculosis and HIV infection are known to be associated with malnutrition, although the picture is more complex, as with the prevalence of overweight/obesity increases among PLWH receiving HAART. Even a patient who has body mass index ,18.5 kg/m2, has been reported to be associated with TB in PLWH(33).

2.4 Isoniazid preventive therapy for PLWH

Isoniazid Preventive Therapy (IPT) was released in 2004 by WHO, and has beneficial preventive properties such as a rapid reduction of onset of TB. Randomized controlled trials have demonstrated that a course of Isoniazid Preventive Therapy (IPT) reduces the incidence of TB disease in HIV-negative populations at risk of developing active disease(18). In addition to early initiation of ART the WHO also recommends initiation of isoniazed preventive therapy (IPT) as a key intervention to prevent TB among PLWH. Furthermore, WHO also reported that IPT taken for 6–12 months has reduced the risk of TB by 33% among all people with HIV and by 64% in HIV infected patients who have a positive tuberculin skin test (TST)(34). Besides early initiation of ART, the main intervention to prevent TB in people living with HIV is isoniazid preventive therapy (IPT). Worldwide, significant progress has been made to minimize morbidity and mortality among people living with HIV/AIDS(21). After controlling for other variables, the overall effect of IPT was found to reduce TB incidence by 55% (29). Among first tuberculosis episodes, 7/58 were resistant to isoniazid in the TB after IPT group, compared with 12/200 in the control clusters and 32/270 in the laboratory sub study(24).

A case control study which s conducted by(35) shows that Among IPT group who have been taking the prophylaxis, 12 (8.7%) of the study participants were infected by TB, whereas the remaining 126 (91.3%) study participants were TB negative after 6 months duration on IPT. According to the meta-analysis done in Ethiopia, The pooled effect of IPT in reducing incident TB among HIV infected patients taking ART was significant compared with no intervention group. Thus, IPT reduced the risk of active TB incidence by 74% in IPT group compared to no IPT intervention group(34). Also IPT prophylaxis users were protected from TB infection with statistically significant difference compared with those who did not use IPT prophylaxis in this study(35).

2.5. Predictors for Incidence of TB in HIV Infected Patients

2.5.1 Anti-Retroviral Therapy and CD4+ Count

The major predictors stated for the risk of TB infection among HIV infected patients were being in pre-ART follow up than on ART(12). With the advent of combined ART it was observed that TB incidence fell in persons on ART in North America and Europe. The fall in TB incidence has been observed to be greater in persons with a higher baseline CD4+ cell count, a lower base line viral load and robust immunological and virological responses cite(36). Baseline CD4+ T-lymphocyte count is an important predictor for development of TB. A retrospective cohort study conducted in Brazil showed that baseline CD4+ count <200 cells/mm3 was independently associated with increased risk of TB(33).

Although the risk of TB is lower in ART groups compared with pre-ART groups, they are still at risk of developing TB. Different studies revealed that the risk of TB in HAART group associated with baseline CD4+ count< 50cells/μL(36). Among those with baseline CD4 cell counts less than 200cells/ μL, the excess risk of TB during early ART might be due to missed TB cases at baseline screening. On the other hand an increase of CD4+ by 100 cells/ μL was associated with 25% lower risk of developing TB. In addition to this, a higher CD4+ cell count at the time of starting HAART was independently associated with a reduced incidence of TB (37).

2.5.2. Isoniazid Preventive Therapy on TB Incidence

Prophylaxis with the isoniazid (INH) has been shown to reduce the incidence of TB in HIV infected persons either by eradicating latent infection and or preventing progression of new infection to active TB(38). A Meta analysis of (seven randomized trials) six months preventive therapy with INH was shown that reduces in incidence of TB in HIV infected people with relative risk (RR) of 0.58 on INH treated Vs placebo for TB(39). Another retrospective study carried out in Rio D Janeiro, Brazil, reported that the combination of ART and IPT has the greatest impact on TB incidence when compared to IPT or ART alone (33)and provides further impetus to provide IPT in all HIV infected persons irrespective of whether they are or are not on ART. This approach would conform with the observation that the risk of TB in HIV infected persons remains higher than that in non-HIV infected persons even when on ART(40)

2.5.3. Personal habits

The other study conducted in India forwarded that People who use chat along with ART medications are at risk to develop OIs than those who don't use khat. Study conducted in resource limited setting in Nigeria also found alcohol consumption and smoking to have no association with occurrence of OIs among HIV patients taking ART. The study conducted in Northwest Ethiopia showed that Patients who used to chew khat was found to be at risk for OIs occurrence. Alcohol use and cigarette smoking were not found to be associated with occurrence of OIs among HIV patients taking ART(41).

2.5.4. Other Important Factors Related to Development of TB in HIV Positive Individual

Regarding to socio demographic factors, the most affected age groups with active tuberculosis are patients between 15 to 44 years old. In this age group, 20 to 70% of the new cases are patients with HIV infection (1). In addition to this male gender is independently associated with at higher risk of TB(22)(31).Evidences also shows that, Infection with HIV, Diabetes mellitus, Low body weight, Head or neck cancer, leukemia, or Hodgkin's disease are related to the development of TB. Some medical treatments, including corticosteroids or certain medications used for autoimmune or vasculitic diseases such as rheumatoid arthritis or lupus, which suppress the immune system are associated with TB incidence(42)

Another important clinical predictor for incidence of TB is WHO clinical staging. A number of studies showed that patients in WHO clinical stage III or IV were in higher risk of developing tuberculosis than stage I or II. The possible reason stated was immune-compromised state due to reduced CD4+ number and advanced HIV disease(36)(43)

2.6 Time of TB Occurrence after IPT Completion

The median follow- up period after IPT completion was 16 months. The majority (79.9%, n=310) of the patients were followed over a 12 month period(11). The median follow-up period between IPT completion and TB diagnosis was 13 months. No TB cases were diagnosed before 6 months after IPT completion. Four TB cases were diagnosed between six and twelve months, and after 12 months of IPT completion, respectively(11). The overall 16 month cumulative survival TB-free and cumulative hazard of TB incidence was 97.5%, and 2.5% after IPT completion, respectively. The

median duration of follow- up was 40 months (inter-quartile range, 28–52 months). From those who completed IPT, active TB has occurred between 6 and 28 months duration. Almost 50% of patients who completed IPT developed active TB at 19thmonth; while in non-exposed patients TB occurred within a month time of enrollment(44).

As cited by Taraz(45), Authors of a recently published prospective trial conducted in South African gold mines indicates that a more than twice of TB incidence almost immediately after a 9 month course of IPT and attributed it to the intense infection pressure of this environment. In contrast to that, an IPT trial conducted among TST-positive HIV-infected participants mostly from the United States a nonendemic setting showed a more than 4-year durability of 12 months' IPT(45) (46). A study which is done at University of Pennsylvania shows that, morbidity during the period of study was more frequent in patients who did not receive Isoniazed Preventive therapy (50/92 or 54%) than in patients who received isoniazid preventive therapy (7/29 or 24%). Median survival was more than 111 months in patients who received isoniazid compared with 75 months in patients who did not receive isoniazid(47).

2.8 OIs prophylaxis

The study conducted in Eastern Ethiopia as cited by (41) showed that participants who were not on co-trimoxazole and INH prophylaxis were more likely develop OIs compared to their counterparts who were on co-trimoxazole prophylaxis. The study conducted in Gondar University Hospital, Northwest Ethiopia reported, Prevalence of OIs was higher among patients who were not on co-trimoxazole prophylaxis compared to their counter parts who were on cotrimoxazole prophylaxis.

2.7 Conceptual frame work

After extensive review and consideration of many literatures(41)(36)(48) to show the potential relationship between TB Incidence, predictors and TB free survival time with factors, this is to show how the particular variables in the study are related to each other and identify the variables required in the research investigation process. Age and sex affect the initiation of Prophylaxis (43) and CD4, clinical stage, Hgb, BMI, Wt affect prophylaxis effectiveness mostly(36).

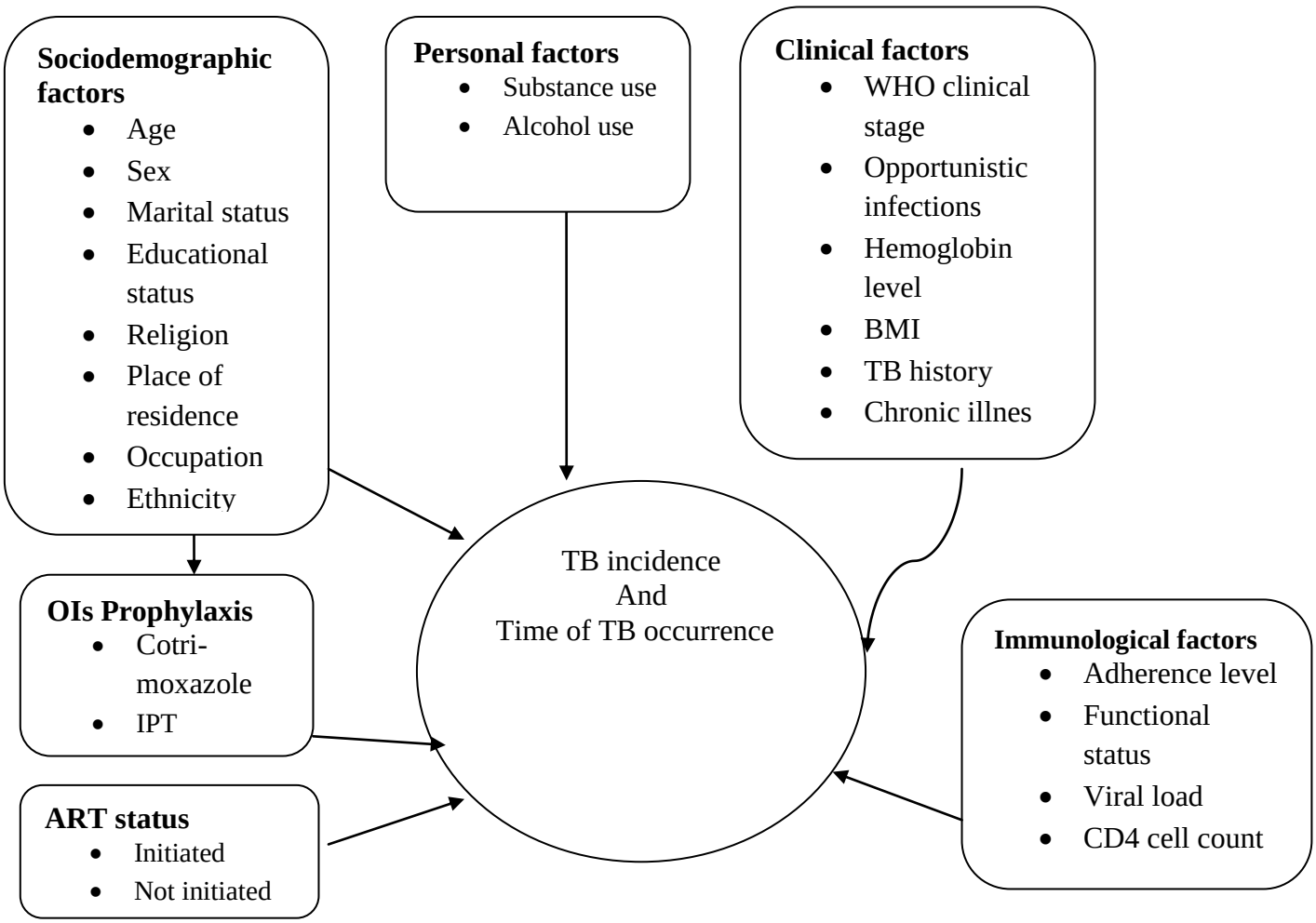

Figure 1: conceptual frame work developed by principal investigator after literature review (47, 36, and 48) for TB incidence, predictors and TB free survival time on adult HIV patients who completed IPT in Hawassa University comprehensive specialized Hospital.

3. OBJECTIVES

3.1 General Objective:

To determine Tuberculosis incidence, predictors and Tuberculosis free Survival time among Human Immune Virus infected adult patients who completed Isoniazid preventive therapy in Hawassa Referral Hospital.

3.2 Specific Objectives:

1. To determine TB incidence rate among HIV positive patients who completed IPT in Hawassa comprehensive specialized Hospital.
2. To determine predictors of TB incidence among HIV positive patients who completed IPT in Hawassa comprehensive specialized Hospital.
3. To determine TB free survival time among HIV positive patients who completed IPT in Hawassa comprehensive specialized Hospital.

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4. RESEARCH METHODOLOGY

4.1. Study setting and Period

The study was conducted in Hawassa University Specialized Hospital providing ART and IPT service in Hawassa City Administration. It is located 273 km (170 mi) south of Addis Ababa via Bishoftu, 130 km (81 mi) east of Sodo, and 75 km (47 mi) north of Dilla. The town servesasthecapitalofthe SidamaRegion andthe SouthernNations,Nationalities,andPeoples'Region.Itli eslongitudeof 7°3′N 38°28′ECoordinates: 7°3′N 38°28′E and an elevation of 1,708 meters (5,604 ft) above sea level. Amharic, sidamuma and Wollaitato is widely spoken in the city.

The study design utilized was a health institution based retrospective cohort study of HIV-positive adults who had completed IPT. Hence, the charts of HIV-positive patients who initiated IPT between May, 2015 to July, 2016 were reviewed retrospectively from the date of IPT completion until the end of data collection date. The totals of 483 samples were included in analysis. The samples were selected with simple random sampling.

4.2 Study Design*:* The study design utilized a Health- institution based retrospective cohort study of HIV-positive patients who had completed IPT. Hence, the charts of HIV-positive patients who initiated IPT between May, 2015 to July, 2016 were reviewed retrospectively from the date of IPT completion until the end of data collection date.

4.3 Population

4.3.1 Source Population: The source population was all PLWH who had initiated IPT in Hawassa comprehensive specialized hospital and are provided with ART and IPT service.

4.3.2 Study Population*:* The study population was all PLWH who had Started IPT Between May 2015 to July 2016 and had completed the six-month regimen of IPT from the date of initiation. Study subjects were stratified based on completion status of IPT (Completed and Non completed).

4.4. Eligibility criteria

4.4.1. Inclusion Criteria

IPT completers-Adult patients enrolled on ART, aged 15 and above, who were free of active TB and who had completed six months of Isoniazid therapy from May, 2015 to July, 2016 with

complete intake form, registers, follow up form were considered eligible candidates and were included in the exposed group and will be included in the study.

IPT non completers- Adult patients enrolled on ART, aged 15 and above, who were free of active TB and never completed IPT were included.

4.4.2. Exclusion Criteria

All individuals on ART follow up who were unexposed to IPT, whose record is incomplete; who have had past history of TB, Active TB or on treatment of TB were excluded on the study.

4.5 Sample Size Determination

Minimum sample size will be determined by using single population proportion sample size calculation formula with the assumption of 9.7% of the overall incidence of TB on ART and IPT exposed patients from previous similar studies(12),

$$n = \frac{\mathrm{Z}\alpha/2^2\ \mathrm{P}q}{(\mathrm{d})^{\ 2}}$$

Where:

n = sample size

P = proportion of tuberculosis incidence among HIV positive adult patients, 9.7 %(36)

q = 1-p

d = Margin of error (5%)

Z α/2 = is the standard normal value at the level of confidence desired, usually at 95% confidence level

N= $(1.96/0.05)^2$ (0.097) (0.903)

= 134 and after adding 10% contingency rate, the final sample size will be 148

For the second objective, the sample size was determined using double population proportion formula by considering CD4, bed ridden and ambulatory functional status and WHO stage as the major predictor variables(48). Moreover, CD4 is considered as independent predictor since it gives the maximum sample size. Sample size will be calculated by using open Epi info version 7 statistical package.

$$n_1 = \frac{\left[Z_{\alpha/2}\sqrt{\left(1+\frac{1}{r}\right)P(1-P)} + Z_{\beta}\sqrt{\frac{P_1(1-P_1)+P_2(1-P_2)}{r}}\right]^2}{(P_1-P_2)^2}$$

$$where, p = \frac{p1 + rp2}{r+1}, if\ r = 1\ then\ p = \frac{p1+p2}{2}$$

P1: is percent of completed with the outcome

P2: is percent of non-completers. with the outcome

Z $_{\alpha/2}$: is taking CI 95%: 80% power

r: is the ratio of non-completers to completers1:1

Table 1: sample size calculation to assess the incidence of tuberculosis and its predictors among HIV positive Adult patients on ART and completed IPT in Hawassa University Comprehensive specialized Hospital based on TB case, Sidamma, Ethiopia from May 2015-Junne 2016. (n=483).

S.N	Variables	CI	Assumptions	Total sample size	Reference
1.	CD4	95%	P1=54% P2=7.5%	483	(12)
2.	WHO stage	95%	P1=65% P2=34%	92	(29)
3.	Bedridden functional status	95%	P1=66% P2=33%	88	(29)

P1: is percent of completed with the outcome
P2: is percent of non-completed with the outcome

Z $_{\alpha/2}$: is taking CI 95%
: 80% power

- r is the ratio of non-completers to completers 1:1
  - ✓Then the largest sample size (n= 483).

Sample size for specific objective three (TB free survival status) was calculated by using power and sample size calculations developed by (Dupont and Plummer, 1998) by using the assumptions:

The researcher used an accrual interval of 0 time units, and additional follow-up after the accrual interval of 60 time units. Prior data indicate that the median survival time on the control treatment

is 111 time units. If the true median survival times on the control and experimental treatments are 111 and 70 time units, respectively, I will need to study 150 experimental subjects and 300 control subjects to be able to reject the null hypothesis that the experimental and control survival curves are equal with probability (power) .800. The Type I error probability associated with this test of this null hypothesis is 0.05.

Considering the following:

α=0.05, P=80% ,A=0 , m1=70months , m2=111months , F=60 months and m=1, then by using this information's and inserting to PS(power and sample size calculations)the calculated sample size become 450.

Where,

m1=median survival time at control group

m2= median survival time at experimental group

α=0.05,

P=80%

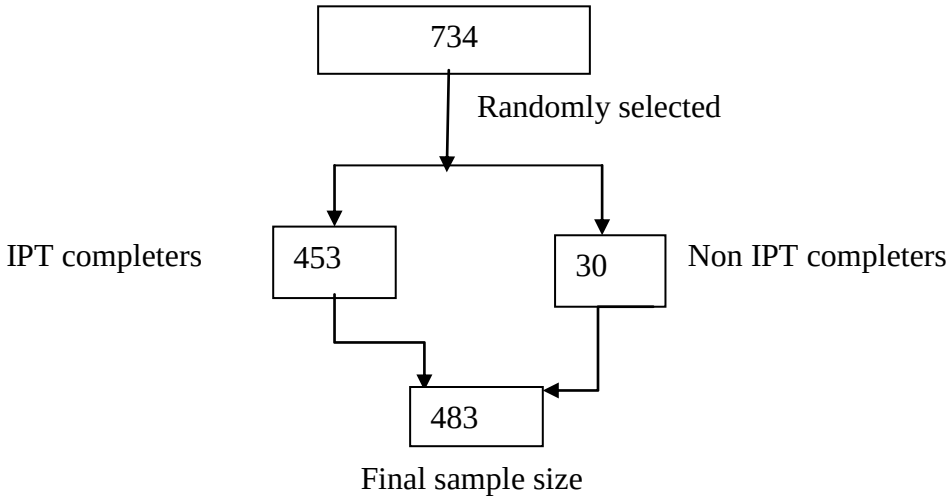
A=Acural time during which patients are recruited=0

F= Additional follow up time after end of recruitment=60

m=Ratio of control to experimental patients=1(47)

4.6 Sampling Procedures and frame

Hawassa University Comprehensive and specialized Hospital was selected for the study purposively to get adequate number of sample and optimal follow up period. For those who fulfill inclusion criteria, unique ID number was given in increasing order for ART groups. Then simple random sampling technique was employed separately to select 483 samples from each group using computer generated random number table. Those patients who started ART and IPT services earlier were selected to have long follow-up data. The calculated final sample size was 483. But because the sample was not inadequate the principal investigator decided to review all eligible adult clients charts who initiated IPT between May, 2015 to July, 2016 and had completed their six month regimens of IPT in HIV-chronic care on the facilities.



4.7 Data Collection Methods and Instrument

4.7.1 Data Collection instrument

The data extraction tool was developed from the format of WHO standardized ART entry and follow up form currently used by the ART clinics. Data collectors used the data collection tool to collect the information from patients' cards and register. To ensure consistency of the data, HIV care forms, ART follow-up forms with the IPT register including the patient intake form, the ART registers, and finally, the patient clinical files were used to extract the study data. The data was collected using an altered and structured checklist from the HIV care ART and IPT follow-up forms.

4.7.2 Data collection method/Procedure: four data collectors and two supervisors who have a bachelor degree in health science (Bsc) in nursing and Public health and been trained with ART and/or are working in ART clinics were recruited for data collection. In addition data collectors were trained on the check list in order to get common understanding and make aware of the context of each question. List of enrolled clients were obtained from ART and IPT follow up chart.

4.7.3 Pre test- The pre test was done in Yiggalem Teaching Hospital using cronbach alpha test for reliability. And values >0.7 were considered for high internal consistency.

Data quality Control: To keep data quality, supervisor and data collectors were oriented on how and what information they should collect from the targeted data sources. The prepared checklist was pretested in on the actual site before actual date of data collection and any correction was made based on the finding. Proper categorization and coding of the data Completeness and consistency of

the collected data was checked on daily bases during data collection by supervisor and the principal investigator. Whenever there appears incompleteness and ambiguity of recording, the filled information formats was crosschecked on daily basis with source data and feedback was given to data collectors to encourage accuracy. Individual records with incomplete data were excluded. Double entry and data cleaning was also considered.

4.9 Entry and Analysis

The Collected data was coded, cleaned and explored to identify outliers, missing values, and inconsistencies. The coded data were checked for completeness and entered into Epidata version 4.6.2. An analysis was done based on 5-year cohort follow up. Finally, data was exported to SPSS version 25.0 for analysis. Descriptive statistics of numeric variables are presented in medians with interquartile range (IQR), categorical variables are presented using frequency and percentages. TB-free survival time was estimated by applying the Kaplan–Meier Log-rank model to estimate the Occurrence time of TB based on explanatory variables. Bivariate and multivariable Cox proportional hazards regression models were performed to the independent predictors of TB incidence.

4.10. Study Variables

4.10.1 Dependent variable

- ✓ Developing TB
- ✓ Time to occurrence of TB

4.10.2 Independent variable

- ✓ Exposure variable: IPT status (IPT Completion)

Socio demographic, Clinical and other variables: Age, sex, gender, education status, marital status, occupation status, weight, CD4+ count at the start of IPT, prophylaxis (IPT and CTX), Hemoglobin level, opportunistic infection, adherence level for IPT, WHO clinical stage at the start of IPT, time of ART initiation, functional status, and a baseline nutritional status using the BMI formula.

4.11. Operational Definitions

The primary outcome variable was 'incident TB', defined as: The diagnosis of TB was defined as either presumptive or definitive. A diagnosis of presumptive pulmonary TB was determined by a consistent clinical picture of more than 30 days, presence of AFB mycobacterium in sputum, bronchoalveolar lavage or other sterile specimen, lack of response to standard antibiotic therapy and/or successful response to standard anti-TB treatment in one month. A diagnosis of definitive TB will be determined by a consistent clinical picture and positive culture for isolation of M. Tuberculosis(19).

Survival- Lack of experiencing TB

Past history of TB: defined as pervious history of TB before the first date of registration on pre ART or ART log book.

IPT eligible: PLHIV without active TB or not diagnosed with TB within 3months of ART registration in whom there is no documented evidence of liver disease, active alcohol use, jaundice, prior isoniazid resistance, peripheral neuropathy and unexplained illness in the 'ART register' during initial assessment.

IPT initiation: IPT is said to be initiated when the eligible PLHIV receives IPT after eligibility assessment.

IPT user: A person on chronic HIV care follow-up, who took full course of IPT (6 month) before diagnosed for TB.

Patient on ART: A person on chronic HIV care follow-up and started taking ART

IPT completion: The IPT is said to be completed if the individual started on IPT receives it during six consecutive visits to ART centre and is indicated as 'IPT completed' in 'IPT register'

Smear negative pulmonary tuberculosis (PTB) - was diagnosed if at least three sputum specimens negative for AFB and radiologic abnormalities consistent with TB, and no response to a course of broad-spectrum antibiotics and decision by a physician to treat with a full course of anti-tuberculosis chemotherapy.

EPTB refers to TB of organs other than the lungs, and diagnosis was based on strong clinical suspicion by a physician.

WHO clinical staging system was considered to staging HIV/AIDS

Functional status

- Working = able to perform usual work in or out of the house

- Ambulatory= able to perform activities of daily living
- Bedridden= not able to perform activities of daily living

Employment status

Working full time = if the patient is full time employee

Working part time = if the patient works on part time base

Not working = if the patient couldn't work due to HIV/AIDS related problems

Unemployed = if the patient doesn't work due to not HIV/AIDS related problems but other factors

Event: - PLWHIV on ART, who developed TB during the study period.

Entry date:- First date for each observation within study period at date of HIV/AIDS confirmation.

End date: - Last date for each observation within the study period that subject visited last.

Incomplete Records: - cards with incomplete information for main variables

Complete Records: - Cards with complete information for main variables

Body Mass Index: A measurement used to assess nutritional status and measured as weight divided by height square. For adult, if not malnourished (BMI>18.5 kg/m2), if malnutrition (BMI<18.5 kg/m2) (40).

Censored= PLWH on ART, who didn't develop TB till the last date of study period, drop out, lost to follow up or death.

There are three categories of censoring.

i) **Right censoring**: Survival time is said to be right censored when it is recorded from its beginning to a defined time before its end time. This type of censoring is commonly recognized survival analysis and also considered in this study.

ii) **Left censoring**: Survival time is said to be left censored if an individual develops an event of interest prior to the beginning of the study; this is not common in survival studies.

iii) **Interval censoring**: Survival time is said to be interval censored when it is only known that the event of interest occurs within an interval of time but the exact time of its occurrence is not known.

High viral load- >1000copies/ml

Anemia- If the participant Hemoglobin level was less than 11

4.12. Ethical Considerations

The study used the routine existing admission and patient record data. Ideally, it was preferable to have informed consent from the subjects of the study, even if there is no direct contact with them, but it is difficult to get them. However, all the necessary measures were taken to maintain and assure the privacy, confidentiality and all benefits of the patients. Charts were reviewed at separate room, no mention is made about the names of the patients and care providers or anything related to the study. Moreover, confidentiality of the information was assured through using anonymous check list and keeping the data in secured place. On the other side, the findings of the study is believed to benefit the patients indirectly through improvement of health care system; which will maximize the benefit and minimize the harm. Ethical clearance and support letter was obtained from Addis Ababa University College of health science school of Nursing and midwifery ethical review committee and written permission will be obtained from the Hospital administration before starting data collection.

4.13 Dissemination of results

The result of this proposal thesis will be disseminated or communicated to Hawassa University Comprehensive and specialized Hospital, Addis Ababa University School of Nursing, and other concerned bodies through Conferences, reports as well as publication on world class journal.

5. RESULTS

5.1 Description of studies

5.1.1 Base line Socio-demographic characteristics of the Study Subjects

The study showed that, a total of 734 HIV-positive patients were initiated IPT between May, 2015 and July, 2016.Out of those 251 were excluded because 133 did not have a patient clinical folder, 20 were less than 15 years of age, and 98 patients had not Initiated the 6 month IPT regimen. Therefore, a total of 483 HIV-positive adults who were on 6 months of IPT prophylaxis were analyzed. The result of the study shows that Female participants of the study account for 54.2% (n=262) (Table2). At the base line, the mean age was 32.8 years [IQR=22- 44] with SD=12.8. The majority of the study subjects were from urban 61.5% (297) and the remaining 186 (38.9%) were from rural area. The study also shows that the majority of study participants 169(35.0%) were Protestants and the least number 11(2.3%) were the followers of other kind of religions such as Adventist or seculars (Table 2).

More than half of the study subjects were married (56.1%, n=271) and 87.2% (n=285) had a primary education and above. Out of the 247(48.9%) patients recorded as substance users, 88(18.2%) were chat chewers, 74(15.3%) alcohol consumers and 43(8.9%) used both (Table 2). The study also reveals that from the study subjects 123 (25.5%) were government employed, Farmers were 27 (11.8%), Trader were 111 (23%), Non-Government Employed were 42 (8.7%), day laborer 44 (9.1%), Jobless 32 (6.6%), Driver 39 (8.1%), and other groups of participants such as Retired/housewives/Student(other)and around 35 (7.5%). Regarding the age demography, young people's whose age category was between 18-39 were scored a large number of patients which is 322 (66.7%) but the middle age and elderly people were less numbered which was 139 (28.8%) and 22 (4.6%) respectively among the research subjects. 391 (81.5%) of the participants were under the category of the family size of <=5 (Table 2).

Table 2 : Socio-demographic characteristics of HIV patients who were enrolled for IPT care at Hawassa University Comprehensive specialized Hospital, Sidamma, Ethiopia from May 2015-Junne 2016. (n=483).

Characteristics	Frequency	%
Age in years [mean=32.8, SD=12.8]		
18-39	322	66.7
40-59	139	28.8
>=60	22	4.6
Sex		
Male	221	45.8
Female	262	54.2
Residence		
Urban	297	61.5
Rural	186	38.9
Marital Status		
Never Married	107	22.2
Married	271	56.1
Separated	35	7.2
Widowed	21	4.3
Divorced	49	10.1
Religion		
Protestant	169	35.0
Orthodox	225	46.6
Muslim	52	10.8
Catholic	26	5.4
Other	11	2.3
Substance Use		
Yes	247	48.9
No	236	51.1
Type of Substance Use		
No	246	50.9
Tobacco/Cigarette	32	6.6
Alcohol	74	15.3
Tobacco and alcohol	43	8.9
Chat	88	18.2
Educational Status		
No education	62	12.8
Primary	150	31.1
Secondary	177	36.6
Tertiary	94	19.5

Occupation		
Farmer	57	11.8
Merchant/Trader	111	23
Government Employed	123	25.5
Non-Government	42	8.7
Employed	44	9.1
Day Laborer	32	6.6
Jobless	39	8.1
Driver	35	7.0
Retired/house w./Student (other)		
Family size		
<= 5	391	81.0
6-8	85	17.6
>=9	7	1.4

The table below (Table 3) shows that half of the participants who are old adults are shown greater increase in the development of Tuberculosis as compared to other age groups 11 (50%). Regarding the sex of the participants, a female patient accounts more of male participants 49 (18.7%). Married individuals are also the ones who develop TB in a larger number between marital status of the patients 25 (9.2%). Patients who are exposed to substance abuse are also contract tuberculosis compared to not exposed 42 (17.2%). Traders develop tuberculosis more12 (11.1%) according to this particular study and the least are nongovernmental organization (NGO) workers 3 (7.1%) respectively.

Table 3: Socio-demographic characteristics of HIV patients who were enrolled for IPT care at Hawassa University Comprehensive specialized Hospital based on TB case, Sidamma, Ethiopia from May 2015-Junne 2016. (n=483).

Characteristics	Status at last contact		Total
	TB Occurred	Censored	
Age in years [mean=32.8, SD=12.8]			
18-39	23 (7.1%)	298 (92.9%)	321 (66.8%)
40-59	21 (15.3%)	116 (84.6%)	137 (28.5%)
>=60	11 (50%)	11 (50%)	22 (4.5%)
Sex			
Male	6 (2.7%)	213 (97.2%)	219 (45.6%)
Female	49 (18.7%)	212 (81.2%)	261 (54.3%)
Marital Status			
Never Married	19 (17.7%)	88 (82.2%)	107 (22.2%)
Married	25 (9.2%)	245 (90.7%)	270 (56.2%)
Separated	2 (5.8%)	32 (94.11%)	34 (7.1%)
Widowed	1 (4.7%)	20 (95.2%)	21 (4.3%)
Divorced	8 (16.6%)	40 (83.3%)	48 (10%)
Religion			
Protestant	15 (8.8%)	154 (91.1%)	169 (35.2%)
Orthodox	33 (14.8%)	189 (85.1%)	222 (46.2%)
Muslim	3 (5.7%)	49 (94.2%)	52 (10.83%)
Catholic	3 (11.5%)	23 (88.4%)	26 (54.2%)
Other	1 (9.2%)	10 (90.9%)	11 (2.2%)
Substance Use			
Yes	42 (17.2%)	202 (82.7%)	244 (50.2%)
No	13 (5.5%)	223 (94.4)%	236 (49.1%)
Type of Substance Use			
No	23 (9.4%)	222(90.6%)	245 (51.04%)
Tobacco/Cigarette	6 (18.7%)	26(81.2%)	32 (6.6%)
Alcohol	11 (14.8%)	63 (85.1%)	74 (15.4%)
Tobacco and alcohol	6 (14.2%)	26 (61.9%)	42 (8.7%)
Chat	9 (10.3%)	78 (89.6%)	87 (18.1%)
Educational Status			
No education	6 (9.6%)	56 (90.3%)	62 (12.9%)
Primary	25 (16.7%)	124 (83.2%)	149 (31.04%)
Secondary	19 (10.7%)	157 (89.2%)	176 (36.6%)
Tertiary	5 (5.37%)	88 (94.6%)	93 (19.3%)
Occupation			
Farmer	7 (12.2%)	50 (87.7%)	57 (11.8%)
Merchant/Trader	12 (11.1%)	97 (88.9%)	109 (22.7%)
Government Employed	11 (8.94%)	112 (91.1%)	123 (25.6%)

Non-Government	3 (7.1%)	39 (92.8%)	42 (8.7%)
Day Laborer	7 (15.9%)	37 (84.1%)	44 (9.1%)
Jobless	5 (16.1%)	26 (83.8%)	31 (6.4%)
Driver	5 (12.8%)	34 (87.1%)	39 (8.1%)
Retired/housewives/Student (other)	4 (14.8%)	30 (88.2%)	34 (7.1%)
Family size			
<= 5	51 (13.2%)	337 (85.5%)	385 (80.2%)
6-8	4 (4.7%)	81 (95.2%)	85 (17.7%)
>=9	0 (0%)	7 (100%)	7 (1.45%)

**** 3 Missing values were considered.***

5.1.2 Base line Clinical characteristics of the Study Subjects

At time of IPT initiation, there were a total of 483 participants who fulfill the information for analysis, more than half 281(58.2%) had a baseline WHO clinical stages I and II 138 (28.6%), were in clinical stage III and 64 (13.3%) were in stage IV. Almost half 258 (53.4%) of the participants were underweight (BMI less than 18.5kg/m^2) (Table 3). The majority of the patients 466 (96.5%) were in the functional status of working, 15 (3.1 %) were ambulatory and 2 (0.4%) were bed ridden. The median CD4 count during enrollment and end of follow up was 456 (IQR, 314-661) and 231 cells/ µL (IQR, 105-400) cells permm^3, respectively and body mass index (BMI) was 20.29 kg/m^2 (IQR, 18.49-22.36). More than three-quarters 390 (80.7%) were not anemic (Hgb >11mg/dl). During the 5-year retrospective follow-up, most 368 (76.2%) of the participants were provided with CPT. The result also shows that most patients 413 (86.04) are under the category of >200ml/mm^3 and almost all patients initiated ART before IPT initiation.

Most patients have no previous TB disease history 386(79.9%). The number of patients who don't have chronic illness is much more 466 (96.5%) than that of who do have. In the follow up the type of TB which was seen in the participants was Pulmonary Positive which accounts around 42 (75%) and the less frequent kind of TB was combined kind 8(14.3%) (Table3). As can be seen from the table, much percentage 407 (84.3%) of the study participants has the minimum viral load. From the study participants 390 (80.7%) are classified under normal range hemoglobin amount which is more than half percentile. The number of participants who developed anemia were less around 93 (19.3%) which is significantly fewer (Table 3).

Table 4: Clinical characteristics of HIV patients who were enrolled for IPT care at Hawassa University Comprehensive specialized Hospital, Sidamma, Ethiopia from May 2015-Junne 2016. (n=483).

Characteristics	Frequency	%
WHO clinical Stage		
I and II	281	58.2
III	138	28.6
IV	64	13.3
CD4 cell count(Cells/µL)		
< =200	67	13.9
>200	413	86.04
Median of current CD4 count=456cells/µL, (IQR, 314-661) and 231 cells/ µL (IQR, 105-400)		
BMI		
<18kg/m^2	258	53.4
>18kg/m^2	225	46.6
Median BMI= 20.29 kg/m^2 (IQR, 18.49-22.36)		
Functional status		
Working	466	96.5
Ambulatory	15	3.1
Bed ridden	2	0.4
CPT use		
Yes	368	76.2
No	115	23.8
IPT Completed		
Yes	454	93.9
No	29	6.0
Previous TB disease		
Yes	97	20.1
No	386	79.9
Chronic illness		
Yes	17	3.5
No	466	96.5
Form of TB		
Pulmonary positive	42	75.5
Pulmonary negative	3	5.4
Extra Pulmonary	3	5.4
Combined	8	14.3
Viral load		
<1000 copies/ml	407	84.3
>1000 copies/ml	76	15.7
Hemoglobin		
>=11mg/dl (Normal)	390	80.7
< 11mg/dl (Anemia)	93	19.3

**** 3 Missing values were considered.***

More than half percentiles of the WHO clinical Stage IV patients were seen developing TB in comparison to other WHO stages 33(52.3%) (Table 5). Study participants whose CD4 cell counts (Cells/µL) were less than 200 were Tuberculosis developers 32(47.7%). Less BMI patients experience TB than more BMI patients 46(17.8%). Patients who have previous history of TB disease were also contract TB disease 35(36.1%). More viral load 33(44.0%) and less Hemoglobin count 35(38.04%) participants develop TB in certain manner (Table 5).

Table 5: Clinical characteristics of HIV patients who were enrolled for IPT care at Hawassa University Comprehensive specialized Hospital, Sidamma based on TB case, Ethiopia from May 2015-Junne 2016. (n=483).

Characteristics	**Status at last contact**		**Total**
	TB Occurred	**Censored**	
WHO clinical Stage			
I and II	9 (3.2%)	271(96.7%)	280(58.3%)
III	13(9.4%)	124(90.5%)	137(28.5%)
IV	33(52.3%)	30(47.6%)	63(13.1%)
CD4 cell count(Cells/µL)			
< =200	32(47.7%)	35(52.2%)	67(13.9%)
>200	23(5.5%)	390(94.4%)	413(84.04%)
Medium of current CD4 count=456cells/µL, (IQR, 314-661) and 231 cells/ µL (IQR, 105-400)			
BMI			
<18kg/m^2	46(17.8%)	211(82.1%)	257(53.5%)
>18kg/m^2	9(4.03%)	214(95.9%)	223(46.4%)
Medium BMI= 20.29 kg/m^2 (IQR, 18.49-22.36)			
CPT use			
Yes	47(12.8%)	319(87.1%)	366(76.2%)
No	8(7.01%)	106(92.9%)	114(23.7%)
Previous TB disease			
Yes	35(36.1%)	62(63.9%)	97(20.2%)
No	20(5.22%)	363(94.7%)	383(79.7%)
Chronic illness			
Yes	11(64.7%)	6(35.2%)	17(3.5%)
No	44(9.5%)	419(90.4%)	463(94.6%)

Form of TB			
Pulmonary positive	42(100%)	0	42(76.3%)
Pulmonary negative	2(66.6%)	1(33.3%)	3(5.45%)
Extra Pulmonary	3(100%)	0	3(5.45%)
Combined	7(100%)	0	7(12.7%)
Viral load			
<1000 copies/ml	22(5.4%)	283(69.8%)	405(84.3%)
>1000 copies/ml	33(44.0%)	42(56.0%)	75(15.6%)
Hemoglobin			
>=11mg/dl(Normal)	20(5.1%)	368(94.8%)	388(80.8%)
< 11mg/dl(Anemia)	35(38.04%)	57(61.9%)	92(19.1%)

**** 3 Missing values are considered.***

The log-rank test was done to validate the occurrence of any significant differences in Tuberculosis (TB) free survival time among various levels of the categorical variables which are considered in the study. According to the Kaplan-Meier analysis indication, significant evidence of differences in survival times in the categories of sex, functional status, WHO clinical staging, Age of the patient, Viral load, Hemoglobin and IPT completion (Table 6). The Kaplan-Meier survival function (Table 6) indicated a significantly higher survival of patients with the baseline characteristics of clinical stage I and II disease (58.36%; 95% CI, 57.30 to 59.43%), working functional status (57.91%; 95% CI, 56.77 to 59.05%), Age of the patient (18-39) (56.57%; 95% CI, 55.14 to 57.95%), Being female (58.46%; 95% CI, 57.23 to 59.70),Viral load (57.38%; 95%CI, 56.25 to 58.51%), IPT completion (59.16%; 95% CI, 59.95 to 57.42%), Hemoglobin (57.50%; 95% CI, 56.39 to 58.61%) and BMI (50.38%; 95% CI, 47.97 to 52.78). The lowest survival probabilities were observed on patients who did not completed IPT prophylaxis with a value of (24.87%), age greater than 60 (32.64%), Bed ridden patients (38.75%), a viral load >1000 copies/ml (37.88%), and WHO stage IV disease (43.7%) (Table 6).

Table 6: Baseline characteristics and probability of TB free survival during 5-year of follow-up (Kaplan-Meier method) of HIV patients receiving IPT, Hawassa University Comprehensive specialized Hospital, Sidamma, Ethiopia from May 2015-Junne 2016. (n=483).

Characteristics (Variables)	**Mean survival time/Probability in month over 5 yr (95% CI)**	**Log rank test**	**Overall 5-year TB-free Survival (%)**	**P-value**
Age of the patient				
18-39	56.57 (55.14,57.95)		74.6	< 0.002
40-59	52.58 (49.57,55.48)		57.2	
>= 60	32.64 (28.36,36.84)	91.22	9.4	
Sex				
Male	58.46(57.23,59.70)		87.0	
Female	51.61(49.50,53.72)	19.66	54.30	< 0.001
WHO clinical stage				
I and II	58.36 (57.30,59.43)	113.37		
III	54.95 (52.32, 57.59)		87.5	0.030
IV	39.85 (35.43, 44.26)		63.6	
			13.9	
BMI				
<18kg/m^2	50.38 (47.97,52.78)	30.14	48.4	
>=18kg/m^2	58.28 (57.06,59.50)		82.9	0.074
Viral load				
<1000 copies/ml	57.38 (56.25,58.51)	130.94		
>1000 copies/ml	37.88 (33.12,42.64)		75.4	< 0.01
			17.5	
Functional status				
Working	57.91 (56.77,59.05)		90.7	
Ambulatory	50.15 (46.53,53.78)	98.86	38	< 0.015
Bed ridden	38.75 (32.79,44.71)		7.8	
IPT completed				
Yes	56.19 (54.95,57.42)	29.7	68.9	
No	24.87 (19.54,30.20)		18.7	< 0.001
Hemoglobin				
	57.50 (56.39,58.61)	88.28	75	
>=11mg/dl(Normal)	41.27 (36.85,45.70)		32.2	0.002
<11mg/dl(Anemia)				

5.1.3 Baseline clinical information of HIV positive patients Based on IPT completion status

As shown in Table 7, most patients who admitted to the retrospective cohort with IPT exposure (completion/non completion) has manifested WHO clinical stage of I and II which is 266(55.1%) while the least number are admitted with stage IV 59 (12.2%). The CD4 count of the patients who were completed the prophylaxis was higher in number 454(93.9%) with medial CD4 count of CD4 count=456cells/µL, (IQR, 314-661) and 231 cells/ µL (IQR, 105-400). Majority of participants whose BMI <18kg/m2 were IPT completers with the number and percent of 454 (93.9%). The CPT coverage among Completers was 364(75.3%) and 454(93.9%) of the patients were screened for TB among IPT completers. The findings of the cohort also indicates that 381(78.8%) of the IPT completer participants were have the viral load > 1000 copies/ml. The overall hemoglobin count of the study participants among IPT completers was 367(75.9%) and the hemoglobin count among IPT completers was high 367(75.9%) (Table 7).

Table 7: Baseline clinical information Based on IPT completion status in Hawassa University Comprehensive specialized Hospital, Sidamma, Ethiopia from May 2015-Junne 2016. (n=483).

Characteristics	IPT completed N (%)	Not completed N (%)	Total N (%)
WHO clinical Stage			
I and II	266(55.1%)	15 (3.1%)	281(58.1%)
III	129(26.7%)	9 (1.9%)	138 (28.5%)
IV	59(12.2)	5(1.03%)	64 (13.2%)
CD4 cell count(Cells/µL)			
< 200	66 (13.6%)	5 (0.6%)	69(14.2%)
>=200	388(80.3%)	26 (5.3%)	414 (85.7%)
Median of current CD4 count=456cells/µL, (IQR, 314-661) and 231 cells/ µL (IQR, 105-400)			
BMI			
<18kg/m^2	247 (51.1%)	11 (2.2%)	258 (53.4%)
>18kg/m^2	207(42.8%)	18 (3.7%)	225(46.5%)
Medium BMI= 20.29 kg/m^2 (IQR, 18.49-22.36)			
CPT use			
Yes	364(75.3%)	4(0.8%)	368(76.2%)
No	114(23.6%)	1(0.2%)	115 (24%)

TB screen			
Yes	454(93.9%)	29(6.01%)	483 (100%)
No	0	0	0
Viral load			
<1000	381(78.8%)	26(5.3%)	407(84.2%)
>1000	73(15.1%)	3(0.6%)	76(15.7%)
Hemoglobin			
>=11mg/dl(Normal)	367(75.9%)	23(4.7%)	390(80.7%)
< 11mg/dl (Anemia)	87(18.04%)	6(1.2%)	93(19.25%)

5.1.4 Profile of IPT exposure

Table 8 describes that the number of female patients 239(49.4%) who were registered and Completed for IPT was high in comparison to that of males 214 (44.3%) respectively. Most Study participants were IPT completers 453(93.7%) and the less number of participants were non completers 30(6.6%) that means they were discontinued. Regarding the concomitant use of ART with IPT, most patients were on both ART and IPT treatments and the completion rate were very high on IPT 730(99.45%) and less percent of the patients were non completers of IPT who are also on ART 729(99.3%). The male IPT completed patients 221(45.7%) was less than that of female patients 257(53.2%), this shows that admission and completion of IPT among female participants/patients in hawassa comprehensive specialized Hospital (Table 8).

.

Table 8: Profile of IPT exposed patients Hawassa University Comprehensive specialized Hospital, Sidamma, Ethiopia from May 2015-Junne 2016. (n=483).

Profile	**N (%)**	**Chi-square (P-value)**
Male	214 (30%)	
Female	239(35%)	0.00
TB screened & tested negative	428(58%)	
Currently on ART	734(100%)	
IPT completed	478(65%)	
IPT not completed	30(3.9%)	
On ART + IPT completed	730(99.45%)	0.00
On ART + IPT in-completed	729(99.3%)	
Male IPT completed	214(45.7%)	0.00
Female IPT completed	239(53.2%)	

5.1.5 Initiation and Completion of IPT

IPT was initiated for 483 patients, Adults, women, those having CD4 count more than 100, those with earlier WHO disease stage and those having initiated ART were more likely to receive IPT. There was documented completion of IPT in 453(93.8%) of those who started treatment and the rest are non completers. The result of this particular study showed that, there was a statistically significant association between IPT completion and TB incidence.

5.1.6 Incidence of Tuberculosis Occurrence

Out of 483 patients who were given IPT, completion rate was 453(93.9%). From the total of 483 Participants who are on IPT, 55 were developed Tuberculosis during the respective follow up period, 20 from Completers and 35 from non completers which is 55/483 (11.3%), survival free of Tuberculosis (TB) was around 89% while 425 were censored (6 Dead, 17 Lost to follow up, 12 drop out and 9 transferred out and the remaining 387 were TB negative up to the end of follow- up period). A total of 483 patients contributed 1490 person-years of observation (PYO) after IPT completion. 55 TB cases were diagnosed during the follow-up period which makes the overall TB incidence in 5 year retrospective follow up was in rate of 3.7 per 100 PYO. The TB incidence rate in a follow-up duration of 6-12 months and more than 12 months after IPT completion was 0.3 per 100 PYO and 3.4 per 100 PYO respectively.

The minimum and maximum follow-up observations were 1 and 60 months, respectively. The median follow-up period was 54 months observation period (IQR=20-41.75). Among TB positive populations, females' number is very high 49 (89.1%). Out of 55 TB cases, the majority were categorized under pulmonary positive which accounts around 42 (75%) while pulmonary negative and extra pulmonary tuberculosis accounts equally 3 (5.4%). Around 4 (7.2%) of the TB incidents occurred within the first year of follow-up. The TB incidence among study subjects in urban and rural dwellers was 34 cases and 21cases, respectively. Regarding TB incidence among IPT completers and non completers was 20(36.3%) and 35 (63.6%) respectively (Table 9). Among IPT non completed group, incidence rate was 2.4 /100PY, while in IPT completer patients; it was 1.3/100P-Y, which shows that TB incidence among Non completers was nearly twice than that of

non completers. This shows that IPT exposure and completing has a major protective effect than that of non-completing (Table 9).

Table 9: Incidence of tuberculosis per 100 person-year according to exposure category among HIV infected individuals on ART follow up in Hawassa University Comprehensive specialized Hospital, Sidamma, Ethiopia from May 2015-Junne 2016. (n=483).

Group	**No. of cases of tuberculosis**	**No. of PY**	**Incidence rate of TB per 100 PY**
IPT completers	20	369	1.3
IPT not completers	35	1122	2.4
Overall TB incidence	55	1490	3.7

According to the explanation given on the (table 10) below, the incidence rate of TB according to the age category, the incidence was high among 18-29 age groups which were 9.4(Table 10). Regarding sex group's female patients were more showed the increased incidence rate of tuberculosis, 3.7. In a marital status category Peoples who were never married showed the more incidence rate (10.2) from married, separated and others. Protestants religion followers were the ones who have had more number of tuberculosis incidence (6.0) than that of the remaining religious followers. Tuberculosis incidence among substance users was more than double (13.6) than that of non substance users. Government employers (1.6) and patients whose family size was more than five (6.9) were showed the large incidence rate than other groups of the study participants respectively. Out of 483 patients who were given IPT, completion rate was 453(93.7%) and the remaining 30(6.2%) were the non completers (Table 10).

Table 10: Tuberculosis incidence rate stratified by socio-demographic characteristics of PLWH on IPT at Hawassa University Comprehensive specialized Hospital, Sidamma, Ethiopia from May 2015-Junne 2016. (n=483).

Characteristics	Total TB	PY	TB	Incidence
Age in years (mean=32.8, SD=12.8)				
18-39	322	1210.08	11	0.9
40-59	139	244.08	23	9.4
>=60	22	110.54	21	19.1
Sex				
Male	221	710.08	6	0.8
Female	262	1242.42	48	3.8
Marital Status				
Never Married	107	185.92	19	10.2
Married	271	608.08	25	4.1
Separated/widowed/divorced	105	850	11	1.2
Religion				
Protestant	169	542.5	15	6.0
Orthodox	225	1073.75	33	1.3
Muslim	52	1787.92	3	0.1
Catholic	26		3	
Other	11		1	
Substance Use				
Yes	247	308.5	42	13.6
No	236	336.25	13	3.6
Type of Substance Use				
No	246	1602.5	23	1.4
Tobacco/Cigarette	32	53.5	6	1.3
Alcohol	74		11	
Tobacco and alcohol	43		6	
Chat	88	123.2	9	7.3
Occupation				
Farmer	57		7	
Merchant/Trader	111	992.67	12	1.2
Government Employed	123	667.67	11	1.6
Non-Government	42		3	
Day Laborer	44		7	
Jobless	32		5	

Driver	39		5	
Retired/housewives/Student(other)	35		4	
Family size				
<= 5	391	729.83	48	6.5
6-8	85	1085.92	4	0.4
>=9	7		3	

Table 11 briefly describes that, in the category of WHO clinical stage III and IV, the incidence rate of Tuberculosis was very high 3.01 and 37.5 respectively. Among CD4 <200 group it was 7.3, in CD4 count greater than or equal to 200 the incidence rate was 1.83. Regarding body mass Index the table shows that in BMI <18kg/m2 there was high rate of incidence (Table 11). In the patients who have previous history of Tuberculosis, there was high incidence rate of tuberculosis as compared to those who don't have tuberculosis. Concerning functional status, patients whose status was bedridden outlines ambulatory and working respectively (Table 11). High burden of viral load; >1000copies/ml were seen developing TB early and in with increased incidence. Regarding Hemoglobin, from the table 9 we can understand that in patients who have hemoglobin number <11 g/dl were highly exposed to TB in relation to those who have greater than 11g/dl (Table 11).

Table 11: Tuberculosis incidence rate stratified by Clinical characteristics of PLWH on IPT Hawassa University Comprehensive specialized Hospital, Sidamma, Ethiopia from May 2015-Junne 2016. (n=483).

Characteristics	Total TB	PY	TB	Incidence (IR)
WHO clinical Stage				
I and II	281	925.5	9	0.9
III	138	427	13	3.01
IV	64	88.4	33	37.5
CD4 cell count(Cells/µL)				
< 200	69	436.5	32	7.3
>=200	414	1359.25	25	1.83
Medium of current CD4 count=456cells/µL, (IQR, 314-661) and 231 cells/ µL (IQR, 105-400)				
BMI				
<18kg/m2	258	1104.58	46	4.16
> =18kg/m2	225	47.92	9	1.91
Medium BMI= 20.29 kg/m^2(IQR, 18.49-22.36)				
IPT Completed				
Yes	454	1459.25	20	1.3
No	29	693.25	35	2.43
Previous TB disease				
Yes	97	436.5	35	8.01
No	386	808.92	20	2.47
Functional status				
Working	348	1168.66	12	1.02
Ambulatory	102	608.5	23	3.77
Bed ridden	32	183.83	30	16.3
Viral load				
<1000	407	1024.58	22	2.14
>1000	76	47.92	33	6.88
Hemoglobin				
>=11mg/dl(Normal)	390	1168.42	20	1.71
< 11mg/dl(Anemia)	93	84.08	35	2.34

5.1.7 Time of TB Occurrence after IPT Completion /TB free Survival time

The median follow-up period after IPT completion was 54 months. The majority (91.5%, n=432) of the patients were followed over a 12 month period. The median follow-up period between IPT completion and TB diagnosis was 29 months. No TB cases were diagnosed before 6 months after IPT completion. Six TB cases were diagnosed between six and twelve months, and after 12 months of IPT completion, respectively. The overall 60 month cumulative TB-free survival and cumulative hazard of TB incidence was 98.4 % and 1.6 % after IPT completion, respectively.

The table below (Table 12) explains the comparison time free survival time between IPT exposed groups, completed and non completed groups. As we can see from the table, the least time for the occurrence of Tuberculosis among completers was 11 months while in non completers it was only 6 months. On the other hand there was a wide time difference in Tuberculosis occurrence between two groups which was 60 (in completers) and 27 (in non completers) respectively (Table 12). The median TB occurrence time of IPT non completers were 6 month and that of completers were 38 which still shows a significance difference. The study also shows that the number of TB case among non completers was very much high 35 than that of the proportion of completers 20; this indicates that the intake and completion of IPT has an excellent protective effect against tuberculosis incidence.

As shown in Table 12, IPT completers were significantly protected for 5 years (AHR = 0.05 (95% CI (0.02-1.74)) compared to IPT in-completed patients.

Table 12: Month of occurrence of active TB among IPT exposed (completed vs. non completed patients) in Hawassa University Comprehensive specialized Hospital, Sidamma, Ethiopia from May 2015-Junne 2016. (n=483).

Variables	No of patients active TB diagnosed	Minimum month TB occurred	Maximum month TB occurred	Mean month TB occurred	Standard Deviation	Median Month
Month TB occurred among IPT completed patients	20	13	60	41	6.71	38
Month TB occurred among patients who notcompleted IPT	35	1	27	18.15	14.8	6

The test of equality for survival distribution for different levels of different categories was performed with Kaplan-Meier, using the log-rank test. The cumulative probability of survival distribution of a patient with TB at the end of 1, 2, 3 and 4 years was 0.99, 0.95, 0.87, 0.76 and 0.65 respectively and the least probability time was 0.65 which is at end of follow-up time. The median survival time was 54.13 months (figure 2). In terms of survival curves, there were significant variations among male and female ($P<0.00$) (figure 3), different WHO clinical stage categories ($P<0.03$) (figure 4), different age groups ($P<0.002$) (figure 5) anaemic and non-anaemic ($P<0.002$) (figure 6), high viral load and low viral load ($P<0.01$) (figure 7), IPT completers and non-completers ($P<0.001$) (figure 8), underweight and normal weight ($P<0.001$) (figure 9), working, ambulatory and bed ridden ($P<0.015$).

5.1.8 Graphical presentation of different categories in Kaplan-Meier analysis

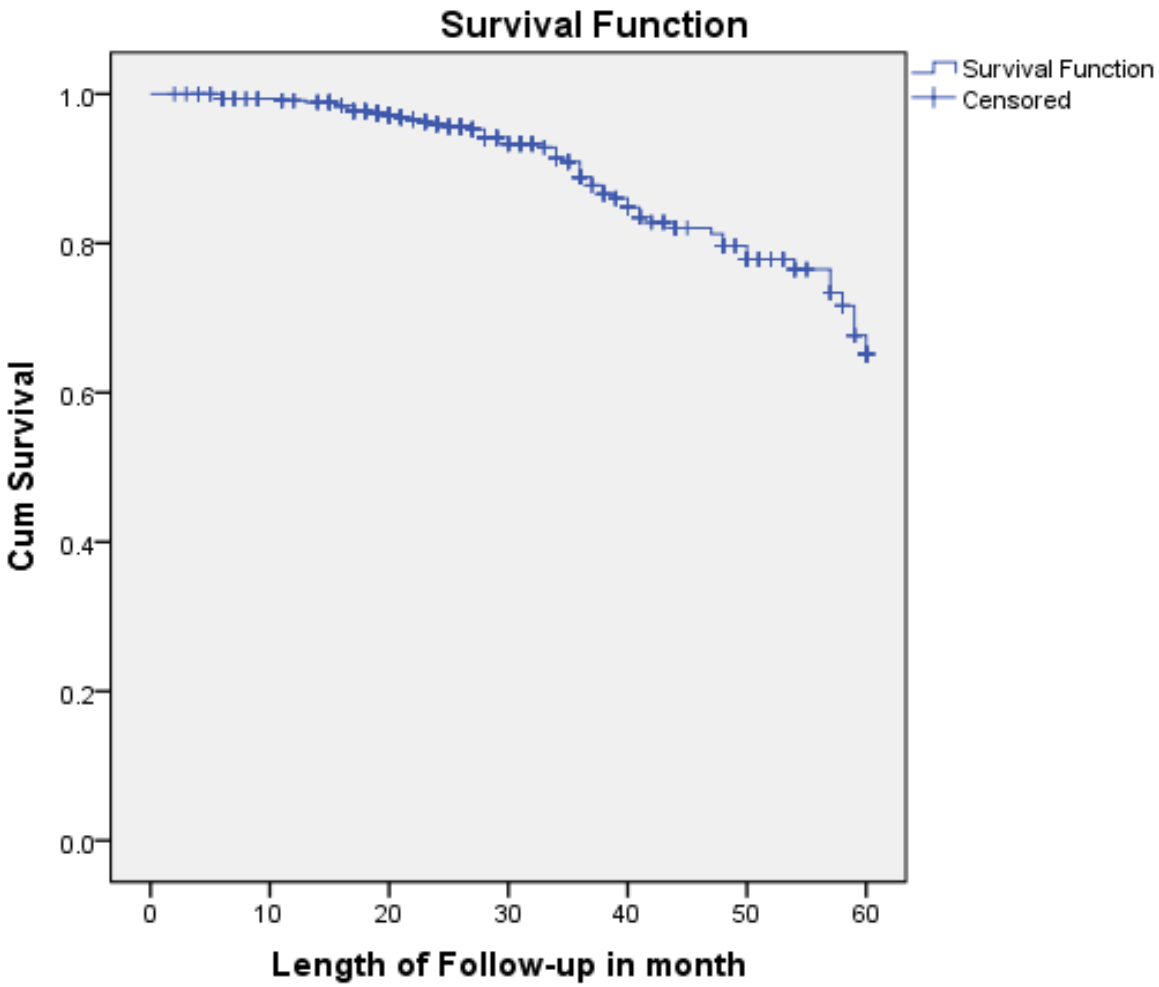


Figure 2 Kaplan-Meier curve of tuberculosis survival proportion of people with HIV/AIDS who are on IPT in Hawassa Comprehensive specialized Hospital, during may 2015-June 2016.

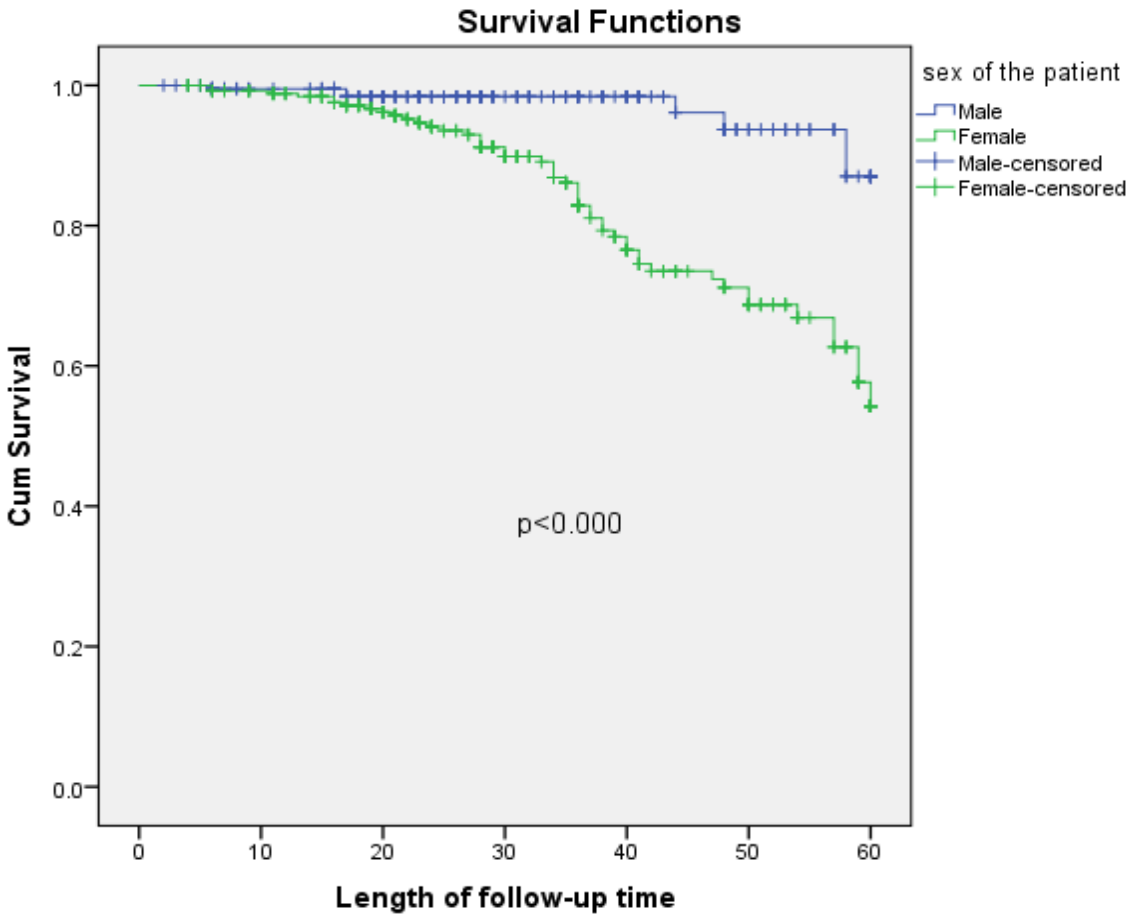


Figure 3 Kaplan-Meier survival curve of patients with tuberculosis based on body mass index (BMI) sex category among people living with HIV who are on IPT in Hawassa Comprehensive specialized Hospital, during may 2015-June 2016.

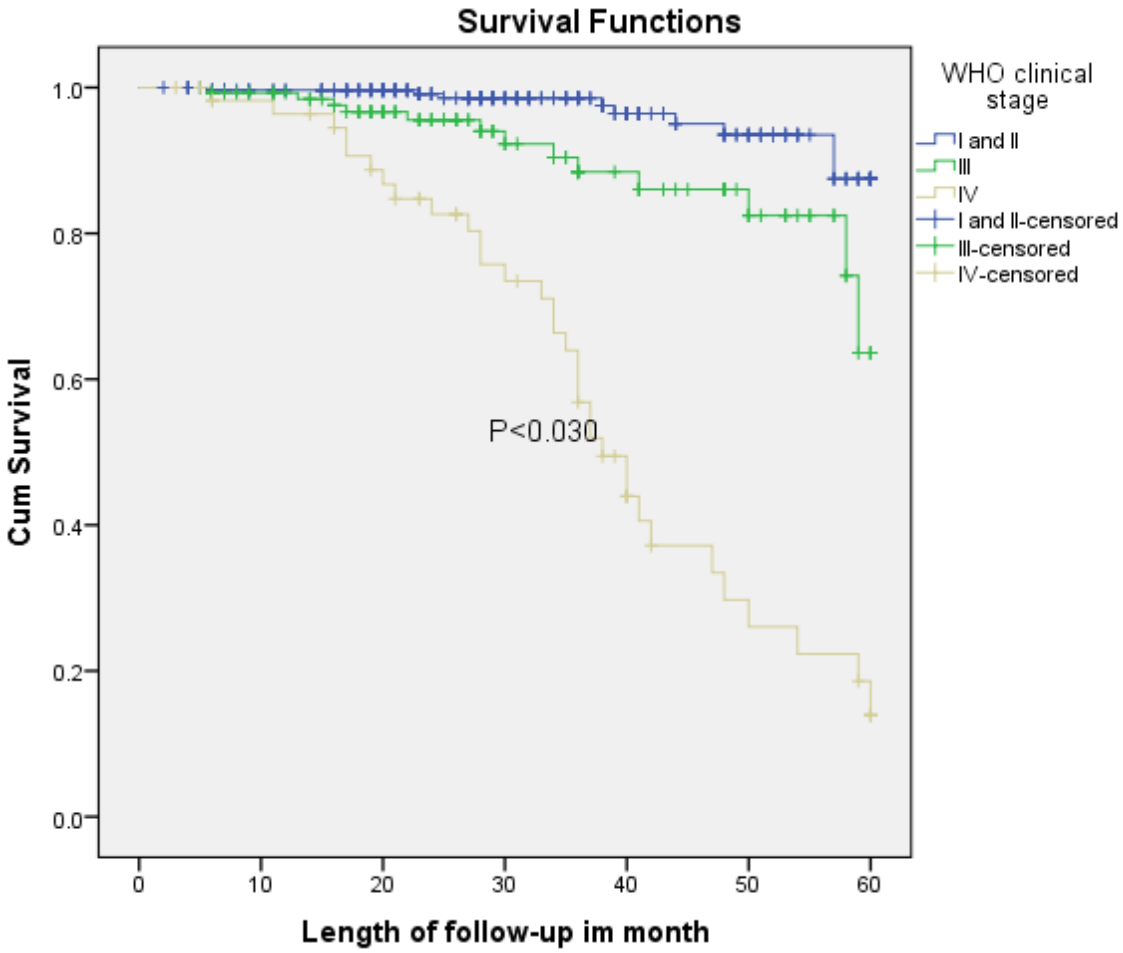


Figure 4 Kaplan-Meier survival curve of patients with tuberculosis based on WHO clinical stage category among people living with HIV who are on IPT in Hawassa Comprehensive specialized Hospital, during may 2015-June 2016.

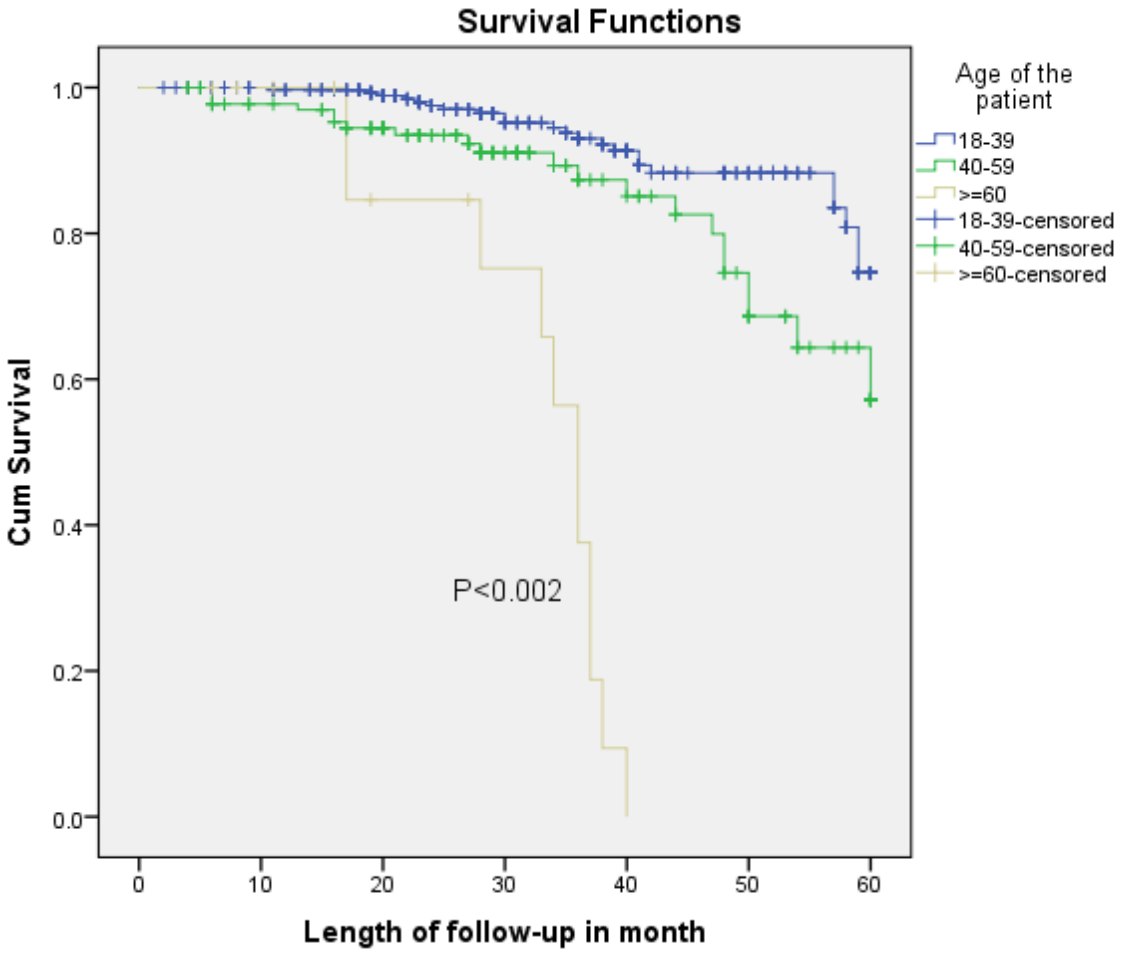


Figure 5 Kaplan-Meier survival curve of patients with tuberculosis based on Age category among people living with HIV who are on IPT in Hawassa Comprehensive specialized Hospital, during May 2015-June 2016.

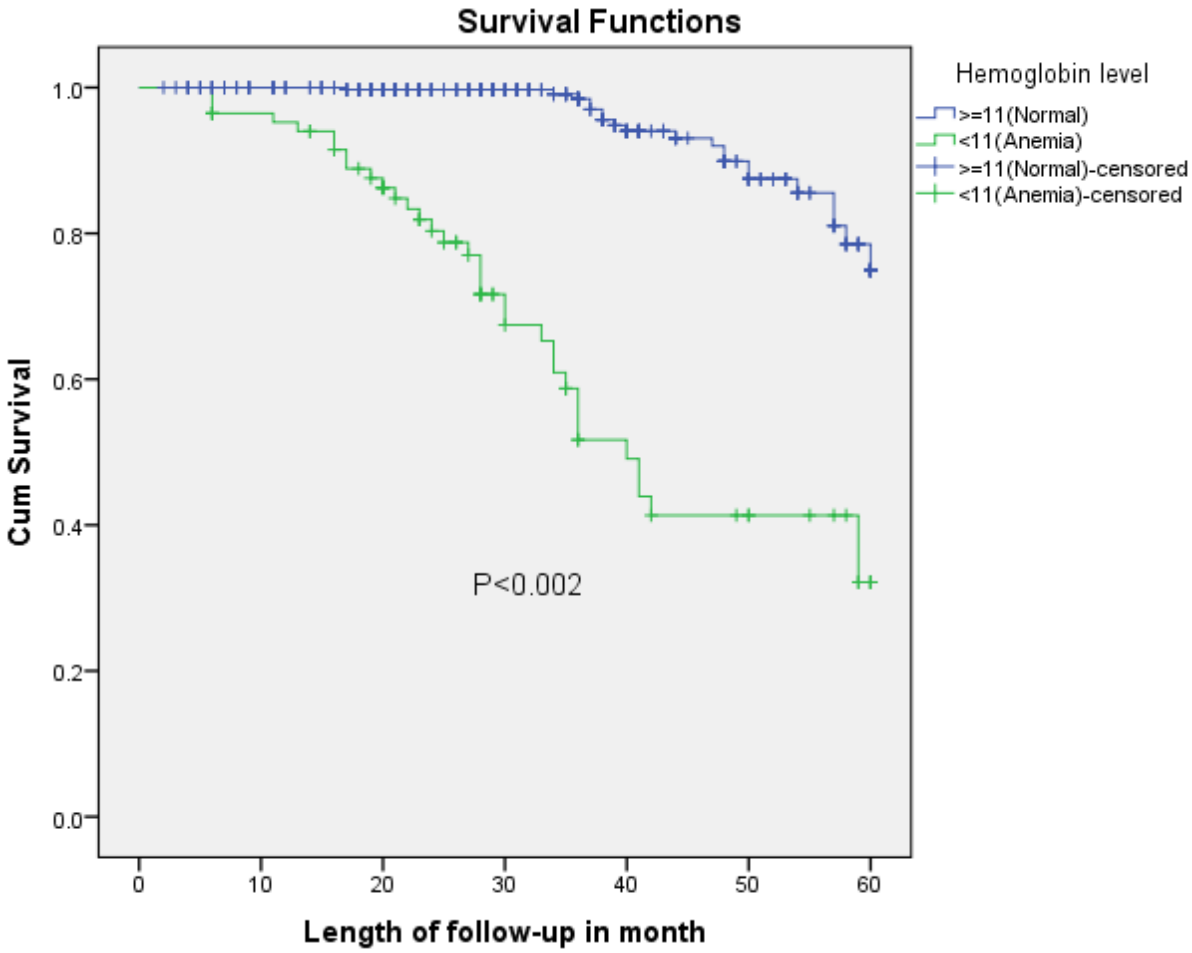


Figure 6 Kaplan-Meier survival curve of patients with tuberculosis based on Hemoglobin (Hgb) category among people living with HIV who are on IPT in Hawassa Comprehensive specialized Hospital, during May 2015-June 2016.

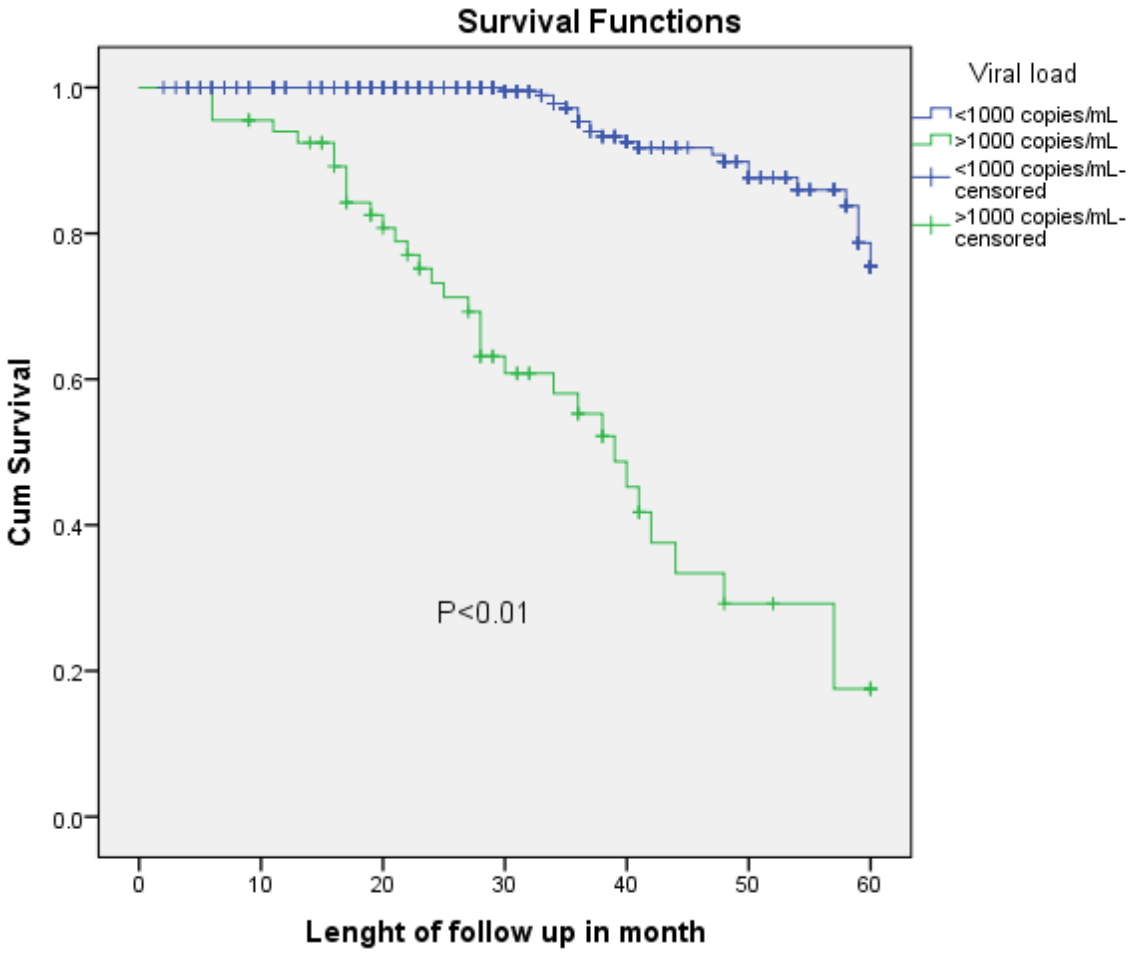


Figure 7 Kaplan-Meier survival curve of patients with tuberculosis based on viral load index category among people living with HIV who are on IPT in Hawassa Comprehensive specialized Hospital, during May 2015-June 2016.

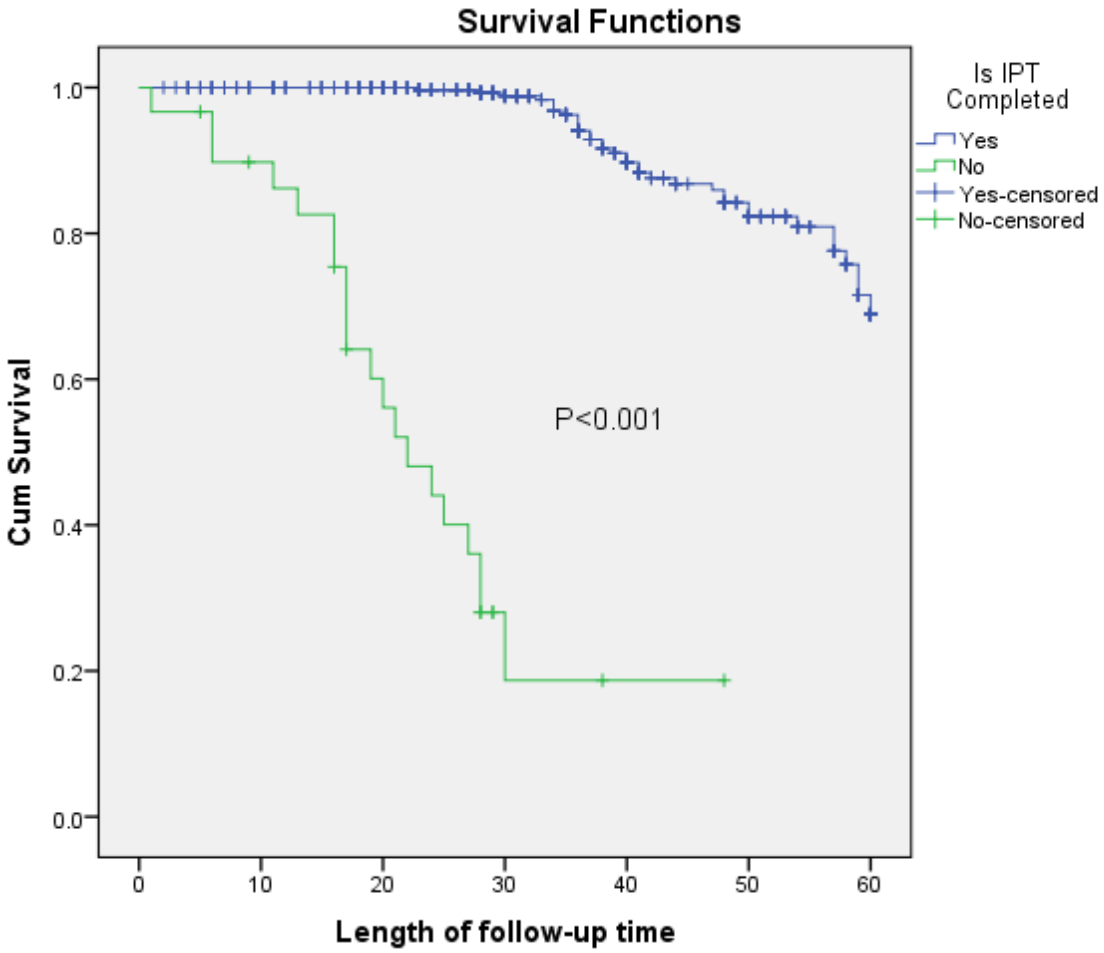


Figure 8 Kaplan-Meier survival curve of patients with tuberculosis based on IPT completion status category among people living with HIV who are on IPT in Hawassa Comprehensive specialized Hospital, during May 2015-June 2016.

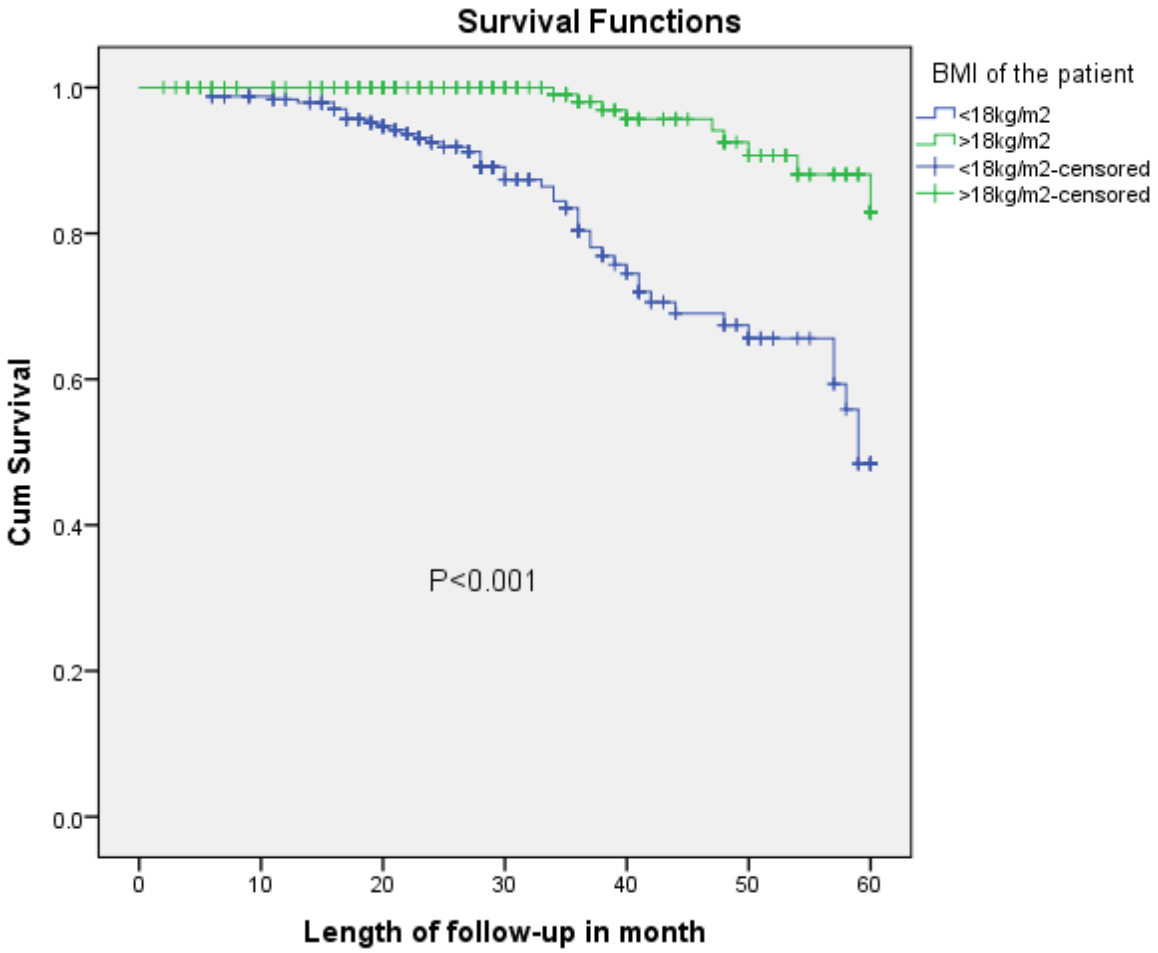


Figure 9 Kaplan-Meier survival curve of patients with tuberculosis based on BMI (Body mass Index) status category among people living with HIV who are on IPT in Hawassa Comprehensive specialized Hospital, during May 2015-June 2016.

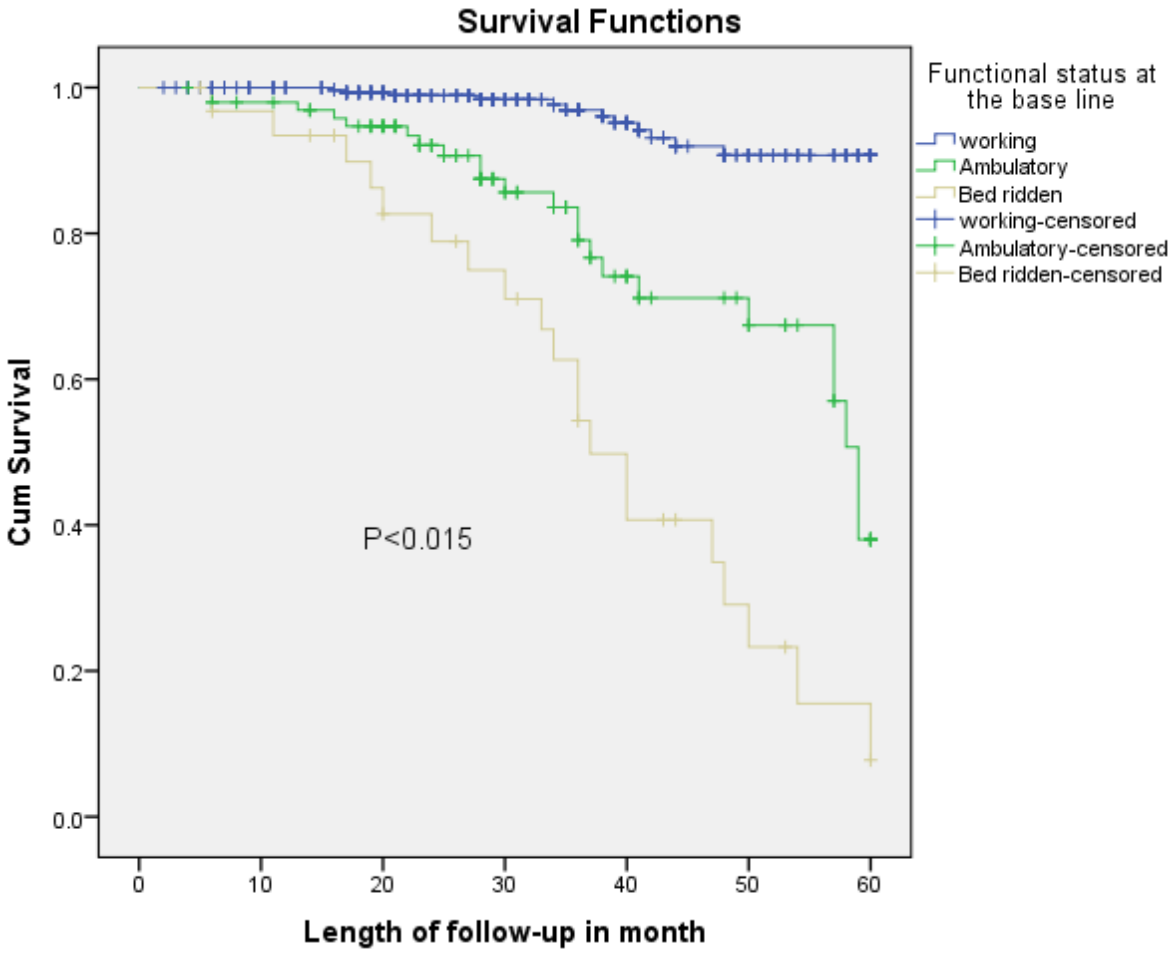


Figure 10 Kaplan-Meier survival curve of patients with tuberculosis based on Functional status scategory among people living with HIV who are on IPT in Hawassa Comprehensive specialized Hospital, during May 2015-June 2016.

5.1.9 Predictors of tuberculosis incidence and time to TB occurrence

The relationship between the baseline variables and the incidence of tuberculosis was analyzed using bivariate Cox proportional Hazard regression model. In the bivariable Cox regression analysis, Age, sex, substance use, history of TB, baseline CD4 count, WHO clinical stage, BMI, Hgb level, IPT status, viral load and Functional status were found to be predictors of the incidence of TB at a P-value of less than 0.25. Consequently, these variables were entered in to multivariate Cox regression analysis, and sex, Hgb, IPT status, advanced WHO clinical stage, Bed ridden functional state and viral load found to be statistically significant and become more determinants of TB-free survival time at a P-value of less than 0.05. HIV infected individuals who are on ART and didn't Completed IPT during the study period had 94% of higher risk of developing TB as compared to those who received IPT, after adjusting for past opportunistic illness(Table13).

The univariate analysis was used to assess the relationship between the baseline variables and the risk of developing TB. Before fitting the covariate into the model all the proportional hazard model assumptions were checked by plotting Schoenfeld residual and by examining log plots. The result showed that most variables plus functional status were significant predictors of TB- free survival time among ART patients who Completed IPT treatment except BMI and baseline CD4 count (Table 13).

To identify independent predictors, a multivariate Cox-proportional hazard adjusted model was fitted with variable having a P-value <0.25 in the Univariate analysis. Accordingly, most variables were remained independent predictors of TB-free survival time after controlling for the other factors. Accordingly, Participants who are female were 2 times exposed to TB than being male (aHR=2.07, 95% CI; 0.78–5.26), the PLWH who were at WHO clinical stage III or stage IV had 3.2 and 4.5 times higher risk of developing TB as compared to those with WHO clinical stage I or II. WHO stage III and IV (aHR = 3.2, 95% CI; 1.15–8.95) and IV (aHR = 4.5, 95% CI; 0.19–1.094). A patient with a Hgb level below 11 mg/dl were three times more likely to have TB than a patient with a Hgb level above 11mg/dl (AHR= 3.17; 95%CI, 0.15 to7.01). But CD4 and BMI were lost their statistical significance in the multivariate analysis (Table 13).

PLWH who were in bedridden functional status at baseline were 3.28 times at more risk of developing TB compared with Working and ambulatory functional status (AHR 3.28; 95%CI, 0.134 to 8.06). Individuals who completed IPT were 94% less likely to develop TB at any time compared with those who did not (AHR 0.60; 95%CI, 0.018 to 0.203). Participants whose viral load was less than 1000copies/ml were 1.96 more likely developed TB than that of greater than 1000 copies/ml (AHR=1.96; 95%CI, 0.04 to 2.20) (Table 13).

Table 13: Cox regression analysis of the determinants of the incidence of TB among adults, who completed IPT care at hawassa university comprehensive specialized hospital in sidamma Regional State, may 2015–May 2016 (n=483)

Characteristics **(Variables)**	**Survival status**		**Total**	**CHR (95% CI)**	**AHR (95% CI)**	**P- Value**
	Event (TB)	**Censored**				
Sex						
Male	6	215	221	1.00 (Ref)		0.001*
Female	48	214	262	1.82 (0.78-4.26)	2.07 (0.78–5.26)	
WHO clinical stage						
I and II	9	272	281	1.00 (Ref)		
III	13	125	138	5.7 (0.027-0.119)	3.2(1.15-8.95)	0.030*
IV	33	31	64	1.93 (0.101-0.368)	4.5 (0.19-1.094)	
Viral load						
<1000 copies/ml	22	385	407	1.00 (Ref)		
>1000 copies/ml	33	43	76	0.83 (0.048-0.143)	1.96 (0.04-.2.20)	0.001*
Functional status						
Working	12	336	348	1.00 (Ref)		
Ambulatory	23	79	102	0.58 (0.028-0.119)		0.015*
Bed ridden	30	2	32	0.371 (0.204-0.678)	3.28(1.34-8.06)	
IPT completed						
Yes	35	419	459	1.00 (Ref)		
No	20	9	29	0.28 (0.015-0.052)	0.60(0.018-2.03)	0.001*
Hemoglobin						
>=11g/dl(Normal)	20	370	390	1.00 (Ref)		
<11g/dl(Anemia)	35	58	93	1.12 (0.065-0.195)	3.17(0.152-0.7)	0.002*

6. DISCUSSION

Four hundred eighty three records of PLWH were analyzed. Their median age was 32 years with [IQR: 22-44] and 322 (66.7%), of them were in the age group of 18-39 years. Over half 262(54.2%) of the PLHIV were females and 271(56.1%) were married. One hundred seventy seven (36.6%) patients had completed secondary school (Table 1). The cumulative probability of TB-free survival at the end of one year was 0.99 and at the end of five years was 0.66.

This retrospective cohort study covering the time from 2015 to June 2020 attempted to assess TB free survival time among patients who completed IPT against active TB in HIV positive adults who were on HIV/IPT care in hawassa university comprehensive specialized hospital. The result of the cohort shows that, at the end of follow up, 6 Dead, 17 Lost to follow up, 12 drop out and 9 transferred out and the remaining 387 were TB negative up to the end of follow- up period. The overall TB incidence rate in HIV-infected adult patients after IPT completion in Hawassa University Comprehensive specialized hospital providing IPT and ART services was 3.7 per 100 PYO. It was similar with that of studies done in Ethiopia and Myanmar, which reported that the incidence rate of tuberculosis was 3.73 & 2.14/100 person years among those on IPT and HAART respectively(49)(50). The result of the study was also along side with the result in other study(12) which indicates the overall incidence of 3.87 among the study subjects. But the incidence rate was a bit less than the result 2.6 PYO of a research which was conducted in Ethiopian among Peoples which are living with HIV(51)(3).

In addition to that the result of this study shows that, the IRs was 1.2/100P-Y and 2.45/100P-Y among IPT completed and in-completed patients, respectively. The Incidence rate among completers of IPT on this study was almost similar to other findings 1.98 per 100 person-years in the study which was conducted in Nekemte Town, Ethiopia (29). The study which was done in Bulawayo, Zimbabwe indicates that the incidence of TB among patients who initiated and completed the INH prophylaxis was 0.9 per 100(52), this is nearly similar to this particular study. Another research which was done in Botswana on Tuberculosis incidence after 6 and 36 months' isoniazid prophylaxis in HIV-infected adults shows the congruent result of 6 month IPT completers, 1.13% TB incidence rates(45) with that of this particular study.

The IR among IPT completed patients was lower when compared with the findings of studies done in different countries (53)(54)(55), But it is higher than other studies which was conducted in Addis

Ababa with TB Incidence Rate of 0.21/100 Person-Year, for IPT completed and uncompleted patients.(44). The Incompatibility in incidence rate among the studies may be due to the difference in follow-up period of the studies and the difference in the overall burden of TB in the general population. Another possible explanation for this cause might be the different characteristics of the population which are included under this follow up.

Moreover, completion of IPT in HIV infected adults' significantly reduced TB incidence by 94.0% when compared to non-exposed patients (AHR 0.60, 95%CI 0.018 to 0.203) which is similar to other studies conducted in Ethiopia (54) which shows the protective effect of Taking of IPT with(aIRR = 0.037, 95% CI 0.016-0.072). This shows that the protective effect was 96.2%. Similar study which is done in Indonesia Jakarta shows nearly similar result with (IRR = 0.31, 95% CI 0.023-0.881, $p<0.008$). In this population, IPT administration reduces 89% risk of PLHIV to suffer TB(39). Other same findings showed that IPT prophylaxis significantly reduces getting of TB with the relative risk =0.31 (95% confidence interval =0.122 to 0.49) in ART patients of this study site where the tuberculosis prevalence is prominent(21)(11).

Another study which was conducted in Arbaminch also shows similar protective effect of Taking and completion of IPT among ART patients in Arbaminch Hospital with the relative risk =0.31 (95% confidence interval =0.122 to 0.49)(35). The difference may be related to good patient adherence rate, difference in TB burden among different countries or better socioeconomic and clinical status of patients might have contributed to such differences among studies conducted in different countries(54).

Regarding TB free survival time Among patients who completed IPT, though TB had occurred after 6 months, almost 50% of them developed TB at 11^{th} month; while in patients who didn't completed IPT, Patients were seen developing TB within a month time. This result was nearly similar to the research which was done in Addis Ababa with 19^{th} month and Diredawa, Ethiopia with 16^{th} month of TB free survival time(44)(11) The study proved that IPT completion has been significantly protecting early occurrence of TB during the first 6 months. This finding was in line with the study conducted in Thailand where IR among IPT completers was 0 and among non-exposed patients 8.60/100 P-Y as cited by mahlet(44). Moreover, the present study indicated that IPT had offered a

significant protective effect until 5 years. The durability of protective effect of IPT documented in the present study concurs with the expected level indicated in Ethiopian guideline(11) (56). But the TB free survival month of this study was less than of the study which was conducted in Pennsylvania, USA with the result of 111^{th} months for IPT completers.

The reason for this kind of discrepancy might be related to socioeconomic and different clinical and other factors. The result; however, better than reports from South East Asian and other Sub-Saharan African countries (3)(57). Also the observed differences in outcomes might relate to study design and geographic setting, a smaller number patient in the current study, and a shorter duration of follow-up after IPT completion. Others could include the criteria established for the diagnosis of TB and the degree of immunodeficiency of the patients studied.

In general, the incidence of TB is usually low in chemoprophylaxis studies. This study showed even a lower incidence of TB after IPT completion. This might be explained, in part, by the smaller sample size and a short follow-up period post IPT completion compared to other studies. Also, Most of the IPT completers took ART before initiation of IPT and there was the protective effect of IPT on the incidence of TB. This lower rate of TB after isoniazid treatment is closer to a previous incidence rate report with 1.6 per 100 patient-years and 1.7 cases per 100 person-years(11)(52).

Concerning to the predicting factors between the study subjects, In Cox regression analysis, the CD4 cell counts were not significantly associated with TB incidence. This was not consistent with the findings observed in other studies. (58)(31) The observed difference could be due to the small sample size and low number of TB cases which limited the power of the study to detect significant differences in the subgroups. But TB Occurrence was significantly associated with other factors such as sex (Being female) (aHR=2.07, 95% CI; 0.78–5.26), WHO clinical stage III or IV (AHR =3.20; 95%CI, 0.115to8.95). Hgb level below 11 mg/dl (AHR= 3.17; 95% CI, 0.15-7.01). Bedridden functional status (AHR 3.28; 95% CI, 0.134 to 8.06),IPT completion (AHR 0.60; 95% CI, 0.018 to 0.203). Viral load less than 1000copies/mL(AHR=1.96; CI, 0.04 to 2.20). These findings are the same as other researches which shows same predictors.(59)(28)(9). In this study TB occurrence among IPT completed/in completed patients as was seen among female patients, this shows the same result as Getahunet.al(60) which reported that in countries with a high prevalence

of HIV, more women than men are affected with TB. Other similar researches which was conducted in Nigeria(59) shows same thing that female were affected with TB than male. But this result was opposes the research which is done in Tanzania and Addis Ababa that indicates male gender were more affected (44)(61). The exact reason for this may not be known by researcher but it might be related to socioeconomic factors and co morbidity during the study period.

One of important predictors for the TB occurrence was baseline clinical variables like WHO clinical stages; Even though TB can occur at any WHO clinical stages it is more common in advanced clinical stages (62). The PLWHIV who were at WHO clinical stage III or IV had 3.2 times higher risk of acquiring TB as compared to those with WHO clinical stage I or II (AHR =3.20; 95%CI, 0.115 to 8.95) which is in line with a studies done in Ethiopia which ranges from 2 to 6 times higher (50)(63). This suggests that, PLWHIV who had WHO clinical stage III or IV might be immune-compromised and predisposed to TB ,which is higher than this finding because it also includes pre ART patients.

PLWH with Hgb level below 11mg/dl were three times more likely to have TB than a patient with an Hgb level above 11mg/dl (AHR= 3.17; 95%CI, 0.15 to7.01). Other studies also showed individuals with Hgb level 11mg/dl or less and anaemic were more likely to have TB and also prone to failing ART (7).This shows that patients having higher haemoglobin level were less likely to develop TB than those with low haemoglobin level. TB and haemoglobin level might be indirectly associated with advanced stage of HIV disease.

Participants whose viral load was greater than 1000copies/ml were 1.96 more likely developed TB than that of greater than 1000 copies/ml (AHR=1.96; 95%CI, 0.04 to 2.20). When HIV positive patients have chronic disease and high viral load copy greater than 1000, it resulted in immune-suppression and suppression of red blood production in bone marrow. This is also consistent with the previous findings that is done in Addis Ababa which shows on ART (pVL > 1000 copies/ml) patients were 3 times more likely to develop incident TB (aHR: 3.05 (95% CI: 2.094, 4.454) after IPT initiation (50)(7)(6). Another study which is conducted in south Africa also showed independent association between increased viral load and occurrence of tuberculosis, viral load >1000copies/ml(30)**.**

Different studies in high TB/HIV burden countries have shown that Isonized preventive treatment reduces the risk of TB infection in PLWHIV. In this study INH prophylaxis has shown a protective effect against TB in HIV infected persons. Patients who had completed IPT had reduced TB incidence by 94% than a patient who hadn't (AHR 0.60; 95%CI, 0.018 to 0.203). Likewise a prospective cohort in South Africa showed a strong reduction in tuberculosis risk (AHR = 0.11; 95% CI 0.02–0.78)(64).

The two studies done in Ethiopia showed PLWHIV who were ambulatory or bed ridden at enrolment, were at higher risk of developing TB as compared to those who were working (50)(62). These results are similar to this particular study which indicated that, PLHIV who were in bedridden functional status at baseline were 3.28 times at more risk of developing TB compared with Working and ambulatory functional status (AHR 3.28; 95%CI, 0.134 to 8.06).

Even though, it was not clear for the researcher why BMI was not associated in multivariate analysis in this research; the researcher believes that body mass Index is/was the strong clinical predictor for the occurrence of TB among HIV patients. Since the syndrome is associated with body immunity it has clinical significance. Many studies also associates BMI with Tuberculosis Occurrence.(29)(27)(65)**.**

6.1 STRENGTH AND LIMITATIONS

6.1.1 Strength

- The study was done in one of Ethiopia's leading hospital in the treatment of AR patients.
- Long follow up period (Five years).
- This study considers time to event for analysis which enables us to consider contribution of censored study subject.

6.1.2 Limitation

- Use of retrospective nature of the cohort study design.
- Narrow scope of the study setting and population being only one hospital set up and population from specific area.
- Inability to address TB contacts (other family member/coinhabitant)
- In this study it was not possible to measure some data such as house hold income, housing condition, and others which might be important predictors
- Since the study was conducted in a single region in Ethiopia, it might not indicate the actual incidence of TB in other regions of the country.
- There was also some scarcity on IPT drug in the hospital.

7. CONCLUSION AND RECOMMENDATIONS

7.1 Conclusion

The result of this study implies that completion of IPT significantly reduced TB incidence by 94.0% and IPT had significantly protected occurrence of active TB for five years among HIV/AIDS infected patients. It also shows indicates that being female, WHO clinical stage of HIV/AIDS III & IV, Bed ridden functional state, Viral load <1000copies/ml, Hemoglobin <11mg/dl, and IPT completion status were predicting factors for TB incidence. The result of this study evidenced and supported the WHO recommendations that the completion of IPT protected the occurrence of active TB and proved the effectiveness of IPT in reducing TB incidence among HIV infected patients in Ethiopia.

7.2 Recommendations

The findings in this study shows that the completion of IPT protected the occurrence of active TB and proved the effectiveness of IPT in reducing TB incidence among HIV infected patients in Ethiopia. The problem requires attention from all stake holders. Therefore,

7.3 FMOH

- Should work more on exposing and completion of IPT
- It should give emphasize widely for HIV-infected patients in all parts of the country so as to improve their quality of life by reducing the TB burden and prevent further transmission of TB in the community.

7.4 HUCS Hospital

- Early TB screening and regular follow up should be done among HIV patients.
- Increasing community awareness may be essential component to improve patient's prognosis.
- Should improve its data management system and work more on increasing the knowledge of the professionals to record the patient's data correctly and fully.

7.5 For Health professionals

- short appointments, effective adherence support

7.6 Researchers

- Further studies should account for exploring factors such as drug adherence and completion status to capture the true effect of IPT on TB incidence as well as involve more geographical regions to represent the whole country.

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7. ANNEX

Annex I- Information Sheet for the Institution

Title of the Research Project: Tuberculosis In HIV Infected Adults Who Completed Isoniazide Preventive Therapy In Hawassa Comprehensive Specialized Hospital. Hawassa, Ethiopia. 2020.

Name of Investigator: Amanuel Fanta (Bsc in Generic nursing)

Name of the Organization: Hawassa University Comprehensive specialized Hospital.

Name of the Sponsor: AAU

Introduction: This information sheet is prepared for Hawassa University Comprehensive specialized Hospital administration and Hospital ART clinic coordinating office. The aim of the form is to make the above concerned office clear about the purpose of research, data collection procedures and get permission to conduct the research.

Purpose of the Research Project: To determine Tuberculosis incidence, Predictors and TB free survival time among Adult patients living with HIV and attending ART clinic in Hawassa Comprehensive Specialized Hospital Procedure: In order to achieve the above objective, information which is necessary for the study was taken from HIV care medical record follow up forms.

Risk and /or Discomfort: Since the study will be conducted by taking appropriate information from medical chart, it would not inflict any harm on the patients. The name or any other identifying information was not recorded on the questionnaire and all information taken from the chart was kept strictly confidential and in a safe place. The information retrieved will be only be used for the study purpose.

Benefits: The research have no direct benefit for one whose document/ record is included in this research. But the indirect benefit of the research for the participant and other clients in the program is clear. This is because if program planners are preparing predicted plan there is a benefit for clients in the program of getting appropriate care and treatment services. Of all, the research work has a paramount direct benefit for health care planners and managers, especially for those on HIV/TB collaborative program planning and management.

Confidentiality: To reassure confidentiality the data on the chart was collected by those individuals who are working on the HIV care clinic in the facility and information was collected without the name of the clients. The information collected from this research project was kept

confidential and was stored in a file. In addition, it was not be revealed to anyone except the investigator and it was kept in key and locked system with computer password.

Person to contact: If you have any question you can contact any of the following individuals (Investigator and Advisors) and you may ask at any time you want.

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Data collection tool and check list

This tool is prepared for the collection of socio-demographic, clinical, laboratory, treatment and outcome related information that are important for the assessment of Tuberculosis incidence and Predictors among Adults living with HIV attending ART clinic in Hawassa University specialized hospital, 2020.

All this information was retrieved from the clients ART registration book and from individual patient card without mentioning the name of clients. This information was collected by health care providers (BSc Nurses) possibly working in the ART clinic of the hospitals. **Contact information :**-Amanuel Fanta, Cell phone: +251-0961457900, E-mail-amanuelfanta@gmail.com

Data collection date----------month----------Year----------

Name of the Hospital ----------

Name of data collector---------- signature----------

Name of supervisor----------signature----------

Code No._____

Annex-II: Check list

Check list for tuberculosis incidence, predictors and TB free survival among HIV infected adults who completed Isoniazid preventive therapy in Hawassa Comprehensive Specialized Hospital. Sidama, Ethiopia.

General information

For each question, make a circle around a Number that corresponds to answer; fill in the blank

Name of Data Collector _____ Date_____

Unique ART number_____

Socio demographic and clinical characteristics of people living with HIV who were enrolled for chronic HIV care at HUCSH, 2012.

Part I: Socio-Demographic Characteristics

NO	VARIABLES	CODING CATAGORIES	REMARK
101	Patient ID number		
102	Unique ART number	_____	For ART initiated
103	Age of the patients	1.18-27 2. 28-37 3. 38-47 4. >=48	
104	sex	1. Male 2. Female	
105	Ethnicity	1. Sidamma 2. Wollaitta 3. Amhara 4. Gurage 5. Other (specify)	
106	Religion	1. Orthodox 2. Protestants 3. Muslim 4. Catholic 5. Other (specify) =5	
107	Educational status	1. No education 2. Primary 3. Secondary 4. Teritiary	

108	Occupational statues	1. Farmer 2. Merchant 3. Government employe 4. Non governmental organization 5. Day Laborer 6. Jobless 7. Driver 8. Other (Specify)	
109	Marital status	1. Never married 2. Married 3. Separated 4. Divorced 5. 110widowed	
110	Residence	1. Urban 2. Rural	
111	Family size	1. <=5 2. 6-8 3. >=9	
112	Monthly income	1. <100 ETB 2. 101–300 ETB 3. 301–500 ETB 4. >500 ETB	
113	Type of substance used	Tobacco2. Alcohol 3. Both tobacco and alcohol 4. Chat 5. Other(Hard or soft drug)	
114	People in the house hold	1. <=2 2. >2	
Section 2: Base line clinical, laboratory and ART information			
	Variable	**Coding Categories**	Remark
203	Confirmed HIV+ date	_____/_____/_____	
204	Is ART initiated	1. Yes 2. No	
205	If yes for question 204, ART initiation date	_____/_____/_____	
206	Durration in monthes since initiation of ART	1. 1 week 2. 2 week 3. 3 week 4. 1 month 5. 2 month	

		6. Other (specify)	
207	Adherence level for ART	1. Good 2. Fair 3. poor	
208	Opportunistic illness/list all mentioned at base line	1. no 2. Candidiasis 3. CMV 4. Crypt.meningitis 5. Kaposisarcoma 6. Cryptosporiodiosisis 7. Diarrehea 8. Diss.atypical myco. 9. Encephalopathy 10. fever 11. herpes simplex 12. Minor mucocuan. 13. Mycosis 14. PGL 15. PCP 16. PML 17. Pneumonia 18. Salmonella 19. EPTB 20. Toxoplasmosis 21. Wasting syndrome. 22. other specify	
209	Height in cm at base line	_____	
210	Weight(kg) at base line	BMI _____	
211	Functional status at base line	1. working 2. Ambulatory 3. Bedridden	
212	WHO Clinical stage of HIV at base line	1. Stage I 2. Stage II 3. Stage III	

		4. Stage IV	
	Hgb at base line	_____	
	CD4 count at base line _____	Date _____	
	Viral load	1. > 1000copies/ml 2. < 1000 copies/ml	
	Section3 : ART and treatment		
	ARV eligibility criteria	1. CD4 below 200 2. WHO stage IV 3. WHO stage I, II, or III with TLC < 200	**For ART initiated patients**
	OI prophylaxis at base line	1. Not given 2. Cotrimoxazole 3. INH 4. Fluconazole 5. others_____	
	Regimen recommended at base line	1. 1a (30) =d4t (30)-3TC-NVP 2. 1a (40) =d4t (40)-3TC-NVP 3. 1b (30) =d4t (30)-3TC-EFV 4. 1b (40) =d4t (40)-3TC-EFV 5. 1c= AZT-3TC-NVP 6. 1d=AZT-3TC-EFV 7. 2nd line regimens(2a/2b/2c/2d)	**For ART initiated patients**
	Part III. Patients follow up information (To be filled from ART follow up form Please document the current or the recent results		
	variables	**Coding categories**	**Remark**
	Latest follow up date	_____/_____/_____E.C	
	Recent weight	Weight in Kg _____	

	Recent functional status	1. Working 2. Ambulatory 3. Bed ridden	
	Recent WHO status	1. Stage I 2. Stage II 3. Stage III 4. Stage IV	
	Recent opportunistic infections	1. no 2. Candidiasis 3. CMV 4. Crypt.meningitis 5. Kaposisarcoma 6. Cryptosporiodiosisis 7. Diarrehea 8. Diss.atypical myco. 9. Encephalopathy 10. fever 11. herpes simplex 12. Minor mucocuan. 13. Mycosis 14. PGL 15. PCP 16. PML 17. Pneumonia 18. Salmonella 19. EPTB 20. Toxoplasmosis 21. Wasting syndrome. other specify	
	Recent ARV adherence	1. Good 2. Fair 3. Poor 4. If fair or poor, skip to	
	Reason for fair or poor adherance	1. Toxicity/side effect 2. Share with others 3. Forgot	

		4. Felt better 5. Too ill 6. Stigma 7. Disclosue 8. Drug stock out 9. Lost/ run out of pills 10. Delivery/travel problems 11. In ability to pay 12. Alcohol 13. Depression 14. Other (specify)	
	Recent dispense (code/dose)	1. 1a (30) =d4t (30)-3TC-NVP 2. 1a (40) =d4t (40)-3TC-NVP 3. 1b (30) =d4t (30)-3TC-EFV 4. 1b (40) =d4t (40)-3TC-EFV 5. 1c= AZT-3TC-NVP 6. 1d=AZT-3TC-EFV 7. 2nd line regimen (2a/2b/2c/2d)	
	Side effects	1. No side effect 2. Nausea 3. Fatigue 4. Diarrehea 5. Head ache 6. Numbness 7. Rush 8. Anemia 9. Abdominal pain 10. Jaundice 11. Fat change 12. Dizzy, anxiety, night mare	
	Reason for regimen change	1. Not changed	

		2. Toxicity/side effect 3. Pregnancy 4. Risk of pregnancy 5. Due to new TB 6. New drug available 7. Drug out of stock 8. Clinical failure 9. Immunological failure 10. Biological failure 11. Other (specify)	
	Recet CD4 count	_____ cells/UL date_____	
	CD4 level	Baseline CD4+ Date_____ At 6 month CD4+ Date_____ At 12 month CD4+ Date_____	
	Recent hemoglobin	_____ date_____	
	Isoniazid prophylaxis initiated	1. Yes 2. no	
	If yes for the above question, for how long doe he/she on it?	Duration _____ in days/months	
	Co-trimoxazole prophylaxis initiated?	1. Yes 2. No	
	If yes for the above question, for how long doe he/she on it?	Duration _____ in days/months	
	Status of the patients at the end of follow up?	Active _____/_____/____EC Dead ___/___/___EC Lost to follow up Drop out Transfer out	
	TB related information		
	Is he/she screened for TB?	1.yes 2. No	
	If yes for the above question, is he/she diagnosed as having TB?	1. Yes	

		2. No	
	If yes for question number 802, Time of Time of diagnosis/Occurrence	____/___/____EC	
	If yes for question number 802, Sputum result	1. Positive 2. Negative	
	If yes for question number 802, site of TB/ TB category?	1. Pulmonary positive 2. Pulmonary negative 3. EPTB 4. Combined	