

**ADDIS ABABA UNIVERSITY  
COLLEGE OF HEALTH SCIENCES  
SCHOOL OF PUBLIC HEALTH**

**THE EFFECT OF HAART ON INCIDENCE OF TUBERCULOSIS  
AMONG HIV INFECTED PATIENTS IN HAWASSA UNIVERSITY  
REFERRAL HOSPITAL, SOUTH ETHIOPIA**

**A RETROSPECTIVE COHORT STUDY**

**BY**

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**ADDIS ABABA UNIVERSITY  
SCHOOL OF GRADUATE STUDIES**

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## **ACRONYMS (ABBREVIATIONS)**

AAU	Addis Ababa University
AFB	Acid-Fast Bacilli
AHR	Adjusted Hazard Ratio
AIDS	Acquired Immune Deficiency Syndrome
ART	Anti Retro Viral Therapy
ARV	Anti Retro Viral Drug
CHCT	Couple HIV Counseling and Testing
CPT	Cotrimoxazole Preventive Therapy
FMOH	Federal Ministry of Health
HAART	Highly Active Anti-Retroviral Therapy
HCT	HIV Counseling and Tasting
HIV	Human Immunodeficiency Virus
IPT	Isoniazid Preventive Treatment
IRB	Institutional Review Board
MDR	Multi Drug Resistant
MPH	Muster of Public Health
OI	Opportunistic Infection
PICHT	Provider Initiated HIV Counseling and Testing
PLHIV	People Living With HIV
PPD	Purified Protein Derivative
PYO	Person Year Observation
RNA	Ribonucleic Acid
SNNPR	Southern Nation Nationality and People Region
TB	Tuberculosis
TLC	Total Lymphocyte Count
VCT	Voluntary Counseling and Testing
WHO	World Health Organization

## ABSTRACT

**Background Information:** Studies of Antiretroviral Therapy program in Africa have shown high incidence rate of tuberculosis in both Antiretroviral Therapy receiving and Antiretroviral Therapy naïve Human Immunodeficiency Virus infected patients. Tuberculosis incidence and factors that contribute for development of tuberculosis in era of Antiretroviral Therapy were poorly described in Ethiopia.

**Objective:** To examine the effect of HAART on incidence rate of tuberculosis and tuberculosis free survival among HIV-positive adults in HAART receiving and HAART naïve groups enrolled to ART clinic in Hawassa University Referral Hospital.

**Method:** A retrospective cohort study design was used on 632 HIV-positive adults with age 15 years old and above enrolled to ART clinic in Hawassa University Referral Hospital over a three-year period. Incidence rate of tuberculosis and TB free survival was calculated and compared for Pre-HAART and HAART follow up HIV/AIDS patients. In this study, patients who followed on Pre-HAART are considered as unexposed and patients who receiving HAART considered as exposed, and was followed for three years from July 2006 to January 2011.

**Result:** A total of 632 patients (316 in ART and 316 in ART cohort) followed for a median of 32.9(IQR=17.6-36.5) months in Pre-HAART and 35.4 (IQR=23.6-36.5) months in HAART cohort. TB incidence rate was 3.5 and 7.2 per 100 PYO in HAART and Pre-HAART cohort respectively. Over all chance of not developing TB was high in HAART cohort (Log rank=8.24, df=1, P=0.004). Being on HAART (AHR=0.182, 95%CI=0.078-0.424, P<0.001), being married (AHR=0.354 95%CI=0.191-0.655, P=0.001) and widowed (AHR=0.375, 95%CI=0.169-0.831, P=0.016) were factors related to decreased TB incidence. WHO stage 3 or 4 (AHR=1.999, 95%CI=1.025-3.896, P=0.042), being bedridden (AHR=4.689, 95%CI=1.715-12.819, P=0.003), and having hemoglobin level less than 10mg/dl (AHR=2.497, 95%CI=1.098-5.679, P=0.036) were factors associated with increased risk of TB at multivariate analysis.

**Conclusion:** HAART decreased new cases of tuberculosis by 81.8% compared to HAART naïve patients and the probability of not developing TB was higher in HAART cohort than Pre-HAART. The finding is similar level with other developing and developed countries, but still gross TB incidence rate was high in both Pre-HAART and HAART cohort when compared with developed countries. More efforts have to be taken to reduce TB incidence as level of most developed countries have achieved many years ago.

## 1. INTRODUCTION

The burden of HIV associated TB continued as the major public health problem in the world. Globally almost one third of HIV infected patients have TB infection concomitantly(1). Although the availability of antiretroviral therapy (ART) has transformed human immunodeficiency virus (HIV) infection into a chronic and manageable disease in those who are able to access treatment, the successes recorded can easily be destroyed by the high burden of tuberculosis (TB) co-infection in the HIV-infected individual. Even after the initiation of ART, the incidence of HIV related TB remains unacceptably high (1, 2).

According to WHO, 2009 report, from 9.27 million incident cases of tuberculosis, about 1.37 million (14.8%) was attributed by HIV infection in 2007 worldwide. Majority of these cases are accounted by African region where 79% HIV positive TB incident cases occurred in 2007. South Africa is the most affected county in Africa, and accounted for 31% of all cases in Africa region. Moreover tuberculosis is the commonest opportunistic infection and number one causes of death in HIV infected patients in the developing countries. In 2008 it killed about 0.5 million HIV infected people globally (3, 4).

Sub-Saharan African countries continued taking the leading position in HIV/TB morbidity and mortality rate, where the TB epidemic is primarily driven by HIV infection. Ethiopia is one among these countries most heavily affected by HIV and TB co-infection. The World Health Organization (WHO) has classified Ethiopia 7<sup>th</sup> among the 22 high burden countries with TB and HIV infection in the world in 2007. According to the same report, in Ethiopia 20% of all TB cases were also co-infection with HIV in 2007. In addition to this TB was the cause of 76 thousand deaths in Ethiopia, out of which 30% were among HIV positive patients(3, 5).

Analysis of the incidence of HIV associated tuberculosis infection in the era of HAART has been another challenging task. Since the clinical presentation of tuberculosis is deviated somewhat from that was known in Pre-HIV and HAART era. Moreover TB and HIV co-infection are associated with special diagnostic and therapeutic challenges and constitute an enormous burden on healthcare systems of heavily infected countries like Ethiopia. However, introduction of provider initiated counseling and testing in most public health facilities of Ethiopia has improved

TB screening among HIV patients. For example, from a total of 24,112 HIV positive people were referred from HCT, chronic HIV and ART clinics for TB screening out of which 4,154 (17.2%) were found to have active TB and 2,403 (10%) with latent TB (6, 7).

AIDS related deaths and illnesses in countries where ART has been available since the mid 1990's have declined considerably(8). This is also true for sub Saharan countries since the rapid scaling-up of antiretroviral therapy and generating considerable public health gains. Antiretroviral therapy (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. The emergence of drug resistant TB in countries with a high HIV prevalence poses an additional public health threat, not only to people with HIV but also to the broader community (9).

In Ethiopia, free antiretroviral therapy (ART) has been started since 2005. Although the rapid expansion of ART services at both hospital and health centers in most parts of the country over the last five years has greatly increased, there are still the coverage of ART was 53% of those in need in 2009 (6, 7).

### **Rationale of the study**

In the era of ART, prevention and treatment of TB in people living with HIV is an urgent priority for both HIV/AIDS and TB programmes. However, there is shortage of studies in Ethiopia, on effect of ART on incidence of tuberculosis, factors associated with development of TB and TB free survival among HIV infected patients. This study is designed to assess and compare the incidence of tuberculosis and TB free survival among HIV infected patients with and without HAART initiation and to find out the determinant factors for the development of TB in both groups while bridging the gaps in literature and it may also help for policy makers to make right decision in TB/HIV prevention.

## **2. LITERATURE REVIEW**

### **2.1. Burden of Tuberculosis and HIV/AIDS**

Globally tuberculosis is the leading causes of morbidity and mortality among HIV/AIDS infected patients. According to the WHO, 2009 report there were 1.37 million (14.8%) new HIV positive TB cases in 2007. In the same year TB accounts for 456,000(23%) deaths from estimated 2 million all HIV/AIDS deaths. Africa is the most affected region in the world with TB and HIV infection. Among 15 countries with highest estimated TB incidence rate, 13 are found in Africa. Africa accounted for 79% of global HIV positive TB cases in 2007. South East Asian region is the second most affected with 11% of global new TB cases in 2007(3, 10).

HIV and TB infection have synergistic effect by accelerating the individuals to the sever form of HIV disease and death. HIV infection increases the risk of developing the active TB by 100 folds. Moreover it has an indirect effect on the incidence of TB by increasing transmission rates of Mycobacterium tuberculosis, with negative consequences for both HIV negative and HIV positive persons. In contrary active TB facilitates the progression of HIV infection into AIDS by increasing plasma level of HIV RNA. This clearly shows that untreated TB can speed up the progression of HIV infection in to its advanced form.

The risk of developing TB disease among HIV infected individuals and the association between TB and AIDS has been well documented. Different studies revealed that the incidence of TB for untreated HIV infection and positive PPD skin test is 7 to 10% per year, representing 50 to 60% life time risk compared to 5 to 10 % per life time in immune competent population (1, 11).

### **2.2. The Impact of HAART on Development of TB**

Combination antiretroviral therapy, or ART, is the single most important way to reduce the incidence of TB in people living with HIV/AIDS. Following the initiation of widespread use of HAART in the United States in 1995 to 1996, marked declines have been noted in the incidence of most AIDS-defining conditions including TB. Suppression of HIV replication is an important component of ART (1).

Different studies illustrate the impact of ART on incidence of TB as follows: a retrospective cohort study conducted in 2003 in Brazilian state showed that TB incidence was 10 folds on ART naïve group than ART treated group ( $P < 0.001$ )(12). Another similar study conducted in 10 Spanish hospitals in 2003, showed similar findings with incidence density rate of 1.56 per 100 PY and 0.5 per 100 PY in ART naïve and ART treated patients respectively(13). However, TB incidence still higher in both pre ART and ART groups in developing countries compared to developed countries. A prospective cohort study conducted in resource limited setting in southern part of Ethiopia revealed this fact. In this study incidence of TB were 3.7 per 100PY and 11.1 per 100PY ( $P < 0.01$ ) in ART and pre ART patients respectively(14). Although the incidence of TB was significantly lower in ART groups than pre ART, it is still higher compared with developed countries. Another study conducted in South Africa had similar finding in resource limited setting with the TB incidence rate of 2.4 and 9.7 PY in ART treated and ART naïve patients respectively(2).

Although the risk of developing TB is reduced by 70–90% among HIV-infected persons receiving HAART compared with untreated individuals(15-17); TB continues to occur, moreover, TB has become relatively more common when considered as a proportion of all AIDS-associated opportunistic infections(10, 18). This is because of the emergence of multi drug resistant TB in countries with a high HIV prevalence poses (9).

To overcome this emerging challenge, early TB screening and identification of cases, followed by adequate treatment services, are beneficial in improving overall clinical outcomes in TB/HIV co-infected patients. In addition to this it helps in reduction of TB transmission from undiagnosed and untreated patients. Moreover, HIV infected patients who screen negative for TB can be assessed for eligibility of isoniazid preventive therapy.

### **2.3. Tuberculosis Free Survival in HIV Infected Patients**

Different studies revealed that tuberculosis free survival were significantly lower in HAART naïve HIV positive patients than patients on HAART. That means; patients on HAART were stay longer period without developing tuberculosis compared with HAART naïve subjects. A prospective study from South Africa showed that the overall median tuberculosis-free survival in

the HAART cohort was significantly greater than that of the non-HAART cohort ( $p < 0.0001$ ). It was further stratified by baseline CD4 count ( $< 200$ ,  $200-350$ , and  $> 350$  cells/ $\mu\text{L}$ ) and WHO clinical stage, and the final result showed that the TB free survival lower in non-HAART cohort across all strata of WHO stages and CD4 counts, but not in the stratum of more than 350 CD4 cells/ $\mu\text{L}$  CD4 count(2, 19). Another study conducted in Brasilia, Federal District in Brazil; the overall TB free survival was significantly lower ( $p < 0.001$ ) among the patients with CD4+ less than 200 and non- HAART user. In this study the analysis was performed by categorizing CD4+ T-lymphocyte counts as  $\leq 200$  and  $> 200$  cells/ $\mu\text{L}$ , as stratified by the use of HAART the final result showed TB free Survival was significantly lower ( $p < 0.001$  using the log-rank test) among the patients with CD4+ T-lymphocyte counts  $\leq 200$  cells/ $\mu\text{L}$  and among those who were not using HAART. Patients who showed both of these characteristics had the worst mean survival and highest hazard ratio for developing TB(20).

## **2.4. Predictors for Incidence of TB in HIV Infected Patients**

### **2.4.1. 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 ( $P < 0.003$ )(14, 19, 21). 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 (22). 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/ $\text{mm}^3$  was independently associated with increased risk of TB ( $p < 0.01$ ) (12).

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  $< 50$  cells/ $\mu\text{L}$  ( $P = 0.0002$ ). Among those with baseline CD4 cell counts less than 200 cells/ $\mu\text{L}$ , the excess risk of TB during early ART might be due to missed TB cases at baseline screening (22-24). On the other hand an increase of CD4+ by 100 cells/ $\mu\text{L}$  was associated with 25% lower risk of developing TB ( $P = 0.007$ )(25). In addition to this, a higher CD4+ cell count at the time of starting HAART was independently associated with a reduced

incidence of TB (22). Moreover incidence of TB decreases with stay longer time in ART treatment (26). A prospective study done in south Africa stated that the adjusted TB rates among those with CD4+ cell counts 0-200 cells/ $\mu$ L were 1.7 times higher in short duration on ART than long duration on ART(P=0.026) This might be due to increased level of CD4+ cells since initiation of ART(27).

#### **2.4.2. 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(28). 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 (95% CI, 0.43-0.80), P=0.03 on INH treated Vs placebo for TB. 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(29) 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(30)

#### **2.4.3. Other Important Factors Related to Development of TB in HIV Positive Individuals**

Regarding to socio demographic factors, the most affected age groups with active tuberculosis are patients between 25 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 (P=0.001) is independently associated with at higher risk of TB (22, 23, 31).

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 (1, 22, 32).

### **3. OBJECTIVES**

#### **3.1.1. General objectives**

- To examine the effect of HAART on the development of tuberculosis and TB free survival among HIV positive adult patients.

#### **3.1.2. Specific objectives**

- To compare the incidence of tuberculosis in HAART and Pre-HAART cohort
- To compare TB free survival between HAART and Pre-HAART cohort
- To identify potential risk factors for the development of TB in HIV positive patients

## **4. METHODOLOGY**

### **4.1. Study Setting**

A retrospective cohort study was conducted in January, 2011 in Hawassa University Referral Hospital, which is located 275 km south of Addis Ababa, in the capital of SNNPR Hawassa. The hospital gives services for approximately one million people and it is the University Teaching Hospital with basic facilities for HIV care and treatment and with established clinical set up and highly trained medical personnel. The hospital has started pre-ART and ART services since July 2006. Any patient diagnosed as having HIV in any of HIV counseling and testing protocols (VCT, PICT, and CHCT etc) referred to the ART clinic for Pre-ART and ART follow up and registered in Pre-ART and ART log books according to the status of the patients on diseases progression.

### **4.2. Study Design**

A retrospective cohort study design was used to compare the incidence of tuberculosis and tuberculosis free survival among patients in Pre-ART and ART follow up. In this study, patients who followed on Pre-ART and ART were retrospectively followed for three years since July 2006 to January 2011. Therefore there were two cohorts of patients: the Pre-HAART and the HAART cohorts. Patient's initiation of HAART was considered as an exposure and diagnosis of TB was considered as the outcome variable. TB incidence density is calculated as number of new TB cases divided by total person time follow up contributed by each subjects in the per-ART and ART group separately from the date of registration in Pre-ART or ART log book to date of TB diagnosis. For the Pre-HAART cohort, TB free survivals is the time from initial clinic visit to the date their diagnosis of tuberculosis, drop out, death, or the last follow-up visit. To the HAART cohort, it is the time from date of HAART initiation to the date of tuberculosis diagnosis, drop out, death, or the last follow-up visit.

### **4.3. Population**

**4.3.1. Source Population:** All HIV positive patients registered in Hawassa University Referral Hospital both in Pre-ART and ART follow up and who are age 15years and above.

**4.3.2. Study population:** All HIV positive patients registered from July 2006 to January 2008 in Hawassa University Referral Hospital both in Pre-ART and ART follow up and who are age 15years and above.

**4.3.3. Study subjects:** All selected HIV infected patients, registered on pre ART and ART log book for chronic care and treatment in the study period.

### **4.4. Starting and End Points of Follow up**

Both the exposed (HAART) and unexposed (HAART naive) HIV positive patients were followed-up from the date of registration for Pre- HAART and initiation of HAART for HAART group until date of TB diagnosis, or death, drop out or the date of the most recent visit prior to the end of follow up. The duration of the follow up period for a subject was three years and the starting point for follow up in records was July 2006 for both cohorts.

### **4.5. Inclusion and Exclusion Criteria**

**4.5.1. Inclusion Criteria:** Any HIV infected patient whether on HAART or Pre-HAART care and treatment who was registered from July 2006 to January 2008 with complete intake form, registers, follow up form and age 15 years or above was included in the study.

**4.5.2. Exclusion Criteria:** All individuals on HAART follow up who were censored from pre HAART follow up during the study period were not included in the study. In addition to this all HIV infected patients in both Pre-HAART and HAART groups who have prior history of TB were not part of the study.

### **4.6. Sampling Procedures**

Hawassa University Referral Hospital was selected for the study purposely to get adequate number of sample and optimal follow up period. A total of 2821(1823 in Pre-ART and 998 in ART) patients were enrolled to the ART clinic from July 2006 to January 2008. Of the total 1823 patients in Pre-ART group 1678 were fulfill the inclusion criteria. Similarly out of 998 patients in ART group 892 patients fulfill inclusion criteria. For these who fulfill inclusion criteria, unique ID number were given in increasing order for both Pre-ART and ART groups separately. Then simple random sampling technique was employed separately to select 316 samples from each group using computer generated random number table.

#### 4.7. Sample Size Determination

The sample size was calculated using two sample proportion formulas in Epi-Info version 3.3.1 for window.

$$n_1 = \frac{\left[ Z_{\alpha/2} \sqrt{(r+1) \bar{p} \bar{q}} + Z_{1-\beta} \sqrt{r p_1 q_1 + p_2 q_2} \right]^2}{r(p_1 - p_2)^2}, n_2 = r \times n_1$$

Where:

$n_1$  = number of HIV infected patients who were on ART (Exposed)

$n_2$  = number of HIV infected patients who were ART naive (non exposed)

$r$  = the ratio of exposed to non exposed HIV infected patients = 1

$P_1$  = proportion of tuberculosis in ART receiving HIV infected patients

$$\bar{p} = \frac{p_1 + r \times p_2}{r+1}; \bar{q} = 1 - \bar{p}$$

$P_2$  = proportion of tuberculosis in ART naïve HIV infected patients

$\alpha$  = Type one error (0.05)

$Z_{\alpha/2}$  = Critical value at 95 % level of significance

$Z_{1-\beta}$  = standard normal distribution value corresponding to power

To determine the sample size, a prospective cohort study conducted at Arbaminch Zonal hospital, South Ethiopia was considered. In the study incidence rate of TB in pre-HAART and HAART were 11.1 and 3.7 person years respectively(14). Therefore, the sample size was calculated using this incidence rate in pre-HAART and HAART. Taking ratio of number of exposed to number of unexposed 1:1 with 90% power and 5% type I error and considering 10% incomplete and inconsistent data, the resulting minimum sample size was 632. (316, pre-ART HIV infected patients and 316, ART HIV infected patients). Therefore, the total sample size (n) was = 632 with  $n_1 = n_2 = 316$

#### **4.8. Data Collection Tools and Procedures**

Data collection format was prepared by principal investigator. Based on it relevant data were collected from patient's pre-ART and ART follow up log books and other clinical records. To ensure the quality of data, data collectors were trained nurses, recruited from ART and TB chronic clinic, on method of extracting the needed data from patient's records and filling on data collection format. Pretest was carried out on 10% of the study subjects and a modification was taken according to the findings. During data collection, baseline, socio-demographic, clinical and laboratory data were collected from standardized patient records and was followed risk factors and outcome events. On the days of data collection, the principal investigator and supervisors were supervised the data collection process by checking completeness of the data.

#### **4.9. Data Entry and Analysis**

The data collection forms were checked for completeness and consistency by the principal investigator before the entry for the analysis. Completed questionnaires were coded by numbers and 20% of the data double entered in computer software EPI info version 3.3.1 statistical package. Cross-checking and data cleaning was done for accuracy, outliers, and consistencies carried out by running frequencies of each variable by principal investigator. Once the data cleaning completed the statistical analyses was performed using SPSS version 16. The risk of developing TB among patients with retrospective follow up in Pre-ART or ART cohort was assessed using the person-time method. Incidence rate was calculated as number of tuberculosis cases per 100 person years observed. Here, all patients were considered to be at risk of developing tuberculosis during follow-up period. Cox proportional hazards model was used to assess predictors of incidence of TB, two-sided P-value  $<0.05$  at 95% confidence level was considered as statistically significant and the Kaplan-Meier technique and the generalized log-rank test were used to construct and compare the tuberculosis-free survival probabilities curves of the two groups.

## **4.10. Study Variables**

### **4.10.1. Dependent variable**

- Developing new TB and time to occurrence of TB

### **4.10.2. Independent variable**

- Exposure variable: HAART status (HAART initiation or not)
- Socio demographic, Clinical and other variables:

Age, sex, education status, marital status, occupation status, weight, CD4+ count, prophylaxis (IPT and CTX), Hemoglobin level, opportunistic infection, adherence level for HAART, WHO clinical stage at baseline

#### 4.11. Operational Definitions

- Past history of TB: defined as previous history of TB before the first date of registration on pre ART or ART log book.
- Anemia classified as hemoglobin level < 10 mg/dl
- Tuberculosis defined and categorized according to the National Tuberculosis and Leprosy control manual of Ethiopia.
  - Smear positive pulmonary tuberculosis (PTB+) if two or more initial sputum examinations were positive for AFB, or one sputum positive for AFB plus radiographic abnormalities consistent with active TB as determined by a physician.
  - 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

- Adherence level

Score	%	of 30 doses	of 60 doses
G(good)	>95%	≤ 2 doses	< 3 doses
F(fair)	85-94%	3-5 doses	3-9 doses
P(poor)	<85%	≥6 doses	>9 doses

- 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
- Drop out= lost to follow up for > 3 months
- Transfer out= moving by taking the full medical record from Hawassa University Referral Hospital to other health institution for care and treatment

#### **4.12. Ethical Considerations**

Ethical clearance was obtained from the Institutional Review Board (IRB) of Addis Ababa University, College of Health Science before conducting the study. After securing ethical clearance from IRB of Addis Ababa University, Hawassa University Referral Hospital was informed about the objective of the study through a support letter from Addis Ababa University, School of Public Health and written permission was obtained from the Hospital administration before starting data collection. Informed consent was obtained from patients who were access in the period of data collection. Otherwise the informed consent not needed from the patients absent during data collection period, since the study is conducted through review of medical records, the individual patients were not subjected to any harm as far as the confidentiality is kept. To keep the confidentiality of the patients, data collectors were recruited from ART clinic and personal identifiers were not included in the data collection format.

## 5. RESULT

### 5.1. Baseline Socio-Demographic Characteristics of the Study Subjects

A total of 632 HIV infected patients (316 Pre-ART and 316 ART cohorts) were followed retrospectively for a median of 32.9 months (interquartile range (IQR) 17.6-36.5) in Pre-ART and 35.4 months (IQR=23.6-36.5) in ART cohort. The follow up period was a little higher in ART than pre-ART groups .The data were retrieved from Pre-ART and ART Logbooks and patient follow up medical records for baseline/ initial and repeated measurements. Repeated values collected for CD4+ count, weight, hemoglobin level, HAART adherence and WHO clinical staging, which were available in the patient's medical record. However, due to the incompleteness the data they have totally excluded from the analysis.

The baseline socio-demographic characteristics of both cohorts are shown in table 1. The median and inter quintile range (IQR) for the age of ART cohort were 31 and 27-38 years respectively. The corresponding values for the Pre-ART cohort were 28 and 24-35 years. High number of women were in both cohort; 189 (59.8%) and 214(67.7%) in ART and Pre-ART cohort respectively. But the proportion of women in the non-HAART cohort was higher than in HAART cohort. Majority of the patients were married in both cohort; 138(43.7%) and 154(48.7%) in ART and Pre-ART respectively. More than three fourth; 277(87.7%) of patients who initiated ART were completed primary school and above whereas in ART naïve patients 238(75.3%) were completed primary education and above. Considerable number of patients in the study were government employees in both ART and Pre-ART cohort; 64(20.3%) and 82(25.9%) respectively. Of the total 316 patients in ART follow up group; 146(46.2%) were unemployed this number is much lower in pre-ART cohort; 87(27.5%).

**Table1:** Baseline socio-demographic characteristics of HIV infected patients in Hawassa University Referral Hospital, 2011

<b>Baseline variables</b>	<b>ART(n=316)</b>	<b>Pre-ART(n=316)</b>	<b>Total(n=632)</b>
<b>Sex</b>			
Male	127(40.2)	102(32.3)	229(36.2)
Female	189(59.8)	214(67.7)	403(63.8)
<b>Age(years)</b>			
15-24	44(13.9)	81(25.6)	125(19.8)
25-34	150(47.5)	150(47.5)	300(47.5)
35-44	93(29.4)	62(19.6)	155(24.5)
45-54	21(6.6)	17(5.4)	38(6.0)
55+	8(2.5)	6(1.9)	14(2.2)
<b>Marital status</b>			
Single	66(20.9)	45(14.2)	111(17)
Married	138(43.7)	154(48.7)	292(46.2)
Separated	14(4.4)	11(3.5)	25(4.0)
Divorced	50(15.8)	49(15.5)	99(15.7)
Widowed	48(15.8)	57(19.8)	105(16.6)
<b>Occupational status</b>			
Farmer	11(3.5)	10(3.2)	21(3.3)
Merchant	73(23.1)	38(12.0)	111(17.6)
Governmental employee	64(20.3)	82(25.9)	146(23.1)
Non-governmental employee	11(3.5)	14(4.4)	25(4.0)
Day laborer	72(22.8)	62(19.6)	134(21.2)
Jobless	21(6.6)	7(2.2)	28(4.4)
House wife	56(17.7)	90(28.5)	146(23.1)
Others <sup>1</sup>	8(2.5)	13(4.1)	21(3.3)

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<sup>1</sup> Student, driver

## **Employment**

Working full time	141(44.6)	205(64.9)	346(54.7)
Working part time	3(0.9)	10(3.2)	13(2.1)
Not working	26(8.2)	14(4.4)	40(6.3)
Unemployed	146(46.2)	87(27.5)	233(36.9)

## **5.2. Baseline Clinical Characteristics of the Study Subjects**

Baseline clinical condition of the two groups was different in many aspects; patients receiving ART had more advanced WHO clinical stage than Pre-ART group. Majority of ART receiving group were in stage III or IV WHO clinical stage 262(82.9%). In contrary, 224(70.9%) in ART naive group were in stage I or II WHO clinical staging. More individuals in Pre-ART group were able to perform usual work in or out of their house (working); 283(89.6%) than in ART cohort; 184(58.2%) at baseline. Nearly three fourth of the ART receiving patients had at least one opportunistic infection at baseline; 230(72.9%). More than half 180(57%) patients had opportunistic infection in Per-ART group. (Table 2)

Baseline immunological status of the two groups assessed using baseline CD4 count at registration. The result shows that patients in ART cohort had much lower CD4+ cell count than patients not receiving ART. The minimum and maximum CD4+ cells in ART group were 1 and 803 respectively with median of 153cells/ $\mu$ l and IQR (91-208). The corresponding value in Pre-ART group was 111 and 1661 respectively with the median of 543cells/ $\mu$ l and IQR (405-710). The difference also more elaborated by dividing the CD4+ level into below 200cells/ $\mu$ l Vs 200cells/ $\mu$ l and above. Of the total 316 patients in ART group; 228(72.15%) patients had CD4+ less than 200cells/ $\mu$ l. In contrary only 8(2.5%) of patients had CD4+ less than 200cells/ $\mu$ l in Pre-ART group.

Measuring hemoglobin level is another important hematologic instrument to assess the progression of HIV disease and to initiate and monitor antiretroviral drugs in HIV positive individuals. All study subjects had measured hemoglobin level at registration in both groups.

Accordingly, the minimum and maximum hemoglobin level in HAART was 7.2 and 17.3mg/dl respectively with the median of 13mg/dl and IQR (11-14.1mg/dl). Whereas in Pre-HAART groups; the minimum and maximum hemoglobin level was 8.9 and 17.5mg/dl respectively with median of 13.2 mg/dl IQR (12.4-13.5mg/dl).

**Table2:** Baseline clinical and immunological characteristics of HIV infected patients in Hawassa University Referral Hospital, 2011

<b>Baseline variables</b>	<b>HAART(n=316)</b>	<b>Pre-ART(n=316)</b>	<b>Total(n=632)</b>
<b>Functional status</b>			
working	184(58.2)	283(89.6)	467(73.9)
Ambulatory	107(33.9)	32(10.1)	139(22.0)
Bedridden	25(7.9)	1(0.3)	26(4.1)
<b>WHO Stage</b>			
Stage I	7(2.2)	83(26.3)	90(14.2)
Stage II	47(14.9)	141(44.6)	188(29.7)
Stage III	205(64.9)	91(28.8)	296(46.8)
Stage IV	57(18.0)	1(0.3)	58(9.2)
<b>Opportunistic infection</b>			
Yes	230(72.8)	180(57)	410(64.9)
No	86(27.2)	136(43.0)	222(35.1)
<b>Hemoglobin level</b>			
<10mg/dl	37(11.7)	7(2.2)	44(7.0)
≥10mg/dl	279(88.3)	309(97.8)	588(93.0)
<b>CD4+ Count</b>			
<200	228(72.2)	8(2.5)	236(37.3)
200-350	79(25.0)	37(11.7)	116(18.4)
>350	9(2.8)	271(85.8)	280(44.3)

### 5.3. Description of the ART Cohort at Baseline

Out of 316 HIV infected patients on treatment about 224(70.9%) of patients were initiated the therapy by CD4 count eligibility criteria and the remaining by clinical and total lymphocyte count. At the time of initiation of antiretroviral therapy, 230(72.8%) of the patients had at least one opportunistic infection. (Table 3)

#### 5.3.1. Antiretroviral Drugs Prescribed at Baseline

At start of antiretroviral treatment, nearly all patients were initiated with first line antiretroviral drugs; 315(99.7%) only one patient started with second line ARV drugs. Out of the total patients initiated with first line drugs; majority 136 (43.2%) of patients started with drug type d4t-3TC-NVP followed by d4t-3TC-EFV; 74(23.5%). Adherence evaluation at the end of first month, showed 304(96.2%) patients had good adherence to the treatment.

**Table 3:** Baseline clinical characteristics of the study participants for HAART cohort, Hawassa University Referral Hospital, 2011

<b>ARV eligibility criteria used</b>	<b>Number</b>	<b>Percent</b>
CD4<200	224	70.9
WHO Stage IV	13	4.1
WHO stage I, II or III with TLC<1200	79	25.0
<b>Regimen Recommended at baseline</b>		
1a <sup>2</sup>	136	43.0
1b <sup>3</sup>	74	23.5
1c <sup>4</sup>	68	21.5
1d <sup>5</sup>	37	11.7
2nd Line Regimen	1	0.3
<b>Adherence level for HAART</b>		
Good	304	96.2
Fair	3	0.9
Poor	9	2.8

<sup>2</sup> Stavudine, Lamivudine, Nevirapine

<sup>3</sup> Stavudine, Lamivudine, Efavirenz

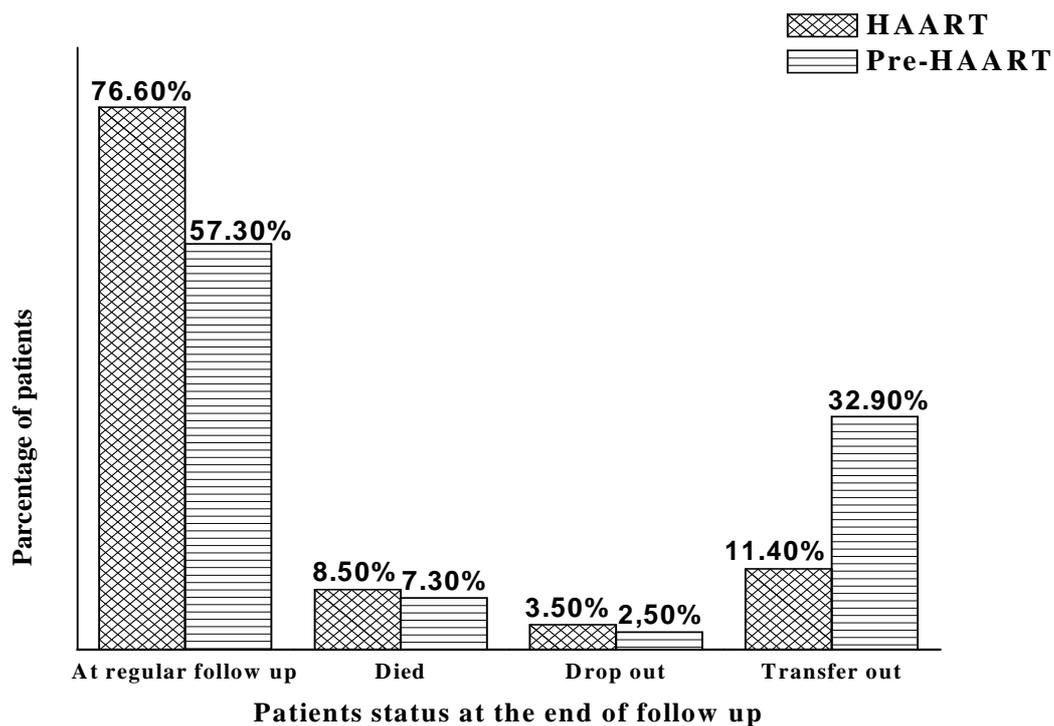
<sup>4</sup> Zidovudine, Lamivudine Nevirapine

<sup>5</sup> Zidovudine, Lamivudine Efavirenz

#### 5.4. Patients Follow Up in Both Pre-HAART and HAART Cohorts

At the end of the follow up period in Pre-HAART group 181(57.3%) of the patients were at regular follow up 23(7.3%) died, 8(8.5%) dropped out and 104(32.9%) were transferred out to other health institution. Similarly, 242(76.6%) of the patients were at regular follow up, 27(7.3%) died, 11(3.5%) drop out and 36(11.4%) were transferred out to other health institution in HAART receiving cohort. (Figure 1)

Both groups had nearly the same mortality rates with 3.6 per 100 PYO (27 per 746.6PYO) in HAART and 3.27 per 100 PYO in Pre-HAART (23 per 703.5PYO). Statistical analysis of the Kaplan Meier survival curve also shows no significant difference in survival between the two groups (log rank test=0.254, df=1, P=0.615)

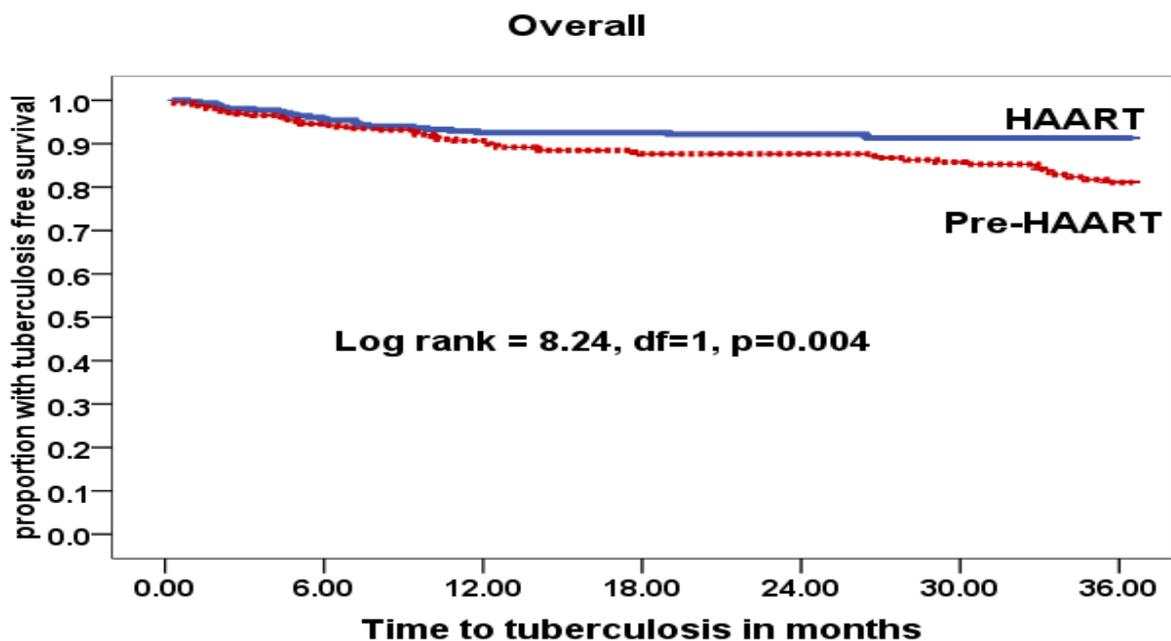


**Figure 1:** Patients' status at the end of the study period, in Hawassa University Referral Hospital, 2011

### 5.5. Comparison of Tuberculosis Incidence Rate and TB Free Survival in Pre-ART Vs ART Cohort

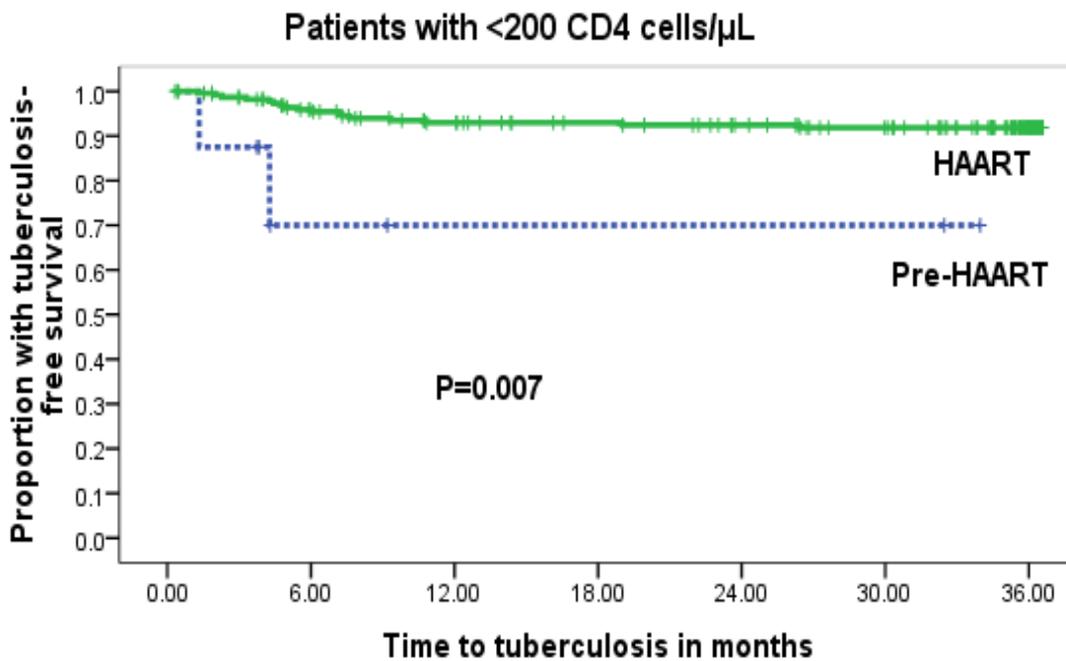
All the 632 study subjects have contributed for their respective group tuberculosis free time follow up observation with 664.76PYO and 711.37PYO in Pre-ART and ART cohort respectively. In Pre-ART cohort more HIV infected patients developed TB; 48(18 male and 30 female) than ART group; 25(13 male and 12 female) with the incidence rate 7.2 per 100PYO and 3.5 per 100PYO respectively. The result showed that ART resulted in statistical significant decreased occurrence of TB cases (AHR=0.168, 95%CI=0.076-0.371, P<0.001)

The Kaplan-Meier analysis and the log-rank test were used to compare the tuberculosis-free survival probabilities of the two groups. All the patients in both groups were included in the analysis. Overall probability of not developing tuberculosis in the HAART cohort was significantly greater than that of the non-HAART cohort, i.e. the risk of developing TB is higher in Pre-HAART group (log rank statistic=8.24, df=1, P=0.004) (Figure 2).

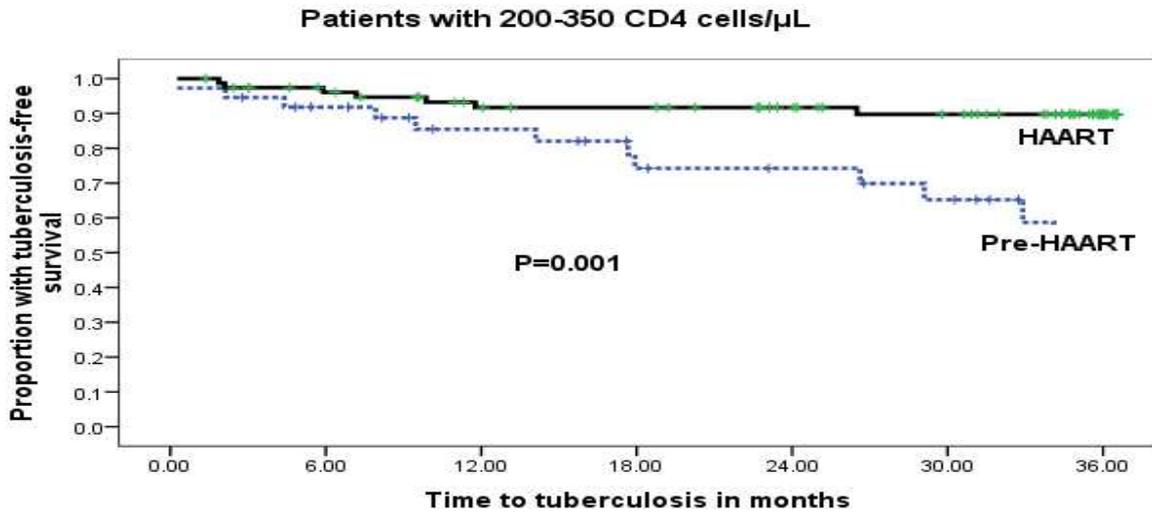


**Figure 2:** Kaplan-Meier estimate of tuberculosis free survival with and without ART, Hawassa University Referral Hospital, 2011

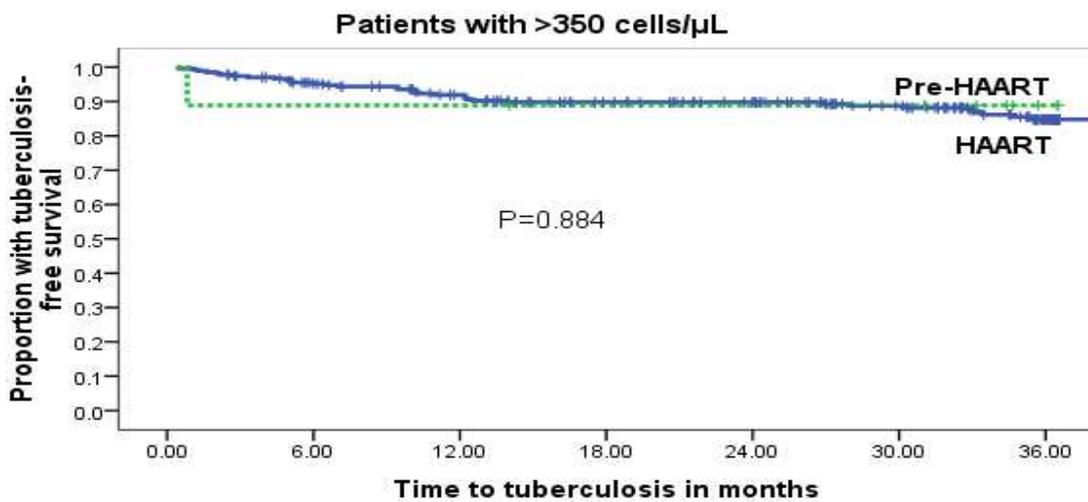
Baseline immunological and clinical status were further stratified based on CD4 count (<200, 200–350, and >350 cells/μL) and WHO clinical stage (WHO stage 1 or 2 and WHO stage 3 or 4) to compare tuberculosis free survival in the both cohorts. The result showed that HAART cohort had significantly greater chance of not developing TB than that of the non-HAART cohort across strata CD4 <200 and 200-350(P=0.007 and P=0.001 respectively), but no significant difference was observed in the stratum of greater than 350 CD4 cells/L (P=0.884). There was no significant difference in both groups in the WHO stages 1 or 2 stratum (P=0.128) but HAART cohort significantly greater probability of not developing TB than non- HAART in WHO clinical stage 3 or 4 stratum (P<0.0001). (Figure 3-7)



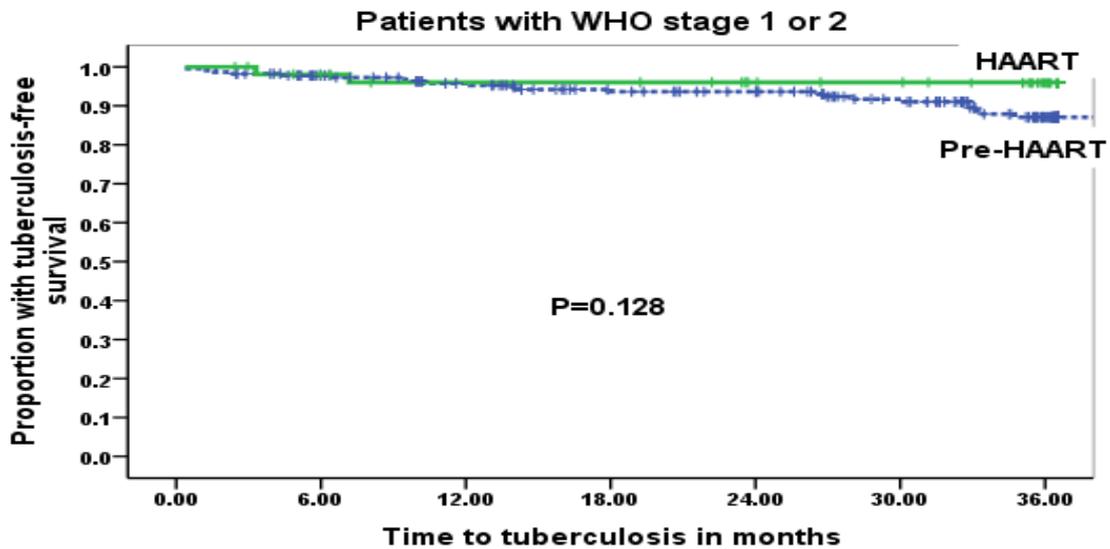
**Figure 3:** Kaplan-Meier estimate of tuberculosis free survival with and without ART, in patients <200 CD4, Hawassa University Referral Hospital, 2011



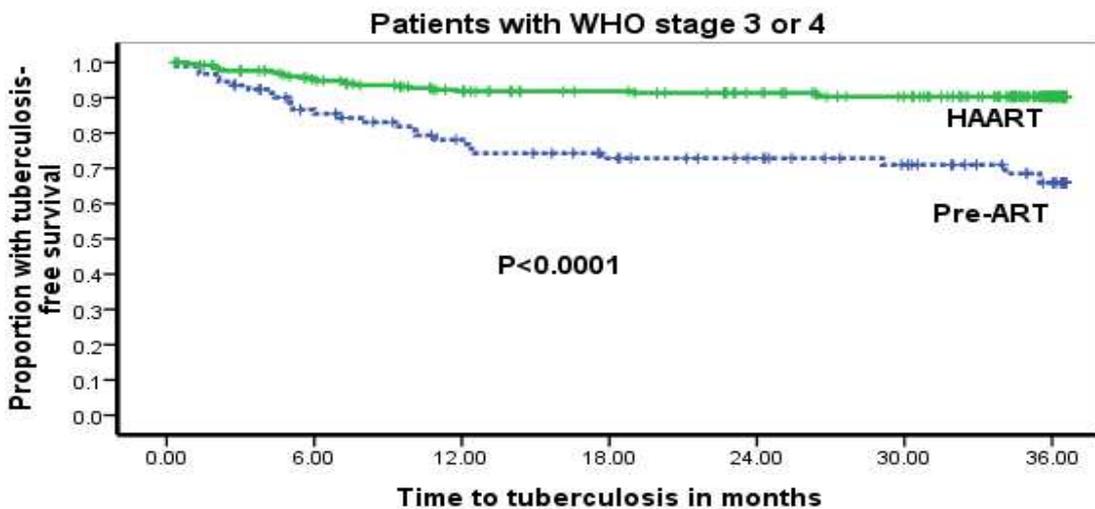
**Figure 4:** Kaplan-Meier estimate of tuberculosis free survival with and without ART, in patients 200-350 CD4, Hawassa University Referral Hospital, 2011



**Figure 5:** Kaplan-Meier estimate of tuberculosis free survival with and without ART, in patients 200-350 CD4, Hawassa University Referral Hospital, 2011



**Figure 6:** Kaplan-Meier estimate of tuberculosis free survival with and without ART, in patients with WHO stage 1 or 2, Hawassa University Referral Hospital, 2011



**Figure 7:** Kaplan-Meier estimate of tuberculosis free survival with and without ART, in patients with WHO stage 3 or 4, Hawassa University Referral Hospital, 2011

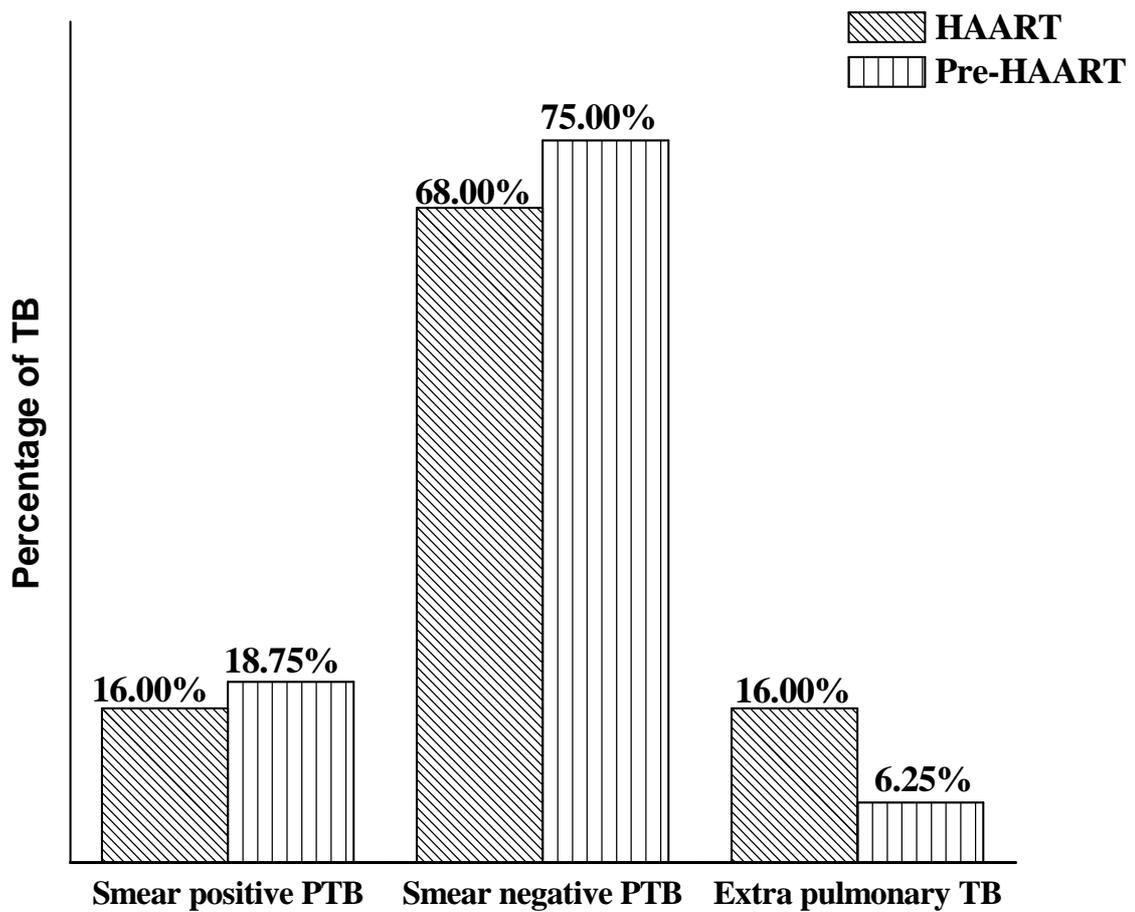
The median time for development of TB also has shown variation between the two groups. In ART group, from those who developed TB, majority of TB cases occur in the first 0 to 12 months with median and IQR 5.9(2.8-9.6) months and decreases in later follow up period. In similar manner, majority of new TB cases occurred in the first 12 months in Pre-ART group, but it continued to occur throughout the follow up period with median and IQR 9.8(4.3-24.4) months. Based on the life table analysis the probability of not developing TB at six, twelve, twenty four and thirty six months in ART cohort were 96%, 93%, 92% and 91% respectively. The corresponding values in Pre-ART cohort were 94%, 91%, 88% and 81% respectively (Table 3). This clearly showed that the probability of not developing TB at the end of study period in Pre-ART cohort was lower than that of ART cohort (81% Vs 91% respectively).

**Table 4:** The life-table showing comparison of the TB cases and TB free survival in HIV infected patients in HAART and Pre-HAART groups, Hawassa University referral hospital, 2011.

ART Status	Time in Months	N <sub>0</sub> at Start	Censored	N <sub>0</sub> at Risk	TB cases	Probability of not Developing TB in interval	Cumulative Probability of not developing TB
PRE-ART	(0-6)	316	20	306	17	0.94	0.94
	(6-12)	279	21	268.5	11	0.96	0.91
	(12-18)	247	21	236.5	8	0.97	0.88
	(18-24)	218	15	210.5	0	1.00	0.88
	(24-30)	203	26	190	4	0.98	0.86
	(30-36)	173	49	148.5	8	0.95	<b>0.81</b>
ART	(0-6)	316	23	304.5	13	0.96	0.96
	(6-12)	280	18	271	9	0.97	0.93
	(12-18)	253	13	246.5	0	1.00	0.93
	(18-24)	240	17	231.5	1	1.00	0.92
	(24-30)	222	15	214.5	2	0.99	0.91
	(30-36)	206	86	163	0	1.00	<b>0.91</b>

### 5.6. Clinical Presentation of Tuberculosis in Pre-HAART and HAART cohorts

Out of the total 48 TB cases in Pre-ART, 9(18.75%) patients had smear positive PTB, 36(75%) had smear negative PTB and the rest 3(6.25%) patients had extra pulmonary TB. The corresponding figure for ART was 4(16%) had smear positive pulmonary TB, 17(68%) had smear negative TB and the rest 4(16%) patients had extra pulmonary TB. (Figure 8)



**Figure 8:** The clinical presentation (category) of tuberculosis in HIV infected patients in Pre-HAART and HAART groups, Hawassa University Referral Hospital, 2011.

## 5.7. Predictors of Tuberculosis Incidence

Bivariate Cox-proportional model was used to assess the relationship between the baseline variables and the risk of developing new TB. Before fitting the covariate into the model all the proportional hazard assumptions was checked by plotting Schoenfeld residual and by examining log plots. The result showed that baseline weight, marital status, religion, WHO clinical stage, functional status, hemoglobin level, ART status (ART Vs Pre-ART), history of pneumonia at baseline were significantly associated with developing new TB in HIV infected patients during follow up period(Table 4).

Compared to the reference in the variable, the result of the bivariate analysis showed that the risk of developing new TB decreased by 63.1% and 55.1% in married and widowed patients respectively, compared with not married. In the study, the risk of new TB decreases for every 1kg increase in weight by 3.1%. Another important predictor of TB incidence was being on ART treatment or not. The risk of developing TB in individuals on Pre-ART follow up is two time higher than that of ART cohort ( $P=0.005$ ) i.e. ART decrease the risk of developing TB. Patients who were bedridden ( $HR=3.936$ ,  $P= 0.001$ ) and ambulatory ( $HR=1.725$ ,  $P= 0.039$ ) by their functional status were at increased risk of developing TB. Study subjects with baseline WHO clinical stage III or IV have about 1.7 times higher risk of developing TB than those in stage I or II ( $P=0.031$ ). Individuals with hemoglobin level  $\geq 10\text{mg/dl}$  has decrease risk of TB by 16.7% than individuals with Hemoglobin level  $< 10\text{mg/dl}$  ( $P= 0.008$ ). Patients with baseline history of pneumonia have about 2.2 times risk of developing TB in the follow up period ( $p=0.002$ ). Variables such as age, educational status,  $CD4+$  count were not associated with development of tuberculosis. In addition to this, neither the co-trimoxazole prophylactic treatment nor IPT were statistically significant in bivariate analysis

**Table 5:** Predictors of developing TB among HIV infected patients Hawassa University Referral Hospital, 2011

<b>Covariates</b>	<b>Number at Risk</b>	<b>Number of TB cases</b>	<b>Crude Hazard Ratio</b>	<b>95% CI</b>	<b>P-value</b>
<b>Gender</b>					
Male	229	31	1		
Female	403	42	0.727	(0.457,1.156)	0.727
<b>Age(years)</b>	632	73	0.984	(0.957,1.012)	0.252
<b>Weight(kg)</b>	632	73	0.969	(0.945,0.994)	0.014*
<b>Marital Status</b>					
Never married	111	23	1		
Married	292	25	0.369	(0.21,0.651)	0.001*
Divorced	124	14	0.580	(0.294,1.145)	0.117
widowed	105	11	0.449	(0.219,0.922)	0.029*
<b>Educational status</b>					
Not read and write	117	14	1		
Primary	256	35	1.153	(0.620,2.143)	0.652
secondary	210	19	0.731	(0.367,1.459)	0.375
Tertiary	49	5	0.798	(0.287,2.214)	0.664
<b>Religion</b>					
Muslim	39	8	1		
Orthodox	369	44	0.493	(0.232,1.048)	0.066
Protestant	211	18	0.336	(0.146,0.773)	0.010*
Others <sup>6</sup>	13	3	1.043	(0.277,3.933)	0.950
<b>INH prophylaxis</b>					
Yes	24	2	1		
No	608	71	0.565	(0.193,2.306)	0.426

<sup>6</sup> Catholic, Jehovah

<b>WHO clinical stage</b>					
Stage I or II	261	24	1		
Stage III or IV	305	49	1.713	(1.051,2.791)	0.031*
<b>Co-trimoxazole prophylaxis</b>					
Yes	384	47	1		
No	248	26	0.814	(0.504,1.314)	0.399
<b>Opportunistic infection</b>					
Yes	410	49	1.17	(0.718,1.907)	0.529
No	222	24	1		
<b>Functional status</b>					
Working	467	45	1		
Ambulatory	139	21	1.725	(1.027,2.896)	0.039*
Bedridden	26	7	3.936	(1.773,8.736)	0.001*
<b>Hemoglobin level</b>					
<10g/dl	44	9	1		
>or= 10g/dl	588	64	0.833	(0.728,0.952)	0.008*
<b>HAART Status</b>					
HAART	316	25	1		
Pre-HAART	316	48	2.003	(1.234,3.248)	0.005*
<b>CD4 count</b>					
<200cells/ $\mu$ l	236	19	0.642	(0.367,1.122)	0.119
200-350cells/ $\mu$ l	116	19	1.401	(0.801,2.449)	0.237
>350	280	35	1		
<b>Pneumonia</b>					
Yes	109	22	2.234	(1.355,3.683)	0.002*
No	523	51	1		

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\* Significant at  $\alpha= 0.05$

To identify independent predictors of developing tuberculosis, a multivariate Cox-Proportional hazard adjusted model was fitted with the variables having a P-value < 0.3 in the bivariate analysis. Accordingly, five variables were remaining independent predictors of new cases of TB after controlling for the other factors. From these factors; receiving HAART, being married and divorced had an independent protective benefit against risk of tuberculosis. In contrary being Bedridden, having WHO clinical stage III or IV and hemoglobin level less than 10mg/dl were independent predictors of increased risk of tuberculosis (table 6)

**Table 6:** Multivariate analysis (Cox-model) of baseline characteristics associated with developing TB among HIV infected patients Hawassa University Referral Hospital, 2011

<b>Covariates</b>	<b>Number at Risk</b>	<b>Number of TB cases</b>	<b>Adjusted Hazard Ratio</b>	<b>95% CI</b>	<b>P-value</b>
<b>Age(years)</b>	632	73	0.869	(0.973,1/032)	0.869
<b>Weight(kg)</b>	632	73	0.977	(0.951,1.003)	0.085
<b>Marital Status</b>					
Never married	111	23	1		
Married	292	25	0.354	(0.191,0.655)	0.001*
separated	25	1	0.189	(0.025,1.431)	0.107
Divorced	99	13	0.524	(0.244,1.125)	0.097
widowed	105	11	0.375	(0.169,0.831)	0.016*
<b>WHO clinical stage</b>					
Stage I or II	261	24	1		
Stage III or IV	305	49	1.999	(1.025,3.896)	0.042*
<b>Functional status</b>					
Working	467	45	1		
Ambulatory	139	21	1.433	(0.773,2.657)	0.253
Bedridden	26	7	4.689	(1.715,12.819)	0.003*
<b>HAART Status</b>					
HAART	316	25	0.182	(0.078,0.424)	0.000*
Pre-HAART	316	48	1		

<b>Hemoglobin level</b>					
<10mg/dl	44	9	2.497	(1.098,5.679)	0.029*
≥ 10mg/dl	588	64	1		
<b>CD4 count</b>					
<200cells/μl	236	19	1.001	(0.375,2.671)	0.999
200-350cells/μl	116	19	1.514	(0.743,3.085)	0.253
>350cells/μl	280	35	1		
<b>Pneumonia</b>					
Yes	109	22	1.667	(0.898,3.095)	0.105
No	523	51	1		

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\*Significant at  $\alpha= 0.05$

## 6. DISCUSSION

In this study, about 91.8% of patients are in age group 15-44 years in both groups. Like other developing countries, the most affected population group by HIV is in the most reproductive age group. Different studies revealed that active TB is most common in HIV positive patients between 25 to 44 years of age. These demographic groups contribute about 20 to 70% of the new cases of active TB in all patients with HIV infection (1). Similarly, in this study about 63% of new TB cases were contributed by this age group.

Study subjects in HAART cohort had median CD4 count 153 cells/ $\mu$ l with (IQR, 91-208) and about three fourth (72.15%) of the patients had less than 200cells/ $\mu$ l at initiation of antiretroviral therapy. This result is consistent with other studies done in developing countries. A prospective study from Uganda showed the median CD4 count was 130cells/ $\mu$ l (IQR 62-170) at initiation of HAART(33). Moreover about 82.9% of patients were in WHO clinical stage III and IV in HAART groups; it is in line with the CD4+ cells count in this study subjects. Because most of advanced HIV diseases are occur at low CD4+ count. The possible reason may be most of the patients seek medical care and treatment after they have developed advanced HIV diseases. In contrary in Pre-HAART cohort median CD4 count 543 cells/ $\mu$ l with (IQR 405-710) and about 97.5% patients had 200 cells/ $\mu$ l and above at registration. In addition to this 70.9% of the patients were in WHO clinical stage I and II in Pre-HAART cohort. These groups of patients in contrary to ART groups, they may be diagnosed as having HIV earlier before their clinical and immunological condition deteriorate. The introduction of provided initiated HIV counseling and testing may be possible reason for this group early diagnosis of HIV and enrollment for Pre-HAART follow up(6, 7).

In this study most of patients developed TB in the first 12 months in both Pre-HAART and HAART groups with median and IQR 5.9 (2.8-9.6) and 9.8 (4.3-24.4) respectively. But the numbers of TB cases continue to occur in non-HAART group whereas in HAART cohort it was lower in the later follow up period. This might be explained by the Pre-HAART groups were become deteriorate in their clinical and immunological condition because of HIV disease progression secondary to increased in viral load. But patients in HAART cohort become

immune-competent due to suppression of viral replication and increase in CD4+ count (22, 26, 27). In line to this study incidence of TB decreases in HAART group with stay longer time on HAART (26).

Active TB often develops relatively early in the course of HIV infection and may be an early clinical sign of HIV disease. In one study, the median CD4+ cell count at presentation of TB was 326cells/ $\mu$ L(1). But in this study it was difficult to get the exact value of CD4 at diagnosis of TB because it was not recorded. However, it was tried to look the baseline CD4 count of patients who develop TB in the course of their follow up. Based on this, patients develop TB in their course of follow up with the overall median CD4+ count 329cells/ $\mu$ L at baseline. However when further stratified by ART status, the HAART cohort had low baseline CD4 count than Pre-HAART with the median CD4 count 132cells/ $\mu$ l and 440 cells/ $\mu$ l respectively.

Although the patients in Pre-HAART group were relatively in good clinical and immunological condition at registration than HAART group at initiation of ARV, there were more TB cases in Pre-HAART group than in HAART (48 in Pre-HAART Vs 25 in HAART) with incidence rate 7.2 and 3.5 per 100PYO in Pre-ART and ART groups respectively. The finding is similar to that reported in two studies from Ethiopia and South Africa. TB incidence rate was 11.1 and 3.7 per 100PYO in Pre-HAART and HAART cohort respectively in Ethiopia and 2.4 and 9.7PYO in Pre-HAART and HAART cohort respectively in South Africa (2, 14, 19). In this study TB incidence is lower in Pre-HAART cohort than that reported from both stated studies above. The possible reason might be most of patients had relatively high CD4+ count with median of 543 with (IQR 405-710) compared with 303cells/ $\mu$ l (IQR 159-468) from South African study(2, 19).

Although the overall incidence of tuberculosis is low in HAART, it is still substantially higher compared with that have been achieved by developed countries. Studies from developed countries showed low tuberculosis incidence in patients receiving HAART (studies from Italy and USA; 0.79 and 0.5 TB cases per 100PYO respectively) (15, 16).

The life table analysis of not developing TB showed that the probability of not developing TB at the end of the study period (36 months) in HAART naïve group was lower than that of HAART group with 81% and 91% respectively. This clearly showed that the overall TB free survival was high in HAART cohort i.e. patients in HAART follow up group have lower risk of developing TB in the study period. Similarly, the Kaplan- Meier estimate of TB free survival showed; TB free survival significantly worse ( $P=0.004$  using the log-rank test) among patients who were not using HAART. It is consistent with the study conducted in Brasilia, Federal District in Brazil; TB free survival was significantly lower ( $p < 0.001$ ) among the patients with CD4+ less than 200 and non- HAART user(20). And another study from South Africa showed overall median tuberculosis-free survival in the HAART cohort was significantly greater than that of the non-HAART cohort ( $P < 0.0001$ ) (2, 19).

Based on the result from the multivariate analysis, being on HAART treatment was independently associated with decreased risk of developing TB (HR= 0.168, 95%CI, 0.076-0.371) i.e. the overall reduction of tuberculosis risk associated with the use of HAART estimated 81.8% (95% CI 62.9- 92.4%), which is consistent with the studies from Ethiopia, south Africa, Italy and USA with 89%, 81%, 92% and 80% respectively(2, 14, 16, 19, 26, 34). Another independent predictor of decreased risk of developing TB in HIV positive patients was being married and widowed in marital status. Patients who were married and widowed have decreased risk of developing TB by 64.6% (95%CI, 34.5%-80.9%) and 62.5 % ( 95%CI, 16.9%-83.1%) respectively compared to never married. It is difficult to explain how married and widowed associated with decreased risk of TB, so it need further study in this area.

Patients who were bedridden and their hemoglobin level less than 10mg/dl were independently associated with increased risk of developing TB. Patients who were bedridden at the initiation of HAART and registration of Pre-HAART have a 4.216 times higher hazard/risk of developing TB than working patients. This might be due to being seriously sick secondary to deteriorated clinical and immunological condition. Patients having a hemoglobin level of  $< 10\text{mg/dl}$  have 2.423 times higher risk of developing TB than those patients having hemoglobin level  $\geq 10\text{mg/dl}$ . This shows that patients having higher hemoglobin level have a low risk of developing TB than those with low hemoglobin level. TB and hemoglobin level might be indirectly associated with

advanced stage of HIV disease, when HIV positive patients have chronic disease and high viral load it resulted in immune-suppression and suppression of red blood production in bone marrow this might lead to both TB due to deteriorated immunity and Anemia due to supersession of RBC production. Other independent predictors of tuberculosis were WHO stage 3 or 4; patients with WHO stage 3 or 4 have higher risk of developing TB than those with WHO stage 1 or 2(AHR=1.999, 95%CI=1.025-3.896, P=0.042). It is consistent with other study done in South Africa (AHR=4.28, 95% CI=2.64–6.95, P<0.0001)(2). This suggests that those who developed TB may have been more immune-compromised at baseline than patients remaining TB free.

Different studies clearly showed that HAART significantly decreases HIV/AIDS related mortality rate, which means mortality rate low in HAART receiving patients (1, 14, 35, 36) . Most of these studies showed the mortality rate of before and after HAART era and some of them from clinical trial during introduction of ARV drugs. In addition to this more or less the clinical and immunological status of the two groups was similar. However, in this study there is no significant difference in mortality rate in both HAART receiving and HAART naïve group. The absence of the difference in mortality rate in both groups might not be due to absence HAART effect on mortality rate. This might be both groups were different in their clinical and immunological status. Patients in Pre-HAART group were relatively in good clinical and immunological condition. In addition to this, they evaluated and treated for opportunistic infection this might be decreases the mortality rate in Pre-HAART cohort. Because of this no significant difference was observed in mortality rate in HAART naïve and HAART receiving cohorts in this specific study.

In both groups deaths occurred in early period of follow up this might be due to delay in medical care and treatment since some patients seek medical care and treatment after their immunological and clinical condition deteriorated. But once the patients adhere for care and treatment the number of patients that died from HIV/AIDS related diseases decreased.

Different studies in high TB/HIV burden countries have showed that isoniazid preventive treatment reduces the risk of TB infection in people living with HIV/AIDS. A controlled clinical trial that conducted in Zambia was showed that 6 months isoniazid preventive therapy reduced TB occurrence by 89% on PPD-positive HIV positive patients(37). Similarly a study conducted in Haiti showed 12 months of therapy with isoniazid resulted in an 83% rate of protection against TB among HIV positive, PPD-positive patients. In the same study significant protection against TB was documented with 71% reduction of TB infection irrespective of PPD reactivity in the total study population(4). In contrary, a randomized, double-blind, controlled trial comparing isoniazid (INH) with placebo among tuberculin skin test negative (TST) with advanced HIV disease, conducted in South African adults not find any association between INH preventive therapy and reductions incidence of TB(38). Similarly in this study there is no significant difference was observed between patients who were on INH preventive therapy and not on treatment. This might be due to low power of the study to identify the difference because of inadequate number (only 24 patients who were on 6 months therapy) of patients who were on INH preventive therapy.

## **7. STRENGTHS AND LIMITATIONS**

### **7.1.1. Strengths**

- Strong power

### **7.1.2. Limitations**

- Use of retrospective cohort study design
- The HAART cohort had more intense follow-up than Pre-HAART this might lead to greater opportunity to diagnose tuberculosis in HAART cohort.
- Incomplete and inconsistent follow up values makes it difficult to see the clinical and immunological responses of the patients.
- Narrow scope of the study setting and population being only one hospital set up and population from specific area.

## 8. CONCLUSION

- ❖ Most of TB cases occurred in the first six months in both Pre-HAART and HAART cohorts.
- ❖ Tuberculosis incidence rate significantly higher in Pre-HAART cohort than HAART cohort.
- ❖ Overall tuberculosis free survival in HAART cohort was significantly higher than Pre-HAART.
- ❖ HAART significantly decreased new cases of tuberculosis in similar level with other developing and developed countries have been achieved but gross TB incidence rate was high in both Pre-HAART and HAART cohort when compared with developed countries.
- ❖ No significant difference observed in mortality rate between the two groups.
- ❖ Being married and widowed were independent predictors of decreased TB incidence. Whereas having WHO clinical stage III or IV disease, being bedridden and having hemoglobin level less than 10mg/dl were factors associated increased risk of TB occurrence at multivariate analysis.

## **9. RECOMMENDATIONS**

- Since most of the TB incident cases occurred at early period, after initiation of HAART, a due attention should be given to treat patients with TB/HIV co-infection because drug adverse effect and high pills burden may lead patients to unwanted poor adherence and outcomes
- Since HAART had significant effect in prevention of new cases of TB, on time initiation of HAART for those eligible for treatment have a paramount effect in reduction of HIV related tuberculosis.
- More efforts have to be taken to reduce TB incidence in HIV infected patients as a level most developed countries have achieved many years ago.
- Furthermore it is recommended that future prospective adult cohort study should be conducted to identify relation b/n marital status and risk of TB and other risk factors such as social and economic status including smoking and alcoholism and TB contact history in order to evaluate their effect in the development of TB among HIV infected patients.

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## 11. ANNEXES

### Annex I: Data Collection Format

Data collection format for Addis Ababa University, MPH research project on effect of HAART on incidence of TB among HIV infected patients, in Hawassa University Referral Hospital, 2011

#### Part I. Study subject's baseline information (to be filled from ART clinic intake form)

##### Section 1: Socio-Demographic Characteristics

NO	VARIABLE S	Coding categories	Remark
101	Patient ID number	_____	
102	Unique ART number	_____	<b>For ART initiated patients</b>
103	Age of the patients	_____	
104	Sex:	1. Male    2. Female	
105	Ethnicity	1. Sidama    2. Wolita 3. Amhara    4. Gurage 99. Other(specify) _____	
106	Religion	1. Muslim    2. Orthodox 3. Protestant    4. Catholic 99. Other(specify)_____	
107	Educational status	1. No education    2.primary 3. Secondary    4. Tertiary	
108	Occupational statuses	1. Farmer    2. Merchant 3. Governmental employee 4. Non-governmental Employee    5. Day laborer 6. Jobless    7. driver 99.Others(specify)_____	
109	Marital status	1. Never married    2. Married 3. separated    4.Divorced 5. widowed	

**Section 2: Base line clinical, laboratory and ART information**

No	Variable	Coding Categories	Remark
201	Confirmed HIV+ date	____/____/____ E.C	
202	Date registered to pre-ART or ART log book	____/____/____ E.C	
203	Is ART initiated	Yes No	
204	If yes for question 203, ART initiation date	____/____/____ E.C	<b>For ART initiated patients</b>
205	Duration in months since initiation of ART	1 week            1=1 month 2 weeks           2=2 month 3 weeks            Other _____	<b>For ART initiated patients</b>
206	Adherence level for ART	Good 2. Fair 3. Poor	<b>For ART initiated patients</b>
207	opportunistic illness(list all mentioned) at baseline	0. no            1.candidiasis 2. CMV        3.Crypt.meningitis 4.Kaposisarcoma 5. Cryptosporiodiosis 6. Diarrehea 7. Diss.atypical myco. 8. Encephalopathy 9.fever 10.herpes simplex 11. Minor mucocuan. 12. Mycosis            13. PGL 14. PCP                15.PML 16.pneumonia        17.salmonella 18.EPTB                19.toxoplasmosis 20. Wasting syndrome. 21.other specify _____	

208	Height(cm) (look Vital signs part) at base line	_____	
209	Weight(kg) at base line	_____	
210	Functional status at base line	W. working A. Ambulatory B. bedridden	
211	WHO Clinical stage of HIV disease at base line	1.Stage I      2.Stage II 3.Stage III    4.Stage IV	
212	Hgb at base line	_____	
214	CD4 count at base line	_____ date ____/____/____ E.C	

### Section 3: Base line Social condition

301	Employment	1.working full time 2.working part time 3. Not working 4. unemployed 6.other specify_____	
303	Religious /supportive care	1. no 2. yes	
304	HIV serostatus disclosure	1.wife/husband 2.own child(ren) 3.parent(s) 4.brother(s)/sister(s) 5.relatives 6.no body knew 7.others specify_____	
305	Spouse information	1.condition of the husband/wife a. health b. chronically ill c. dead d. unknown 2.HIV tested a. not asked b. negative c. positive d. unknown 3.TB tested a. not asked b. negative c. positive d. unknown 4.was/is on Tb treatment a. yes b. no 5. was/is on ART treatment a. yes b. no	
306	General concern identified	1.financial issue 2.about the children 3.marital relationship 4.family relations 5.beravement/grief 6.HIV status disclosure 7.adherence to treatment 8.dietary problems 9.other specify_____	

**Section 4: ART and treatment**

601	ARV eligibility criteria used	1. CD4 below 200 2. WHO stage IV 3. WHO stage I, II, or III with TLC <1200	<b>For ART initiated patients</b>
602	OI prophylaxis at baseline	0 .not given 1.cotrimoxazole 2.INH 3.fluconazole 4. others _____	
603	Regimen Recommended at baseline	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)	<b>For ART initiated patients</b>

**Part II: Patient's follow up information (to be filled from pre-ART and ART follow up Form).Please document the current or the recent results**

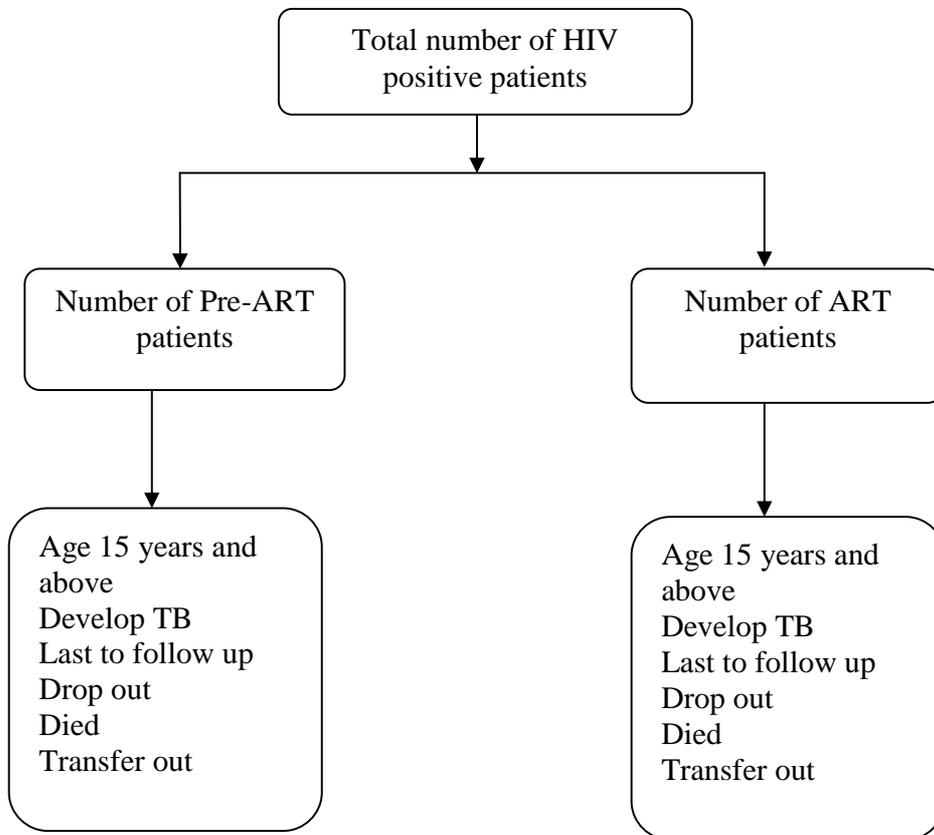
No	variables	Coding categories	Remark
701	Latest follow up date	_____/_____/_____.E.C	
702	Recent weight	_____(in kg), date_____/_____/_____.E.C	
703	Recent functional status	W. working A. Ambulatory B. bedridden	
704	Recent WHO staging	1.Stage I            2.Stage II 3.Stage III        4.Stage IV	
705	Recent Opportunistic infections	0. no 1.Zoster 2.bacterial pneumonia 3.Pulmonary Tb 4.Extrapulmonary Tb 5.oral /vaginal thrush 6.mouth/genital ulcer 7.chronic or acute diarrhea 8.pneumocystis carini pneumonia 9.CNS toxoplasmosis 10.Cryptococcal meningitis 11. others specify-----	
706	Recent ARV adherence	1. good 2. fair 3. poor If 1,skip to 714	<b>For ART initiated patients</b>
707	Reason for fair or poor adherence	1.toxicity/side effect 2.share with others 3.forgot 4.felt better	<b>For ART initiated patients</b>



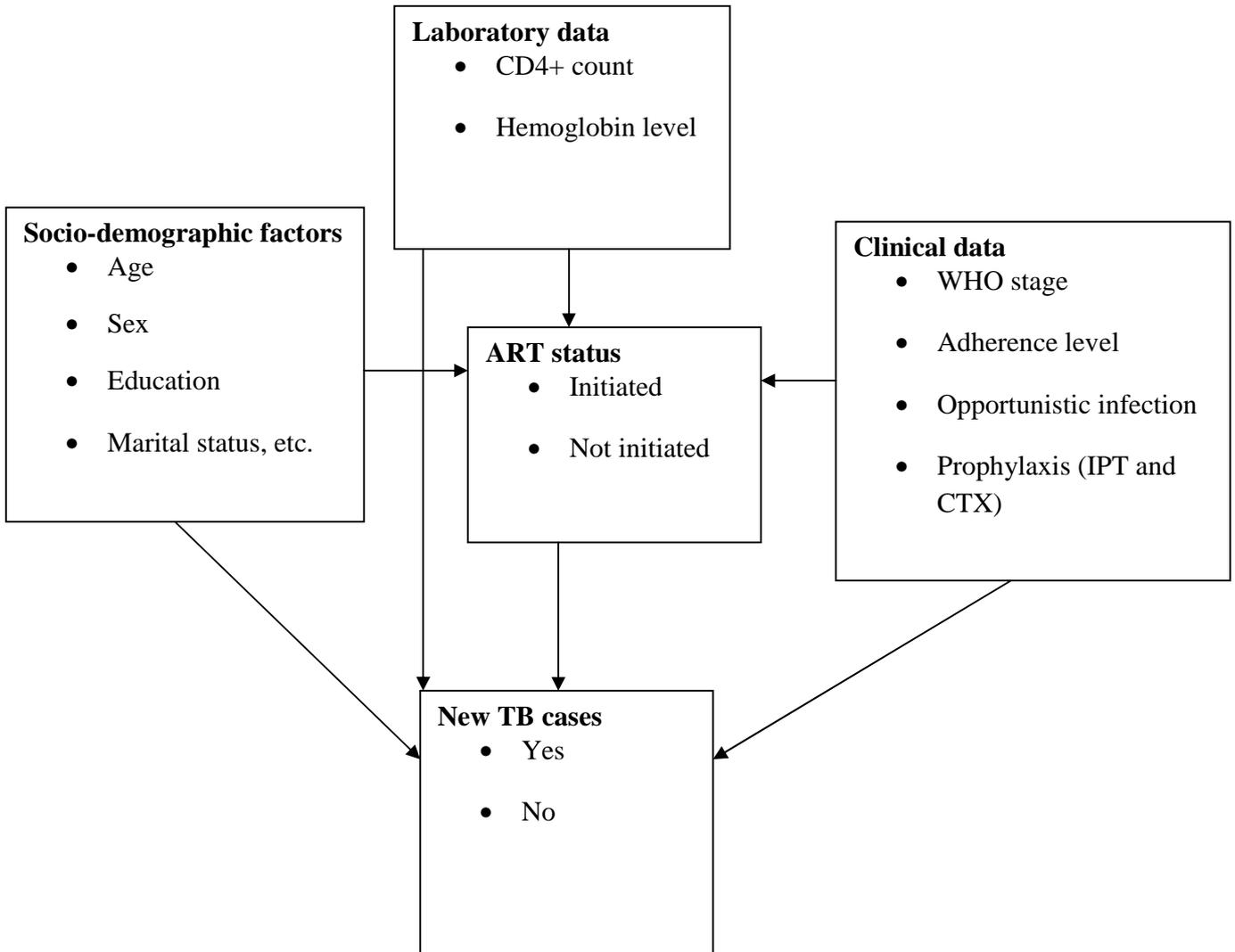
712	CD4+ level	Baseline CD4+ count _____ Date ____/____/___ E.C At 6 month CD4+ count _____ Date ____/____/___ E.C At 12 month CD4+ count _____ Date ____/____/___ E.C At 18 month CD4+count _____ Date ____/____/___ E.C At 24 month CD4+count _____ Date ____/____/___ E.C At 30 month CD4+count _____ Date ____/____/___ E.C At 36 month CD4+count _____ Date ____/____/___ E.C	
713	Recent Hgb	_____ Date ____/____/___ E.C	
714	Isoniazid prophylaxis initiated?	Yes No	
715	If yes for question number 6 for how long has he/she been on it?	Date started ____/____/___ E.C Duration _____ (days, weeks, months)	
716	Co-trimoxazole prophylaxis initiated?	Yes No	
717	If yes to question number 517, for how long has he/she been on it?	Date started ____/____/___ E.C Duration _____ (days, weeks, months)	
718	Status of the patients at the end of follow up	Active ____/____/___ E.C Dead ____/____/___ E.C Lost to follow up Drop out Transfer out	

<b>TB related Information</b>			
801	Is he/she Screened for TB?	Yes No	
802	If yes for question 801, is he/she diagnosed as having TB?	Yes No	
803	If yes for question number 802, Date of diagnosis	____/____/____ E.C	
804	If yes for question number 802, Sputum result	Positive Negative	For PTB
805	If yes for question number 802, Site of TB or TB Category	Pulmonary positive Pulmonary negative EPTB Combined	

**Annex II: Conceptual frame work for data collection, January, 2011**



**Annex III: Conceptual Frame Work for Analysis, January, 2011**



## **Annex IV: English Patient Information Sheet**

### **Participant information sheet**

#### **Description of the study**

**Title of the study:** The effect of HAART on incidence of tuberculosis among HIV infected patients in Hawassa Referral Hospital, South Ethiopia.

**Objective of the study:** To measure the effect of HAART on incidence of TB and TB free survival among HIV infected patients with and without HAART initiation in HIV positive patients

#### **Introduction:**

The burden of HIV associated TB continued as the major public health problem in the world. Although the availability ART has transformed HIV infection into a chronic and manageable disease in those who are able to access treatment; the successes recorded can easily be destroyed by the high burden of tuberculosis co-infection in the HIV-infected individual. Even after the initiation of ART, the incidence of HIV related TB remains unacceptably high.

#### **Rationale of the Study and its benefits**

In the era of ART, prevention and treatment of TB in people living with HIV is an urgent priority for both HIV/AIDS and TB programmes. However, there is shortage of studies in Ethiopia, the impact of ART on incidence and determinants of tuberculosis among HIV infected patients. This study is designed to assess and compare the incidence of tuberculosis among HIV infected patients with and without HAART initiation and to find out the determinant factors for the development of TB in both groups. And it also assesses the TB free survival in both groups while bridging the gaps in literature and it may also help for policy makers to make right decision in TB/HIV prevention. Information which is necessary for the study will be taken from pre ART and ART log books and other clinical and laboratory records. As the study will be conducted through review of medical records alone, the individual patients will not be subjected to any harm as far as the confidentiality is kept. To keep the confidentiality of the patients, personal identifiers will not be included in the data collection format. For any questions about this study contact principal investigator Tarekegn Solomon with (Tel: 0911 94 57 90 or E-mail: [tarekegn2solomon@yahoo.com](mailto:tarekegn2solomon@yahoo.com))

## Annex V: Amharic Patient Information Sheet

### ለጥናቱ ተሳታፊዎች መረጃ የመስጫ ቅጽ

#### **የጥናቱ መግለጫ**

**የጥናቱ ርዕስ** -የፀረ-ኤች.አይ.ቪ/ኤድስ መድኃኒቶች ሕክምና በቲቢ በሽታ ክስታት(incidence) ላይ ያለው ተጽዕኖ ከኤች.አይ.ቪ/ኤድስ ጋር በሚኖሩ ሰዎች ላይ በሐዋሳ ዩንቨርስቲ ሪፈራል ሆስፒታል ደቡብ ኢትዮጵያ

**የጥናቱ ዓላማ**- የፀረ-ኤች.አይ.ቪ/ኤድስ መድኃኒቶች ሕክምና በቲቢ በሽታ ክስታት(incidence) ላይ የምኖረቸውን ተጽዕኖ ከኤች.አይ.ቪ ጋር በሚኖሩና የፀረ-ኤች.አይ.ቪ/ኤድስ መድኃኒቶች በመውሰድ ላይ በሉና መድኃኒቶችን በልጀመሩ የሐዋሳ ዩንቨርስቲ ሪፈራል ሆስፒታል ታካሚዎች መካከል ማነፃፀር ነው።

**መግቢያ**: ከኤች.አይ.ቪ/ኤድስ ጋር ተያያዥነት ያለው የቲቢ በሽታ የዓለም አቀፍ ዋነኛ የሕብረተሰብ ጤና ችግር ሆኖ ቀጥሎታል። ምንም እንኳን የፀረ-ኤች.አይ.ቪ/ኤድስ መድኃኒቶች መኖር በሽታውን ለማከምና ከበሽታውን ጋር ለሚኖሩ ሰዎች ዕድሜ ለመረዳም ከፍተኛ አስተዋጽኦ ቢያደርጉም የቲቢ በሽታ ተጓደኝ ክስታት(incidence) በቀለብ ይህንን ጥሩ እምርታ በማሰነክል ላይ ይገኛል። በአገር ውስጥና ከአገር ውጭ የተሰሩ የተለያዩ የጥናት ውጤቶች እንደምያሰዩ ከሆነ የፀረ-ኤች.አይ.ቪ/ኤድስ መድኃኒቶች ከተጀመሩ በኋላም ከኤች.አይ.ቪ/ኤድስ ተያያዥነት ያለው የቲቢ በሽታ ክስታት(incidence) አሁንም ተቀባይነት በሌለው መልኩ በከፍተኛ ደረጃ በመከሰት ላይ ይገኛል።

**የጥናቱ አስፈላጊነት**: የፀረ-ኤች.አይ.ቪ/ኤድስ መድኃኒቶች ባሉበት በአሁኑ ወቅት የቲቢ በሽታ ከኤች.አይ.ቪ/ኤድስ ጋር በሚኖሩ ሰዎች ላይ እንደይከሰት መከለከልና ማከም የኤች.አይ.ቪ/ኤድስና የቲቢ በሽታ ፕሮግራሞች አፋጣኝ ኤርምጃ መሆን አለበት። ነገር ግን በሀገራችን ውስጥ የፀረ-ኤች.አይ.ቪ/ኤድስ ህክምና በቲቢ በሽታ ክስታት(incidence) ላይ ያለውን አስተዋጽኦ የሚያሰዩ ጥናቶች በጣም ውስን በመሆናቸው ይህንን ጥናት ማድራግ አስፋለግ ሆኖታል። በመሆኑም ይህ ጥናት የፀረ-ኤች.አይ.ቪ/ኤድስ መድኃኒት በጀመሩና በልጀመሩ ከኤች.አይ.ቪ/ኤድስ ጋር በሚኖሩ ሰዎች መካከል ያለውን የቲቢ በሽታ ክስታት(incidence) ልዩነት እና የክስታቱን መንስኤዎችን ያጠናል። ይህም የመረጃ ክፍተትን ከማሙላቱ በሻገር ለፖሊሲ አወጪዎች ትክክለኛውን የኤች.አይ.ቪ/ኤድስና የቲቢ በሽታ መከላከያ አቅጣጫ በመጠቀም ረገድ ሚናው ለቅ ያለ ነው።

ስለዚህ ለጥናቱ አስፈላጊ የሆኑ መረጃዎች ከሐዋሳ ዩንቨርስቲ ሪፈራል ሆስፒታል ከቅድመ ፀረ-ኤች.አይ.ቪ/ኤድስ ታካሚዎች መዝገብ፣ ከፀረ-ኤች.አይ.ቪ/ኤድስ ታካሚዎች መዝገብ፣ እንዲሁም ከምርመራና ለብራቶር መዝገቦች ላይ ይሰበሰባሉ። ጥናቱ የሚደረገው ምስጢራዊነቱን በጠበቀ መልኩ በታካሚዎች መረጃ ላይ ስለሆነ ግለሰቦችን የሚገቡ ምንም ነገር አይኖርም። ምስጢራዊነቱን ለመጠበቅ እዚያው በኤች.አይ.ቪ/ኤድስ ክሊኒክ ውስጥ ሕክምና የሚሰጡ የጤና ባለሙያዎች መረጃውን ከመዝገብ እንዲሰበሰቡ ይደረጋል። በመረጃ ስብሰባ ወቅት ለሚመጡ ታካሚዎች ፈቃደኝነታቸውን በመጠየቅ መረጃ ይወሰዳል።

በተጨማሪም የኤች.አይ.ቪ/ኤድስ ታካሚን ማንነት የሚገልጽ ምንም አይነት መረጃ መጠይቁ ላይ አይሞላም። የተወሰደው መረጃ ምስጢራዊነቱ ተጠብቆ ሙሉ በሙሉ ጠቀሜታው ለምርምር ሥራው ብቻ ይውላል። ጥናቱን በተመለከተ ጥያቄ ካለዎት አጥኚውን አቶ ታረቀኝ ሰለሞንን በስልክ ቁጥር 09 11 94 57 90 ወይም በኢሜል አድራሻ tarekegn2solomon@yahoo.com መጠየቅ ይቻላል።

## **Annex VI: English Consent Form**

My name is \_\_\_\_\_, I am a ART clinic nurse working here in Hawassa referral hospital ART clinic and now I am collecting data from our patients pre ART and ART logbook for the research being conducted to determine the effect of HAART on incidence of TB, by Ato Tarekegn Solomon who is the Master of public Health student in Addis Ababa University. You are selected as one of study subject by chance. The investigator employed me (from this ART clinic) for this data collection to maintain your data strictly confidential. We believe that the findings of this study will have paramount for evaluation of TB/HIV programs and to find out proper way for prevention of TB in HIV positive patients.

Information which is necessary for the study will be taken from your pre ART or ART log book. As the study will be conducted through review your medical records alone, it will not harm you as far as the confidentiality is kept. The information will be taken when you give permission, participation is totally voluntary.

Your willingness for your pre ART or ART record information to be utilized in this study will help us achieve the stated benefits of the study. Your name and other personal identifiers will not be recorded on data collection format and the information that you give us will be kept confidential and will also be used for this study purpose alone. You have full right not to let your information on pre ART or ART logbook to be consumed for this study. But the information that would be taken will be quite useful for the study. You will not face any problem if you do not allow the information to be taken from your records and you will not also be denied of getting any medical services from the hospital. If you have any questions about this study you may ask me or the principal investigator Tarekegn Solomon (Tel: 0911 94 57 90 or E-mail: tarekegn2solomon@yahoo.com)

Are you willing to let your information to be utilized for this study?

1. Yes
2. No

Signature of the interviewer which shows that the respondent has consented (verbally) to take part in the study \_\_\_\_\_

**Annex VII: Amharic consent form**

**ለጥናቱ ተሳታፊዎች የፈቃደኝነት መጠየቂያ ቅጽ**

ስሜ \_\_\_\_\_ ይባላል። በዚህ በሐዋሳ ዩንቨርስቲ ረፈራል ሆስፒታል በኤች.አይ.ቪ/ኤድስ ክሊኒክ ውስጥ የሚሠራ የጤና ባለሙያ ስሆን አሁን የፀረ-ኤች.አይ.ቪ/ኤድስ መድኃኒቶች ሕክምና በቲቢ በሽታ ክስታት(incidence) ላይ የምኖረቸውን ተጽዕኖ ከኤች.አይ.ቪ ጋር በሚኖሩ ሰዎች ላይ በሚል ርዕስ በአዲስ አበባ ዩኒቨርሲቲ ድህረ ምረቃ ተማሪ የሆኑት አቶ ታረቀኝ ሰለሞን ለሚሰሩት ጥናት መረጃ ከ ኤች.አይ.ቪ/ኤድስ ጋር በሚኖሩ ታካሚዎች መዝገብ ላይ እየሰበሰቡ ነው። አንተ/ቺ የጥናቱ አካል በመሆን ተመርጧል/ሻል። አጥኚው እዚህ ኤች.አይ.ቪ/ኤድስ መዝገብ ላይ የሚሠራውን እኔን ለመረጃ ሰብሳቢነት ሲመርጠኝ የመረጃውን ምስጢራዊነት ለመጠበቅ ብሎ ነው። ማለትም ከክሊኒኩ ውጪ ያሉት በመረጃ ስብሰባ ወቅት ስምዎንና ሌሎች መረጃዎችን እንዳያዩ ሲባል ነው። የዚህ ጥናቱ ውጤት የቲቢ በሽታ /ኤች.አይ.ቪ መከላከያና መቆጣጠሪያ ፕሮግራሞችን ለመገምገምና ለኤች.አይ.ቪ እና ቲቢ ታካሚዎች የተለየ ጥንቃቄ እንዲደረግ አስተዋጽኦ የጎላ እንደሚሆን ይታመናል። በመሆኑም ለጥናቱ አስፈላጊ የሆኑ መረጃዎች ከእርስዎ ከቅድመ ፀረ-ኤች.አይ.ቪ/ኤድስ መዝገብ ወይም ከፀረ-ኤች.አይ.ቪ/ኤድስ መዝገብ፣ እንዲሁም ከምርመራና ለብራቶር መዝገቦች ላይ ይወሰዳሉ። ጥናቱ የሚደረገው ከቅድመ ፀረ-ኤች.አይ.ቪ/ኤድስ መዝገብ ወይም ከፀረ-ኤች.አይ.ቪ/ኤድስ መዝገብ፣ እንዲሁም ከምርመራና ለብራቶር መዝገቦች ሕክምና መዝገብ ላይ ስለሆነ በእርስዎ ላይ ምንም ዓይነት ጉዳት አያመጣም። መረጃዎ እንዲወሰድ መፍቀድ ለተጠቀሰው የጥናቱ ዓላማ መሳካት የጎላ አስተዋጽኦ ይኖረዋል። ከሕክምና መዝገብ ላይ መረጃ ሲወሰድ የእርስዎን ማንነት የሚገልጽ ስም እና ሌላ ምንም ዓይነት ነገር ወደ መጠይቁ አይሞላም። የተወሰደውም መረጃ ምስጢራዊነቱ ተጠብቆ ሙሉ በሙሉ ለምርምር ሥራው ብቻ ይሆናል። የሕክምና መረጃዎ ለምርምር ሥራ እንዳይውል የማድረግ መብት አለዎት። ነገር ግን መረጃዎ ለምርምር ሥራው ቢውል ጠቀሜታው የጎላ ነው። በጥናቱ ለመሳተፍ ፈቃደኛ ባይሆኑ በሕክምናዎት ላይ ምንም ዓይነት ጉዳት አይፈጠርም። በሌላ በኩል መረጃዎን በመስጠትዎ የሚያገኙት የተለየ ጥቅም አይኖርም። ጥናቱን በተመለከተ ጥያቄ ካለዎት እኔን ወይም አጥኚውን አቶ ታረቀኝ ሰለሞንን በስልክ ቁጥር 09 11 94 57 90 ወይም በኢሜል አድራሻ tarekegn2solomon@yahoo.com መጠየቅ ይቻላል።

መረጃው ለምርምር ሥራ ቢውል ፈቃደኛ ነዎት?

- 1. አዎ
- 2. አይደለም

መረጃቸውን ለጥናቱ ሥራ እንዲውል ፈቅደዋል። የመረጃው ሰብሳቢ ስምና ፊርማ \_\_\_\_\_

## DECLARATION

I, the undersigned, declare that this thesis is my original work and has not been presented for a degree in this or another university and all the sources of materials used for the thesis have been fully acknowledged.

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Signature: \_\_\_\_\_

Date \_\_\_\_\_

This thesis work has been submitted for the examination with my approval as a university advisor

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Signature: \_\_\_\_\_

Date: \_\_\_\_\_