ADDIS ABABA UNIVERSTY

COLLEGE OF HEALTH SCIENCES

SCHOOL OF PUBLIC HEALTH

INCIDENCE AND FACTORS PREDICTING ACTIVE TB OCCOURANCE AMONG PATIENTS ENROLLED IN ART, ZEWDITU HOSPITAL, ADDIS ABABA, RETROSPECTIVE COHORT STUDY.

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LIST OF ACRONYMS

Symbols	Definition
AFB	Acid Fast Bacilli
AHR	Adjusted Hazard Ratio
AIDS	Acquired Immunodeficiency Syndrome
AOR	Adjusted Odds Ratio
ART	Anti Retroviral Therapy
CI	Confidence Interval
COR	Crudes Odds Ratio
CPT	Co-trimoxazole Preventive Therapy
DOT	Directly Observed Treatment
EDHS	Ethiopian Demographic Health Survey
EPTB	Extra Pulmonary Tuberculosis
HAART	Highly Active Antiretroviral Therapy
Hgb	Haemoglobin
HIV	Human Immunodeficiency Virus
IPT	Isoniazid Preventive Therapy
MDR-TB	Multi-Drug Resistant TB
OIs	Opportunity Infections
OR	Odd Ratio
PLWHIV	People Living With Human Immunodeficiency Virus
PTB	Pulmonary Tuberculosis
TB	Tuberculosis
TB/HIV	HIV-related TB
TBL	Tuberculosis & Leprosy
UNAIDS	United Nations Program of HIV /AIDS

ABSTRACT

Background: Tuberculosis is a major opportunistic infection among people living with HIV (PLWH). Antiretroviral Therapy (ART) was introduced in National AIDS Control Programme to reduce the morbidity and mortality among those affected with HIV/AIDS. Even though ART reduces tuberculosis (TB) incidence, risk of TB remains high after ART initiation. However determinants of active TB among HIV patients on ART are not well described in resource limited settings like Ethiopia.

Objectives: To determine incidence and factors predicting active TB occurrence among patients enrolled in ART, in Zewditu Hospital, Addis Ababa.

Methods: A five year institution based retrospective follow up study was conducted by chart review. All adult PLWHs newly enrolled on ART at Zewiditu hospital from September 11, 2009 to August 31, 2010, was identified from electronic data base and register. And those who fulfilled the inclusion criteria were retrospectively followed for different periods in five years until March, 2015. The pretested data collection tool was used in order to extract information's from patient chart. Incidence rate of tuberculosis was calculated. Cox proportional hazard regression model was used to identify predictors.

Results: A total of 480 patients were followed and produced 1952.5 Person-Years (PY) of observation, and 70 new TB cases observed during the follow up period. The overall incidence density of TB was 3.59 per 100 PY. It was high (76.59/100PY) in the first year of enrolment. The cumulative proportion of TB- free survivals was 90% and 80% at the end of the first and fifth years, respectively. After adjustment for potential confounders the presence of INH prophylaxis (AHR=0.49, 95%CI=0.26-0.94), baseline WHO clinical stage III or IV (AHR =2.37, 95%CI = 1.41-3.96), CD4 count <100 cell/ul (AHR 7.48,CI=2.86-19.5), CD4 count between 101-200 cell/ul (AHR 3.53, CI=1.33-9.34), Hgb level less than 10 mg/dl (AHR= 2.32, CI=1.13-4.78), being addicted (AHR = 1.78, CI=1.07-2.96) and poor adherence (AHR=2.98, 95%CI 1.36-6.52) were predictors of time to TB occurrence in multivariate analysis.

Conclusions: IPT associated in reducing TB incidence so IPT service should be strengthening among PLWHIV. Intensified screening is highly recommended during treatment follow up for those who have advanced disease condition (WHO clinical stage III/IV, CD4 count below 200 and having hemoglobin level below10 mg/dl) and in the first year of follow up. Strengthen ongoing adherence and positive living counseling also recommended.

1 INTRODUCTION

1.1 Background

Tuberculosis is an infectious disease caused by the bacillus Mycobacterium tuberculosis. It typically affects the lungs (Pulmonary Tuberculosis) but can also affect other organs (extra pulmonary TB)[1].

Tuberculosis remains a major global health problem. It affects millions of people each year and ranks as the second leading cause of death from an infectious disease worldwide, after the human immunodeficiency virus (HIV), specially in low and middle-income countries [1-3]. Globally total number of people living with HIV was 35 million in 2012, from those 24.7 million (nearly 71%) people live in sub-Saharan Africa [3-5].

In 2012 an estimated 8.6 million people developed Tuberculosis and 1.3 million died from the disease (including 320,000 deaths among HIV-positive people, which is 25% of all TB deaths). An estimated 1.1 million (13%) of 8.6 million peoples who developed TB were HIV positives. More than 75% of all estimated HIV incident live in sub-Saharan Africa which includes Ethiopia [1, 3].

In Ethiopia, efforts to control tuberculosis began in the early 1960s with the establishment of TB centres and sanatoriums in three major urban areas [6]. The Central Office of the National Tuberculosis Control Programme (NTCP) was established in 1976 specifically to tuberculosis. TB/HIV collaborative activities was piloted in 2004 and then scaled up nationally and integrated into the Tuberculosis & Leprosy and TB/HIV control program [6].

To reduce the burden of TB among PLWH, World Health Organization (WHO) recommends Intensified Case Finding (ICF), Isonizid Preventive Therapy (IPT), Infection Control (IC) and early initiation of Anti Retroviral Therapy (ART). Of these, ART is the most potent and widely implemented TB preventive intervention among PLWHIV [7].

1.2 Statement of the problem

HIV infection has been identified as a major risk factor for developing tuberculosis. The life time risk of HIV positive individuals to develop TB was 20-37 times greater than HIV negative individuals [6].

According to WHO 2014 report, TB-related deaths among people living with HIV have fallen by 33% worldwide since 2004 due to the result of important improvements in the quality and integration of HIV and TB services [8].

According to the WHO Global TB Report 2011, there were an estimated 9 million incident cases of TB globally, in 2010, of which 1.2 million were among people living with HIV. The African region accounted for 82% of TB cases among people living with HIV [9].

Tuberculosis is a major cause of morbidity and mortality and HIV/AIDS pandemic presents a major challenge to the control of TB in Ethiopia. The TB & HIV epidemic has a number of impacts on the health sector. It increases TB and HIV burden, demand for care and worsen the situation of the already overstretched health care delivery system in the country [6].

According to the 2012 world health organization (WHO) report, Ethiopia ranks 8th among the 22 high TB burden countries with 277 TB cases per 100,000 people per year [10] as well as high HIV burden country with Adult HIV prevalence of 1.5% [11].

A Study conducted at Gonder revealed that the overall TB incidence density was 7.89 per 100 PY among PLWHs [12] and other study conducted at Assela showed that the incidence of tuberculosis was 3.73/100 person years among those on HAART [13]. However the predicting factors of TB after ART initiation is not well described in order to emphasize on other TB preventive interventions in addition to ART.

1.3 Rational of the study

Accelerated the response to TB/HIV is one of the five priority actions required to accelerate progress towards 2015 targets. Even though TB-HIV collaborative service are expanding, global targets are not yet in sight. The probability of developing TB is much higher among PLWH [1]. What are the best infection control interventions that effectively reduce M. Tuberculosis transmission in health care setting, at home and in the community is one of the primary research questions in the area of TB prevention [14].

Prevention and treatment of TB in PLWH is an urgent priority for both HIV/AIDS and TB programs [15]. There are some studies done in predictors of TB among PLWH and most of them recommend ART initiation. Even though ART known to minimize incidence of TB, still studies have reported high TB incidence among PLWH on ART in poor-resource and high TB burden countries [16]. But as to the knowledge of this research, there is one study done in Ethiopia on factors associated with occurrence of TB among PLWH after ART. So this five year retrospective follow up study will provide basic information to contribute for the development of effective TB control strategies for the organization, who work on this area and helps for further studies.

2 LITERATURE REVIEW

2.1 Overview of TB-HIV co-infection

TB is a leading killer among PLWH, at least one in four deaths among PLWH can be attributed to TB and many of these deaths occurred in resource limited settings [17]. The overall incidence of TB among PLWH is high and pulmonary TB is more dominant than extra pulmonary TB [12, 18-20].

A five year cohort study done in Brazil has shown out of 5,451 individuals reported with TB 320 (5.9%) died, after adjustment, relative risk of dying from TB/HIV co-infection was 9.0 [21]. Similarly a study done at Ambo hospital has also shown that the mortality rate was very high in the earlier months of TB treatment initiation and stabilized in later stages. There was 79/501 (15.7%) deaths among the pulmonary and extra-pulmonary PLWH patients [22].

To prevent TB, as well as other HIV-related illnesses and death, WHO recommends initiation of highly active antiretroviral therapy (HAART) when the CD4+ lymphocyte count is below 500cells/mm. In addition to this HIV testing and provision of cotrimoxazole is the main intervention to reduce the burden of HIV in TB patients [1].

WHO also recommends, Adults and adolescents living with HIV should be screened for TB with a clinical algorithm and those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered Isoniazid Preventive Therapy (IPT) [7]. TB can be diagnosed using bacteriological, molecular, histopathology and radiological diagnostic methods so all TB suspects are evaluated using the national standard TB diagnostic algorithm [6].

All TB patients are initiated on anti-TB drugs provided by Ministry of health, Ethiopia and they put on DOTS for the duration of TB treatment [6, 23]. For the first two months (Intensive phase) Ethambutol (275mg), Rifampicin (150mg), Isoniazid (75mg), and Pyrazinamide (400mg) are given and for the next four months (continuation phase) Rifampicin(150mg) and Isoniazid (75mg) are given and the dosage is settled according to their weight in kilogram.

2.2 Predicting factors for the occurrence of TB/HIV co-infection

Different studies have shown that socio-demographic, clinical, immunological, environmental factors, INH and cotrimoxazole prophylaxis's therapy had association on the occurrence of TB.

2.2.1 Socio-demographic related factors

TB is more common among men than women and mostly affected adults in the economical productive age group [1, 24]. Study done in India revealed , Post HAART TB occurred predominantly in men (67.6%) and in 31- 44 years age group (69.8%) with 100-person year risk being 3.26 and 2.83 respectively [18]. A prospective cohort study done in South Africa also revealed that men were more likely to develop tuberculosis than women (IRR = 1.46; 95% CI 1.09–1.94) and compared to patients <30 years of age, those who were 30–39 years (IRR = 1.34; IQR 0.98–1.85) or were 40–49 years (IRR = 1.77; 95% CI 1.26–2.51) were at greater risk [19]. In contrary a cross-sectional study conducted in Cameron and A cohort study done in 15 countries shows younger age were associated with virologic failure and TB in low-income settings countries [12, 24].

A case-control study done in Addis Ababa has demonstrated, higher proportion of male patients (COR = 1.73; 95% CI: 1.23, 2.46) develop TB compared to female patients and those who lived in households having a size of 6–10 members were more likely to develop TB compared with the number of persons in the household between 1 and 5 (COR = 1.914; 95% CI: 1.23, 2.99 [25].

Income and place of residence also other factors of TB incidence, for instance a cohort study done in 15 countries shows incidence rates in the first year on HAART were 7.4 (95% CI 6.6 to 8.4) in low-income settings and 1.0 (0.88 to 1.2) in industrialized settings per 100 person-years [24] and the rural site had an increased tuberculosis risk (IRR = 1.51; 95% CI 1.13–1.98) compared to the urban site [19].

2.2.2 Clinical and immunological factors

Studies shows that baseline CD4 cell count, WHO clinical stage, follow up period and functional status were significant predictors of TB among PLWHIV [12].

HAART decreases TB risk in HIV-infected populations. However, TB risk is high in 3–6 months following HAART initiation. For instance, a cross-sectional study in Cameron, while patients on ART for < 12 months had higher odds (OR 4.24, 95% CI 2.49 – 7.23) than those who have been on ART for 12–36 months and > 36 months [26]. Another cohort done in India, a total of 144 patients (54.9%) developed tuberculosis within six months and this number increased to 202 (77%) by 12 months [18].

Likewise retrospective cohort done in Gonder, Ethiopia, the highest incidence of TB was observed in the first year of enrolment (95.9/100 PY) and then decreased in the subsequent years of follow up (34.0 and 1.6 per 100 PY in three and five years, respectively [12]. Similar study done in SNNPR demonstrates the first six months on ART represented the period with the highest risk (TB incidence 8.0 per 100 PY; 95% CI: 6.0–10), followed by Pre-ART period (TB incidence 3.9 per 100 PY; 95% CI: 3.3–4.6). After the first 6 months it decreased progressively with increase in length of time on ART [20].

The risk of new TB event was increased substantially in patients with low CD4 counts at base line. An observational cohort study done in Nashville showed that low recent CD4+ lymphocyte count influences TB risk during the first 180 days of HAART [27]. A cohort study done in 15 countries shows that the hazard ratio for patients with a CD4 count of less than 100 cells/μL as compared to those with a count of 100 cells/μL or more was 1.82 (95% CI 1.40 to 2.36) and 3.47 (2.62 to 4.60), respectively [24].

Similarly, A retrospective cohort done in Gonder reveals patient with a CD4 count of less than 50 cell/ul was 2.47 times more likely to have TB at any time than a patient with a CD4 count greater than 200 cell/ul (AHR =2.47,95% CI 1.49-4.09) [12]. Another retrospective cohort study conducted at Assela and a case-control study done in Addis Ababa was also demonstrated TB risk is higher among HIV-infected persons with CD4+ lymphocyte counts is lower than 100 cells/μl . Whereas the risk was lower for patients with higher initial CD4 cell count [13, 18, 19].

Individuals with haemoglobin level 10 mg/dl or less and anaemic were more likely to have TB and also prone to failing ART [25, 26].

Studies done in Ethiopia (Addis Ababa and Gonder) show PLHIV who were ambulatory or bed ridden at enrolment, were at higher risk of developing TB than those who were working [12, 25].

Other important predictors for the TB occurrence were baseline clinical variables like WHO clinical stage. A retrospective cohort study conducted at Assela showed PLWHIV presented with WHO clinical stage III or IV at base line were developing TB at a rate of 6.29 times higher risk than base line WHO clinical stage I or II [13]. TB patients are more likely to have baseline WHO clinical stage III or IV (COR = 4.51; 95% CI: 3.032, 6.70) [25].
The PLWH who were at WHO clinical stage III had about three times higher risk of acquiring TB at any time compared to those with WHO clinical stage I or II. Similarly, PLHIV with WHO clinical stage IV were about four times at higher risk of TB acquisition at any time than those with WHO clinical stage I or II [12].
Patients with a previous diagnosis of tuberculosis infection had 2.9 times great risk of virologic failure [28]. HIV/TB co-infected patients had remarkably higher odds (OR 3.24, 95% CI: 1.80 – 5.84) of experiencing virologic failure than HIV mono-infected patients [26].

2.2.3 Environmental and Behavioural factors

The Tuberculosis cases were more likely to be smoker, alcohol drinker as well as Khat chewer. However, tuberculosis was not associated with diabetes and history of asthma [25]. ART adherence also one of predictor of TB [29].

2.2.4 Isonizid Preventive Therapy (INH) and TB in PLWHIV

INH and cotrimoxazole prophylaxis has shown a protective effect against TB in HIV infected persons. A prospective cohort in South Africa, patients who received both IPT and HAART showed a strong reduction in tuberculosis risk (AHR = 0.11; 95% CI 0.02–0.78) [19]. Furthermore a retrospective study in Canadian tertiary centre showed, initiating LTBI (latent TB

infection) treatment proved to be the most crucial. The incidence rate of TB among the tuberculin skin test (TST)-positive patients who failed to initiate LTBI treatment was 122 cases per 1000 person-years [30].

Likewise A retrospective cohort study done in SNNPR Ethiopia shows the combined effect of IPT and ART when started at the same time reduced TB incidence by 57% (IRR: 0.43; 95%CI 0.18–0.86) as compared to those who took ART only [20]. Correspondingly a cross-sectional study done in Addis Ababa has also shown presence of INH prophylaxis and cotrimoxazole prophylaxis had an independent protective benefit against tuberculosis [25].

Studies have shown that Socio demographic, environmental, behavioural, clinical, and immunological factors were associated with the development of TB among PLWHs. However there is only one case control study done in Ethiopia on predicting factors of TB after HAART initiation, in my findings. And this case control study, because of its study design it didn't include the incidence of TB among HAART users and also faced recall biased. So this five year retrospective follow up will incorporate different factors from well recorded patient charts.

3 OBJECTIVES

3.1 General Objective:

- To determine the incidence and factors predicting active TB occurrence among patients enrolled in ART, in Zewditu Hospital, Addis Ababa.

3.2 Specific objectives:

- To calculate the incidence of TB occurrence after ART initiation.
- To determine and compare the TB free survival time of patients under certain predictor variable.
- To identify potential risk factors of active TB in PLWH after ART initiation.

4 METHODS

4.1 Study area and period

The study was conducted in Addis Ababa, in Zewditu hospital from August, 2014 to May, 2015. Addis Ababa is the capital city of the Federal Democratic Republic of Ethiopia and hub of political, economical and cultural activities of the country. According to 2007 census the city has close to three million inhabitants.

Zewditu Hospital is Ethiopia's leading hospital in the treatment of ART patients and operated by the Ministry of Health. As of November 2014, there were a total of 18,394 patients ever enrolled in to the chronic HIV care and follow-up services, 11,879 ever-started on ART and currently 6,932 PLWH on ART at Zewditu hospital. The hospital also deals with palliative care, HIV counseling and testing, STI services and Post-exposure prophylaxis (PEP) services. Two sub cities, Kirkos and Akaki, which have 13 health centers, have also served by this hospital.

4.2 Study design

A five-year institution based retrospective follow up study was conducted at Zewiditu hospital, Addis Ababa. Patients, who have been enrolled in ART from September 11, 2009 to August 31, 2010, were followed until March 30, 2015.

4.3 Population

4.3.1 Source population

The source population were the entire HIV positive patients who have been enrolled on Anti retroviral treatment in Zewditu hospital.

4.3.2 Study population

All Adult HIV positive patients enrolled for ART from September 11, 2009 to August 31, 2010 in Zewditu hospital of Addis Ababa city Administration.

Inclusion and exclusion Criteria

Inclusion criteria

- All adults (15 or more year's age) enrolled for ART from September 11, 2009 to August 31, 2010 in Zewditu hospital were included in the study.

Exclusion Criteria

- PLWH who developed TB before ART initiation
- Transferred in patients
- Patient whose charts were missed (unable to find) and cards with incomplete information for main variables

4.4 Sample size determination

All Adult PLWHs enrolled on ART from September 11, 2009 to August 31, 2010 in Zewditu hospital, Addis Ababa, who fulfilled the inclusion criteria, were included in the study. This period was selected in order to have the nearest five year follow up study period. A total of 670 PLWH were registered in this Period.

4.4.1 Sampling procedures

Study facility was selected purposively in order to get high HIV/TB client load facility which has a good data management system and computerized data base among Addis Ababa public hospitals, to get adequate number of sample. Accordingly Zewiditu Hospital was selected. All eligible adult PLWHs enrolled in HAART at Zewiditu Hospital from September 11, 2009 to August 31, 2010 were included in the study.

Out of 670 patients registered, 65 were excluded because they were transferred in; a further 75 (11%) were excluded from the study because either Patient cards were not found (60) or incomplete information (n=15). Others were excluded either diagnosed to have TB before ART initiation (7 patients) or were on TB treatment (43 patients). Thus, there were 480 patients studied (Figure 1).

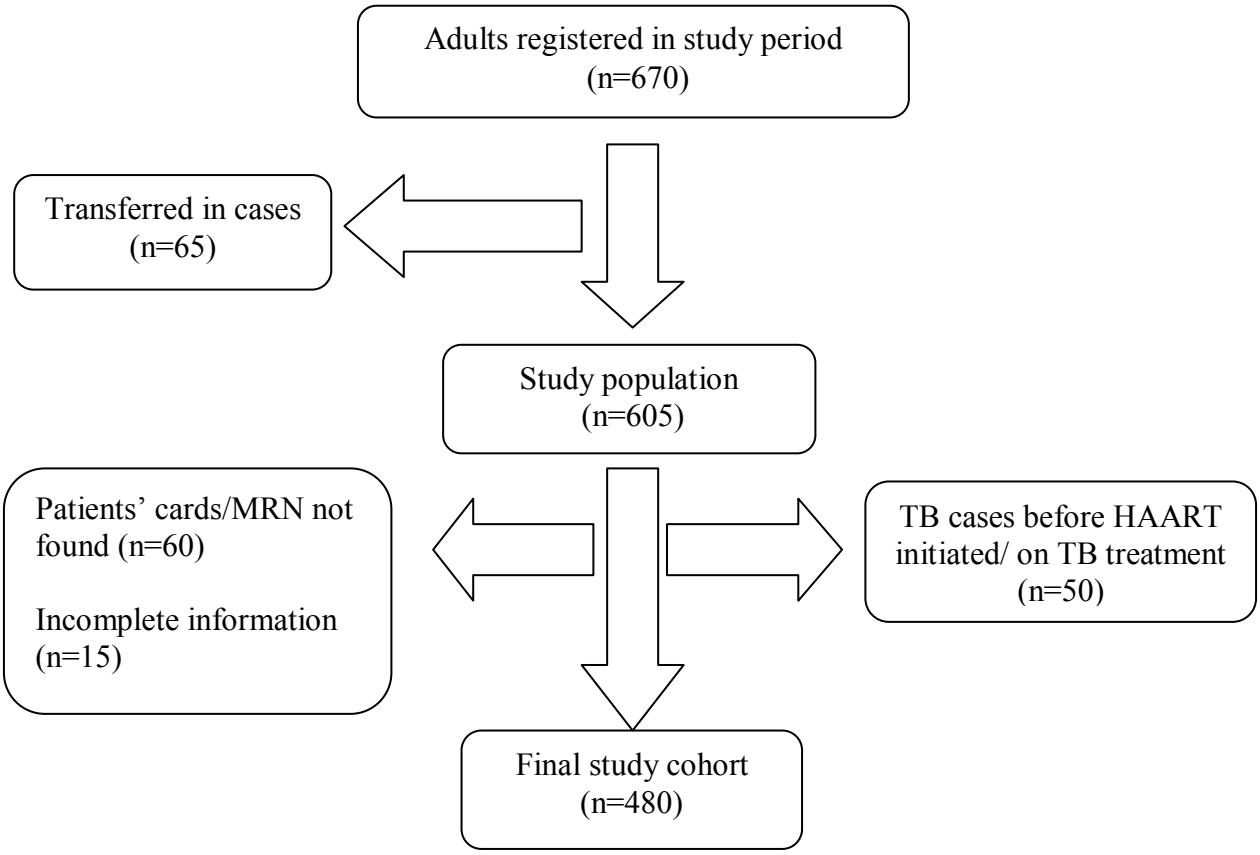

Figure 1- Cohort profile of study population, Zewiditu hospital, Addis Ababa, Ethiopia, ART cohort from September 11, 2009 to August 31, 2010.

4.5 Data collection procedures

All available information on patient records were checked and formats from other literatures were reviewed then appropriate data extraction format was adopted in English in order to extract all the relevant variables to meet the study objectives from patient charts.

The data clerks identified patient cards that were enrolled on ART from September 11, 2009 to August 31, 2010 from the register/electronic data base by using MRN and unique ART number.

Then, the data was extracted from patients' charts by two nurses who have been working in Zewditu Hospital ART clinic by using the prepared formats. The principal investigator supervised all data collection processes.

Study variables

In dependent variable

Socio-demographic characteristics (age, sex, religion, ethnicity, employment, marital and educational status), clinical and immunological variables (CD4, WHO stage, haemoglobin level, functional status, and OIs), Prophylaxis (IPT and CPT), Substance use (smoking, alcohol, and other drugs), past medical history and contact history of TB.

Dependent variable

TB development after ART initiation

4.6 Conceptual definitions

A case of tuberculosis: A patient with mycobacterium tuberculosis identified from sputum smear positive for AFB (Acid fast bacilli), culture positive for mycobacterium tuberculosis, radiological or histological diagnosis of TB.

New case: A patient who has never had treatment for tuberculosis.

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

CPT users: A person on chronic HIV care follow up who has been taking CPT before diagnosed for TB.

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

Treatment failure: A person on chronic HIV care follow-up and on ART but had a history of clinical/immunological/virological failure confirmed by medical personal and registered on card.

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

ART 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

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

Censored= PLWHIV on ART, who didn't develop TB till the last date of study period, drop out, or death.

WHO clinical staging system was considered to staging HIV/AIDS.

4.7 Data quality management

The quality of data was ensured in the point of data collection tool, data collection and data entry. Emphasis was given in designing data collection format based on relevance, logically sequenced, and availability in patients chart. Pre-test was undertaken on the format before the actual data collection started and amendment was made on the formats. The data collectors were provided with intensive training on the objective of the study and contents of the format.

Data collection was done by well experienced ART nurses' with data clerks and the principal investigator supervised. The investigator examined the completeness, concordance and correctness of completed data and for incompleteness and/or inconsistency data, correction was made by going back to patient cards. After coding, data were entered and analysed with Statistical Package for the Social Sciences (SPSS-version 20) by investigator. Cross-checking and data cleaning were done for accuracy, outliers, and consistencies before analysis.

4.8 Data Analysis procedures

Descriptive statistics was used to describe the study population by independent variables in terms of frequencies and percentages. The risk of developing TB among patients on ART cohort was assessed using the person time method. Incidence rate of tuberculosis was calculated as number of tuberculosis cases per 100 person years observed. TB free survival was calculated by months.

TB incidence density was calculated as number of new TB cases divided by total person time follow up contributed by each subjects. TB free survival was calculated from date of ART initiation to the date of tuberculosis diagnosis, drop out, death, or the last follow-up visit.

The Kaplan-Meier curve (an intuitive graphical presentation which describes survivorship of the study population) was used to estimate the median duration of TB occurrence. The Log rank test was used to compare survival curves between different categories of explanatory variables. Cox proportional hazards models was used to examine factors associated with time to TB development after initiation of ART. Factors that associated with outcome variables at 20 % significant level in the univariate analysis were included in the final Multivariate analysis.
Hazard Ratios (HR) with 95% confidence intervals were computed and statistical significance was accepted at the 5% level ($p < 0.05$). The necessary assumptions for Cox Proportional hazard model were checked using the Schoenfield residuals test.

4.9 Ethical consideration

Ethical clearance was obtained from research and ethical committee (REC) of school of public health, Addis Ababa University. In order to maintain confidentiality, study subjects were not identified by name and data collection was done by data clerks and ART nurses, who have been working in ART clinic.

4.10 Dissemination of results

The result of this study will be presented to the School of Public Health of Addis Ababa university College of Health Sciences as partial fulfillment of a master's degree in public health. Furthermore, the result of this study will be shared for Zewiditu Hospital, where the study was conducted.

5 RESULTS

5.1 Base line socio demographic characteristics of study participants

Four hundred eighty records of PLWHIV were analyzed. The median age of the patients was 36 years with [IQR: 31.2-42]. The study findings revealed that 304(63.3%) study participant were female and 176(36.7%) were male. Out of total study subjects, 264(55%) were married and 77(16%) were single. Two hundred five (43%) patients had completed secondary school and 144(30%) patients had completed primary school. Almost half of occupational status were not recorded, and from those recorded, 165 (34.4%) patients were employed.

A total of 442 (92.1%) patients disclosed their HIV status, to their wife/husband 227 (47%), to brothers/sisters 104 (22%), and to parents 90(19%). Ninety one patients (19%) were addicted, to alcohol 82(17%), to tobacco 49(10%) or to other drugs 41 (8.5%) (Table 1).

Table 1: Baseline socio demographic characteristics of PLWHIV on ART at Zewditu Hospital from September 11, 2009 to March 31, 2015.

Variables		Number	Percent
Age	15-29	66	13.8
	30-44	315	65.6
	>44	99	20.6
Sex	Male	176	36.7
	Female	304	63.3
Level of education	No formal education	51	10.6
	Primary	144	30.0
	Secondary	205	42.7
	Tertiary	80	16.7
Marital Status	Single	77	16.0
	Marred	264	55.0
	Separated/Divorced/Widowed	139	29.0
Occupation	Employed	165	34.4
	Unemployed	91	19.0
	Not recorded	224	46.7
Disclosure status	Yes	442	92.1
	No	11	2.3
	Not recorded	27	5.6
Addiction	Yes	91	19.0
	No	387	80.6
Family size	1-3	239	49.8
	4-6	173	36.0
	>6	37	7.7
	Not recorded	31	6.5
No of rooms	1-2	271	56.5
	>=3	178	37.1
	Not recorded	31	6.5

5.2 Baseline clinical characteristics of the study subjects

The eligibility criteria for initiation of ART were mainly with both CD4 count and WHO clinical stage in 311(66%). More than half 363(75%) of them were at WHO clinical stage 1 & 2 and 198(41%) had a CD4 count between101& 200 during ART initiation. Four hundred twenty nine (89%) of the participants were on working functional status at baseline. The median CD4 count during enrollment and end of follow up was 166 [IQR: 98–237] and 426[IQR: 317–546] cells per mm3, respectively. The predominant regimens initially prescribed were a combination of Lamivudine , Tenofovier and Efavirenz (3TC-TDF-EFV) 221(46%), followed by zidovudine, Lamivudine and Efavirenz (AZT-3TC-EFV) 110 (23%). Fifty nine patients (12%) had changed their initial regimen to first line ART during the follow up period. Forty(8.3%) and 9(1.9%) patients regimens were changed due to drug side effect and new drug availability, respectively. Out of total study subjects, 347(72.3%) of patients had BMI above18 kg/m^2 at baseline. While only 19(4%) patients BMI was below 16 Kg/m^2 during initiation of treatment and 62(12.9) patients' heights were not recorded.

Most of patients 453(94.4%) had more than 10 Hg level. During the follow up period most of patients 441(92%) had taken CPT but only 160(33%) had taken IPT and their ART adherence was good 463(96.5%). Fifty (71%) TB patients presented with pulmonary TB, followed by 20(29%) extra pulmonary TB. Sixty six (94%) patients developed TB for the first time during the follow up period (Table 2).

Table 2: Clinical characteristics of PLWHIV on ART at Zewditu Hospital from September 11, 2009 to March 31, 2015.

Variables		Number	Percent
WHO clinical stage	Stage I or II	363	75.6
	Stage III or IV	117	24.4
Base line CD4	<=100	125	26.0
	101-200	198	41.3
	>200	157	32.7
Functional status	Working	429	89.4
	Ambulatory/Bed redden	51	10.6
Hg level	<=10	27	5.6
	>10	453	94.4
Adherence	Good	463	96.5
	Fair/Poor	17	3.5
IPT	Yes	160	33.3
	No	320	66.7
CPT	Yes	441	91.9
	No	39	8.1
Eligibility criteria	WHO clinical stage	23	5
	CD4 count	139	29
	Both	311	66
ART initial regimen	3TC-TDF-EFV	221	46.0
	1d=AZT-3TC-EFV	110	22.9
	3TC-TDF-NVP	90	18.8
	Others	59	12.3
Regimen change during follow up	To 1st line	59	12.3
	To 2nd line	1	0.2
	Not changed	420	87.5
Reason for switch first regimen	Toxicity/side effect	40	8.3
	New drug available	9	1.9
	Pregnancy	3	0.6
	Not recorded	8	1.7
BMI (Kg/m^2**)**	<16	19	4.0
	16-18.49	52	10.8
	>=18.5	347	72.3
	Not recorded	62	12.9
Type of TB	PTB	50	71
	EPTB	20	29
TB case definition	New	66	94.3
	Re-treatment	4	5.7

5.3 Tuberculosis incidence density

Four hundred eighty study participants who were followed for different periods in five years produced 1952.5 PY of observation. Within the follow up period, 70 patients were found to have post HAART TB. The overall TB incidence density was 3.59 per 100 PY (70/1952.5). Among the new TB cases, 27 were males and 43 females. Of these, 50(71%) were pulmonary TB and 20(29 %) were Extra-pulmonary TB. Thirty six (51.4%) of the TB cases occurred within the first year of follow up. The highest incidence of TB was observed in the first year of enrolment (76.59/100 PY) and then decreased in the subsequent years of follow up (18.4 and 1.03 per 100 PY in three and five years, respectively). As by life table method, the cumulative probability of TB-free survival at the end of one year was 0.90; at the end of two years 0.89; at the end of three years 0.88; at the end of four years 0.84 and at the end of five years 0.80.

Table 3: Tuberculosis incidence density rate stratified by socio-demographic characteristics of PLWHIV on ART at Zewditu Hospital from September 11, 2009 to March 31, 2015.

Covariates	Total	PY	TB	TB IDR
Age				
15-29	66	244.08	10	4.09
30-44	315	1310.08	45	3.43
>44	99	398.33	15	3.77
Sex				
Male	176	710.08	27	3.8
Female	304	1242.42	43	3.46
Level of education				
No formal education	51	185.92	9	4.84
Primary	144	608.08	23	3.78
Secondary	205	850	26	3.05
Tertiary	80	308.5	12	3.89
Marital status				
Single	77	336.25	7	2.08
Married	264	1073.75	38	3.54
Separated/Divorced/Widowed	139	542.5	25	4.61
Disclosure status				
Yes	442	1787.92	66	3.69
No	11	53.5	2	3.73
Addiction				
Yes	91	342.42	23	6.71
No	387	1602.5	47	2.93
Family size(n=449)				
1-3	239	992.67	33	3.32
4-6	173	667.67	32	4.79
>6	37	155.42	4	2.57
No of rooms(n=449)				
1-2	271	1085.92	46	4.24
>=3	178	729.83	23	3.15

Table 4: Tuberculosis incidence density rate stratified by clinical characteristics of PLWHIV on ART at Zewditu Hospital from September 11, 2009 to March 31, 2015.

Covariates	Total	PY	TB	TB IDR
WHO clinical stage				
Stage I or II	363	1525.5	35	2.29
Stage III or IV	117	427	35	8.19
CD4 count				
<=100	125	436.5	40	9.16
101-200	198	808.92	25	3.09
>200	157	707.08	5	0.71
Functional status				
Working	429	1768.66	55	3.11
Ambulatory/Bed redden	51	183.83	15	8.16
Hg level				
<=10(mg/dl)	27	84.08	9	10.7
>10(mg/dl)	453	1868.42	61	3.26
Adherence level				
Good	463	1904.58	62	3.26
Fair/Poor	17	47.92	8	16.69
IPT				
Yes	160	693.25	12	1.73
No	320	1259.25	58	4.61
CPT				
Yes	441	1780.83	65	3.65
No	39	171.67	5	2.91
Year of follow up				
<1	47	47	36	76.59
1-3	41	81.33	15	18.44
>3	392	1852.58	19	1.02

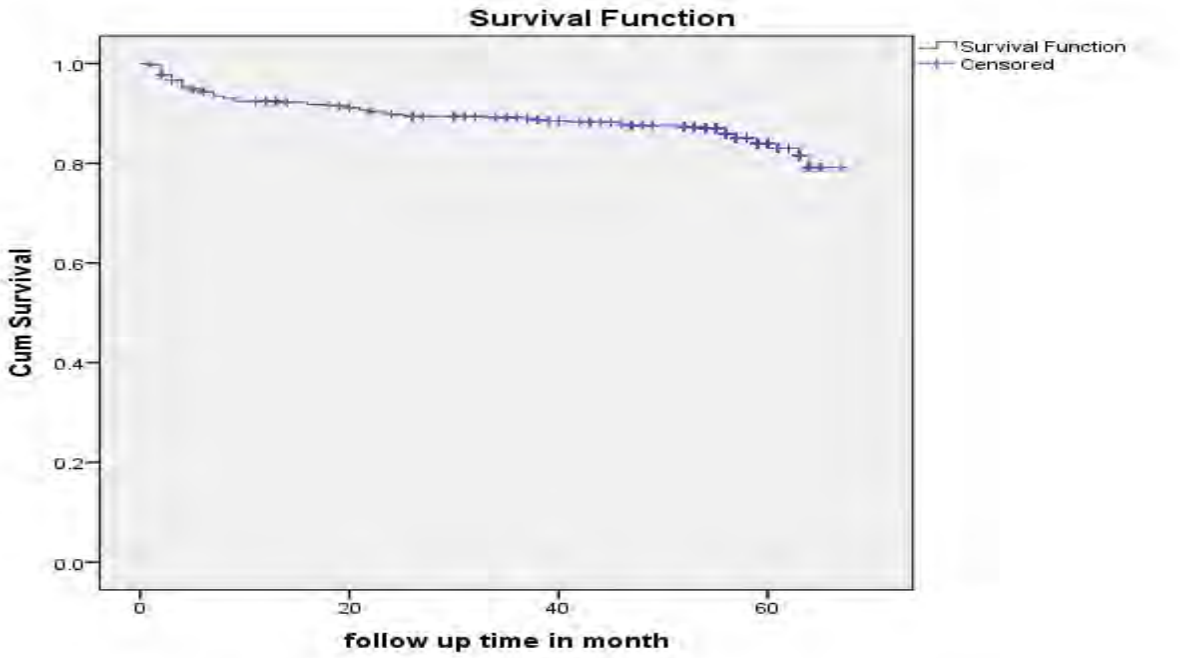

Figure 2 Kaplan-Meier curve of TB survival proportion for PLWHIV on ART at Zewditu hospital, September 11, 2009 to March 31, 2015.

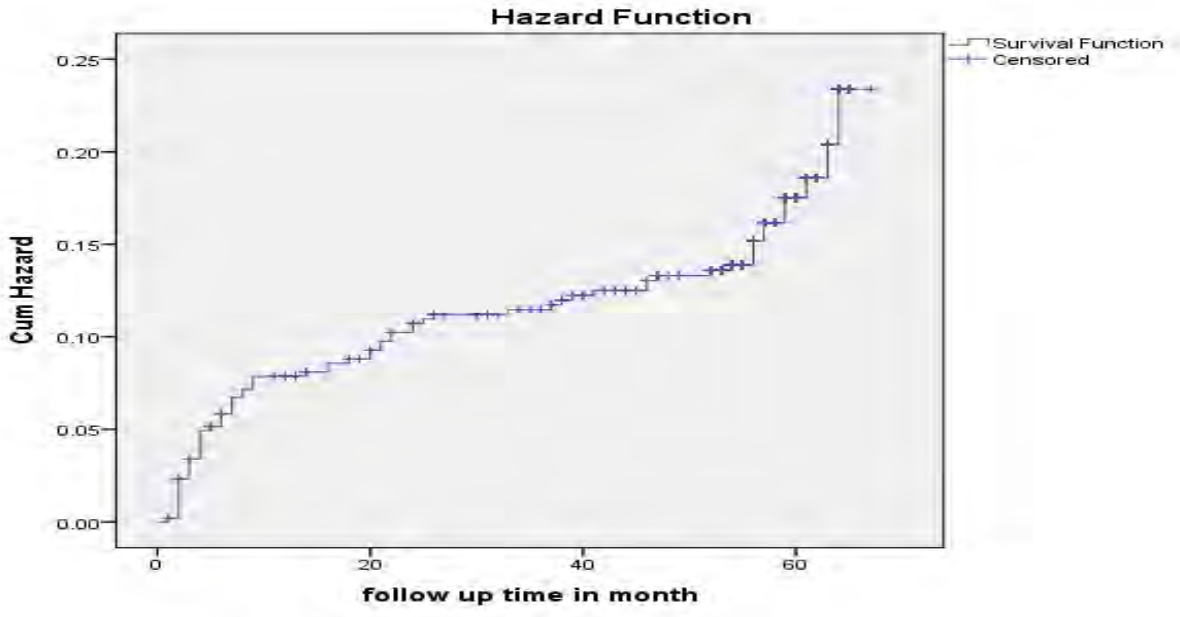

Figure 3 Kaplan-Meier curve of TB hazard proportion for PLWHIV on ART at Zewditu hospital, September 11, 2009 to March 31, 2015.

The Kaplan-Meier analysis and the log-rank test were used to compare the tuberculosis- free survival probabilities of HAART cohort in WHO clinical stages (log rank statistic= 31.49, df=1,p=<0.001) and in CD4 count(log rank statistic= 50.9, df=2, p=<0.001)

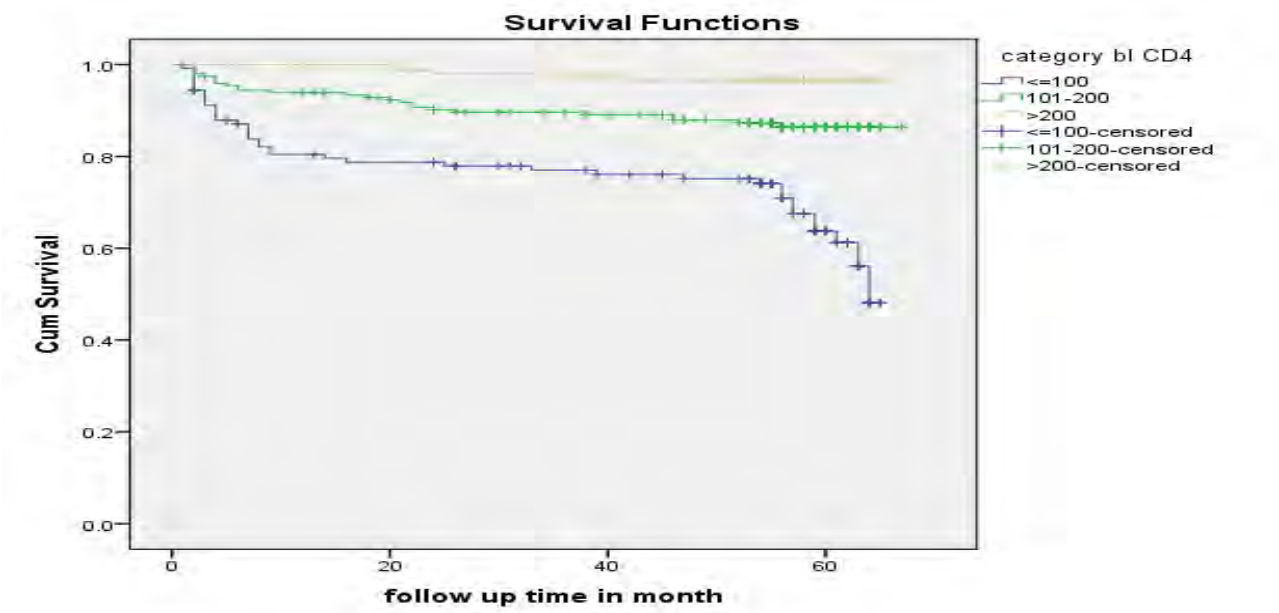

Figure 4 Kaplan-Meier curve of Tuberculosis -free survival proportion based on baseline CD4 cell count among PLWHIV on ART in Zewditu hospital, September 11, 2009 to March 31, 2015.

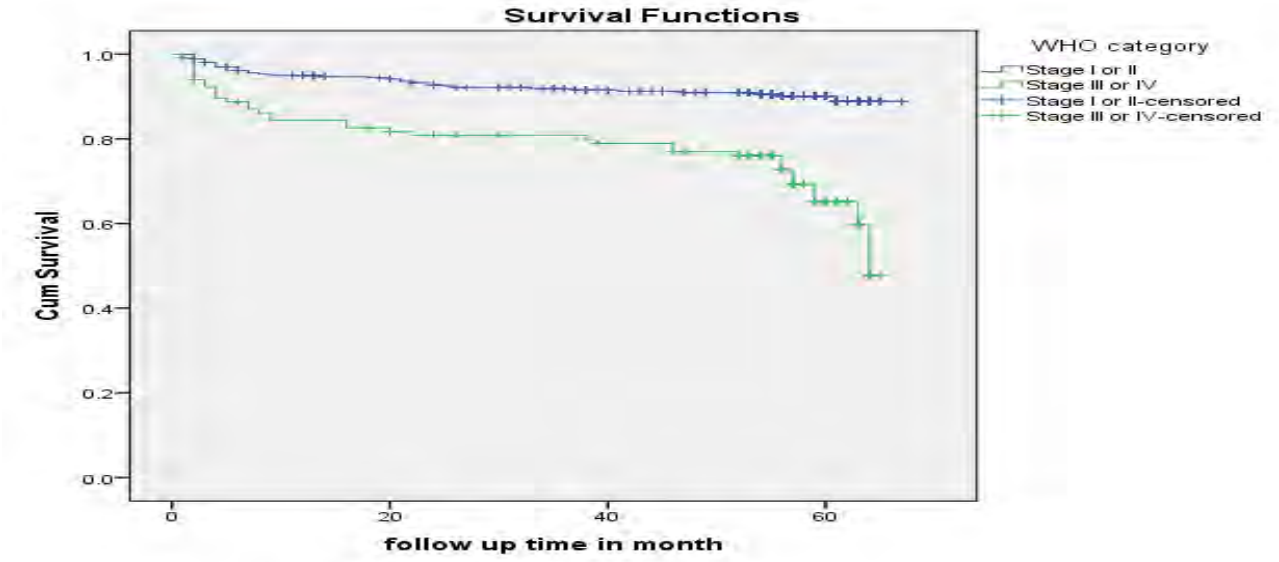

Figure 5 Kaplan-Meier survival curve of TB-free proportion based on WHO Clinical Stage among PLWHIV on ART in Zewditu hospital, September 11, 2009 to March 31, 2015.

5.4 Predictors of time to TB occurrence

Univariate and Multivariate analysis

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 being addicted to tobacco/alcohol, poor adherence, CD4 count below 200 cell/ul, functional status, WHO clinical stage III and IV, hemoglobin level below 10 mg/dl, and had taken IPT were significant predictors of TB- free survival time (Table 5).

Table 5: Univariate and Multivariate analysis of predictors of tuberculosis among PLWHIV cohorts on ART at Zewditu Hospital from September 11, 2009 to March 31, 2015.

Covariates	Survival status		Total	CHR(95% CI)	AHR(95% CI)	p-value
	Event (TB)	Censored				
Age						
15-29	10	56	66	1.00		
30-44	45	270	315	0.86(0.43-1.71)		
>44	15	84	99	0.93(0.41-2.07)		
Sex						
Male	27	149	176	0.90(0.56-1.46)		
Female	43	261	304	1.00		
Level of education						
No formal education	9	42	51	1.00		
Primary	23	121	144	0.8(0.373-1.74)		
Secondary	26	179	205	0.66(0.31-1.42)		
Marital status						
Single	7	70	77	1.00		
Married	38	226	264	1.67(0.74-3.75)		
Separated/Widowed	25	114	139	2.07(0.89-4.79)		
Disclosure status						
Yes	66	376	442	0.98(0.24-4.01)		
No	2	9	11	100		
Addiction						
Yes	23	68	91	**2.19(1.33-3.61)**	**1.78(1.07-2.96)**	0.02*
No	47	340	387	1.00		
WHO clinical stage						
Stage I or II	35	328	363	1.00		
Stage III or IV	35	82	117	**3.48(2.18-5.57)**	**2.37(1.41-3.96)**	0.001*
CD4 count						
<=100	40	85	125	**11.9(4.69-30.19)**	**7.48(2.86-19.5)**	<0.001*
101-200	25	173	198	**4.1(1.56-10.71)**	**3.53(1.33-9.34)**	0.011*
>200	5	152	157	1.00		
Functional status						
Working	55	374	429	1.00		
Ambulatory/Bedridden	15	36	51	**2.52(1.42-4.47)**	1.20(0.64-2.24)	.565
Hg level						
<=10(mg/dl)	9	18	27	**3.11(1.54-6.27)**	**2.32(1.13-4.78)**	.022*
>10(mg/dl)	61	392	453	1.00		
Adherence level						
Good	62	401	463	1.00		
Fair/Poor	8	9	17	**4.49(2.15-9.4)**	**2.98(1.36-6.52)**	.006*
IPT						
Yes	12	148	160	**0.39(0.21-0.73)**	**0.49(0.26-0.94)**	.032*
No	58	262	320	1.00		
CPT						
Yes	65	376	441	1.22(0.49-3.03)		
No	5	34	39	1.00		

***Significant at P<0.05**

To identify independent predictors, a multivariate Cox-proportional hazard adjusted model was fitted with variable having a P-value <0.2 in the Univariate analysis. Accordingly, most variables were remained independent predictors of TB-free survival time after controlling for the other factors.

In the multivariate Cox-regression analysis, baseline addiction, adherence, CD4 cell count, WHO clinical stage, hemoglobin level, and IPT remained significant predictors of TB- free survival time. Accordingly, PLWHIV who were addicted to tobacco/alcohol/other drug ,were 1.78 times at higher risk of developing TB as compared to those who were not addicted (AHR = 1.78, CI=1.07-2.96). The PLWHIV who were at WHO clinical stage III or stage IV had 2.37 times higher risk of acquiring TB as compared to those with WHO clinical stage I or II (AHR =2.37, 95%CI = 1.41-3.96). A patient with a base line CD4 count of below 100 cell/ul were seven times more likely to have TB than a patient with a CD4 count greater than 200 cell/ul (AHR 7.48,CI=2.86-19.53). Similarly, PLWHIV with a CD4 count of between 101 & 200 were 3.5 times more likely to have TB than a patient with a CD4 count greater than 200 cell/ul (AHR 3.53, CI=1.33-9.34) even though CI is wide. A Patient who had poor adherence had three times more likely to have TB than a patient who had good adherence (AHR=2.98, 95%CI 1.36-6.52). A patient with a Hgb level below 10 mg/dl were two times more likely to have TB than a patient with a Hgb level above 10 mg/dl (AHR= 2.32, CI=1.13-4.78). IPT had a protective effect, patients who had taken IPT were lower hazard of developing TB than a patient who hadn't taken (AHR=0.49, 95%CI=0.26-0.94). But functional status lost their statistical significance in the multivariate analysis (Table 5).

6 DISCUSSION

Four hundred eighty records of PLWHIV were analyzed. Their median age was 36 years with [IQR: 31.2-42] and 315 (65.6%), of them were in the age group of 30-44 years. Over half 304(63.3%) of the PLHIV were females and 264(55%) were married. Two hundred five (43%) patients had completed secondary school (Table 1). The cumulative probability of TB-free survival at the end of one year was 0.90 and at the end of five years was 0.80.

In this study, the overall incidence of TB was 3.59 per 100 PY among patients on ART. It was similar with that of studies done in Ethiopia and India, which reported that the incidence of tuberculosis was 3.73 & 2.83/100 person years among those on HAART, respectively [13,18]. Another study conducted in Ethiopia and south Africa also revealed that the overall TB incidence density was 7.89 & 6.2 per 100 PY among PLWHIVs, respectively [12,19] which is higher than this study because those studies include pre ART patients, this also indicates ART reduces the incidence of TB [13,20].

The highest incidence of TB was observed in the first year of enrolment. This observation was in line with the evidence of declining TB incidence after enrolment and HAART initiation reported in different studies done in Cameron, India and Ethiopia [12, 18, 20,26]. In this study the highest incidence of TB was observed in the first one year of enrolment 76.59/ 100PY and then decreased in the subsequent years of follow up (18.4 and 1.03 per) in three and five years, respectively. The Peak TB incidence shortly after enrolment may have several explanations. It may represent the progression of a subclinical disease that remained undetected during enrolment, a rapid progression of either a newly reactivated disease or an exogenous infection, and also immune reconstitution inflammatory syndrome (IRIS) may have been responsible for some of these cases. TB is the most frequently reported IRIS associated infection [31]. The result of this study showed that patients who started HAART led to the development of IRIS within the first year of follow up. The finding also showed a significant decrease in TB incidence in the subsequent years of follow up. These indirectly indicated that the reduction in TB incidence following the introduction of HAART can be particularly linked with HAART induced prevention [31].

The other possible reason for increased TB- free survival within the duration of enrolment could be the result of progressive increase in CD4 cell count which builds the immune system and may

decrease the viral load over time. Although TB risk has decreased with time following enrolment, it was still significantly higher than that of the general population of Ethiopia, even after 5 years of follow up [32].

This retrospective study has also identified several determinant factors for the occurrence of TB among HIV infected people enrolled on ART. Adherence, addiction and isoniazid preventive therapy were predictor factors for TB in this setting. Patients who have advanced condition (WHO clinical stage III or IV, having CD4 count <200 cell/ul and haemoglobin level below 10 mg/dl) were also associated with development of new TB infection.

The Tuberculosis cases were more likely to be smoker, alcohol drinker as well as Khat chewer [25] which is similar to this study, PLWHIV who were addicted to tobacco/ alcohol ,were two times at higher risk of developing TB as compared to those who were not addicted (AHR = 1.78, CI=1.07-2.96).

A study showed that poor adherence was also one of predictor of TB [29]. In this study a Patient who had poor adherence had three times more likely to have TB than a patient who had good adherence (AHR=2.98, 95%CI 1.36-6.52).

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 [6]. The PLWHIV who were at WHO clinical stage III or IV had 2.37 times higher risk of acquiring TB as compared to those with WHO clinical stage I or II (AHR =2.37, 95%CI = 1.41-3.96) which is in line with a studies done in Ethiopia which ranges from 2 to 6 times higher [12,13,20]. A study conducted in Assela showed PLWHIV presented with WHO clinical stage III or IV at base line were developing TB at a rate of 6.29 times higher risk than base line WHO clinical stage I or II [13]. 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.

A lower baseline CD4 count before initiation of HAART has consistently been indicated as an independent risk factor for the occurrence of TB during the course of HIV treatment and care in different settings [13, 18, 19]. In this study a patient with a base line CD4 count of less than 100 cell/ul is seven times more likely to have TB than a patient with a CD4 count greater than 200 cell/ul (AHR 7.48,CI=2.86-19.5). Similarly, PLWHIV with a CD4 count of between 101 & 200 cell/ul were 3.5 times more likely to have TB than a patient with a CD4 count greater than 200

cell/ul (AHR 3.53, CI=1.33-9.34) even though the confidence interval was wide. This result was similar to the study done in Ethiopia and in Nashville, which is between two to three times higher.

PLWHIV with Hgb level below 10mg/dl were two times more likely to have TB than a patient with a haemoglobin level above 10 mg/dl (AHR= 2.32, CI=1.13-4.78). Other studies also showed individuals with Hgb level 10 mg/dl or less and anaemic were more likely to have TB and also prone to failing ART [25, 26] .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. 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 is also consistent with the previous findings that predict the occurrence of TB which implied that advance disease condition in HIV patients may predict occurrence of Tuberculosis after ART initiation [13, 18, 19].

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 taken IPT reduced TB incidence by 51% than a patient who hadn't taken (AHR=0.49, 95%CI=0.26-0.94). Likewise A prospective cohort in South Africa, patients who received both IPT and HAART showed a strong reduction in tuberculosis risk (AHR = 0.11; 95% CI 0.02–0.78) [19]. A study done in SNNPR Ethiopia shows the combined effect of IPT and ART when started at the same time reduced TB incidence by 57% as compared to those who took ART only [20]. Correspondingly a cross-sectional study done in Addis Ababa has also shown presence of INH prophylaxis and cotrimoxazole prophylaxis had an independent protective benefit against tuberculosis [25].

But in this study significant difference was not observed between, patients who had taken CPT and were not taken CPT. It might be due to low power of the study to identify the difference, because of inadequate number (only 39(8%) patients who were not taken CPT).

In this study, about 65.6% of patients were in age group of 30-44 years. 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 PLWHIV between 30-49 years of age. Similarly, in this study about 64% of new TB cases were contributed by this age group.

From the study population 63.3% were female and 61.4% of TB cases were contributed by females.

But In this study, socio-demographic factors, sex, age, marital status and educational level were not significantly associated with TB which is inconsistent with other reports in South Africa and Ethiopia, which showed that TB is more common among men than women and mostly affected adults in the economical productive age group [18, 19, 25]. In contrary a cohort study done in 15 countries shows younger age were associated with TB in low-income settings countries [24]. So it needs further study to clear out.

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 [12, 25]. But in this study, functional status was not significance that might be in our case 429(89%) of patients were working status. The main limitation of our study was the retrospective nature of the cohort. The study participants whose charts were lost and incomplete were not included in the study so the incidence rate of TB might be underestimated. Besides this, BMI, occupational status, OIs and past history of TB were not included in the analysis due to missed data in most of the documents.

7 STRENGTH AND LIMITATIONS

Strength

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

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.
- Some of data (occupational status, TB contact history, OI, and BMI) were incomplete and inconsistent so it wasn't analysed.
- In this study it was not possible to measure some data such as house hold income, housing condition, viral loads and others which might be important predictors.

8 CONCLUSION

Incidence of TB was high among people living with HIV, especially in the first year of ART cohort. WHO clinical stage III and IV, low CD4 count (<200 cell/ul), being addicted to tobacco/alcohol, poor adherence, and low haemoglobin level (<10) were found to be independent predictors of increased incidence of TB. Whereas taking INH was positive factors associated with decreased risk of TB occurrence at multivariate analysis.

9 RECOMMENDATIONS

- Since most of the incidence cases occurred at early period, after initiation of HAART, a due attention should be given to screen and treat patients with TB/HIV infection as early as possible, because drug adverse effect and high pill burden may lead patients to unwanted poor adherence and outcome.
- Increasing coverage of INH.
- More effort and special attention should be given to patients who have advanced clinical condition at ART clinic (WHO clinical stage III & IV, low CD4 count and Hgb level less than 10 mg/dl in order to reduce the risk of TB incidence.
- Health facilities should strengthen ongoing adherence and positive living counselling as long as ART is a lifelong treatment.
- Moreover, it is recommended that further prospective cohort study should be conducted to make clear relations between other risk factors such as social and economic factors.

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11 ANNEXES

Annex- I Conceptual Frame work

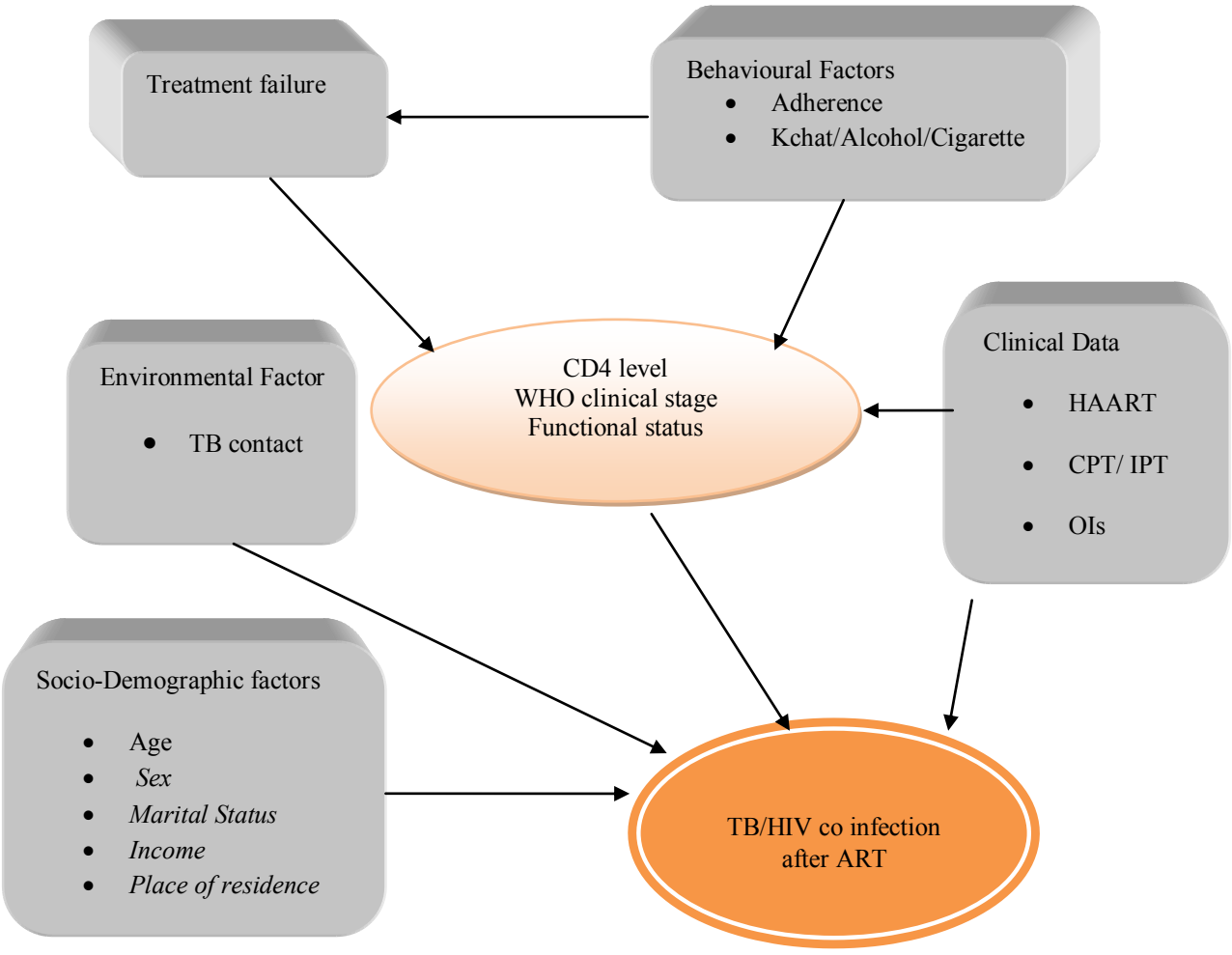

Figure 1: Determinant factors for the development of active TB in PLWHIV after ART initiation.

Annex- II Data collection format

This patient information data collection format was intended to determine incidence and factors predicting occurrence of TB among patients enrolled in ART, in Zewditu Hospital, Addis Ababa, Ethiopia. The data collection was conducted through patients chart review.

Name of data collector_____ Date _____

Medical record number _____ Patient unique ART number_____

No	Variable	Description/categories	Remark
Part 1:Socio-demographic Characteristics(from intake form A)			
101	Age	_____Years	
102	Sex	1.Male 2.Female	
103	Marital Status	1.Single 2.Married 3.Divorced 4.Separated 5.widowed	
104	Level of education	1.No formal education 2.Primary 3.Secondary 4.Tertiery	
105	Religion	1. Muslim 2. Orthodox 3.Protestant 4.Catholic 5.Other	
From intake form E			
106	Employment	1.Working full time 2.Working part-time 3.Not working/studying due to ill health 4.Un employed	
107	Number of rooms		
108	Running water	1.No 2.Yes	
109	Electricity	1.No 2.Yes	
110	Number of people in the house hold		
111	Disclosure Status	1.Not disclosed 2.Wife/Husband 3.Own child 4. Parents 5. Brothers/Sisters 6.Relatives 7.Friends	
112	Any addiction(from intake form F)	1.No 2.Tobacco 3.Alcohol 4.Other drug	
Part 2: Clinical and immunological characters (filled from patient ART follow-up form)			

Base line = at the time of ART initiation			
201	Date of ART initiated	____/____/_____E.C	
202	Latest follow up date	____ /____/_____E.C	
203	ARV eligibility criteria used	1.Clinical only 2.CD4 3.TLC 4.Transfer in(TI)	
204	Height(meter)		
205	Base line weight(kg)		
206	Functional status at ART initiation	1.Working 2.Ambulatory 3.Bedridden	
207	WHO clinical staging at time of ART initiation	1.Stage I 2.Stage II 3.Stage III 4.Stage IV	
208	TB screen	1.Posetive 2.Negative 3.Not screened	
209	Isoniazid preventive therapy (IPT) initiated	1.No 2.Yes	
210	Date of IPT started and duration	____/____/_____E.C Duration_____(days, weeks, months)	
211	Cotrimoxazol preventive therapy(CPT) initiated	1.No 2.Yes	
212	Date of CPT started and duration	____/____/_____E.C Duration_____(days, weeks, months)	
213	Any opportunistic infection (list all mentioned at base line)	0.No 1.Zoster 2.Bacterial pneumonia 3.Pulumenary TB 4.Extrapulumunary TB 5.Oral/vaginal trash 6.Mouth/genital ulcer 7.Chronic/acute diarrhoea 8.Pneumocystis carini pneumonia 9.CNS toxoplasmosis 10.Cryptococal meningitis 11.Others specify----------	
214	Any opportunistic	0.No 1.Zoster 2.Bacterial pneumonia	

	infection (list all mentioned after ART initiation)	3.Pulumenary TB 4.Extrapulumunary TB 5.Oral/vaginal trash 6.Mouth/genital ulcer 7.Chronic/acute diarrhoea 8.Pneumocystis carini pneumonia 9.CNS toxoplasmosis 10.Cryptococal meningitis 11.Others specify----------	
215	Initial ART regimen	1.1a(30)=d4t(30)-3TC(30)-NVP 2.1a(40)=d4t(40)-3TC(30)-NVP 3.1b(30)=d4t(30)-3TC(30)-EFV 4.1b(40)=d4t(40)-3TC(30)-EFV 5.1c=AZT-3TC-NVP 6.1d=AZT-3TC-EFV 7. 3TC-TDF-EFV 8.2nd line regimens(2a/2b/2c/2d)	
216	ARV adherence	1. Good 2. Fair 3. Poor	
217	ARV Side effects	0.No side effects 1.Nausea 2.Diarrhea 3.Fatigue 4.Headache 5.Numbness/tingling 6.Rash 7.Anemia 8. Abdominal pain 9. Jaundice 10.Fat change 11.Dizzy,anxiety,nightmare	
218	Regimen change during follow up	1. Not changed 2.To first line 3. To 2nd line	
219	Reason for switch first regimen.	0.Not changed 1.Toxicity/side effect 2.Pregnancy 3.Risk of pregnancy 4.Due to TB 5.New drug available 6.Drug out of stock 7.Clinical failure 8.Immunological failure 9.Virological failure 10.Other----------	
220	Hgb level at base line		

221	CD4 count	Base line CD4 _____ Date____/____/_____E.C At 6 month _____ Date____/____/_____E.C At 12 month _____ Date____/____/_____E.C At 18 month _____ Date____/____/_____E.C At 24 month _____ Date____/____/_____E.C At 30 month_____ Date____/____/_____E.C Latest CD4 count ____Date____/____/___E.C	
222	TB diagnosed	1. Yes 2. No	
223	Status of the patient at the end of follow up	1. Active 2. Dead 3. Lost to follow up 4.Drop out 5. Transfer out	
From patient history sheet			
224	Past TB treatment history	1.Yes 2.No 3.Not available	
225	History of TB contact	1.Yes 2.No 3.Not available	
Part 3:TB related information(only filled for those who developed TB)			
301	Date of TB diagnosed		
302	Month on ART when TB diagnosed		
303	TB investigation /diagnosed were done by	1. Sputum microscopic exam. 2.x-ray 3. Sputum culture 4. Clinical 5.FNA	
304	Types of TB/Sputum result	1. Smear positive pulmonary TB 2. Smear Negative pulmonary TB 3. Extra pulmonary TB 4. Combined	
305	TB case definition	1. New 2. Re-treatment (relapse, failure, default)	

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.

Name: Mahlet Nigussie (Bsc)
Signature: _____
Date: _____

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

Name: Wondimu Ayele (BSc, MSc)
Signature: _____
Date:_____

ASSURANCE OF PRINCIPAL INVESTIGATOR

The undersigned agrees to accept responsibility for the scientific ethical and technical Conduct of the research project and for provision of required progress reports as Per terms and conditions of the Research Publications Office in effect at the time of Grant is forwarded as the result of this application.

Name of the student: _____

Date._____ Signature _____