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EFFECT OF TUBERCULOSIS ON THE SURVIVAL OF HUMAN IMMUNODEFICIENCY VIRUS INFECTED ADULTS INITIATED ANTIRETROVIRAL THERAPY IN PUBLIC HOSPITALS OF HARAR AND DIRE DAWA TOWN, EASTERN ETHIOPIA.

MPH THESIS

BY: TADESSE SIME (BSc)

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HARAMAYA UNIVERSITY, HARAR, ETHIOPIA

Effect of Tuberculosis on The Survival of Human Immunodeficiency Virus Infected Adults Initiated Antiretroviral Therapy in Public Hospitals of Harar and Dire Dawa town, Eastern Ethiopia

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In Partial Fulfillment of the Requirements for Master's Degree
OF PUBLIC HEALTH IN EPIDEMIOLOGY

Tadesse Sime (BSc)

Major Advisor: Lemessa Oljira (PhD, Associate professor)

Co-Advisor: Tadesse Alemayehu (PhD, Assistant professor)

June, 2019

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I hereby certify that I have read and evaluate thesis entitled with Effect of Tuberculosis on The Survival of Human Immunodeficiency Virus Infected Adults Initiated Antiretroviral Therapy in Public Hospitals of Harar and Dire Dawa town, Eastern Ethiopia: retrospective cohort study prepared under my guidance by Tadesse Sime. I recommend that it be submitted as fulfilling the thesis requirement.

Lemessa Oljira (Associate professor, PhD) _____ _____

Major Advisor Signature Date

Tadesse Alemayehu (PhD, Assistant professor) _____ _____

Co-Advisor Signature Date

As members of the Examining Board of the Final MPH Open Defense, we certify that we have read and evaluated the thesis prepared by Tadesse Sime and examined the candidate. I recommend that the thesis be accepted as fulfilling the thesis requirements for the degree of master of public health in Epidemiology.

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BIOGRAPHICAL SKETCH

I was born in 1991 in Gerba Guracha town, North shoa Zone, central Ethiopia. I have completed my elementary school in Gerba Guracha No-3 primary school. I have attended my Secondary school in Gerba Guracha Secondary school and preparatory in Gerba Guracha preparatory school. After completion of my Preparatory School I have joined Ambo University by the year 2012. I got my first degree BSC in nursing from Ambo University on June 2015. I am serving as assistant lecturer at Mettu University since January 2016.

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ACRONYMS AND ABBREVIATIONS

AFB	Acid fast bacilli
ABC	Abacavir
AIDS	Acquired Immune Deficiency Syndrome
AHR	Adjusted Hazard Ratio
ART	Antiretroviral Therapy
AZT	Zidovudine
BMI	Body mass index
CD4	Cluster of differentiation 4
CDC	Centre for Diseases Control
CEO	Chief executive officer
CI	Confidence interval
CPT	Cotrimoxazole Prophylaxis Treatment
CSA	Central statistical agency
DOT	Direct observaed therapy
EFV	Efavirenz
EPTB	Extra-pulmonary Tuberculosis
FMOH	Federal Ministry of Health
HAART	Highly Active Antiretroviral Treatment
HIV/TB	Human Immunodeficiency Virus/Tuberculosis
HRHB	Harari Regional Health Bureau
IQR	Interquartile range
IHRERC	Institutional Health Research Ethical Review Committee
3TC	Lamivudine
NVP	Nevirapine
PLHIV	People living with Human Immunodeficiency Virus
PMO	Person month observation
PTB	Pulmonary tuberculosis
PYO	Person year observation
TB	Tuberculosis
TDF	Tenofovir
WHO	World health organization
VIF	Variance inflation factor

ABSTRACT

Background: Tuberculosis is considered to be the leading cause of death in people living with human immunodeficiency virus in low-income countries. Although the effect of tuberculosis on survival of human immunodeficiency virus infected patient is setting specific, in Ethiopia the effect of tuberculosis co-infection on the survival of human immunodeficiency virus patient is poorly understood in antiretroviral therapy era.

Objective: To determine the effect of tuberculosis co-infection on survival of human immune deficiency virus infected adults initiated antiretroviral therapy in public hospitals of Harar and Dire Dawa town, eastern Ethiopia, March 1-15, 2019.

Methods: Retrospective cohort study was conducted. Human immunodeficiency virus infected patients with and without tuberculosis co-infection was selected by simple random sampling. Kaplan-Meier test was used to estimate the probability of death and the median time to death among patients with tuberculosis and without tuberculosis. Cox proportional hazard model was used to determine the effect of tuberculosis on survival of human immunodeficiency virus infected patients and p-value < 0.05 declares the significance of the variables at 95% confidence level.

Result: Out of 566 patients included in the study, 76 were dead with an overall mortality rate of 6.55 per 100 person years (95% CI: 5.28, 8.16 per 100 person years). The incidence of death was 11.04 per 100 person years and 2.52 per 100 person years in tuberculosis co-infected and not tuberculosis co-infected respectively. In multivariable Cox regression analysis, patients with tuberculosis co-infection had 2.19 times higher hazard of death (AHR: 2.19; 95% CI: 1.17, 4.12) compared to those without tuberculosis. Advanced clinical stage (stage IV) (AHR: 3.06; 95% CI: 1.16, 8.09), low CD4+ cell count (<50 cells/mm3) (AHR: 3.7; 95% CI: 2.00, 7.03), and past episode of opportunistic illness other than TB (AHR: 1.65; (95% CI: 1.01, 2.68) were also independent predictors of mortality.

Conclusion: Being tuberculosis co-infected at antiretroviral therapy initiation increase the hazard of death approximately by two folds as compared to those without tuberculosis. This illustrates tuberculosis and human immunodeficiency virus collaborative activities need to be strengthened

Key words: Antiretroviral therapy, Tuberculosis, Human immunodeficiency virus, Co-infection, Retrospective cohort, Ethiopia

1. INTRODUCTION

1.1. Background

The synergistic interaction between the human immunodeficiency virus and tuberculosis epidemics has had deadly consequences around the world and extremely affects people in Africa (Kwan and Ernst, 2011). People living with HIV and latent tuberculosis infection are at much higher risk for progressing to active TB disease than people with latent TB infection alone (WHO, 2013). In 2016 an estimated 1 million people living with HIV worldwide fell ill with TB and TB is the leading cause of death accounting for 370,000 death (WHO, 2017b). In Ethiopia the 2014 TB/HIV Surveillance report showed that among HIV infected clients newly enrolled to HIV Care 9.1 % were found to have active TB and from this Harari region and Dire Dawa accounts for 14.2% and 11.5% respectively (EPHI, 2015)

According to WHO guidelines, all clients attending HIV testing centers or people living with HIV (PLHIV) attending anti-retroviral therapy (ART) centers should be clinically screened for TB symptoms and all TB diseased patients should be screened for HIV infection (WHO, 2010a). Early diagnosis and timely treatment among people living with HIV are essential for minimizing TB associated mortality (WHO, 2015b). Tuberculosis infection among people living with HIV complicates management of both diseases(Abdool Karim et al., 2010) as the simultaneous administration of antitubercular and antiretroviral agents to patients with severe underlying disease is associated with frequent adverse events (McIlleron et al., 2007).

Early initiation of ART during TB treatment is associated with better survival through restoring immune function and preventing opportunistic infections (Ismail and Bulgiba, 2013) . Between 2000 and 2016, TB treatment and antiretroviral therapy saved 9 million lives among HIV-positive people (WHO, 2017a). Consequently the World Health Organization (WHO) recommends that ART should be initiated for all TB co- infected HIV patients irrespective of their CD4 counts (WHO, 2010b). Human immunodeficiency virus patients with active TB disease should receive treatment support, including adherence counseling and DOT, corresponding to their needs (Montales et al., 2015). Currently, in Ethiopia ART should be started for all TB patients within first 8 weeks, irrespective of their CD4 count(FMOH, 2017)

1.2. Statement of the Problem

Tuberculosis is leading killer of HIV-positive people. In 2017, from an estimated 1.6 million death from TB about 0.3 million were among people living with HIV. The risk of developing tuberculosis is estimated to be between 20-30 times greater in people living with HIV than those without HIV infection (WHO, 2018a). In 2015 from an estimated 10.4 million cases of tuberculosis disease globally 1.2 million (11%) cases were among people living with HIV and 60% of tuberculosis cases among people living with HIV were not diagnosed or treated, resulting in 390 000 tuberculosis-related deaths among HIV patients (WHO, 2018b). A recent study conducted in United Kingdom assessing the effect of TB on mortality in persons with HIV infection found that TB increase overall mortality of HIV patients by 4.7 folds (Zenner et al., 2015).

Different studies in Africa have showed that TB is the leading cause of death among HIV-infected patients. Sub-Saharan Africa bears the burden of the dual epidemic, accounting for approximately 86% of all deaths from HIV-associated TB in 2016 (WHO, 2018b; Au-Yeung Christopher et al., 2011). According to study conducted in South Africa Prevalent and incident TB among ART were strongly associated with increased risk of mortality (Gupta et al., 2013). In Uganda the proportion of death were high (10.5%) among Patients with TB co-infected HIV patients as compared to not TB co-infected HIV patients (6.4%) and being TB co-infected increase the death of HIV infected patients by 37% when compared to those not co-infected with tuberculosis (Chu et al., 2013)

Ethiopia is one of 30 high burden countries with TB/HIV coinfection globally and from total of 36,761 HIV positive patients newly enrolled to ART in 2016 about 5.9 were co-infected with tuberculosis (WHO, 2017a). Different studies conducted in Ethiopia in the last five years showed that mortality rate among TB co-infected HIV patients ranges from 14% (Teklu et al., 2017) to 29.3% (Sileshi et al., 2013) and about 67.3% of deaths among TB/HIV co-infected were occurred during TB treatment (Teklu et al., 2017). Several studies in Ethiopia have analyzed survival and predictors of mortality among people living with HIV (Fekade et al., 2017 ; Tachbele and Ameni, 2016 ; Setegn et al., 2015 ; Damtew et al., 2014) and a few studies take into account on long-term outcome of antiretroviral treatment in patients with and without concomitant tuberculosis by holding potential explanatory variables (Reepalu et al., 2017).

Several predictors of mortality among HIV infected patients like; age, educational status, functional status, base line CD4 count, BMI, ART adherence, TB co-infection and WHO clinical stage (Damtew et al., 2014 ; Abebe et al., 2014) were identified in previous studies. Tuberculosis mortality among HIV-positive patients is one of the key indicators that measures the impact of collaborative TB/HIV activities (WHO, 2015a) and Ethiopia is implementing national collaborative activities between TB and HIV/AIDS control programs according to world health organization (WHO) recommendation like: routine HIV testing among presumptive and diagnosed TB cases; TB screening among people living with HIV; early ART; improved infection control; and provision of TB preventive treatment to decrease the burden of tuberculosis in people living with HIV (FMOH, 2017).

Although the review of cohort studies showed that, currently available data are insufficient to draw definite conclusions about the causal effect of TB on mortality in PLWH exposed to HAART and Mortality among TB-HIV co-infected patients were strongly associated with the absence of ART (Straetemans et al., 2011) yet, a few analytical study was conducted on effect of tuberculosis on survival of HIV patients in Ethiopia. From previous study conducted in the study area there is limitation on not including opportunistic infection like TB as predictors of mortality among HIV patients due to incomplete information (Biadgilign et al., 2012) and effect of TB co-infection on mortality of HIV patient is not conclusive in ART era. Therefore this study was aimed to determine effect of TB co-infection at ART initiation on survival of HIV infected adults initiated ART in public hospitals of Harar and Dire Dawa town, eastern Ethiopia. The study was based on the hypothesis that there is no significant difference on survival of HIV infected individuals with TB and without TB at ART initiation.

1.3. Significance of the study

The result of this study may help the public hospitals of Harar and Dire Dawa town to understand the need for active TB case finding among people living with HIV and the need to strength and recommend early HIV testing to improve survival from these two deadly diseases. Moreover, findings from this study will help the Harari regional health bureau and Dire Dawa town health office as the body of knowledge that informs TB-HIV program planners to accurately plan for TB and HIV/AIDS co-management activities. The result of this study will also be used as a reference by other researchers who are interested on related topic.

1.4. Objectives of the Study

To determine the effect of TB co-infection on survival of HIV infected adults initiated ART in public hospitals of Harar and Dire Dawa town, eastern Ethiopia, March 1-15, 2019.

2. LITERATURE REVIEW

2.1. Effect of TB on survival of people living with HIV

Human immunodeficiency virus -associated TB contributes substantially to the burden of TB-associated morbidity and mortality among HIV patients (WHO, 2014). Retrospective cohort conducted on Impact of TB on the survival of people living with HIV infection in United Kingdom showed that the survival probability after one year of HIV diagnosis were 93.2% among TB co-infected compared with 98% for those without TB ($p<0.001$). Being TB co-infected increase the hazard of death 4.8 times when compared to not TB co-infected (Zenner et al., 2015). Similarly prospective cohort study conducted in USA on Effect of tuberculosis on the survival of HIV-infected men showed that, TB was associated with more than a two-fold increase in the hazard of AIDS-related mortality (López-Gatell et al., 2008).

Prospective cohort study conducted in Uganda revealed that proportion of death were high in TB co-infected (10.5%) when compared to not TB co-infected (6.4%) and being TB co-infected increase hazard of death by 37% when compared to not TB co-infected HIV patients (Chu et al., 2013). While retrospective cohort study conducted in South Africa showed PTB have no effect on mortality of HIV patients following initiation of HAART. This may be due to the difference in study area setting and care given to the patients (Westreich et al., 2009). Another study conducted in south Africa showed that Mortality rate was substantially greater among patients with prevalent TB at baseline compared to those who were TB free 4.84 and 2.62 deaths/100 PY among those without TB respectively (Gupta et al., 2013).

Study conducted in Tanzania showed that incidence of death among HIV patients on HAART was 4.32/100 person-years at risk (Mageda et al., 2012). similarly prospective cohort study conducted nationally in Ethiopia showed that all-cause mortality rate was 5.4/100PYO and 70% of death were occurred within six months of starting ART (Fekade et al., 2017). While study conducted in South Omo among 350 study participants showed that the overall incidence of death were 1.75 deaths per 100 person-years and overall survival probability of patients on HAART was 64% (Tachbele and Ameni, 2016).

A retrospective cohort study conducted on Time to death predictors of HIV/AIDS infected patients in Southwestern Ethiopia being tuberculosis co-infected increase the hazard of death by 2.8 folds when compared to non-co-infected patients (Tadege, 2018). Similarly retrospective Cohort Study conducted in southeastern Ethiopia being TB co-infected increase hazard of death by 4.5 times as compared to not TB co-infected patients (Setegn et al., 2015).

Retrospective cohort studies conducted in Somali region on Survival and determinants of mortality in adult HIV infected patients showed that overall mortality rate of the cohort were 5.15/100 and TB co-infection increase the hazard of death 2.3 times when compared to not TB co-infected HIV patients (Damtew et al., 2014). However, prospective cohort study conducted in Ethiopia among 141 TB cases and 588 non TB cases showed that Concomitant TB have no impact on outcomes of adults investigated for active TB before starting ART and proportion deaths were (9%) and (8%) among TB and non TB cases respectively (Reepalu et al., 2017). This difference may be due to small number of patients with TB in latter study.

2.2. Predictors of mortality among HIV infected patients

2.2.1. Sociodemographic risk factors

According to retrospective cohort study conducted in UK being aged >55 years increase the hazard of death by 3.6 times and being female decrease the hazard of death by 30 % (Zenner et al., 2015). Similarly study conducted in Tanzania revealed that being male and rural resident increase the hazard of death by 4.7 and 2.2 times respectively (Mageda et al., 2012).

Longitudinal study conducted in Ethiopia, nationally among 355 patients showed being Male increase hazard of death nearly by two folds (Teklu et al., 2017) and retrospective cohort study conducted in Aksum showed that primary level of education increase the hazard of death and 2.6 times when compared to those who have no formal education (Tadesse et al., 2014). While retrospective Cohort Study conducted in southeastern Ethiopia showed that being primary and secondary educated reduce probability of death by 72% and 66% respectively. This difference may be due to difference in study setting (Setegn et al., 2015).

Retrospective cohort study conducted in south western Ethiopia showed that being a rural resident and being aged between 35–44 years increase the hazard of death 3.4 times and three times respectively (Gesesew et al., 2016). Retrospective cohort study conducted in eastern Ethiopia showed that being single marital status increase the hazard of death approximately by two folds (Damtew et al., 2014).

2.2.2. Base line clinical, prophylactic and laboratory related risk factor

According to retrospective cohort conducted in United Kingdom, CD4 count less than 100cells/mm3 and opportunistic infection other than TB increase the hazard of death 3.5 times and 7.3 times respectively (Zenner et al., 2015). Similarly study conducted in Tanzania revealed that CD4 cells between 50-199cells/mm3 and WHO clinical stage 4 at the start of ART increase the hazard of death approximately by two and four folds respectively (Mageda et al., 2012).

Retrospective cohort study conducted in northwestern Ethiopia showed that Lower baseline hemoglobin increase the hazard of death by 86%. Being in Ambulatory and bedridden functional status increase the hazard of death nearly by three and two folds. Presenting with Advanced WHO clinical stage at ART initiation also increase the hazard of death by two folds among people living with HIV (Abebe et al., 2014). Similarly Prospective cohort study conducted in Ethiopia showed that WHO stages III&IV hazard of and CD4 count <100 increase hazard of death approximately by 76% and 2 folds respectively (Fekade et al., 2017).

Retrospective cohort study conducted in South Omo, on Survival and predictors of mortality of HIV patients showed that, ambulatory and bedridden functional status increase the hazard of death approximately three and five times (Tachbele and Ameni, 2016). Similarly study conducted in south eastern Ethiopia revealed that being bedridden functional status increase the hazard of death 4.4 times as compared to working functional status (Setegn et al., 2015).

Retrospective cohort study conducted in Aksum showed that being in hemoglobin level <11 mg/dl and CD4 counts lower than 50 cells/µl increase the hazard of death approximately by two folds (Tadesse et al., 2014). Similarly retrospective cohort study conducted in eastern Ethiopia showed that advanced WHO clinical stage and CD4 count < 50 cells/µL increase the hazard of death nearly 7 and 3 times respectively. Being in BMI < 18.5 Kg/m2 also increase the hazard of death by two folds (Damtew et al., 2014).

Retrospective cohort study conducted in eastern Ethiopia: showed that WHO clinical stage IV and bedridden functional status increase the hazard of death by 3 and 4 folds respectively (Biadgilign et al., 2012). Similarly retrospective cohort study conducted in Harar showed that; CD4 count lower than 50 cells/µl and not taking Cotrimoxazole Prophylaxis Treatment (CPT) at base line increase the hazard of death by 2.3 and 2.4 times respectively (Digaffe et al., 2014).

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2.3. Conclusion and Conceptual Frame Work

Generally the literature review showed that there is a variation of mortality among HIV infected patients with and without TB co-infection. The base line predictors that are associated with mortality among people living with HIV include: sex, age, occupation, educational status, marital status, and place of residence, patient functional status, WHO clinical stage, cotrimoxazole prophylaxis status, hemoglobin level, TB co-infection, CD4 count level, BMI and adherence to ART. The main predictors of mortality that are identified by literature review were in the conceptual frame work (**fig.1**)

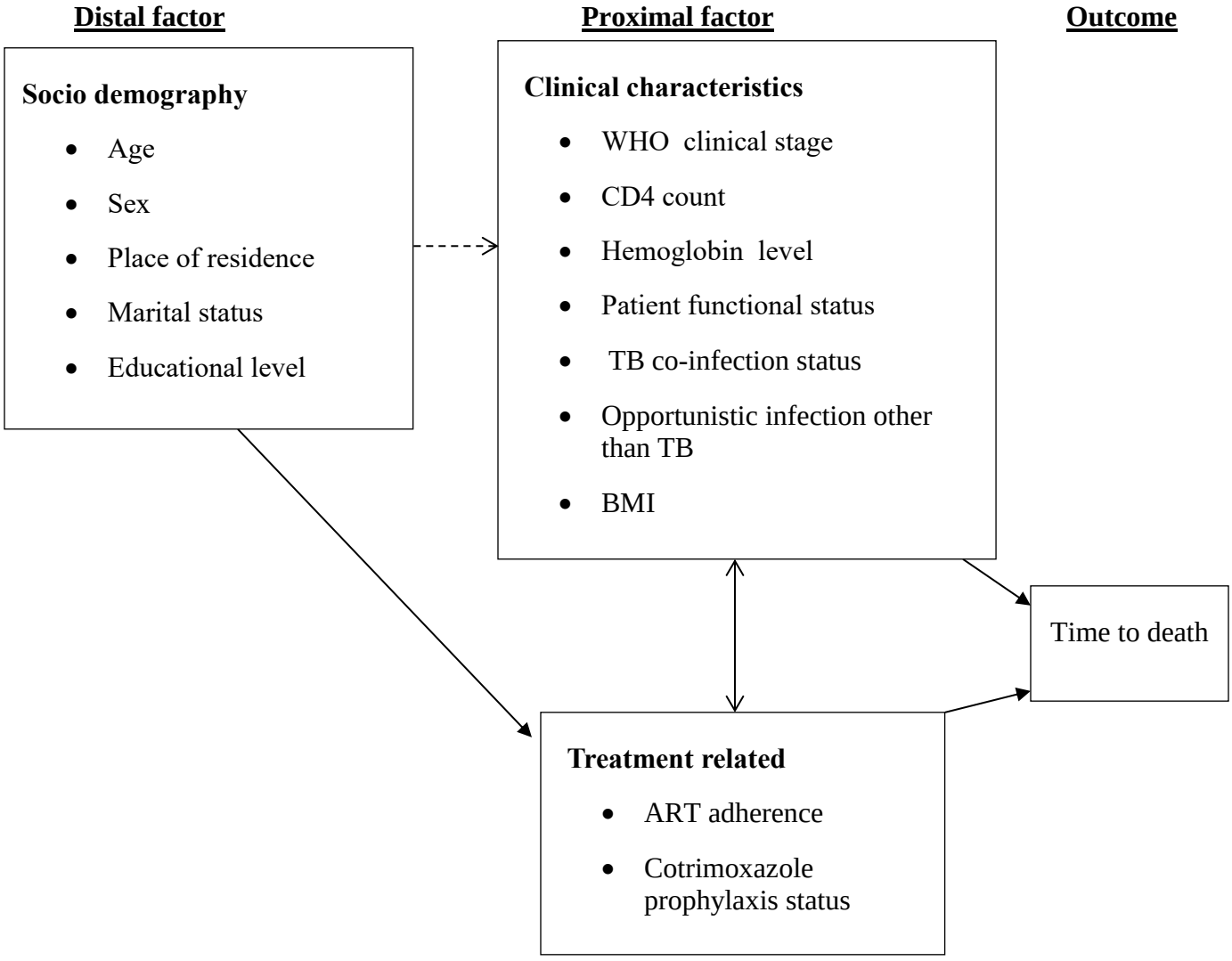


Figure 1Conceptual frame work describing predictors of mortality among HIV infected patients initiated ART source: Researcher Own Construction (2018) based on Review of Literatures.

3. METHODS AND MATERIAL

3.1. Study Area and Period

The study was conducted in public hospitals of Harar and Dire Dawa town, eastern Ethiopia: Hiwot Fana specialized university hospital; Jugol hospital, Dil Chora referral hospital and Sabian general hospital were included. Hiwot Fana specialized university hospital and Jugol hospitals are located in Harar town 525 KM away from Addis Ababa. From most recent demographic data the projection of population in the Harar town was 230,000 in 2014, and comprised of 3 rural and six administrative woredas. The adult HIV provenance of the town 2.95% with the estimation of 4,874 PLHIV in the year 2017. There are also an estimated 199 new all age HIV infection in 2017 (EPHI, 2015). Nine health facilities have been providing ART service in addition to other comprehensive HIV service for the population living in and near by community living outside the region. Hiwot Fana specialized university hospital is the region high load hospital which accomplish more than 50% of HIV treatment and follow up services the hospital runs HIV clinics that was started early in 2004, and currently 2327 patients are attending their ART follow up at ART clinic. Jugol hospital runs HIV clinics that was started early in 2004, and currently 1200 patients are attending their ART follow up at ART clinic. The electronic medical record is done in the ART clinic by the assigned data clerks and patient physical file is updated in computer at the end of each clinic day (HRHB, 2015).

Dil Chora referral hospital and Sabian general hospital are located in Dire Dawa town which is located at the distance of 515 km from Addis Ababa, capital city of Ethiopia. Based on 2007 estimates Dire Dawa has the total population of 342,827 of whom 171.930 were men and 170,897 were female. Dire Dawa town have two public hospital, one army hospital and four private hospitals and in the hospital all HIV positive people from any service area were enrolled to ART clinic for comprehensive HIV care also there are multidisciplinary professional's team that include physician, nurses and volunteer ART adherence supporters. Currently 2604 patients and 1008 patients are attending their ART follow up at Dil Chora referral hospital and Sabian general hospital respectively. In both hospitals the electronic medical record is done in the ART clinic by the assigned data clerks and patient physical file is updated in computer at the end of each clinic day (CSA, 2007). Data was extracted from March 1 to 15, 2019.

3.2. Study Design

Retrospective cohort study was used.

3.3. Source Population

The source population was all HIV infected adults initiated ART in public hospitals of Harar and Dire Dawa town.

3.4. Study Population

The study population was all HIV infected adults initiated ART in public hospitals of Harar and Dire Dawa town, between January 1, 2014 and June 30, 2018. Patients who co-infected with TB at ART initiation were included in exposed cohort and those who didn't co-infected with TB at ART initiation were included in non-exposed cohort.

3.5. Inclusion and exclusion criteria

3.5.1. Inclusion criteria

All HIV infected patients aged 15 years or older at ART initiation and those who naïve to antiretroviral therapy before January 1, 20014 were included in the study.

3.5.2. Exclusion criteria

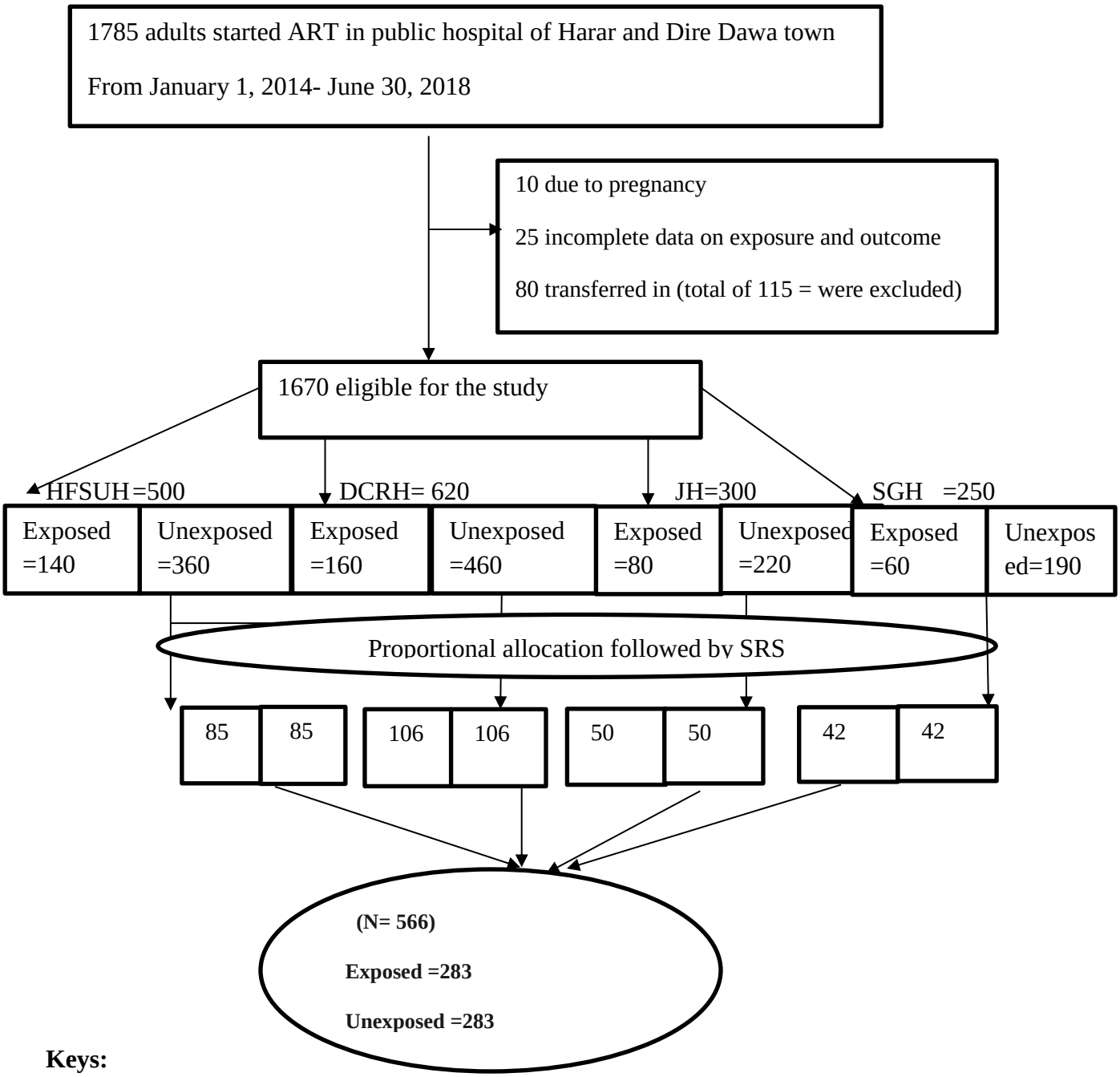
Patient with incomplete registration cards on date of TB diagnosis for exposed group and date of death for both exposed and non-exposed, who started ART from other healthcare institutions (transferred in) and pregnant mother at ART initiation were excluded from the study.

3.6. Sample Size Determination

Sample size was calculated by Stata using sample sizes for Cox PH regression, assuming 95% confidence interval, Power =80, α =0.05, β = 0.2 and by considering 20% loss to follow up, by taking the overall probability of event 0.1 and AHR of 2.3 from the study conducted in Ethiopia, Somali Region (Damtew et al., 2014). Finally minimum sample sizes of 566 patients were included in the study which means 283 in exposed and 283 in non-exposed group.

3.7. Sampling Procedure

All public hospitals in Harar and Dire Dawa town were included. From January 1, 2014 to June 30, 2018, 1785 adults initiated ART in public hospitals of Harar and Dire Dawa town, Hiwot Fana specialized university hospital (30%), and Dil Chora referral hospital (37%), Jugol hospital (18%) and Sabian hospital (15%). Latter 115 patient cards were excluded due to eligibility criteria. Human immunodeficiency virus infected patients was categorized based on their TB status. Proportional allocation followed by simple random sampling was applied to select to select TB co-infected and not TB co-infected from each hospital (**Fig: 2).**



Keys:

HFSUH: Hiwot Fana Specialized University Hospital JH: Jugol Hospital

SGH: Sabian General Hospital DCRH: Dil Chora Referral Hospital

SRS: Simple Random Sampling

Figure 2 Schematic presentation of sampling procedure on effect of tuberculosis on survival HIV infected adults initiated ART from public hospitals of Harar and Dire Dawa town, eastern Ethiopia, March 1-15, 2019

3.8. Data collection methods

3.8.1. Data collection tools

In this study, for the purpose of collecting the required study data, a data collection instrument was developed by the principal investigator based on the standardized national ART entry and follow up form employed by the ART clinic and literature reviewed. All ART registration, lab requests, follow-up forms, ART intake forms, and patient cards was reviewed using data collection tool prepared for this purpose.

3.8.2. Data collectors and collection procedures

Data was extracted by eight nurses who work in ART clinics and supervised by two BSc nurses. All profiles of HIV infected patients between January 1, 2014 and June, 30 2018; lab requests, follow-up forms, ART intake forms, and patient cards were reviewed. If there were no laboratory tests at ART initiation, results obtained within one month of ART initiation were used as baseline. The patients' date of death was extracted from ART follow up registration form and from patient death summary sheet for hospital death.

3.9. Variable

3.9.1. Dependent variable

Time to death from all-causes during follow up time.

3.9.2. Independent variable

Socio-demographic characteristics

Age, Sex, Place of residence, marital status, Educational status and Occupation.

Clinical and treatment related characteristics

WHO clinical stage, CD4 count level, Hemoglobin level, Adherence to ART, TB co-infection status, co-trim oxazole prophylaxis status, BMI, functional status and opportunistic infection other than TB .

3.10. Operational Definition

Event; All-cause mortality ascertained from death certificates if patients died in hospital and from ART registration reported through phone calling by adherence supporters (Fekade et al., 2017 ;Reepalu et al., 2017 ; Chu et al., 2013).

Censor: patient was censored on their last visit if they lost to follow up, date of transfer for transferred out or at the end of the study (on December 31, 2018) if they still alive.

Time scale: the survival time was calculated in months using the time between the dates of treatment initiation and the date of the event (death) or date of censoring. The maximum and the minimum follow up will be 60 months and 6 months respectively.

TB co-infection; was any confirmed active tuberculosis of at ART initiation or within first three months of ART initiation (Chang et al., 2015;Reepalu et al., 2017). Tuberculosis (pulmonary as well as extra pulmonary) (1) definitive: diagnosed through (Gen Xpert test, acid fast bacteria in sputum or body fluid/tissue by microscopy or culture positive for Mycobacterium tuberculosis or chest radiography) (2) presumptive: clinically suggested TB and initiated anti-TB was considered as the main exposure.

Adherence to ART: Adherence to ART was evaluated by the percentage of missed doses documented by the ART physician and ranked as good (if <5% (<2 doses of 30 doses or <3 dose of 60 doses), fair (if between 5−15% (3-5 doses of 30 doses or 3−9 doses of 60 doses) or poor (if >15% (>6 doses of 30 doses or >9 dose of 60 dose) as documented by ART physician (Damtew et al., 2014)

Initiation of cotrimoxazole prophylactic therapy; patient who have taken co-trim oxazole for longer than 1 month for a prophylaxis purpose (Ahmed et al., 2018)

Patient functional status;

Working “able to perform usual work in or out of the house” ;
Being ambulatory patient - “able to perform activities of daily living

Being bedridden patient -“not able to perform activities of daily living” (Damtew et al., 2014)

WHO staging of AIDS (Annex I)

3.11. Data Quality Control

To ensure data quality training was provided for data extractor and supervisors. Two BSc nurses who trained on ART were recruited to provide continuous supervision and monitoring. Supervisors, data clerks and investigator were checked completeness and consistency of data before and after data entry. Moreover double data entry was performed to prevent data entry error.

3.12. Methods of data analysis

Completed questionnaire were coded and entered to Epi Data version 3.1 computer program and Stata version 14.2 was used for analysis. Data was cleaned and edited by simple frequencies and cross tabulation before analysis. The clinical and demographic characteristic of the HIV cohort with and without TB coinfection was described. Mean (with standard deviation), median (with inter quartile range [IQR]) and frequencies (as percentages) were used to describe patients' characteristics at baseline. Chi-square test (Fisher's exact) and T- test was used to compare categorical and continuous variables between the two cohorts respectively. Survival time was calculated from date of ART initiated to death among HIV patients initiated ART from January 1, 2014 to June, 30 2018 and retrospectively followed for additional six months until December 31, 2018. Patient exited on last follow up date if patient loss to follow up or transferred out and December 31, 2018 if patient is still alive or date of death if patient was dead. The Kaplan-Meier test was used to estimate the probability of death and the median time to death among HIV patients co-infected with TB and patients not co-infected with TB at initiation of ART. The log-rank test was used to compare the median time to death between patient with TB and without TB. Life table was used to calculate the cumulative survival probability of the cohorts. Cox proportional hazard model fitness was checked using schoenfield residuals test and graphically and the result showed that none of the predictors violated the proportional hazard assumption. Multicollinearity was checked (VIF < 10) indicating non-existence of multicollinearity among the variables in this study. Crude hazard ratio test was used for inclusion of variables into multivariable analysis with cut off p-value ≤ 0.20 and by this cut off value eight variable were included in multivariable analysis. The multivariable model was built using backward elimination method of variable selection and confounding was checked and percentage change in the regression coefficients (β) less than 20% reveals absence of confounder (Hosmer Jr et al., 2008). Cox proportional hazard model was used to identify factors associated with mortality and p-value < 0.05 declares the significance of the variables at 95% confidence level.

3.13. Ethical considerations

Ethical clearance was obtained from Institutional Health Research Ethical Review Committee of Haramaya University College of health and medical science. Following the approval official letter of cooperation was written to public hospitals of Harar and Dire Dawa town. Informed voluntary written and signed consent was obtained from medical directors of the Hiwot Fana specialized university hospital, Jugol hospital, Dil Chora referral hospital and Sabian hospital. To preserve patient confidentiality nurses working in the ART clinics were extracted the data from patient's medical records at each hospital. Moreover, no personal identifiers were used on the data collection form

3.14. Information Dissemination

First the result of this study will be submitted and presented to Haramaya University and later the findings of this study will be disseminated to Harari regional health bureau, Dire Dawa city health bureau, Hiwot Fana specialized Haramaya university hospital, Jugol hospital, Dil Chora referral hospital and finally the finding will be published to reach the scientific community

4. RESULT

4.1. Socio-Demographic Characteristics of the participants.

A total of 566 HIV infected patients (283'TB co-infected' and 283 'Not TB co-infected' cohorts) were followed retrospectively for a median of 18.8 months with (IQR =7.0 - 36.3) months in TB co-infected and 24.3 months (IQR = 13.7 - 40.2) months among not TB co-infected cohorts. Both cohorts were statistically different for place of residence (X^2 =8.955; df (1) p = 0.003), sex (X^2 =8.784; df (1) p =0.003) and occupation (X^2 =25.083; df (6) p = 0.001) attribute of the socio-demography. Majority of study subjects were urban resident 238(84.1%) and 261(92.2%) in TB co-infected and not TB co-infected cohorts respectively. The median age of study subjects was 35 years with inter-quartile range (IQR) 28-42years and 34 with IQR 28-40 years in TB co-infected cohorts and not TB co-infected patients respectively.

Among patients with TB 139 (49.1%) were female, whereas among not TB co-infected, female accounted for 176 (62.2%). In both cohorts majority of patients were orthodox; 147 (52%) and 164(58.7%) in TB co-infected and not TB co-infected respectively. Majority of study subjects were married in both cohorts; 115(40.6%) and 128(45.2%) in TB co-infected and not TB co-infected respectively. In both cohorts majority of the patients were in primary level of education 112(40.1%) and 103(37%) in TB co-infected and not TB co-infected respectively. Majority of the study subjects were jobless in both cohorts 117(41.3%) and 118(41.8%) in TB co-infected and not TB co-infected respectively **(Table: 1)**.

Table 1 Sociodemographic characteristics of the study participants initiated ART in public hospitals of Harar and Dire Dawa town, 2019, N = 566

Variables	Categories	TB co-infected	Not TB co-infected	X^2 Value (df)	p-value
Residence	Urban	238(84.1%)	261(92.2%)	8.955	**0.003**
	Rural	45(15.9%)	22(7.8%)	(1)	
Age	Mean **(** ± SD)	35 ± 10	35.13 ± 10.92	♦ - 0.116	0. 907
	Median **(** IQR)	35(28-42)	34(28-40)		
Sex	Male	144 (50.9%)	107 (37.3%)	8.784	**0.003**
	Female	139 (49.1%)	176 (62.2%)		
Religion	Muslim	113 (40%)	87(30.7%)	5.897	0.117
	Orthodox	147 (52%)	164(58.7%)	(3)	
	Protestant	20 (7%)	24(8.5%)		
	Other [4,5]	3 (1%)	6(2.1%)		
Marital status	Married	115(40.6%)	128(45.2%)	5.664	0.226
	Never married	71(25.1%)	50(17.7%)	(4)	
	Divorced	55(19.4%)	54(19.1%)		
	Widowed	33(11.7%)	37(13%)		
	Separated	9 (3.2%)	14(5%)		

Level of education	No formal education	68(24.4%)	55(19.8%)	3.765	0.288
	Primary	112(40.1%)	103(37%)	(3)	
	Secondary	69(24.7%)	84(30.2%)		
	Tertiary and above	30(10.8%)	36(13%)		
Occupation	Merchant	43(15.2%)	38(13.5%)	25.083	**0.001**
	Government employee	30(10.6%)	59(20.9%)	(7)	
	Non-governmental employee	16(5.7%)	6(2.1%)		
	Day laborer	39(13.8%)	31(11%)		
	Driver	8(2.8%)	12(4.3%)		
	Farmer	18(6.4%)	4(1.4%)		
	Jobless	117(41.3%)	118(41.8%)		
	Other [1,2,3]	12(4.2%)	14(5%)		

4 Catholic 5 Adventist 1 student 2 housewife 3 commercial sex worker ♦ T – test statistics used for two independent samples.

4.2. Baseline Clinical and immunological characteristics

In this study there was statistical difference on WHO clinical stage(X^2 =230.367; df (2) p<0.001) between the two cohorts**.** Majority of TB co-infected group patients were in WHO clinical stage III at ART initiation 202(71.4%) and among cohort without TB only 69(24.4%) were in WHO clinical stage III. Both cohorts were also statistically different on functional status (X^2 =53.430; df (2) p<0.001) and BMI level (X^2 =41.798; df (2) p<0.001).

The median hemoglobin level showed statistical difference (T= -5.453; p<0.001). The median hemoglobin level of study subjects was 11.4g/dl with inter-quartile range (IQR) 9.7-13.3g/dl and 12.6 g/dl with IQR 11- 14.4g/dl in patient with TB and without TB respectively. Study subjects in TB co-infected cohort had lower CD4 count (T= -8.475; p<0.001), with median of 137 cells/mm3and IQR 69 – 262 cells/mm3 than no TB co-infected cohort with median of 304 cells/mm3 and IQR 137 – 489 cells/mm3. The result showed that TB co-infected and not TB co-infected were also statistically different on cotrimoxazole prophylaxis status (X^2 =7.524; df (1) p=0.006) and adherence to ART (X^2 =6.015; df (2) p=0.049).

Majority patients had at least one episode of opportunistic illness in the past, 156 (55.1%) of them were from TB co-infected and 126 (42.86%) were from not TB co-infected group (X^2 =16.824; df (1) p<0.001)**.** Almost all of the study subjects (99%) were initiated ART with (TDF+3TC+EFV). During the follow up period, 76 (13.4%) patients were deceased, thirty six patients (6.4%) patients were transferred to other facilities and 46 (8.1%) were lost-to follow up. The remaining 408 (72.1%) were active until the last censoring date. **(Table 2)**

Table 2 Base line Clinical and immunologic characteristics of the study participants of the study participants initiated ART in public hospitals of Harar and Dire Dawa town, 2019, N = 566

Variables	Categories	TB co-infected	Not TB co-infected	X^2 Value (df)	p-value
WHO clinical stage	Stage I/II	13(4.6%)	185(65.4%)	230.367	< 0.001
	Stage III	202(71.4%)	69(24.4%)	(2)	
	Stage IV	68(24%)	29(10.3%)		
BMI	<16kg/m^2	66 (23.4%)	29(10.4%)	41.798	< 0.001
	16-18.5kg/m^2	105 (37.2%)	66(23.6%)		
	>= 18.5kg/m^2	111(39.4%)	185(66%)		
Functional status	Working	140(49.5%)	221(78.1%)	53.430	< 0.001
	Ambulatory	96(33.9%)	50(17.7 %)	(2)	
	Bedridden	47(16.6%)	12(4.2%)		
Hemoglobin	Mean (± SD)	11.3 ± 2.46	12.5 ± 2.52	♦ -5.453	< 0.001
	Median (IQR)	11.4(9.7 – 13.2)	12.6 (11- 14.4)		
CD4 count level in cells/mm3 (n=552)	Mean (± SD)	189.8 ± 178.2	352.9 ± 265.6	♦ -8.475	< 0.001
	Median (IQR)	137(69 – 262)	304(137 – 489)		
Initial ART regimen	1c=AZT+ 3TC + NVP	4 (1.4%)	5 (1.8%)	○	0.395
	1d=AZT+ 3TC + EFV	1 (0.4%)	3 (1%)		
	1e=TDF + 3TC + EFV	276 (97.4%)	271 (95.8%)		
	1f=TDF + 3TC + NVP	1(0.4%)	3 (1%)		

	1g=ABC_+3TC_+EFV	1(0.4%)	1(0.4%)		
ART adherence	Good	229 (82.1%)	250 (88.7%)	6.015	0.049
	Fair	13(4.7%)	12 (4.3%)	(2)	
	Poor	37(13.3%)	20 (7%)		
Cotrimoxazole prophylaxis	Yes	257(90.8%)	235(83%)	7.524	0.006
	No	26(9.2%)	48(17%)	(1)	
OPI other than TB	Yes	156(55.1%)	203(71.7%)	16.824	< 0.001
	No	127(44.9%)	80(28.3%)	(1)	
Follow-up outcome	Dead	60(21.2%)	16(5.7%)	31.468	< 0.001
	Transferred out	18(6.4%)	18(6.4%)	(3)	
	Loss to follow up	25(8.8%)	21(7.4%)		
	Alive / On treatment	180(63.6%)	228(80.6%)		

♦ – Test statistics used for two independent samples. ○ Fisher's exact test

4.3. Comparison of survival based on TB co-infection status.

There were 76 (13.4%) deaths in this study cohort with majority of deaths 50 (65.7%) occurring in the first 6 months. All the study subjects (566) had contributed a total of 13910.8 person months; 6455.8 person months in TB co-infected cohort and 7455 person months in not TB co-infected respectively. In this study more patients died among TB co-infected 60(21.2%) than not TB co-infected patients 16(5.6%) with overall mortality rate of 6.55 per 100 PY of follow up (95% CI: 5.28, 8.16 per 100 PYO). The incidence of death in TB co-infected cohorts was 11.04 per 100 PY follow up (95% CI: 8.64, 13.2 per 100 PY) and 2.52 per 100 PY follow up (95% CI: 1.56, 4.2 per 100 PY) in not TB co-infected cohorts.

The median time to death during follow-up has shown variation between the two groups. The median time to death was 2.5 months and 12.2 months in TB co-infected cohort and not TB co-infected cohort respectively. Based on actuarial life table analysis the estimated survival probability of the whole cohort at 6, 12, 24, 36, 48 and 60 months was 91%, 89.4%, 86.2%, 84.6%, 84.6% and 80%, respectively. The survival probability at 1 year of ART initiation was 81.6% (95% CI: 76.4% to 85.7%) and 97 %(95% CI: 94.1% to 98.5%) among those with TB and without TB respectively. The cumulative survival probability at 60 months of follow-up was approximately 69% (95% CI: 57% - 78.9%) in TB co-infected and 93% (88.5% -95.6%) among not TB co-infected groups. (**Table: 3**)

Table 3Actuarial life table analysis of TB co-infected and not TB co-infected patients initiated ART in public hospital of Harar and Dire Dawa town, eastern Ethiopia, 2019 (N= 566)

TB status	Time Interval in months	Number entering the interval	Number withdrawing during interval	Number of death	Cumulative Probability of not developing death
TB co-infected	0-6	283	17	44	**0.84**
	6-12	222	43	5	**0.82**
	12-24	174	47	5	**0.79**
	24-36	122	47	4	**0.76**
	36-48	71	32	0	**0.76**
	48-60	39	37	2	**0.69**
Not TB co-infected	0-6	283	5	5	**0.98**
	6-12	273	44	3	**0.97**
	12-24	226	73	8	**0.93**
	24-36	145	61	0	**0.93**
	36-48	84	53	0	**0.93**
	48-60	31	31	0	**0.93**

The Kaplan-Meier analysis and the log-rank test were used to compare survival probabilities of the two groups. Survival probability in the TB co-infected was significantly lower than not TB co-infected group throughout the study period (log rank statistic = 31.01, df =1, P < 0.001). **(Fig: 3, Fig: 4).** In addition to TB, functional status (Log rank, p<0.001, adherence to ART (Log rank, p = 0.028),, WHO clinical stages (Log rank, p<0.001), BMI (Log rank, p<0.001), CD4 count (Log rank, p<0.001) and opportunistic infection other than TB (Log rank, p<0.001), were variables that showed the significant association with the survival of patients on ART with Log rank test.

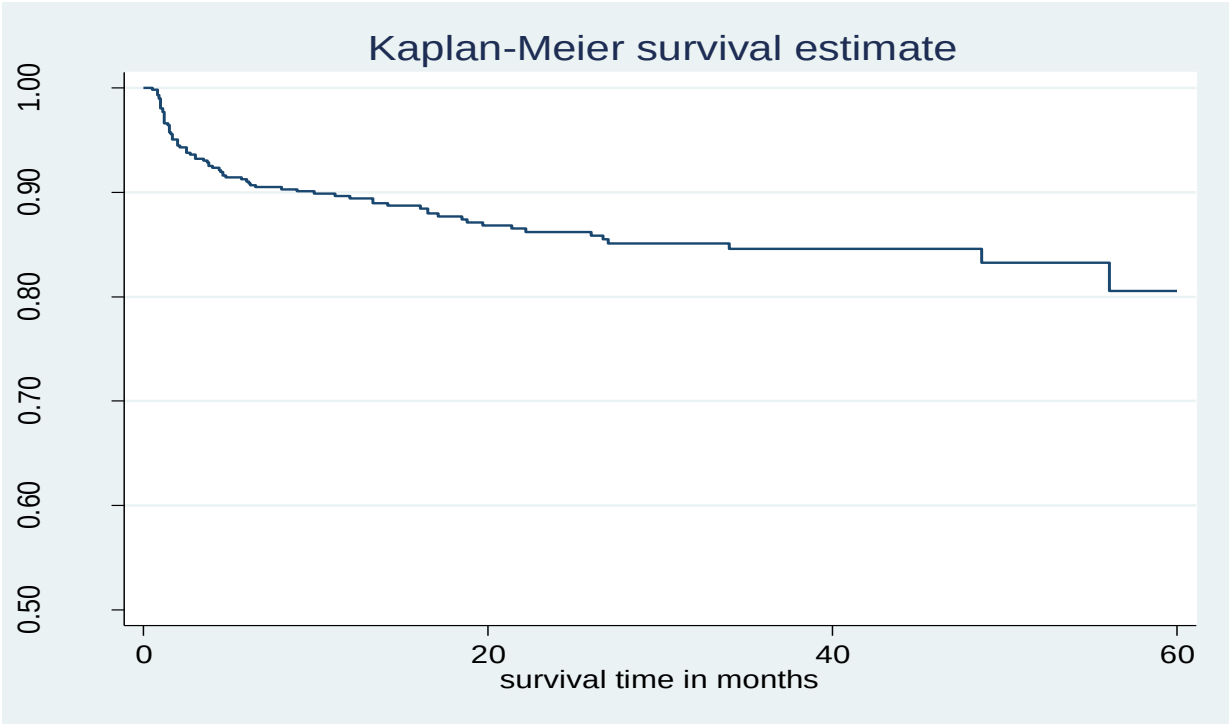


Figure 3 Kaplan-Meier estimate of overall survival probability among HIV infected patients initiated ART in public hospitals of Harar and Dire Dawa town, 2019.

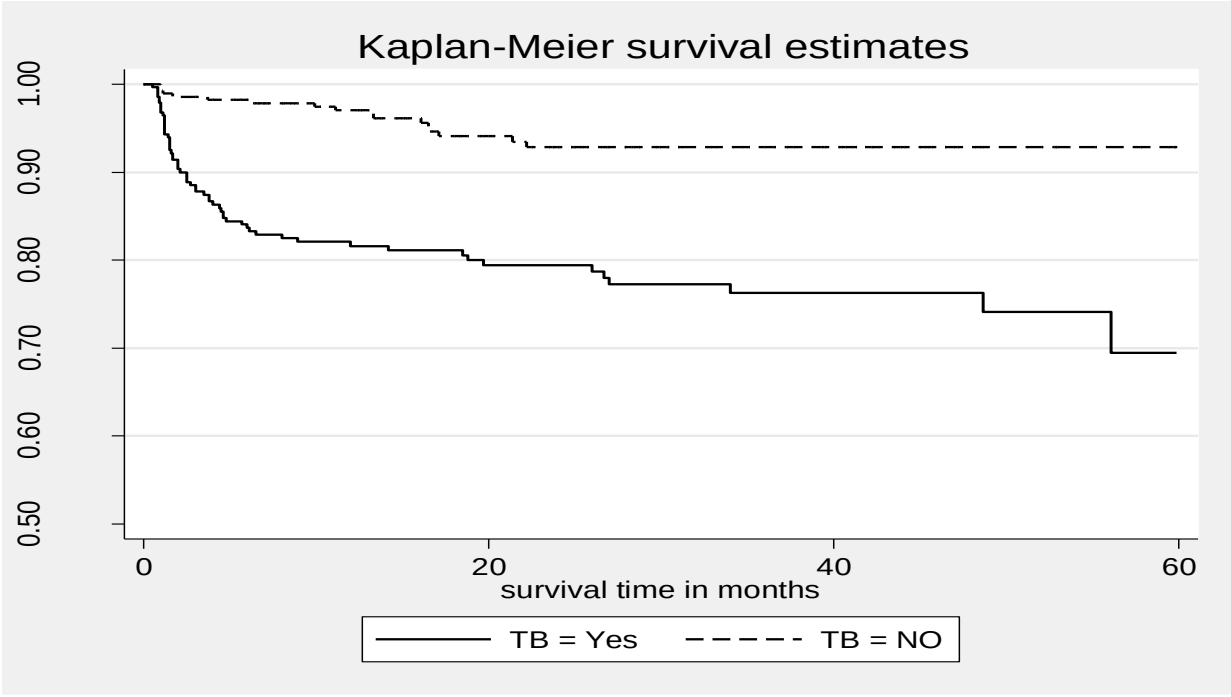


Figure 4Kaplan-Meier estimate of survival probability among TB co-infected and not TB co-infected HIV patients initiated ART in public hospitals of Harar and Dire Dawa town, 2019

4.4. Predictors of mortality

In bivariate Cox regression analysis, TB co-infection increase the hazard of death approximately by four folds (HR: 4.22 95% CI; 2.43-7.32) when compared to not TB co-infected. Patient functional status, WHO clinical stage, BMI, CD4 count, ART adherence and past opportunistic infection other than TB were all associated with mortality on bivariate cox regression ($P < 0.05$) (**Table: 4**).

Table 4Results of the bivariate Cox regression analysis of mortality in HIV infected patients initiated ART in public hospitals of Harar and Dire Dawa town, 2019 (N=566)

Variable	Categories	Survival status		Crude HR	95% CI	P –value
		Dead	Censored			
TB co-infection	Yes	60 (79%)	223 (45.5%)	4.22	(2.43, 7.32)	<0.001
	No	16 (21%)	267 (54.5%)	(1)		
Age	15-24	12 (15.8%)	61 (12.5%)	(1)		
	25-34	26 (24.2%)	187 (33.1%)	0.74	(0.38 , 1.48)	0.400
	35-44	18 (23.7%)	143 (30.2%)	0.65	(0.31 , 1.35)	0.250
	>=45	20 (26.3%)	94 (19.2%)	1.1	(0.53 , 2.21)	0.830
Sex	Male	40(52.6%)	209 (42.6%)	1.45	(0.93 , 2.28)	0.101
	Female	36(47.4%)	281 (57.4%)	(1)		
Residence	Urban	64(84.2%)	435(88.8%)	(1)		
	Rural	12(15.8%)	56(11.2%)	1.4	(0.75, 2.58)	0.290
Marital status	Married	28 (36.8%)	215 (43.9%)	(1)		
	Never married	22 (29%)	99 (20.2%)	1.69	(0.96, 2.94)	0.268
	Divorced	16 (21%)	98 (19%)	1.38	(0.75, 2.55)	0.304
	Widowed	6 (7.9%)	64 (13.2%)	0.71	(0.32, 1.87)	0.573
	Separated	4 (5.3%)	19 (3.9%)	1.49	(0.52, 4.25)	0.455

Level of education	No formal education	21 (28%)	102 (21.2%)	1.20	(0.56, 2.56)	0.620
	Primary	23 (30.7%)	192 (39.8%)	0.69	(0.33, 1.46)	0.344
	Secondary	21 (28%)	132 (27.4%)	0.88	(0.42, 1.88)	0.752
	Tertiary and above	10 (13.3%)	56 (11.6%)	(1)		
Occupation	Have a job	43 (56.6%)	287 (58.7%)	(1)		
	Jobless	33 (43.4%)	202 (41.3%)	1.07	(0.68 , 1.68)	0.778
WHO clinical stage	Stage I/II	7 (9.2%)	191 (39%)	(1)		
	Stage III	42 (56.3%)	229 (46.7%)	4.79	(2.15, 10.66)	<0.001
	Stage IV	27 (35.6%)	70 (14.3%)	9.26	(4.03, 21.28)	<0.001
BMI(n=562)	<18.5 kg/m2	49 (66.2%)	228 (46.3%)	2.21	(1.37, 3.58)	0.001
	>= 18.5kg/m2	25 (33.8%)	260 (53.3%)	(1)		
Functional status	Working	36 (47.3%)	325 (66.3%)	(1)		
	Ambulatory	20 (26.3%)	126 (25.7%)	1.47	(0.85, 2.54)	0.164
	Bedridden	20(26.3%)	39 (8%)	4.40	(2.55, 7.62)	<0.001
Hemoglobin (515)	<11g/dl	27 (40.9%)	141 (31.4%)	1.48	(0.91, 2.43)	0.112
	>= 11g/dl	39 (59.1%)	308 (68.6%)	(1)		
CD4 count level in cells/mm3 (n=552)	< 50	23 (30.7%)	49 (10.2%)	6.23	(3.39, 11.46)	<0.001
	50-199	33 (44%)	160 (33.5%)	2.86	(1.63, 5.04	<0.001
	>= 200	19 (25.3%)	268 (56.2%)	(1)		
ART adherence	Good	58 (77.3%)	421 (86.6%)	(1)		
	Fair	5 (6.7%)	20 (4.1%)	1.73	(0.69, 4.32)	0.239
	Poor	12 (16%)	45 (9.3%)	2.18	(1.17, 4.07)	0.014
Cotrimoxazole prophylaxis	Yes	68 (89.5%)	424 (86.5%)	(1)		
	No	8 (10.5%)	66 (13.5%)	1.21	(0.58, 2.52)	0.606
OPI other than TB	Yes	43 (56.4%)	164 (33.5%)	2.45	(1.56, 3.86)	<0.001
	No	33 (43.4%)	326 (66.5%)	(1)		

In multivariable Cox regression analysis, HIV patients with TB at ART initiation increase the hazard of death approximately by two folds (AHR 2.19: 95% CI 1.17, 4.12) when compared to those without TB, after adjusting for WHO clinical stage, past opportunistic illness other than TB and CD4 cell count. Individual with baseline WHO clinical stage IV had nearly three times (AHR 3.06 95% CI: 1.16, 8.09) higher hazard of death when compared to those in WHO clinical stage (I/II). Patients with CD4 count less than 50 cells/mm3 at ART initiation had higher hazard of death by 3.7 times (AHR 3.75: 95% CI: 2.00, 7.03) when compared to those in CD4 count greater than 200 cells/mm3. Presence of at least one opportunistic infection other than TB also increase the hazard of death by 65% (AHR 1.65 95% CI: 1.01, 2.68) compared to those without opportunistic infection other than TB **(Table: 5).**

Table 5 Results of the multivariable Cox regression analysis of mortality in HIV infected patients initiated ART in public hospitals of Harar and Dire Dawa town, 2019 (N= 566)

Variable	Categories	Survival status		Crude HR	Adjusted HR
		Dead	Censored		
TB co-infection	Yes	60 (79%)	223 (45.5%)	4.22(2.43, 7.32)	**2.19 (1.17, 4.12)***
	No	16 (21%)	267 (54.5%)	(1)	
Sex	Male	40(52.6%)	209 (42.6%)	1.45 (0.93 ,2.28)	1.41 (0.87, 2.27)
	Female	36(47.4%)	281 (57.4%)	(1)	
WHO clinical stage	Stage I/II	7 (9.2%)	191 (39%)	(1)	
	Stage III	42 (56.3%)	229 (46.7%)	4.79(2.15,10.66)	1.80 (0.72, 4.52)
	Stage IV	27 (35.6%)	70 (14.3%)	9.26(4.03,21.28)	**3.06 (1.16, 8.09)***
BMI(n=562)	<18.5 kg/m2	49 (66.2%)	228 (46.3%)	2.21 (1.37, 3.58)	1.54 (0.93, 2.55)
	>= 18.5kg/m2	25 (33.8%)	260 (53.3%)	(1)	
Functional status	Working	36 (47.3%)	325 (66.3%)	(1)	
	Ambulatory	20 (26.3%)	126 (25.7%)	1.47(0.85 , 2.54)	0.79 (0.44-1.42)
	Bedridden	20(26.3%)	39 (8%)	4.40 (2.55, 7.62)	1.70 (0.90, 3.23)

CD4 count level in cells/mm3 (n=552)	< 50	23 (30.7%)	49 (10.2%)	6.23(3.39,11.46)	**3.75 (2.00, 7.03)*** **
	50-199	33 (44%)	160 (33.5%)	2.86(1.63, 5.04)	1.78 (0.99, 3.19)
	>= 200	19 (25.3%)	268 (56.2%)	(1)	
ART adherence	Good	58 (77.3%)	421 (86.6%)	(1)	
	Fair	5 (6.7%)	20 (4.1%)	1.73(0.69 , 4.32)	2.08 (0.79, 5.44)
	Poor	12 (16%)	45 (9.3%)	2.18(1.17 , 4.07)	1.60 (0.84, 3.03)
OPI other than TB	Yes	43 (56.4%)	164 (33.5%)	2.45(1.56, 3.86)	**1.65 (1.01, 2.68)***
	No	33 (43.4%)	326 (66.5%)	(1)	

*p-value<0.05 ** p-value <0.01 *** p-value <0.001

5. DISCUSSION

In this study, the overall mortality rate was 6.55 per 100 PY and the majority of deaths (65.7%) were occurred in the first six months of ART initiation. The mortality rate was 11.04 /100 PY and 2.52/100 PY in TB co-infected and not TB co-infected cohorts respectively. The estimated survival probability of the whole cohort at the end of follow-up was 80% and survival probability at 1 year of ART initiation was 81.6% and 97 % among those with TB and without TB respectively. This study showed that being TB co-infected at ART initiation increase the hazard of overall mortality approximately by two folds, after controlling for potential baseline confounders. Additionally, advanced disease stage (WHO clinical stage IV), CD4 counts less than 50 cells/mm3 and past opportunistic infection other than TB were independent predictors of mortality.

In the current study the overall mortality rate was 6.55 per 100 PY in the entire follow-up period. This finding was comparable with the study conducted in Ethiopia (Fekade et al., 2017 ; Damtew et al., 2014), but other studies conducted in Africa, including Ethiopia revealed that the mortality rate were smaller than this finding (Tachbele and Ameni, 2016 ; Biadgilign et al., 2012 : Mageda et al., 2012). This difference may be due to the fact that, in this study over 65% of study participants were started antiretroviral therapy while at the WHO stage III or IV of the disease severity and small number of TB co-infected patients in latter studies.

Mortality rate among TB co-infected and those without TB was 11.04/100PYO and 2.52/PYO respectively. This finding showed higher mortality rate among TB co-infected cohorts when compared to another study conducted in South Africa (Gupta et al., 2013), in which mortality rate among TB prevalent patients on ART were 4.84/100PYO. This difference might be due to the country has made robust efforts to tackle the two diseases simultaneously and stipulated integration of HIV and TB services nationwide, by the co-location of services.

In this study, the estimated survival probability of the cohort at the end of follow-up was 80%, and majority of death were occurred in the first six months of ART initiation (65.7%). The survival probability at 1 year of ART initiation was 81.6% and 97 % among those with TB and without TB respectively. This survival probability is lower than study conducted in Somali region in which overall survival probability were 85.9% (Damtew et al., 2014). This difference may be due to less follow up time and higher loss to follow up in the latter study. On the other hand, the death rate in first six months was comparable to retrospective cohort studies conducted in Ethiopia (Fekade et al., 2017 ; Damtew et al., 2014). Current study revealed that, one year survival probability of TB co-infected is lower than those without TB. This finding is in agreement with retrospective cohort study conducted in the united kingdom (Zenner et al., 2015).

This study showed that being TB co-infected at ART initiation increase the hazard of overall mortality approximately by two folds, after controlling for potential baseline confounder. This finding is consistent with other studies conducted in the USA, United Kingdom, Uganda and Ethiopia (López-Gatell et al., 2008 ; Zenner et al., 2015 ; Chu et al., 2013 ; Damtew et al., 2014 ; Setegn et al., 2015 ; Tadege, 2018). This finding is in contrary to study conducted in South Africa and Ethiopia indicating that active TB at ART initiation was uncorrelated to the overall survival of HIV infected patients, after adjusting for multiple confounders (Westreich et al., 2009 ; Reepalu et al., 2017). This difference might be due to variation in study setting and level of care given. The country has also provided integrated HIV/TB services for people in correctional facilities, the communities surrounding industry and community-based TB/HIV screening and early linkage to care where transmission of both HIV and TB is high. Moreover the difference might be due to small number of TB co-infected patients participated in latter study.

This study showed that patients presenting with advanced disease stage (WHO clinical stage IV) are associated with higher hazard of death nearly three times as compared to patients with not in advanced disease stage (WHO clinical stage I and II). The result was in agreement with study conducted in Tanzania (Mageda et al., 2012) and several studies conducted in Ethiopia (Abebe et al., 2014 ; Tachbele and Ameni, 2016 ; Damtew et al., 2014 ; Digaffe et al., 2014). This might be due to the fact that HIV weakens the immune system and leads to more opportunistic infections are likely to occur which adversely affect survival of the HIV patients.

In this study, among the independent predictors, having lower CD4 count was associated with increased relative hazard of death. The hazard of death increased nearly by four folds among patients with CD4 count less than 50 cells/mm3 when compared to patient with CD4 count >=200 cells/mm3. This result is consistent with several cohort studies conducted in Ethiopia (Tadesse et al., 2014 ; Damtew et al., 2014 ;Digaffe et al., 2014). This might be due to the fact that late ART initiation is pervasive problem in sub-Saharan Africa, which faster prognosis of disease and increase opportunistic infection (Lahuerta et al., 2013)

In the present study patients who suffered from opportunistic infection other than TB had 65% higher hazard of death as compared to those free of the infections in the past. This effect is smaller when compared to the study conducted in United Kingdom which showed that having other opportunistic infection in past increased the hazard of death by 7.4 folds (Zenner et al., 2015). This difference might be due to difference in base line exposure to ART, in this study patient followed after ART initiation while in the latter study follow up of patients were started from HIV diagnosis.

6. STRENGTH AND LIMITATIONS

6.1. Strength

This is one of the few studies in Ethiopia that explored effect tuberculosis on survival of HIV patients in ART era. Since this study was time to event analysis it enables us to consider contribution of censored study subjects.

6.2. Limitation

This study had some limitations. First, uncontrolled confounding can never be fully excluded in observational cohort studies. Although deaths ascertained from patient death certificate and through telephone by ART adherence supporters reported as all deaths were due to illness and not attributable to accidents or other unnatural causes, cause-specific mortality was not reported because of unavailability of data on cause of death. This may slightly overestimate the mortality rate. Factors such as patient social condition are incomplete for most patients, therefore not included in the analysis. Exclusion of patients who transferred out may slightly create bias in this result.

7. CONCLUSION AND RECOMMENDATION

7.1. Conclusion

This study demonstrated high rates of mortality among HIV patients co-infected with TB (11.04/100PY) when compared to patients not co-infected with tuberculosis (2.52/100PY). Having active TB at ART initiation increase the hazard of death nearly by two folds, in HIV-infected patients initiated ART in public hospitals of Harar and Dire Dawa town, after adjusting for potential confounders. The study also revealed that, advanced clinical WHO stage (stage IV), low CD4+ cell count (<50 cells/mm3) and past episode of opportunistic illness, were independent predictors of mortality.

7.2. Recommendation

Public hospitals of Harar and Dire Dawa town should need to strengthen efforts for early detection and intervention for both HIV and TB.

The health care providers in Harar and Dire Dawa town health facilities should need to provide counselling on benefit HIV testing for all persons attending the health facility, to reduce the burden of late ART initiation.

Health personnel and data clerks in the ART clinic should be supported to properly record information especially on patient social condition.

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9. APPENDICES

Appendix A: Information sheet and informed consent for health facilities medical director/CEO

My name is ---------- I am working as a data collector for the study being conducted in this health facility by Tadesse Sime who is studying masters' degree of public health in epidemiology at Haramaya University College of health and medical sciences. I kindly request you to lend me your attention; explain about the study and your health facility being selected as the study participant

The study title

Effect of tuberculosis on survival HIV infected patients initiated ART in public hospital of Harar and Dire Dawa, eastern Ethiopia.

Purpose of the study

The study will be conducted through collection of secondary data already collected on patients follow up card and ART register and the aim of the study is to determine the effect of TB co-infection on survival of HIV patients initiated ART in selected public hospitals of Harar and Dire Dawa, eastern Ethiopia.

Data collection procedure and duration

Data will be collected from randomly selected patients based on their medical record number and information will be gathered from patient's medical card, ART follow up card and ART register and it may take 30 to 50 min to collect data for single patient.

Risk and benefit of the study

The risk of collecting information in this way is very minimal, but the finding from this study will contribute to the body of knowledge that informs the hospital and zonal/regional TB-HIV program planers and decision makers by providing effect of tuberculosis co-infection among HIV infected adults receiving ART in public hospitals of Harar and Dire Dawa, eastern Ethiopia.

Confidentiality

The information collected in the way explained above will be confidential. There will be no information to be collected on particular study subject identification. The nurse who work on ART clinic of the facility will be selected for data collection to preserve patient confidentiality

Rights

Participation for this study is fully voluntary. You have the right to declare to participate or not to participate. Moreover, you have the right to withdraw from the study at any time.

Contact address

If there is any question or enquiries at any time about the study or procedure please contact the investigator;

Tadesse Sime: mobile phone; 0921211408.

Email address simetadesse2@gmail.com

Haramaya University Institutional Health Research Ethical Review Committee Office Phone number; 0254662011 P.O.Box 235, Harar, Ethiopia.

Declaration of informed voluntary consent

I have read the participant information sheet. I have clearly understood the purpose, procedure of the research, confidentiality and risk and benefit issue of this study I have been given the opportunity to ask questions for things that may have been unclear. I was informed that I have the right to decide a withdrawal from the study at any time. Therefore, I declare the facility I am responsible to participate in this study with my signature below.

Name and Signature of medical director /CEO---------- Date----------

Name and Signature of data collector---------- Date----------

Appendix B: Questionnaire

Q.NO. ---------- Name of hospital ----------

Name and signature of data collector---------- Date ----------

Section I: Socio-Demographic characteristics.

NO;	QUESTION	Coding and categories	REMARK
101	Age of the patient during ART initiation	_____	
102	Sex	1. Male 2. Female	
103	Religion	1. Muslim 2. Orthodox 3. Protestant 4. Others specify----------	
104	Place of residence	1) Urban 2) rural	
105	Current Marital status:	1. Married 2. Never married 3. Divorced 4. Widowed 5 Separated 9 Not recorded	
106	Educational status:	1. No formal education 2. Primary 3. Secondary 4. Tertiary 5. Other, specify---------- 9 Not recorded	
107	Occupation	----------	

Section II; Baseline Clinical and laboratory information

NO;	QUESTION	Coding and categories	REMARK
201	Patient weight	----------kg	
202	Height	----------cm	
203	Body mass index	----------kg/m^2	
204	Patient WHO clinical stage while initiating ART	1. Stage I 2. Stage II 3. Stage III 4. Stage IV 9.Not recorded	
205	Was the patient TB o-infected at ART initiation?	1. Yes 2. No	If 2 skip to 208
206	Type of tuberculosis the patients developed	1. Pulmonary tuberculosis 2. Extra pulmonary tuberculosis	If 2 or 9 skip to 208
207	Pulmonary tuberculosis	1. Smear positive 2. Smear negative	
208	Patient functional status	1. Working 2. Ambulatory 3. Bedridden 9 Not recorded	
209	Hemoglobin level in g/dl	----------	
210	CD4 count level in cells/mm3	----------	

211	Past opportunistic infections related to AIDS other than TB	1. Zoster 2. Bacterial pneumonia 3. Thrush(oral/vaginal) 4. Diarrhea (chronic/acute) 5. Pneumocystis pneumonia 6. Ulcers (mouth/genital) 7. Cryptococcus meningitis 8. Other (specify)…… 9. No OPI	

Section; III Anti-TB, ART and Prophylactic medication

NO;	Variable	Coding and categories	REMARK
301	Date ART started	_____/_____/__ dd/mm/yy E.C ------/------/----------dd/mm/yy G.C	
302	Was the patient co-infected with tuberculosis during follow up?	1. Yes 2. No	If 2 skip to 306
303	Date of TB diagnosis	_____/_____/__dd/mm/yy E.C ------/------/----------dd/mm/yy G.C	
304	Date of anti-TB initiation	_____/_____/__dd/mm/yy E.C ------/------/----------dd/mm/yy G.C	

305	Date of TB treatment completed	_____/_____/__dd/mm/yy E.C ------/------/----------dd/mm/yy G.C	
306	Initial ART regimen given	1. 1c=AZT+3TC+NVP 2. 1d= AZT+3TC+EFV 3. 1e= TDF+3TC+EFV 4. 1f= TDF+3TC+NVP 5. 1g=ABC+3TC+EFV 6. 1h=ABC+3TC+NVP 7. Other(specify)--------	
307	Regimen change during the follow up time	1. Yes 2. No	**If 2 skip to q.no 309**
308	Reason for regimen change	---------- ------	
309	Adherence to ART drug	1. Good 2. Fair 3. Poor 9 Not recoded	
310	Did the patient prescribed cotrimoxazole prophylactic therapy	1. yes 2. No	

Section IV: Patient's follow up information to be filled from ART register and patient card.

No.	VARIABLE	Coding and categories	REMARK
401	Patient last visit before December 31,2018	_____/____/_____ dd/mm/yy E.C ------/------/----------dd/mm/yy G.C	
402	Patient status on December 31,2018	1. Dead 2. Transferred out 3. Loss to follow up 4. Alive / On treatment	If 2 or 3 or 4 or 5 skip to next section
403	Date of death	____/_____/____ dd/mm/yy E.C ------/------/----------dd/mm/yy G.C	

Section V: Base line Social condition

NO;	Variable	Coding and categories	REMARK
501	HIV serostatus Disclosure	1. Husband/ wife 2. Own child 3. Parents 4. Brother /sister 5. Relative 6. Nobody knew 9. Not recorded	
502	Condition of husband/ wife	1. Health 2. Chronically ill 3. Dead 4. Unknown 5. Not recorded	If married
503	HIV status of husband or wife	1. Positive 2. Negative 3. Unknown 9. Not recorded	If positive
504	Was he/she on ART?	1.Yes 2. No	

Appendix C: WHO Staging System for HIV Infection and Disease in Adults and Adolescents

WHO Antiretroviral therapy for HIV infection in adults and adolescents. Geneva: (WHO; 2010)

Clinical Stage	Clinical Description	Performance Scale
I	Asymptomatic Persistent generalized lymphadenopathy	1: Normal Activity
II	Weight loss <10% Minor symptoms and infections	2: Normal activity
III	Weight loss >10% Symptomatic Diarrhoea/fever >1 mont h	3: Bedridden >50% of days/month
IV	Symptomatic AIDS-Wasting syndrome Severe opportunistic infections	4: Bedridden ?50% of days/month

Detailed description of the clinical stages of HIV/AIDS

Clinical stage 1: a person with confirmed HIV infection who is asymptomatic and/or Persistent generalized lymphadenopathy (PGL)

Clinical stage 2:

A person with confirmed HIV infection and having:

- Moderate unexplained weight loss (<10% of presumed or measured body weight)
- Recurrent respiratory tract infections (RTIs, sinusitis, bronchitis, otitis media, pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulcerations
- Papular pruritic eruptions
- Seborrhoeic dermatitis
- Fungal nail infections of fingers

Clinical stage 3:

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations:

- Severe weight loss (>10% of presumed or measured body weight)
- Unexplained chronic diarrhoea for longer than one month
- Unexplained persistent fever (intermittent or constant for longer than one month)
- Oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis (TB) diagnosed in last two years
- Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

Clinical stage 4:

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations*:*

- HIV wasting syndrome
- Pneumocystis Carinii pneumonia
- Recurrent severe or radiological bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration)
- Esophageal candidiasis
- Extra pulmonary TB
- Kaposi's sarcoma
- Central nervous system (CNS) toxoplasmosis
- HIV encephalopathy

Appendix D; Curriculum vitae of principal investigator

1. **Personal Information**

- Name ; Tadesse Sime Garedow
- Year Of Birth; 1983 E.C
- Place Of Birth ; Gerba Guracha Town
- Nationality ; Ethiopia
- Sex; Male
- Marital Status; Single
- Health ;Normal
- Contact Address:- 0921211408/ simetadesse2@gmail.com

2. **Educational Background**

Year	Level Of Education	Name Of The School	Certified
1992-1999	Primary	G/G No-3	Grade 8th
2000-2001	Secondary	G/G High School	Grade 10th
2002-2003	Preparatory	G/G Preparatory School	Grade 12th
2004-2007	Higher Education	Ambo University	Bsc Degree
2010-Present	Higher Education	Haramaya University	Candidate Of Mph Specialty In Epidemiology

3. **Qualification**

BSc in Nursing

4. **Work Experience**

From 2008-2010 served as assistant lecturer at Mettu University

5. **Language ability skill**

No.	Language	Reading	Writing	Speaking	Listening
1	Afan Oromo	Excellent	Excellent	Excellent	Excellent
2	Amharic	Excellent	Excellent	Excellent	Excellent
3	English	Excellent	Excellent	Excellent	Excellent

6. **Additional Skill**

Interpersonal and communicative skills, team work skill, problem solving and leadership skill Computer software skill

7. **Hobbies**

Reading Books, Articles and News Papers

Playing Football

8. Reference

Shelema Likassa: 0975974996/0917679662, yadawak24@gmail.com