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COLLEGE OF HEALTH SCIENCES

SCHOOL OF PUBLIC HEALTH

PREDICTORS OF MORTALITY AMONG TB-HIV CO-INFECTED PATIENTS DURING TB TREATMENT IN BAHIRDAR TOWN GOVERNMENTAL HEALTH INSTITUTION, ETHIOPIA.

A RETROSPECTIVE COHORT STUDY

BY

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ACRONYMS AND ABBREVATIONS

AIDS	Acquired Immune Deficiency Syndrome
AOR	Adjusted Odd Ratio
ART	Antiretroviral Therapy
AZT	Zidovudine
CI	Confidence Interval
CPT	Cotrimoxazole Prophylactic Therapy
d4t	Stavudine
df	Degree of Freedom
EFV	Efavirenz
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IQR	Inter Quartile Range
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
OR	Odd Ratio
PCP	Pneumocystis Carini Pneumonia
PI	Protease Inhibitor
PMO	Person Month Observation
PTB	Pulmonary Tuberculosis
SNNPR	Southern Nations Nationalities Peoples Region
TB	Tuberculosis
3TC	Lamivudine
TLC	Total Lymphocyte Count
WHO	World Health Organization

ABSTRACT

Background: The synergy between tuberculosis and human immunodeficiency virus is strong in high human immunodeficiency virus prevalence population, in which tuberculosis is a leading cause of mortality and human immunodeficiency virus is driving the tuberculosis epidemic in many countries especially in sub-Saharan Africa.

Objective: To assess predictors of mortality among TB-HIV co-infected patients during tuberculosis treatment in Bahirdar town governmental health institutions.

Methods and Materials: Institution based retrospective cohort study was conducted between April, 2009 and January, 2012. Based on TB, Pre-ART and ART registration log book records of TB-HIV co-infected patients were categorized into On ART and Non-ART cohorts. Chi-square test and T- test were used to compare categorical and continuous variables between the two groups, respectively. Kaplan-Meier test was used to estimate the probability of death after tuberculosis diagnosis. The log-rank test was used to compare overall mortality between the two groups. The Cox proportional hazard model was used to determine factors associated with death after tuberculosis diagnosis.

Results: A total of 422 TB-HIV co-infected patients (272 On ART and 150 Non-ART cohorts) were followed retrospectively for a median of 197 days (IQR: 140-221) in On ART and 191 days (IQR: 65.5-209.5) in Non-ART cohort. In Non-ART cohort more TB-HIV co-infected patients died during TB treatment; 44(29.3%) than On ART cohort 49(18.0%) with incidence rate of 6.03Per 100PMO (95%CI: 4.5, 8.1) and 3.20 per 100PMO (95% CI: 2.40, 4.20). Receiving ART (AHR=0.35 (0.19-0.64)), not initiation of CPT (AHR=3.03 (1.58-5.79)), being ambulatory (AHR=2.10 (1.22-3.62)), CD4 count category 0-75cells/µl, 75-150cells/µl and 150-250cells/µl (AHR=4.83 (1.98-11.77), 3.57 (1.48-8.61) and 3.07 (1.33-7.07) respectively) and treatment in hospital (AHR=2.64 (1.51-4.62)) were independent predictors of mortality during TB treatment.

Conclusions: Despite the availability of free ART from health institutions, mortality was high and was strongly associated with the absence of ART during TB treatment. In line with other studies risk of death was over 65% lower in TB-HIV co-infected patients treated with ART compared with those not treated with ART.

1. BACKGROUND

The human immunodeficiency virus (HIV) pandemic presents a massive challenge to the control of tuberculosis (TB) at all levels. This unprecedented scale of the epidemic of HIV-related tuberculosis demands concerted and urgent action. The synergy between TB and HIV is strong i.e., in high HIV prevalence population, TB is a leading cause of morbidity and mortality, and HIV is driving the tuberculosis epidemic in many countries, especially in sub-Saharan Africa. The spread of TB and HIV is aggravated by socio-economic factors such as poverty and low levels of literacy(1). TB is often the first clinical indication that a person has underlying HIV infection and TB services can be an extremely important entry point to HIV prevention, care and treatment (2).

The syndemic interaction between the human immune deficiency virus (HIV) and tuberculosis (TB) epidemics has had deadly consequences around the world. The TB-HIV syndemic has had a major impact on human health and disproportionately affects people in Africa (3).

In patients with advanced acquired immune deficiency syndrome (AIDS) and active TB, highly active antiretroviral therapy (HAART) may be administered concurrently with the TB treatment because if antiretroviral therapy (ART) is deferred another opportunistic infection may superimpose and accelerate HIV disease progression (4).The World Health Organization (WHO) currently recommends that all HIV infected TB patients receive co-trimoxazole and that patients with clinical evidence of AIDS or CD4+ T-lymphocyte counts (CD4) <350 cells/μL initiate ART during TB treatment (5). ART should be initiated for all people living with HIV with active TB disease irrespective of CD4 cell count (6).

Despite international recommendations and the proven benefit of ART, physicians remain reluctant to prescribe ART to HIV-infected TB patients, because of concerns about overlapping toxicity, drug-drug interactions, pill burden, and immune reconstitution inflammatory syndrome (IRIS) (7).

Major research questions also remain unanswered, including the optimum time to initiate ART, the optimum ART regimen in HIV-infected TB patients, and the added

value to ART of co-trimoxazole and other opportunistic infection prophylaxis medications in reducing mortality during TB treatment (8).Though, mortality rate from HIV associated TB in developing countries is high, it is not clear whether it is due to failure of anti TB treatment or complications of HIV (9).

To date, there have been inadequate data on predictors of mortality among TB-HIV co-infected patients in Ethiopia. The aim of this study was to answer some of the above questions directly or indirectly and fill the information gap by assessing the predictors of mortality among TB-HIV co-infected patients. And also it provided empirical evidence for TB-HIV program planners, decision makers and implementers at the different level by enabling them to access a base line data on risk factors of mortality on TB-HIV co-infected patients. The study also aimed to compare the survival rate among TB-HIV co-infected patients who received and did not receive ART.

2. LITRATURE REVIEW

2.1. General burden of TB-HIV co-infection

Worldwide 33.3 million people live with HIV and 1.8 million deaths occur due to AIDS related illnesses. Sub-Saharan Africa still bears an inordinate share of the global HIV burden accounted for 68% of HIV infections worldwide and 72% of the world's AIDS-related deaths in 2009 (10).

The annual risk of developing TB in people living with HIV/AIDS (PLWHA) who are co-infected with M. tuberculosis ranges from 5 to 15% as compared to 5 to 10% life time risk for HIV negative individuals. It also increases the likelihood of re-infections and relapses of TB (1). In 2010, there were an estimated 8.8 million incident and 12 million prevalent cases of TB globally. Approximately 1.4 million people died of TB in 2009. Of the 8.8 million incident TB cases in 2010, an estimated 1.1 million (13%) were HIV-positive with 0.35 million deaths. Of these HIV-positive TB cases, approximately 80% were in the African Region (11).TB is a leading cause of morbidity and mortality in patients with HIV/AIDS (1, 5, 12). Sub-Saharan Africa carries the overwhelming share of the global burden of HIV/AIDS and of HIV-associated TB (13).

In Ethiopia 1.2million people live with HIV causing for about 28,073 annual AIDS deaths (14). Ethiopia stands 7th place in the global rank by estimated number of cases of TB with incidence of 261 per 100,000 populations for all forms of TB and case detection rate of 72. The prevalence of Tuberculosis of all forms in the same period is estimated at 394 per 100,000 populations (11). About 40-70% of HIV patients in Ethiopia are co-infected with TB (15).

A total of 56,040 TB patients were tested for HIV in 2009, of which 11,118 (20%) were found to be HIV positive. In addition, a total of 24,112 HIV-positive people were referred from chronic HIV and ART clinics for TB screening out of which 4,154 (17.2%) were found to have active TB (16).

TB-HIV co-infected patients had a lower quality of life in all domains as compared to HIV infected patients without active TB (17).

2.2. Global and national consideration in response to the dual epidemic

Tuberculosis and HIV programs should collaborate closely with general healthcare providers to improve the quality and continuity of care of HIV-infected TB patients. As well as ensuring effective TB treatment and promoting access to ART, improving the quality of care of HIV infected TB patients involves preventing and treating common HIV-related infections, avoiding unwanted drug effects and avoiding over-crowding of hospital wards. The impact of HIV on TB patients and programs has implications for TB control policies (13).

ART is recommended in all HIV-infected TB patients with CD4 counts <200 cells/mm3 and should be considered for patients with CD4 counts <350 cells/mm3. In cases where CD4 cell counts cannot be assessed, a total lymphocyte count of 1200/mm3 or below can be used as a substitute indication for treatment in the presence of symptomatic HIV disease. In the absence of CD4 counts and total lymphocyte counts, which may be the case in most of sub Saharan Africa, ART is recommended for all TB patients with documented HIV infection (18).

Current international guidelines also recommend that patients with advanced immune-suppression begin ART within two weeks to two months of beginning TB treatment (19).

After the establishment of TB-HIV Advisory Committee in 2002 key collaborative TB-HIV activities being implemented by Ethiopia includes routine HIV testing and counseling for TB patients and suspects, Co-trimoxazole Preventive Therapy (CPT), HIV prevention services at TB clinic, HIV care and support, Provide ART for eligible TB-HIV co-infected patients, routine offer of TB screening for all HIV positive clients, INH preventive therapy (IPT) and TB infection control in health care and congregated setting (1).

In Ethiopia from July 2008 through June 2009, 68% of HIV-positive TB patients were put on Cotrimexazole Prophylaxis Therapy (CPT) and 41% of HIV-positive TB patients have started ART (16).

2.3. Magnitude of mortality and Survival time due to TB-HIV co-infection

Studies showed that the rate of death among TB-HIV co-infected patients prior to successful completion of TB treatment ranges from 8.5% to 29% (4, 20-22). In a meta-analysis study the pooled percentage of deaths during TB treatment was 3.5% (95% CI: 2.5%–7.2%) in HIV uninfected persons and 18.8% (95% CI: 14.8%–22.8%) in HIV infected persons (22). Death occurred in 43 of 380 (11.3%) patients exposed to ART during TB treatment, compared with 87 of 354 patients (24.6%) without ART (RR 0.46, 95% CI 0.33–0.64) (23).

A retrospective study in Thailand found that the overall mortality rate was 7.7% in ART+ group and 67.7% in ART- group ($P < 0.001$) (24). A prospective, multi-center observational study of HIV-infected TB patients in Thailand showed that patients who took ART had one-fifth the risk of dying than those who did not take ART (25). Many of the adverse events observed occurred within the first 2 months of starting TB therapy [hepatitis (91%), rash (85%), GI disturbance (79%), and peripheral neuropathy (65%), other neurological (65%)] (4). The median time from treatment initiation to death was 51 days (range 0–443 days) (26).

Another study in northern Thailand showed that HIV-positive patients are more likely to die in the first month of TB treatment (AOR 3.24, CI 2.46–4.26) than HIV-negative patients. Their observation of surveillance data over 12 years revealed that the highest proportion of TB deaths happened during the first month of TB treatment (27).

2.4. Predictors of mortality among TB-HIV co-infected patients

2.4.1. Socio-demographic risk factors

Lower median survival times were observed in the 40-49 year age bracket and in males (45.4 and 51.5 months, respectively). Survival time was visibly reduced among patients with no schooling (41.6 months) (28). Factors which remained independently associated with death in the multivariate model include increasing age HR 1.02 (95% CI: 1.00–1.04) (26). In multivariable survival analysis, age greater than 45 years (HR 1.44, 95% CI 0.96–2.15) was independently associated with long-term survival after TB diagnosis (21). HIV-infected female patient had a lower risk of death than males

(adjusted relative risk: 0.55, 95% CI 0.37–0.83) (23). A study in Ethiopia showed that age over 45 years at presentation (HR [95%CI] =1.7 [1.2, 2.4]) and men had higher mortality rates than women (HR [95%CI] =1.4 [1.1, 1.8]) (29).

2.4.2. Base line clinical and lab risk factors

Factors which remained independently associated with death include CD4 10-24 HR 3.4 (95% CI: 2.0–6.1), CD4 25-49 HR 3.0 (95% CI: 1.6–5.7), CD4 50-99 HR 2.6 (95% CI: 1.4–4.8) or missing CD4 count HR 3.8 (95% CI: 1.7–8.2) (26). In another study baseline CD4 count was independently associated with long-term survival after TB diagnosis (HR 0.76 per 100 cell increase, 95% CI 0.65–0.88) (21). In contrary study done in south India showed that lower CD4 count of 200/mm3 indicating advanced immunosuppressant was not associated with mortality (30). TLC<= 750/mcL at baseline was the strongest predictor of overall mortality [HR (95%CI) = 3.4 (1.5–7.6) (31). Higher mortality was associated with advanced clinical stage [95%CI] =2.4 [1.5, 4]) and WHO stage IV [HR (95%CI) = 9.2 (1.8–45.8), P = 0.007] at start of treatment (29, 31).

2.4.3. TB location site, type and category risk factors

Study done in south India showed that disease classification as ‘pulmonary TB’ [(OR 2.21, CI (1.26–3.88)], type as ‘retreatment cases’ [OR 2.05, CI (1.01–4.18)] and ‘treatment irregularity’ [OR 2.07, CI (1.14–3.78)] were potential risk factors for death (30). The other risk factors associated with a higher probability of death were gastrointestinal TB (HR 9.2, 95% CI: 1.10-78.02, P = 0.042), multidrug-resistant TB (HR 2.0, 95% CI: 1.04-3.78, P = 0.038) and ineffective TB regimen (HR 5.0, 95% CI 2.0–12.6) (20, 24). TB-HIV co-infected patients with mixed clinical presentation, extra pulmonary and treatment dropout have reduced survival time (22.2, 39.6 and 45.4 months, respectively) (28).

Diagnosis of mixed TB (HR 1.4, 95% CI: 1.0–2.0) and multidrug-resistant TB (HR 3.3, 95% CI: 1.2–9.2) were factors which remained independently associated with death (26). Having pulmonary TB was also independently associated with a greater risk of

death, and there was a trend towards greater risk of death in those with prior anti-TB treatment (23).

2.4.4. Medication and regimen type risk factors

In the logistic regression analysis the treatment related factors independently associated with death were 'non initiation of ART' [AOR-2.80, CI (1.15–6.81)] and of 'CPT' [AOR-3.46, CI (1.47–8.14)] (30). A prospective, multi-center observational study of HIV-infected TB patients in Thailand showed that the risk of dying was further reduced with early ART initiation and concomitant use of fluconazole. The choice of non-nucleoside reverse transcriptase inhibitor (NNRTI) in the ART regimen did not alter the risk of adverse events or death (25). A study done in Ethiopia showed that HAART resulted in a decrease of mortality (adjusted HR [95%CI] = 0.35 (0.19–0.63) (32).

The use of HAART during treatment for tuberculosis significantly protected against mortality when compared to HIV-infected patients who either did not receive any anti-retroviral medications or received regimens other than HAART (RR 0.36, 95% C.I. 0.14-0.91, p = 0.01) (33).Not receiving ART was associated with a higher probability of death (HR = 20.0, 95% CI = 8.62-45.45, P = 0.001)(24). In another study ART remained strongly associated with reduced mortality during TB treatment. In multivariate analysis of patients who did not receive ART and adjusting for CD4 count, smear status, and hospital providing treatment, co-trimoxazole was not associated with survival (AOR 0.9, CI 0.5–1.9) (34). The risk for death caused by TB was lower for persons who took ART (HR 0.2, 95% confidence interval [CI], 0.1–0.5) (20).

Factors which remained independently associated with death in the multivariate model include ART use with HR of 0.17 (95% CI: 0.12 to 0.24). Use of fluconazole after TB diagnosis remained statistically protective against death (HR 0.7, CI: 0.5 to 1.0) (26). Having HAART started during TB treatment (HR 0.43, 95% CI 0.26–0.72) was independently associated with long-term survival after TB diagnosis (21). ART exposure at any time during TB treatment remained independently protective against death (adjusted hazard ratio [HR] 0.41, 95%CI 0.28–0.60) (22).

3. OBJECTIVES

3.1. General objective

To assess predictors of mortality among TB-HIV co-infected Patients during TB treatment.

3.2. Specific objectives

1. To estimate the time to death of TB-HIV co-infected Patients during TB treatment.
2. To assess the mortality rate of TB-HIV co-infected patients during TB treatment.
3. To determine independent predictors of mortality among TB-HIV co-infected Patients during TB treatment.

4. METHODS AND MATERIALS

4.1. Study area and period

The study was conducted in Bahirdar town governmental health institutions, located in northwest Ethiopia 565Km far from Addis Ababa. Felege Hiwot Refferal hospital gives different specialized clinical services for approximately 7-9 million people in Amhara regional state. It is a teaching Hospital for Bahirdar University with basic facilities for HIV care and treatment and with established clinical set up and highly trained medical personnel. Any patient diagnosed as having HIV in any of HIV counseling and testing protocols (VCT, PICHT) and referrals from other health facilities referred to the ART clinic for Pre-ART and ART follow up and registered in Pre-ART and ART log books according to the status of the patients on diseases progression. The hospital and Bahirdar health center have started pre-ART and ART services since 2005 and other health centers have started the service in 2009. The 2003 E.C annual report of the hospital showed that 1600 TB cases detected, 13,590 PLWHA ever enrolled in ART clinic, 9,222 ever started ART and currently 5,547 PLWHA are taking ART.

The study was conducted from August, 2011 to January, 2011.

4.2. Study design

Institution based retrospective cohort study was used.

4.3. Population

4.3.1. Source population

All TB-HIV co-infected patients in Felege Hiwot referral hospital and three health centers in Bahirdar town.

4.3.2. Study population

Those TB-HIV co-infected patients who started ART before TB treatment initiation or during TB treatment were included in exposed cohort (on ART) and patients who

didn't receive ART till completion of TB treatment were included in non-exposed cohort (non-ART).

Those patients fulfilling the following inclusion and exclusion criteria at TB and ART clinic

Inclusion criteria

- TB-HIV co-infected patients aged 15 years or older who have diagnosed TB at any time during Pre-ART and ART follow up since April, 2009 and completed TB treatment before January, 2012.
- Patients who had diagnosed both TB and HIV during initial visit
- Patients who had diagnosed TB during follow up care for HIV/AIDS
- TB-HIV co-infected patients with complete intake form, registers, and follow up form from TB diagnosis to completion of TB treatment.

Exclusion Criteria include

- Transferred in and transferred out patients

4.4. Sample size determination

The sample size was calculated using two sample proportion formulas in Epi-Info version 3.5.1 for windows. Calculation was based on the assumption that type I error of 5%, power of 80% and two exposed (ART during anti-TB treatment) to one non-exposed (Not taking ART during anti-TB treatment).

To calculate the sample size proportion of deaths in the non-exposed cohort (24.6%) and in the exposed cohort (11.3%) was taken from retrospective cohort study done in India (23). The minimum sample size was 312 (208 exposed and 104 non-exposed), adding 10% for incomplete records the final sample size was 342 (228 exposed and 114 non-exposed). But we took all eligible records from April, 2009 to January, 2012. We reviewed 422 records of TB-HIV co-infected patients (272 exposed and 150 not exposed).

[Let $P= p_1+ rp_2/1+r$ and $r =n2/n1$

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

Where; P1=proportion of death among exposed

P2=proportion of death among non-exposed

α=level of significance, Zα/2=1.96 at 95% CL

Power=80%=1-β, Zβ=1.28

n=the minimum required sample size in each group]

4.5. Sampling Procedures

Felege Hiwot Referral Hospital and three health centers were selected for the study purposely to get adequate number of sample. Profiles of all TB-HIV co-infected patients between April 2009 and January, 2012 in TB, Pre-ART and ART registration log book and patient's card were reviewed. Then based on TB, Pre-ART and ART registration log book records of TB/HIV co-infected patients were categorized into on ART and non-ART. All records after the introduction of HMIS that fulfills the inclusion criteria were included.

4.6. Data collection procedures

4.6.1. Variables

4.6.1.1. Independent variables

The independent variables were

- ✓ Socio-demographic characteristics including age, religion, sex, educational level, marital status and occupational status.
- ✓ Base line and recent clinical and laboratory information
- ✓ Past opportunistic illness
- ✓ TB type and treatment
- ✓ ART treatment
- ✓ cotrimoxazole chemoprophylaxis,
- ✓ WHO clinical staging
- ✓ Liver function tests (ALT/AST).

4.6.1.2. Dependent variables

The dependent outcome was time to death from TB diagnosis to treatment completion.

4.6.2. Instruments

The data collection instruments were prepared by the principal investigator by reviewing pre-ART, ART, HIV care follow up form and TB-registration book in ART and TB clinic. It had included the following parts

- Socio demographic data
- Base line and recent clinical and laboratory data
- Medication and treatment
- TB location site and category

4.6.3. Data collection

Nurses who work in TB and ART clinic were selected to collect the data. Two day training was given for all supervisors and data collectors. Pre-test was undertaken before we collect the actual data. The data was collected by reviewing pre-ART register, lab request, monthly cohort form, and follow up form, Anti-TB record form, ART intake form and patients' card. Date of death was extracted from TB registration logbook. The most recent laboratory results during TB diagnosis and before were used as a base line value. Supervisors monitored activities of data collectors daily and checked completeness of each questionnaire. The overall activity was controlled by the principal investigator of the study. All completed data collection form was examined for completeness and consistency during data management and storage.

4.6.4. Data Quality control

Data quality was assured by Pre-tested instrument, trained data collectors and supervisors, continuous supervision and monitoring. Data completeness and consistency was checked before and after data entry.

4.7. Measurement of variables

Any death that occurred during TB treatment was classified as ‘‘death during treatment’’. If the date of ART or CPT treatment initiation was more than 1 week before TB treatment initiation, that person was said to be on ART or CPT prior to TB treatment. Patients who initiated ART at any time before TB treatment was completed were classified as having received ART during TB treatment.

Since the 2010 guideline was not implemented during the study period we used the former definition.

Smear positive pulmonary tuberculosis (PTB+) if two or more initial sputum examinations were positive for acid fast bacilli (AFB), or one sputum positive for AFB plus radiographic abnormalities consistent with active TB as determined by a physician.

Extra pulmonary tuberculosis (EPTB) refers to TB of organs other than the lungs and diagnosis was based on strong clinical suspicion by a physician.

Functional status was measured at base line, and a person is categorized into working = “able to perform usual work in or out of the house”; Ambulatory= “able to perform activities of daily living” and Bedridden= “not able to perform activities of daily living”.

4.8. Data analysis procedures

Completed data collection instruments coded using numbers. Data was entered to EpiData 3.1(EpiData Association, Odense Denmark) for windows. SPSS version 16.0 for windows and STATA version 11.0 were used for analysis. Data was cleaned and edited by simple frequencies and cross tabulation before analysis. Date of deaths were recorded by reviewing TB registration logbook, medical registration in the hospital, or registration by ART adherence supporter through calling using the registered phone number and individuals alive at the end of TB treatment completion were censured. Finally, the outcome of each subject was dichotomized into censored or death. Death

from any cause during TB treatment was listed as on-treatment TB death according to the WHO TB treatment outcome definition (35).

The response variable was survival time, defined as time in days transpired from the date of initial TB treatment to death or, in the case of individuals who did not die, the time to completion of the TB treatment.

Mean (with standard deviation), median (with inter quartile range, IQR) and frequencies (%) were used to describe patients' characteristics in each cohort. Chi-square test and T- test were used to compare categorical and continuous variables between the two cohorts, respectively. Actuarial life table was used to estimate survival after initiation of anti-TB and the Kaplan-Meier test was used to estimate the probability of death and the median time to death after TB diagnosis. The log-rank test was used to compare time to death between the two groups. The Cox proportional hazard model was used to determine the chance of death after TB diagnosis by adjusting for confounding factors. All statistically significant factors in the bivariate analysis were included in the final model. The crude and adjusted hazard ratio (HR) and its 95% confidence interval (CI) were estimated. A p-value less than 0.05 was considered statistically significant.

4.9. Ethical Considerations

Ethical clearance was obtained from Review Ethics Committee (REC) of School of Public Health, Addis Ababa University. Following the approval official letter of co-operation was written to concerned bodies by the School of Public Health. Permission letter was obtained from Amhara regional health bureau. As the study was conducted through review of medical records, the individual patients was not be subjected to any harm as far as the confidentiality was kept. Informed consent was obtained from each participant during home visiting or calling. To preserve the confidentiality, nurses working in ART clinic of Felege Hiwot referral hospital and three health centers extracted the data from the medical records. Moreover, no personal identifiers were used on data collection form. The recorded data was not accessed by a third person except the principal investigator, and was kept confidentially.

5. RESULTS

5.1. Enrollment of TB-HIV co-infected patients in the study

From April 2009 – September 2011, 2,773 adult TB patients were registered for treatment in Felege Hiwot Referral hospital, Bahirdar health center, Han health center and Abay health center and 849 (30.6%) were known to be HIV-infected, of which 488 (57.5%) were eligible for the study [Figure 1]. We later excluded 29 patients whose card was not found and 37 patients whose ART status was not determined. The remaining 422 TB-HIV co-infected patients were eligible for the study. A total of 422 TB-HIV co-infected patients (272 'On ART' and 150 'Non-ART' cohorts) were followed retrospectively for a median of 197 days with IQR 140-221days among on ART and 191 days with IQR 65.5-209.5 days among non-ART cohorts. The follow up period was slightly higher in on ART cohorts.

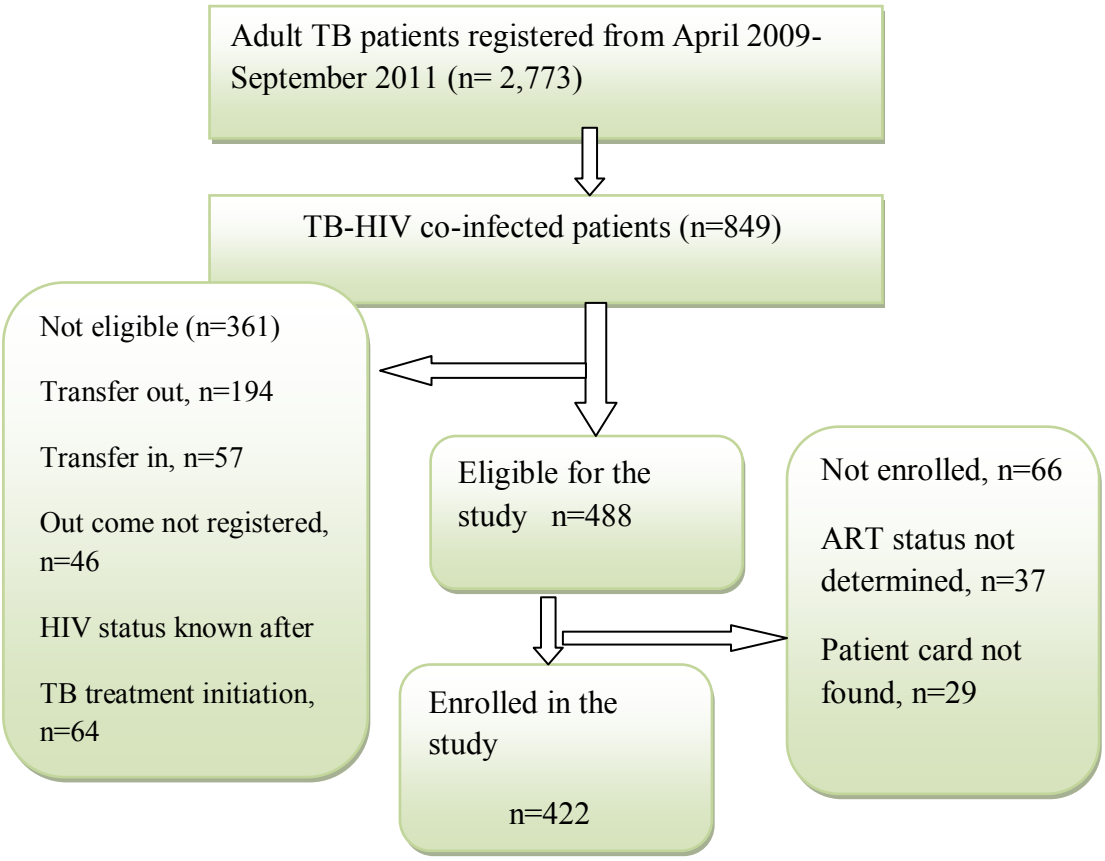

Figure 1: Enrollment of TB-HIV co-infected patients in the study, 2012

5.2. Baseline Socio-Demographic Characteristics of the Study Subjects

In this study both cohorts were not statistically different for each attribute of the socio-demography. The median age of study subjects in both cohorts was 30 years with inter quartile range (IQR) 27-37.5years and 25-38years in On ART and Non-ART cohorts respectively. Majority of study subjects were urban resident 235(90.7%) and 129(87.2%) in On ART and Non-ART cohorts respectively. Females account for a majority of study subjects; 141(53.4%) and 83(56.5%) in On ART and Non-ART cohorts respectively (Table 1).

In both cohorts majority of patients were orthodox; 226(85.3%) and 117(80.2%) in On ART and Non-ART respectively. Majority of study subjects were married in both cohorts; 108(40.0%) and 57(39.0%) in On ART and Non-ART respectively. More than one third of patients in both cohorts were secondary school completed; 93(34.8%) and 50(35.7%) in On ART and Non-ART respectively. More than one fourth of study subjects in On ART cohorts were nongovernmental employees; 73(29.2%) and 32(23.4%) study subjects were government employees in Non-ART cohorts (Table 1).

Table 1: Baseline socio-demographic characteristics of TB-HIV co- infected patients during TB treatment in Bahirdar town governmental health institutions, 2012

Base line variable	On ART (n=272)	Non-ART (n=150)	X2 Value (df)	P-Value
Address(n=407)				
Urban	235(90.7%)	129(87.2%)	1.271	0.260
Rural	24(9.3%)	19(12.8%)	(1)	
Age(n=408)				
Mean ± SD	32.58±9.123	31.98±9.837	0.753♦	0.452
Median(IQR)	30yrs(27-37.5)	30yrs(25-38)		
Sex(n=411)				
Male	123(46.6%)	64(43.5%)	0.355	0.551
Female	141(53.4%)	83(56.5%)	(1)	
Religion(n=411)				
Orthodox	226(85.3%)	117(80.2%)	5.962	0.183
Muslim	26(9.8%)	18(12.3%)	(2)	
Others	13(4.9%)	11(7.5%)		
Marital status(n=415)				
Single	76(28.1%)	55(37.9%)	7.901	0.131
Married	108(40.0%)	57(39.3%)	(3)	
Divorced/Separated	52(19.2%)	24(16.6%)		
Widowed	34(12.6%)	9(6.2%)		
Educational status(n=407)				
Not educated	77(28.8%)	40(28.6%)	0.765	0.858
Primary	61(22.8%)	35(25.0%)	(3)	
Secondary	93(34.8%)	50(35.7%)		
Tertiary	36(13.5%)	15(10.7%)		
Occupational Status				
House wife	18(7.2%)	5(3.6%)	7.932	0.239
Merchant	39(15.6%)	16(11.7%)	(6)	
Government employee	46(18.4%)	27(19.7%)		
Nongovernment employee	73(29.2%)	32(23.4%)		
Day laborer	43(17.2%)	31(22.6%)		
Jobless	19(7.6%)	16(11.7%)		
Others [1,2,3]	12(4.8%)	10(7.3%)		

1. Student 2. Farmer 3.Commercial sex worker, ♦=T-test Statistic for independent sample test used

5.3. Clinical and immunological characteristics of the Study Subjects

When we see clinical condition of study subjects, there was no statistical difference in both cohorts in most variables except for history of prophylactic medication in which higher proportion (51.6%) of patients on ART had history of prophylactic medication compared to patients not on ART (27.1%) (X^2=21.721; df (1); p=0.000). Among the study subjects more than one third had at least one past opportunistic infection; 105(43.6%) and 55(44.0%) in On ART and Non-ART cohorts respectively. And also 58(22.4%) and 31(21.7) study subjects had history of past TB treatment in On ART and Non-ART cohorts respectively (Table 2).

Majority of study subjects were able to perform their usual work (working); 159(60.9%) and 80(58.8%) in On ART and Non-ART cohorts respectively. Majority of study subjects were in WHO clinical stage III during initiation of TB treatment; 181(67.3%) and 94(62.7%) in On ART and Non-ART cohorts respectively (Table 2).

The result showed that On ART and Non-ART cohorts were statistically different in CD4 count (T=10.305; p=0.000) and liver function tests (T=2.081; p=0.039 and T=2.904; 0.004 for ALT and AST respectively). But both cohorts were not different in hemoglobin level. Study subjects in On ART cohort had much lower CD4+ cell count with median of 114cells/µl and IQR 58-185cells/ µl than Non- ART with median of 291cells/µl and IQR 183.5-448cells/µl. In this study hemoglobin level is not statistically different in both cohorts (T=0.063; p=0.950) with the median of 11.3mg/dl (IQR 10.0-13.0) and 12.0 mg/dl (IQR 10.1-13.0) in On ART and Non-ART cohorts respectively (Table 2).

Table 2: Baseline clinical and immunological characteristics of TB-HIV co- infected patients during TB treatment in Bahirdar town governmental health institutions, 2012

Base line variable	On ART (n=272)	Non-ART (n=150)	X^2 Value (df)	P-Value
Past OIs(n=366)				
Yes	105(43.6%)	55(44.0%)	0.006	0.937
No	136(56.4%)	70(56.0%)	(1)	
Past TB Treatment(n=402)				
Yes	58(22.4%)	31(21.7%)	0.027	0.869
No	201(77.6%)	112(78.3%)	(1)	
Past Prophylactic medication(n=387)				
Yes	131(51.6%)	36(27.1%)	21.372	0.000*
No	123(48.4%)	97(72.9%)	(1)	
Functional status (n=397)				
Working	159(60.9%)	80(58.8%)	1.363	0.506
Ambulatory	72(27.6%)	44(32.4%)	(2)	
Bedridden	30(11.5%)	12(8.8%)		
WHO Staging(n=419)				
Stage III	181(67.3%)	94(62.7%)	0.911	0.34
Stage IV	88(32.7%)	56(37.3%)	(1)	
CD4 count(cells/μl) (n=408)				
Mean ± SD	132.9±94.42	312.78±192.8	10.305♦	0.000*
Median(IQR)	114(58-185)	291(183.5-448)		
Hgb level (mmHg)(n=357)				
Mean ± SD	11.36±2.3	11.46±1.83	0.063♦	0.95
Median(IQR)	11.3(10.0-13.0)	12.0(10.12-13.0)		
ALT(n=336)				
Mean ± SD	35.6±20.86	42.73±25.84	2.081♦	0.039*
Median(IQR)	29(22.0-40.025)	34(51.76-61.25)		
AST(n=303)				
Mean ± SD	42.05±23.11	51.76±29.27	2.904♦	0.004*
Median(IQR)	36(27.0-54.0)	47(26.0-69.0)		

*** Significant at α=0.05, ♦=T-test Statistic for independent sample test used**

5.4. Characteristics of study subjects on type of TB diagnosis, type and medication

There was great difference to statistically significant level in type of TB diagnosis between the cohorts. Majority of study subjects in On ART group had smear negative PTB; 107(39.3%) whereas only 36(24.0%) had smear negative PTB in Non-ART group (X^2 =10.434; df=2; p=0.005) (Table 3).

In both cohorts majority of study subjects had new form of TB; 258(94.9%) and 146 (97.6%) in On ART and Non-ART groups respectively. More than three fourth of study subjects had taken 2HRZE/6EH anti-TB regimen; 214(78.7%) and 119(79.3%) in On ART and Non-ART cohorts. Higher proportion (93.3%) of study subjects in On ART cohort had got cotrimoxazole prophylactic therapy compared to Non-ART cohorts (77.0%) (Table3).

5.5. Base line social condition

There was statistical difference in the groups regarding to religious/supportive care (X^2=7.977; df=1; p=0.005). Among On ART group only 49(20.4%) had religious/supportive care whereas 43(33.9%) of study subjects in Non-ART group had religious/supportive care. Majority of study subjects in both cohorts had disclosed their HIV sero status; 209(83.6%) and 97(77.0%) in On ART and Non-ART groups respectively. Similarly; at least one general concern was identified in majority of study subjects; 164(69.2%) and 93(72.7%) in On ART and Non-ART cohorts respectively. (Table 4)

Table 3: Type of TB diagnosis and medication of TB-HIV co-infected patients during TB treatment in Bahirdar town governmental health institutions, 2012

Variable		On ART (n=272)	Non-ART (n=150)	X^2 Value (df)	P-Value
TB diagnosis					
	Smear Positive PTB	53(19.5%)	40(26.7%)	10.434	0.005*
	Smear Negative PTB	107(39.3%)	36(24.0%)	(2)	
	Extra PTB	112(41.2%)	74(49.3%)		
TB Type					
	New	258(94.9%)	146(97.3%)	1.457	0.227
	Not new	14(5.1%)	4(2.7%)	(1)	
Anti-TB Regimen					
	2HRZE/6EH	214(78.7%)	119(79.3%)	12.587	0.002*
	2HRZE/4RH	26(9.6%)	26(17.3%)	(2)	
	Other	32(11.7%)	5(3.3%)		
CPT (n=397)					
	Prescribed	239(93.0%)	109(77.9%)	19.19	0.000*
	Not Prescribed	18(7.0%)	31(22.1%)		
Outcome of TB Treatment(n=417)					
	Cure	37(13.7%)	16(11.0%)	8.039	0.045*
	Treatment completed	167(61.6%)	77(52.7%)	(3)	
	Defaults	18(6.6%)	9(6.2%)		
	Death	49(18.1%)	44(30.1%)		

*** Significant at α= 0.05**

Table 4: Baseline social condition of TB-HIV co- infected patients during TB treatment in Bahirdar town governmental health institutions, 2012

Variable	On ART (n=272)	Non-ART (n=150)	X^2 Value (df)	P-Value
Religious/supportive care(n=367)				
Yes	49(20.4%)	43(33.9%)	7.977	0.005*
No	191(79.6%)	84(66.1%)	(1)	
HIV Serostatus disclosure(n=376)				
Yes	209(83.6%)	97(77.0%)	2.424	0.120
No	41(16.4%)	29(23.0%)	(1)	
General concern Identified(n=365)				
Yes	164(69.2%)	93(72.7%)	0.479	0.490
No	73(30.8%)	35(27.3%)	(1)	

***Significant at α= 0.05**

5.6. Comparison of mortality between On ART and Non-ART cohorts

All 422 study subjects had contributed a total of 2274.4person months; 1545.03person months in on ART cohort and 729.37person months in non-ART cohort respectively. In Non-ART cohort more TB-HIV co-infected patients died during TB treatment; 44(29.3%) than On ART cohort; 49(18.0%) with incidence rate of 6.03Per 100Person month observations (95%CI: 4.5, 8.1) and 3.20 per 100PMO (95% CI: 2.40, 4.20). The overall incidence rate of mortality during TB treatment is 4.09 per 100person month observations (95% CI: 3.34, 5.01). The result showed that incidence of mortality in the first month of TB treatment is 5.40 per 100PMO and 4.8 per 100PMO in second month of TB treatment in On ART cohort. The corresponding value in Non-ART cohort is 16.90 per 100PMO and 5.90 per 100PMO in the first and second month of TB treatment respectively.

The median time for development of mortality during TB treatment has shown variation between the two groups. The median time to develop death was 29.5 days and 59 days in On ART cohort and non-ART cohort respectively. In both cohorts majority of deaths occur in the first month of TB treatment (0-28 days) and decreases in later follow up period. Based on actuarial life table analysis the probability of not developing death at 28 days and 56 days in On ART cohort were 95% and 91%

respectively. The corresponding values in Non-ART cohort were 86% and 80% respectively (Table 5).

Table 5: Actuarial life table analysis of TB-HIV co- infected patients during TB treatment in Bahirdar town governmental health institutions, 2012

ART status	Time interval in days	Number entering interval	Number with drawing during interval	Number exposed to risk	Number of deaths	Probability of not developing death	Cumulative Probability of not developing death
	0-28	272	5	269.5	13	0.95	**0.95**
	28-56	254	0	254	10	0.96	0.91
	56-84	244	4	242	7	0.97	0.89
On ART	84-112	233	2	232	6	0.97	0.86
	112-140	225	13	218.5	7	0.97	0.84
	140-168	205	24	193	3	0.98	0.82
	168-196	178	33	161.5	1	0.99	0.82
	196-224	144	84	102	1	0.99	0.81
	224-252	59	57	30.5	1	0.97	**0.78**
	0-28	150	5	147.5	20	0.86	**0.86**
	28-56	125	0	125	10	0.92	0.80
	56-84	115	0	115	5	0.96	0.76
Non-ART	84-112	110	2	109	3	0.97	0.74
	112-140	105	11	99.5	2	0.98	0.72
	140-168	92	10	87	1	0.99	0.72
	168-196	81	17	72.5	1	0.99	0.71
	196-224	63	40	43	1	0.98	0.69
	224-252	22	21	11.5	1	0.91	**0.63**

The Kaplan-Meier analysis and the log-rank test were used to compare survival probabilities of the two groups. Overall probability of survival in On ART cohort was significantly greater than Non-ART cohort, i.e. the risk of developing death is higher in Non-ART cohort (log rank statistic=8.93, df=1, P=0.003) (Figure 2, 3).

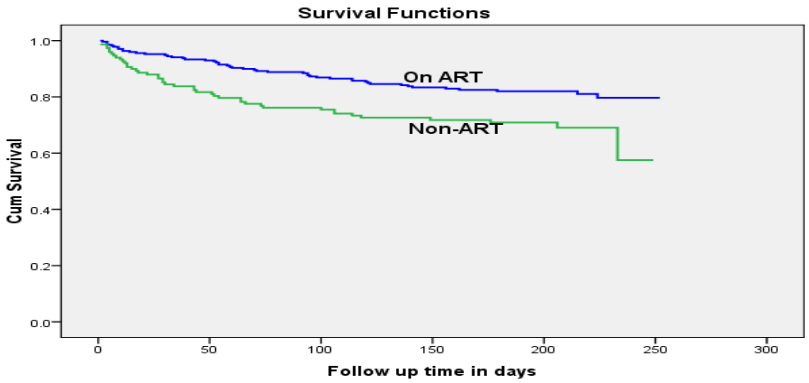

Figure 2: Kaplan-Meier estimate of survival among TB-HIV co-infected patients during TB treatment with and without ART in Bahirdar town governmental health institution, 2012

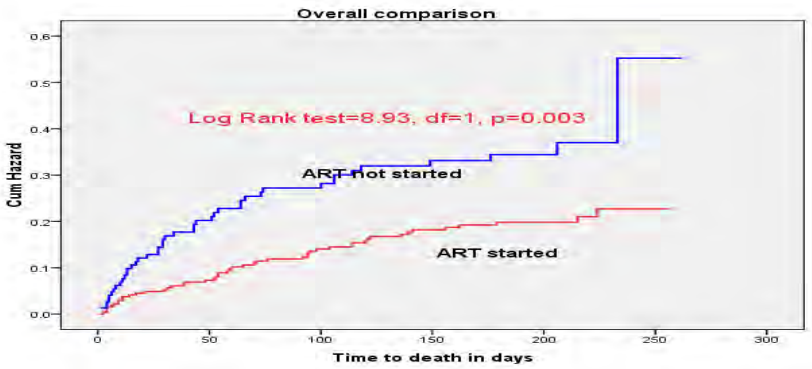

Figure 3: Kaplan-Meier estimate of mortality among TB-HIV co-infected patients during TB treatment with and without ART in Bahirdar town governmental health institution, 2012

After stratification of the cohorts based on type of TB diagnosis, the result showed that On ART cohort had significantly greater chance of not developing death during TB treatment than Non-ART cohort across strata smear positive and smear negative PTB (P=0.030 and P=0.003 respectively), but significant difference was not observed in the stratum of extra PTB (P=0.732). Furthermore; stratification by CD4 count showed that

On ART cohort had significantly greater chance of not developing death during TB treatment than Non-ART cohort across strata CD4 level 0-75cells/µL and CD4 level 75-150cells/ µL (p=0.000 and 0.014 respectively). There was no significant difference in both cohorts in developing death during TB treatment in CD4 level 150-250cells/µl, and >=250cells/µl stratums (p=0.233 and p=0.593 respectively) (figure 3-6).

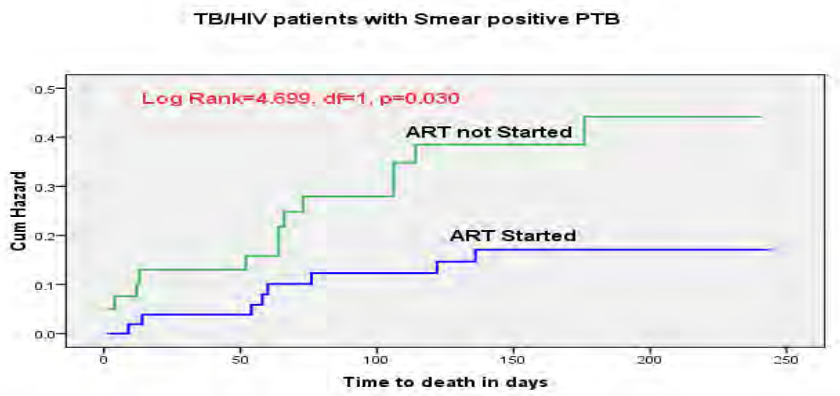

Figure 4: Kaplan-Meier curve of mortality among TB-HIV co-infected patients during TB treatment with and without ART among smear positive PTB patients in Bahirdar town governmental health institutions, 2012

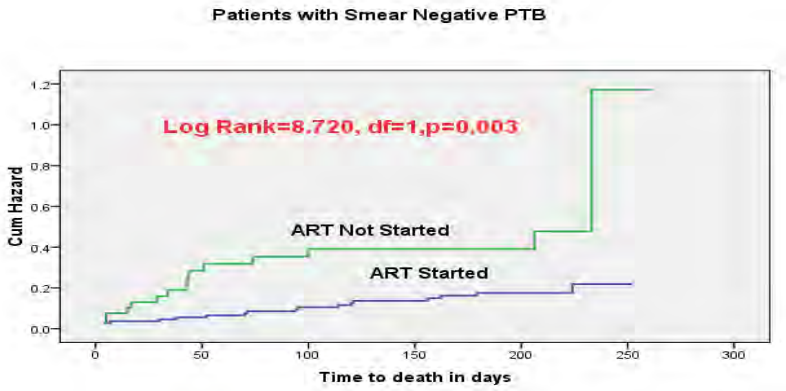

Figure 5: Kaplan-Meier curve of mortality among TB-HIV co-infected patients during TB treatment with and without ART among smear negative PTB patients in Bahirdar town governmental health institutions, 2012

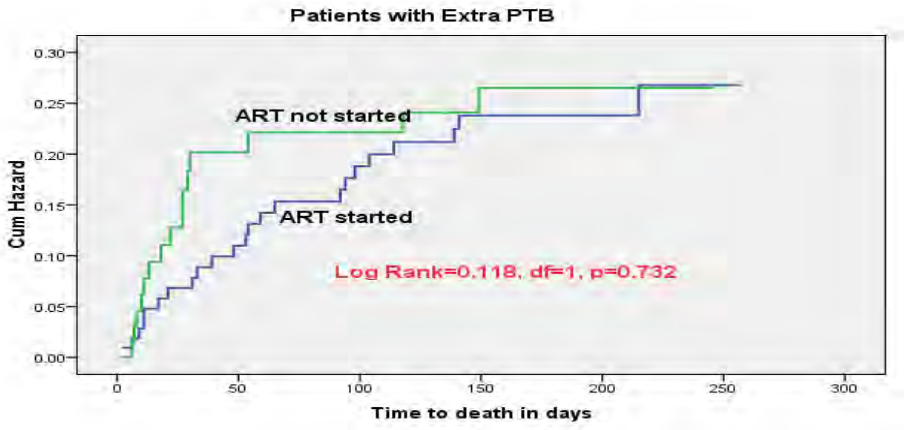

Figure 6: Kaplan-Meier estimate of mortality among TB-HIV co-infected patients during TB treatment with and without ART among extra PTB patients in Bahirdar town governmental health institutions, 2012

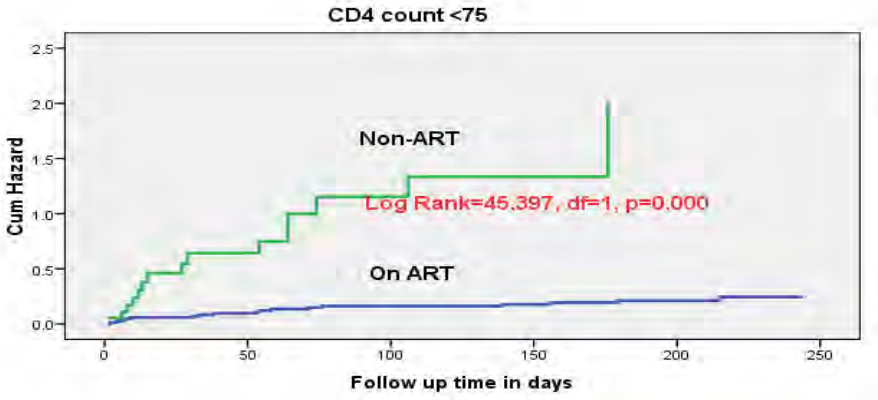

Figure 7: Kaplan-Meier estimate of mortality among TB-HIV co-infected patients during TB treatment with and without ART among CD4 level 0-75cells/µL patients in Bahirdar town governmental health institutions, 2012

5.7. Predictors of mortality in TB-HIV co-infected patients during TB treatment

Bivariate Cox-proportional model was used to assess the relationship between variables and the risk of developing mortality. Before fitting the covariate into the model proportional hazard assumption was checked by examining log (-log) S (t) plots. The result showed that health institution type, educational status, functional status, CD4 level, hemoglobin level, ALT level, AST level, type of TB diagnosis, ART treatment and CPT prophylaxis were significantly associated with developing mortality in TB-HIV co-infected patients during TB treatment (Table 6-8).

The bivariate analysis showed that the risk of developing death in patients treated TB at hospital is 2.18 times (95% CI: 1.43-3.33) higher compared to TB patients at health center. Compared to the reference group; TB patients in the age category 45years and above (HR=2.58, 95% CI: 1.34-4.92), ambulatory and bedridden functional status (HR=2.76, 95% CI: 1.71-4.47 and HR=3.88, 95% CI: 2.15-7.02 respectively) and CD4 count less than 75cells/µl (HR=2.08, 95% CI: 1.17- 3.70) increased risk of mortality during TB treatment. In the study, completing primary education reduced risk of death by 55% (HR=0.45, 95% CI: 0.22-0.90) compared to not educated TB-HIV co-infected patients. In addition the risk of mortality decreased for every 1mmHg increase in hemoglobin by 9.5%.

In this study the risk of death increased by 1.4% for 1unit increase in ALT and AST (p=0.001 and p=0.000) respectively. The result showed that compared to smear negative PTB patients; smear positive PTB patients and extra PTB patients had 2.02 (95% CI: 1.07-3.83) and 2.77 (95% CI: 1.61-4.75) times higher risk of death respectively. In addition patients who didn't start CPT were 3.15 times higher at risk of developing death (95% CI: 1.95-5.11).

ART is another important predictor of mortality. The result showed that the risk of death decreased by 46.0% (HR=0.54, 95% CI: 0.36-0.82) in TB-HIV co-infected patients who have started ART. In the bivariate analysis sex, religion, past history of OIs, past TB treatment, weight and WHO staging were not associated with risk of death during TB treatment.

Table 6: Medication and TB location associated predictors of mortality among TB-HIV co-infected patients during TB treatment in Bahirdar town governmental health institutions, 2012

Variable	Number at risk	Number of death	Incidence of Mortality per 100 person month observation (95% CI)	Crude Hazard Ratio (95% CI)
ART				
Started	272	49	3.17 (2.39, 4.19)	**0.54 (0.36, 0.82)***
Not started	150	44	6.03 (4.49, 8.11)	1
CPT prophylaxis				
Prescribed	348	60	3.59 (2.66, 4.87)	1
Not prescribed	49	23	10.18 (6.77, 15.32)	**3.15 (1.95, 5.11)***
TB Location Site				
Smear negative PTB	143	17	2.02 (1.26, 3.25)	1
Smear positive PTB	93	21	4.31 (2.81, 6.61)	**2.02 (1.07, 3.83)***
Extra PTB	186	55	5.81 (4.46, 7.57)	**2.77 (1.61, 4.78)***

***Significant at α= 0.05**

Table 7: Clinical and immunological associated predictors of mortality among TB-HIV co-infected patients during TB treatment in Bahirdar town governmental health institutions, 2012

Variable	Number at risk	Number of death	Incidence of mortality per 100 person month observation	Crude Hazard Ratio (95% CI)
Past OIs				
No	206	50	4.62 (3.50, 6.09)	1
Yes	160	31	3.53 (2.48, 5.02)	0.77 (0.49, 1.20)
Past TB treatment				
No	313	66	3.95 (3.10, 5.03)	1
Yes	89	18	3.58 (2.25, 5.68)	0.91 (0.54, 1.54)
Functional status				
Working	239	31	2.21 (1.55, 3.14)	1
Ambulatory	116	36	6.39 (4.61, 8.87)	**2.77 (1.71, 4.47)***
Bedridden	42	17	7.31 (3.81, 14.05)	**3.88 (2.15, 7.02)***
WHO Staging				
Stage III	275	56	3.69 (2.84, 4.80)	1
Stage IV	144	36	4.86 (3.51, 6.74)	1.30 (0.86,1.98)
CD4 count				
< 75	107	33	6.22 (4.42, 8.75)	**2.08 (1.17, 3.30)***
75-150	91	21	4.44 (2.90, 6.81)	1.50 (0.80, 2.82)
150-250	95	19	3.57 (2.28, 5.59)	1.24(0.65, 2.37)
>=250	115	18	2.89 (1.82, 4.59)	1
Hgb count	357	88	4.66 (3.69, 5.63)	**0.90 (0.82, 0.99)***
ALT	336	79	4.41 (3.44, 5.38)	**1.01 (1.01, 1.02)***
AST	303	71	4.35 (3.34, 5.36)	**1.01 (1.01, 1.02)***

***Significant at α= 0.05**

Table 8: Socio-demography associated predictors of mortality among TB-HIV co-infected patients during TB treatment in Bahirdar town governmental health institutions, 2012

Variable	Number at risk	Number of death	Incidence of Mortality per 100 person month observation (95% CI)	Crude Hazard Ratio (95% CI)
Health Institution				
Health center	226	34	2.67 (1.91, 3.72)	1
Hospital	196	59	5.89(4.57, 7.61)	**2.18 (1.43, 3.33)***
Age(n=408)				
15-24	100	18	3.30 (2.08, 5.24)	1
25-34	193	40	3.79 (2.78, 5.17)	1.15 (0.66, 2.01)
35-44	69	16	4.40(2.70, 7.18)	1.30 (0.66, 2.55)
>=45	46	19	8.97 (5.72, 14.06)	**2.58 (1.34, 4.92)***
Sex				
Male	187	45	4.53 (3.36, 6.07)	1
Female	224	45	3.69(2.75, 4.94)	0.82 (0.54, 1.24)
Religion				
Orthodox	343	66	3.52 (2.76, 4.48)	1
Muslim	44	13	5.53 (3.21, 9.52)	1.58 (0.87, 2.87)
Others	24	8	6.81 (3.40, 13.61)	1.93 (0.93, 4.02)
Educational status				
Not educated	117	26	4.47 (3.05, 6.57)	1
Primary	96	11	1.93 (1.07, 3.49)	**0.45 (0.22, 0.90)***
Secondary	143	37	4.82 (3.49, 6.66)	1.10 (0.66, 1.81)
Tertiary	51	13	4.48 (2.60, 7.72)	1.05 (0.54, 2.05)

***Significant at α= 0.05**

To identify independent predictors of mortality during TB treatment, a multivariate Cox-Proportional hazard adjusted model was fitted with the variables having a P-value

< 0.05 in the bivariate analysis. Before running the final model multicollinearity was checked using variance inflation factor (VIF). When hemoglobin level and liver function tests (ALT and AST) were included in the model, numbers of valid cases were inadequate to have appropriate power of the study. These variables were excluded from multivariate analysis even if they were statistically significant in the bivariate analysis.

Accordingly, receiving ART, CPT, CD4 count, functional status, type of TB diagnosis and health institution type were independent predictors of mortality after controlling for the other factors. From these factors; receiving ART during TB treatment had an independent protective benefit against risk of mortality and decreased risk of mortality by 65% (AHR=0.35, 95% CI: 0.19-0.64). In addition CPT remained important factor in reduction of mortality during TB treatment in which patients without CPT were 3.03 times higher at risk of mortality (95% CI: 1.58, 5.79). CD4 count category 0-75cells/µl, 75-150cells/µl and 150-250cells/µl, extra PTB type, being ambulatory, and treatment in hospital were independent predictors of increased risk of mortality during TB treatment (Table 9).

Table 9: Multivariate analysis of variables associated with mortality among TB-HIV co-infected patients during TB treatment in Bahirdar town governmental health institutions, 2012

Variable		Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95%) CI)
ART			
	Started	0.54 (0.36, 0.82)	**0.35 (0.19, 0.64)***
	Not started	1	1
CPT prophylaxis			
	Prescribed	1	1
	Not prescribed	3.15 (1.95, 5.11)	**3.03 (1.58, 5.79)***
TB diagnosis			
	Smear negative PTB	1	1
	Smear positive PTB	2.02 (1.07, 3.83)	2.11 (0.95, 4.65)
	Extra PTB	2.77 (1.61, 4.78)	**2.39 (1.23, 4.66)***
CD4 count			
	< 75	2.08 (1.17, 3.30)	**4.83 (1.98, 11.78)***
	75-150	1.50 (0.80, 2.82)	**3.57 (1.48, 8.61)***
	150-250	1.24(0.65, 2.37)	**3.07 (1.33, 7.07)***
	>=250	1	
Functional status			
	Working	1	1
	Ambulatory	2.77 (1.71, 4.47)	**2.10 (1.22, 3.62)***
	Bedridden	3.88 (2.15, 7.02)	2.11 (0.98, 4.53)
Health Institution			
	Health center	1	1
	Hospital	2.18 (1.43, 3.33)	**2.64 (1.51, 4.62)***
Age(n=408)			
	15-24	1	1
	25-34	1.15 (0.66, 2.01)	1.17 (0.60, 2.29)
	35-44	1.30 (0.66, 2.55)	0.98 (0.43, 2.23)
	>=45	2.58 (1.34, 4.92)	2.20 (0.97, 4.59)
Educational status			
	Not educated	1	1
	Primary	0.45 (0.22, 0.90)	0.49 (0.22, 1.12)
	Secondary	1.10 (0.66, 1.81)	0.88 (0.49, 1.58)
	Tertiary	1.05 (0.54, 2.05)	0.65 (0.29, 1.47)

***Significant at α= 0.05. ART, health institution, age, educational status, functional status, CD4 count, type of TB diagnosis and CPT prophylaxis were included in the model.**

6. DISCUSSION

This study provides information on the overwhelming problem of the high mortality of TB-HIV co-infected patients during TB treatment. In this resource limited setting, more than 1 in 5 TB-HIV co-infected individuals died during TB treatment. The results from this study demonstrated that ART remained independently protective against mortality during TB treatment.

In this study, the median age of TB-HIV co-infected patients was 30 years consistent with other study (34). This is slightly lower compared to similar studies in developing countries (23, 25, 26, 36) and in the age group 25-44 years contributed around two third of study subjects in both groups. Like other developing countries, the most affected population group by HIV is in the most reproductive age group. Different studies revealed that active TB is most common in HIV positive patients between 25 to 44 years of age.

More than half (54.5%) of the study subjects are females. This result is inconsistent with other studies in developing countries (23, 24, 26, 36). A study done in India showed that 67% were males (23) and another study in Thailand showed that only 34% of study subjects were females (26). This difference may be due to high prevalence of HIV among females.

It was difficult to get the exact value of CD4 at diagnosis of TB. However, it was tried to look CD4 count of patients during TB treatment in the course of their follow up. In our study the median CD4 count was more than twice in Non-ART cohort compared to On ART cohort (291cells/µl (IQR: 183.5-448) and 114cells/µl (IQR: 58-185)) respectively). These groups of patients may be diagnosed as having HIV and TB earlier before their clinical and immunological condition deteriorate. The median CD4 count in this study is much higher compared to other studies (20, 21, 23-26, 36, 37). The difference may be due to in this study CD4 count was taken during TB treatment or one month before TB treatment initiation and most study subjects were started ART before TB diagnosis which may improve their immunological status. In addition the result showed that 86.3% of study subjects had CD4 count below 350cells/µl indicating

progressive immunodeficiency. This is similar with a study done in Zimbabwe 84.6% had CD4 count below 350cells/µl (38).

Although there was no statistica1 difference on type of TB diagnosis in cohorts, 55.9% and 44.1% of study subjects diagnosed with PTB and extra PTB respectively. This is in line with other studies (24, 26, 30) but proportion of extra PTB in this study is high compared to two studies done in India (22.9% and 31%) and study done in Thailand reported 31% of study subjects had extra PTB (23, 25, 34). The variation may be due to difference in TB location site classification and diagnosis of TB.

We found that mortality rate was high (22%) among TB-HIV co-infected patients during TB treatment. In line to this, previous study have reported high mortality among TB-HIV co-infected patients prior to successful completion of TB treatment ranges from 8.5% to 30% (4, 20-23, 25, 26, 30, 34, 37). In this study, death occurred in 49 of 272 (18.0%) patients exposed to ART during TB treatment compared with 44 of 150 (29.3%) patients without ART. The finding is similar with a study reported in India where death occurred in 11.3% and 24.6% patients respectively (23). In this study the proportion of death in patients who didn't start ART was lower (29.3%) compared with 46% reported from a study done in Thailand (26). Another study in Thailand also reported that 5 (7%) of 71 patients who received ART died compared with 94 (43%) of 219 patients who did not receive ART (RR 0.2; 95% CI: 0.1–0.4) (34). In Malawi a total of 132 (20%) patients died during the 8-month course of anti-tuberculosis treatment which is consistent with our finding (22%) (39).

In this study, we have documented risk of mortality was high in the first month of TB treatment with incidence rate of 9.3 per 100PMO (95% CI: 6.8-12.9). This may be due to delayed presentation of patients and thus advanced TB and HIV/AIDS, late diagnosis of TB within health institutions and life-threatening HIV-related complications. This is similar with a study done in Thailand (27). Another study conducted in Sub-Saharan Africa also documented the rationale for starting ART soon after TB diagnosis is that case-fatality among HIV-TB patients occurs mainly in the first 2 months of TB treatment (40).

This study showed that nearly two third (64.5%) of TB-HIV co-infected patients had access to ART during TB treatment. This is much higher compared to studies in Thailand 41% and India 52% TB-HIV patients had access to ART (23, 27). The difference may be due to emphasis of recommendations to initiate ART during TB treatment and their study was done before some years ago which may not be the case at this time.

In this retrospective institution based study we found that TB-HIV co-infected patients provided ART during TB treatment had low risk of death as those not provided ART(AHR=0.35, 95% CI: 0.19-0.64). This is consistent with other several settings (20-24, 26, 30, 33, 34, 37, 41) in which plenty of studies precisely demonstrate the impact of ART on the survival outcomes among TB-HIV co-infected patients with successful immune restoration and reductions in morbidity and mortality.

International guidelines recommend that HIV-infected persons initiate treatment with nevirapine, zidovudine, and lamivudine; because rifampin can alter drug levels of nevirapine, guidelines recommend that efavirenz replace nevirapine in patients receiving rifampin during TB treatment (19, 42). In line with this our finding showed that 70.2% of patients have got efavirenze based ART regimens during TB treatment. This may have effect on mortality by reducing risk of adverse reactions.

In addition to ART, we found other immunological factors associated with death. Mortality rates increased in patients with lower CD4 category. In this study, TB-HIV co-infected patients with CD4 count category 0-75cells/µl, 75-150cells/µl and 150-250cells/µl had increased risk of mortality (AHR=4.83, 95%CI: 1.98-11.77, AHR=3.57, 95% CI: 1.48-8.61 and AHR=3.07, 95%CI: 1.33, 7.07 respectively). This finding is consistent with other studies in Thailand (26, 34) and in Zimbabwe CD4 count of <50 cells/µl associated with a 13-fold increased risk of death (38). In contrary, study done in south India showed that lower CD4 count of 200/mm3 indicating advanced immunosuppressant was not associated with mortality (30). The difference may be in our study CD4 count categorized in small interval which can enable to see effect of CD4 count on mortality.

The risk of death during TB treatment was higher in patients treated at hospital compared to health center. But in other study hospital providing treatment strongly associated with reduced mortality during TB treatment (34). We didn't conclude that hospitalization increases mortality but the possible reason may be patients who get worse and clinically deteriorated during TB diagnosis admitted to hospital and those who are not severely ill transferred to health centers for TB treatment. Patients who were ambulatory had increased risk of developing death compared to working patients. This may be due to being seriously sick secondary to deteriorated clinical and immunological condition. Unfortunately bedridden patients didn't show association in multivariate analysis. This might be due to small proportion of bedridden TB-HIV co-infected patients.

In this study TB-HIV co-infected patients with extra PTB were at increased risk of mortality during TB treatment compared to smear negative PTB patients. WHO also documented that case-fatality is higher in people living with HIV with smear-negative pulmonary and extra pulmonary TB, as these patients are generally more immune-suppressed than those with smear-positive TB (43). Our finding is not consistent with other studies (26, 34). In other studies PTB is associated with high risk of mortality (23). The possible reason may be HIV infected patients with extra PTB were highly immune-compromised.

In one study conducted in Thailand risk of death during TB treatment increases as the age of patient increase (26). But in our study age was not associated with mortality during TB treatment. This might be due to majority of TB-HIV co-infected patients in this study were in the younger age group.

Not initiation of CPT was associated with high risk of mortality. In line to this, studies in district of South India and Sub-Saharan Africa showed that CPT was significantly associated with mortality (30, 40). But in our study likelihood of not taking CPT may be due to early deaths after diagnosis of TB and HIV. This may over estimate benefit of cotrimoxazole prophylactic therapy.

7. STRENGTH AND LIMITATIONS

Strength

This study considers time of event for analysis which enables us to consider contribution of censored study subjects.

Limitations

Our study was subjected to several important limitations.

Information about other biomedical predictors for death that may have confounded this study, such as drug resistance, severity of immune suppression, or co morbidities, were not available.

We were also unable to collect adequate information about specific type of extra pulmonary TB, patient recent CD4 count.

Data about adverse events and causes of death, which are critical to assessing the risks of combined ART and TB treatment, were not collected.

Since most deaths occur at home, it was difficult to trace all deaths.

Exclusion of patients who transferred out may bias our results slightly.

8. CONCLUSIONS

Significant difference was observed in mortality rate during TB treatment between on ART and non-ART cohorts. Incidence rate of mortality during TB treatment is significantly higher in ART not started TB-HIV co-infected patients. In both On ART and Non-ART TB-HIV co-infected patients mortality was high in the first month of TB treatment.

Despite the availability ART from health institutions, death was common and was strongly associated with the absence of ART during TB treatment.

Risk of death was over 65% lower in TB-HIV co-infected patients treated with ART compared with those not treated with ART.

In multivariate analysis being ambulatory, CD4 count category 0-75cells/µl, 75-150cells/µl and 150-250cells/µl, extra pulmonary TB, not initiation of CPT and treatment in hospital were independent predictors of increased risk of mortality during TB treatment.

9. RECOMMENDATIONS

The country should move to start ART for all TB-HIV co-infected patients irrespective of CD4 levels as per the WHO recommendation.

Expanding use of ART is critical to improve the survival of TB-HIV co-infected patients.

Reducing mortality in this population will require intensive collaboration between HIV and TB programs and should target high levels of ART uptake and closely monitor progress in implementation.

Further prospective studies should be conducted to identify risk of mortality during TB treatment.

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11. ANEXES

ANEX I Data collection format

INTRODUCTION

This patient information collection format is intended to assess risk factors of mortality in TB-HIV co-infected patients with and without ART in Bahirdar town governmental health institutions. The study will be conducted through reviewing patient records in TB and ART clinic and visiting the home/calling if the status of the patient is not recorded or found in the ART follow up form and TB registration book. The study is aimed to fill the information gap and provide evidence for planners, decision makers and program implementers related to ART and TB activities.

Date_____/_____ /_____ Questionnaire code_____

Name of the health institutions_____

Name of data collector_____ signature_____

Name of supervisor_____Date_____ signature_____

Part-I SOCIO DEMOGRAPHIC CHARACTERISTICS (to be filled from ART form)

No	**Variables**	**Coding categories**	
101	Year	_____	
102	Address	1. Urban 2. Rural 9. Unknown	
103	Age(years)	_____	
104	Sex	1. Male 2. Female 9. Not recorded	
105	Religion	1. Orthodox.	

		2. Muslim 3. Protestant. 4. Catholic 5. Others specify_____ 9. Not recorded	
106	Marital status	1. Single 2. Married 3. Divorced 4. Widowed 5. Separated 9. Not recorded	
107	Educational status	1. Not educated 2. Primary 3. Secondary 4. Tertiary 9. Not recorded	
108	Occupational status	1. Farmer 2. Merchant 3. Government employee 4. Non government employee 5. Day laborer 6. Driver 7. Commercial sex worker 8. Jobless 9. Other specify---------- 99. Not recorded	

Part II: Base line Clinical, laboratory and ART information

No	**Variables**	**Coding categories**	
201	Past opportunistic illness(list all mentioned)	1. Zoster 2. Bacterial pneumonia 3. Thrush(oral/vaginal) 4. Diarrhea (chronic/acute) 5. Pneumocystis pneumonia 6. Ulcers (mouth/genital) 7. Extra pulmonary TB 8. Cryptococcus meningitis 9. Other (specify)……. 99. Not recorded	
202	Past TB treatment	1. Yes 2. No 9. Not recorded	**If 2 and 9 skip to 204**
203	Past TB treatment type	1.2SRHZ/6EH 2.2HRZES/1HRZE/5HRE 3.2HRZE/6HE 4. 2SRHZ/4RH 5. Not determined 9. Not recorded	
204	Past prophylactic medications (check all)	1. Not given 2. Cotrimoxazole 3. Fluconazole 4. Other medication-------- 9. Not recorded	
205	Weight at base line	_____Kg	
206	Height at base line	_____cm	

207	Body mass index	_____ kg/m^2	
208	Functional status	1. Working 2. Ambulatory 3. Bed ridden 9. Not recorded	
209	WHO clinical staging	1. Stage III 2. Stage IV 9. Not recorded	
210	CD4 count	_____ cells/µl	
212	Hemoglobin level	_____ mmHg	
212	ALT	_____	
213	AST	_____	
214	Acid Fast Bacilli result during TB diagnosis	1. Positive 2. Negative 3. Not determined	

Part III: TB location and category

No	Variables	Coding categories	
301	TB location site	1. Smear +ve PTB 2. Smear -ve PTB 3. Extra PTB(Specify_____) 9. Not recorded	
302	TB type	1. New 4. Failure 2. Defaulter 5. Chronic 3. Relapse 6. Retreatment 7. Other 9. Not recorded	
303	Treatment Regimen	1. Category I 2. Category II 3. Category III 9. Not recorded	

Part-IV Anti-TB, ART and Prophylactic medication

No	**Variables**	**Coding categories**	
401	Date of TB diagnosis	_____/_____/_____	
402	Date of anti-TB initiation	_____/_____/_____	
403	Confirmed HIV+(date)	_____/_____/_____	
404	Anti-TB regimen	1. 2HRZE/6HE 2. 2HRZES/1HRZE/5HRE 3. 2RHZ/6EH 4. 2HRZE/4RH 9. Not recorded	
405	Missed days during DOTS	_____	
406	ART treatment	1. Started 2. Not started	**If 2 skip to 412**
407	Time of ART initiation	1. Before TB treatment 2. Less than 2 weeks 3. 2 weeks-2month 4. 2-4 month 5. Greater than 4 month	
408	ART eligibility criteria	1. CD4<200 2. WHO stage IV 3. WHO stage III with TLC<1200 4. Not recorded	
409	Date of ART initiation	___/_____/_____	
410	ART Regimens given	1. la=d4t-3TC-NVP 2. lb=d4t-3TC-EFV 3. lc=AZT-3TC-NVP 4. ld=AZT-3TC-EFV 5. Tdf-3TC-NVP	

		6. Tdf-3TC-EFV 7. 2nd line regimens	
411	Adherence to ART drugs	1.Good 2.Fair 3.Poor 9.Not recorded	
412	CPT prophylaxis	1. Prescribed before TB treatment 2. Prescribed during TB treatment 3. Not started 9. Not recorded	**If 1 and 3** **Skip to 413**
413	Date of initiation of CPT	_____/_____/_____	
414	Flucaonazole treatment	1. Prescribed before TB treatment 2. Prescribed during TB treatment 3. Not recorded	

Part V Patient's follow up information (to be filled from ART follow up form and TB logbook).Please document the current or the recent results.

No	**Variables**	**Coding categories**	
501	Latest follow up date	____/___/_____	**For ART started**
502	Duration since initiation of ART	_____(months)	
503	Recent weight in KG	_____	
504	Recent functional status	1. Working 2. Ambulatory 3. Bedridden 4. Not recorded	
505	Recent WHO staging	1. Stage III 2. Stage IV	
506	Recent Opportunistic infections	1. Zoster 2. Bacterial pneumonia	

		3. Thrush(oral/vaginal) 4. Diarrhea (chronic/acute) 5. Pneumocystis pneumonia 6. Ulcers (mouth/genital) 7. Extra pulmonary TB 8. Cryptococcus meningitis 9.Other (specify)……	
507	ART Drug side effect	1. No 2. Nausea 3. Diarrhea 4. Fatigue 5. Headache 6. Numbness 7.Rash 8.Anemia 9. Fat change 10. Night mare 11. Dizziness 12. Others	
508	Recent CD4 count	_____	
509	Outcome of TB treatment	1. Cure 2. Treatment completed 3. Default 4. Failure 5. Death	
510	Date of time of completion	_____/_____/_____	

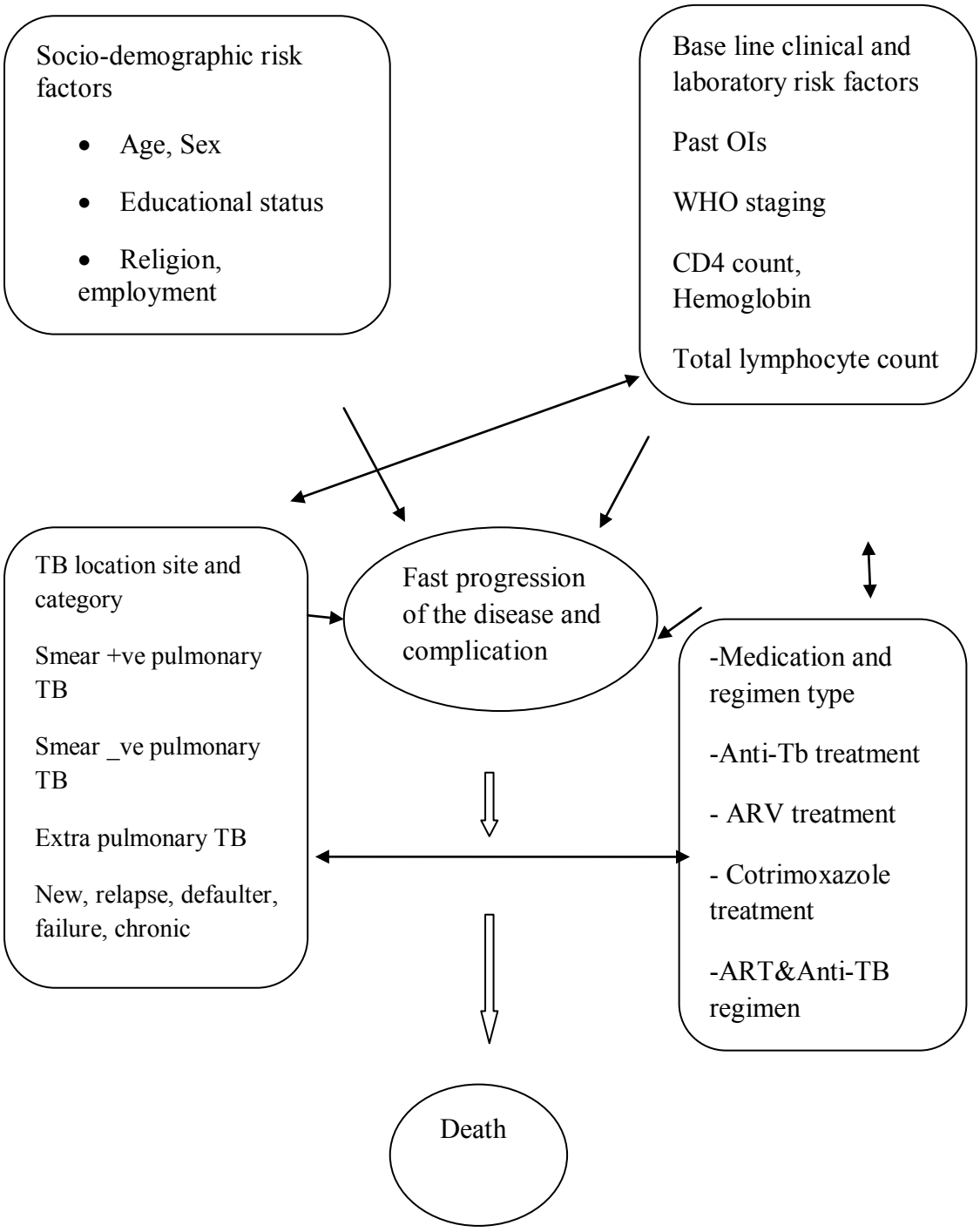
Part VI: Base line Social condition

NO	Variable	Coding category	
601	Religious/supportive	1. Yes 2. No 9. Not recorded	

602	HIV serostatus disclosure	1. Wife/husband 5. Relatives 2. Own child 6. Nobody knew 3. Parent(s) 7. Others specify___ 4. Brother(s)/sister(s) 9. Not recorded	
603	Condition of the husband/wife	1. Health 2. Chronically ill 3. Dead 4. Unknown 9. Not recorded	**Ask if Married and skip to 608 if 3**
604	HIVstatus of husband or wife	1. Not asked 2. Positive 3. Negative 4. Unknown 9. Not recorded	If 1,3,4 skip to 606
605	Was/is on ART	1. Yes 2. No 9. Not recorded	
606	TB status of husband or wife	1. Not asked 2. Positive 3. Negative 4. Unknown 9. Not recorded	If 1,3,4 skip to 606
607	Was/is on TB Rx	1. Yes 2. No 9. Not recorded	
608	General concern identified	1. Financial issue 6. HIV status disclosure 2. About the children 7. Adherence to	

		treatment 3. Marital relationship 8. Dietary problems 4. Family relations 9. Other specify__ 5. Bereavement/grief 99. Not recorded	

Annex II. Conceptual framework



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: Balewgizie Sileshi

Signature: _____

Date _____

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

Name: Dr. Nigussie Deyessa (MD, MPH, PhD)

Signature: _____

Date: _____