ADDIS ABABA UNIVERSITY

FACULTY OF MEDICINE

SCHOOL OF PUBLIC HEALTH

CLINICAL PRESENTATION AND TREATMENT OUTCOME OF TB AMONG HIV POSITIVE TB PATIENTS ON SHORT COURSE DOTS IN HAWASSA HEALTH CENTER

A RETROSPECTIVE COHORT STUDY

By

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Approved by the Examining Board

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ACRONYMS(ABBREVIATIONS)

AAU	Addis Ababa university
AIDS	Acquired Immune Deficiency Syndrome
ART	Anti Retro viral treatment
CPT	Co trimoxazole Prevented Treatment
DOTs	Directly Observed Treatment, Short course
EHNRI	Ethiopian Health and Nutrition Research Institute
EPTB	Extra-pulmonary Tuberculosis
FMOH	Federal Ministry of Health
HAART	Highly Active Anti-Retroviral Treatment
HBCs	High Burden countries
HCT	HIV Counseling and Tasting
HIV	Human Immuno Deficiency Virus
HHC	Hawassa Health Center
IPT	Isoniazed Preventive Therapy
MDGs	Millennium Development Goals
MOH	Ministry of Health
NGOs	Non Governmental Organizations
NTCP	National Tuberculosis Control Program
NTLCP	National Tuberculosis and Leprosy Control Program
OI	Opportunistic Infection
PIHCT	Provider Initiated HIV counseling and Testing
TB	Tuberculosis
VCT	Voluntary counseling and Testing
WHO	World Health Organization

ABSTRACT

Background information: In contrast to, many initiatives implemented to tackle Tuberculosis, many countries have not so far reached the targets set by WHO. The main reason mentioned so far was the impact of HIV infection. Therefore, it is essential to determine the impact of HIV/AIDs on the clinical presentation and treatment outcome of tuberculosis locally.

Objectives: To compare clinical presentation, treatment outcome of TB and on treatment survival among HIV positive and negative TB patients who are through (DOTs).

Methods: A retrospective cohort study design was employed to compare the clinical presentation of TB and its respective treatment outcome between the exposed; HIV positive (n=370) and non exposed; HIV negative TB patients (n=370) who were through the short course DOTs in Hawassa Health Center from 2006-2010. Patient's HIV status during the diagnosis of TB or initiation of DOTs was considered as an exposure and TB treatment outcome was considered as the outcome variables. Standard WHO definition, is used to classify tuberculosis cases and TB treatment outcomes.

Results: Smear negative PTB was significantly the frequent presentation, 0.32, 95%CI (0.25, 0.39; Z=8.76, P=0.000) among HIV positive study subjects, while significant difference in proportion of smear positive PTB; (-0.26; 95%CI (-0.33 -0.19; Z=-6.25, P=0.000) was in favor of HIV negative individuals. Compared to HIV negative TB patients ,cure rate was substantially lower in HIV positive TB patients (73% vs. 87.9%, z=-2.5, P=0.04), and the risk of death was statistically higher among TB/HIV co infected patients; AHR=1.6, 95%CI(1.01-2.6) during the course of DOTs. Regarding survival of TB patients, the survival probability was lower for HIV/TB co infected patients (Log rank test= 6.90, df= 2,P= 0.008).When adjusted for covariates, the survival probability is below 15% for HIV positive but above 85% in HIV negative TB patients at the end of DOTs period(8^{th} month). The independent predictors of death, while on treatment are age, weight and HIV infection.

Conclusion: On TB treatment survival probability and cure rate are substantially lower in HIV infected TB patients due to an increased death and unfavorable treatment out comes for the former and the later respectively. Therefore targeted and comprehensive management of TB should be considered in this group of patients.

Key words: Clinical presentation, treatment outcome, survival of TB patients, Hawassa health center

1. INTRODUCTION

Tuberculosis and HIV infection are the major ongoing public health problems throughout the world. Globally, there were an estimated 9.27 million incident cases of TB in 2007. This is an increase by 30,000 from its 2006 incidence cases. In the same year, an estimated 1.32 million HIV-negative people died from TB, and there were an additional 456 000 TB deaths among HIV-positive people. Deaths from TB among HIV-positive people account for 23% of the estimated 2 million HIV deaths that occurred in 2007**(1)**.TB is often the first opportunistic infection and a leading cause of death in HIV infected persons (2-5).

The primary reason for failure to meet the tuberculosis control targets (at least 70% for detection and 85% for cure among new sputum smear positive TB) set by WHO(6)in countries with high HIV prevalence is infection by HIV(7)**.** This is because of over diagnosis of sputum smear-negative TB; under diagnosis of sputum smear-positive TB; low cure rates; high morbidity, mortality and default rates during treatment (5, 7, 8) and atypical clinical presentation of TB in HIV infected patients(9)**.** By doing so, HIV-infection leads to diagnostic challenges and delays in identifying TB which subsequently places a profound impact on treatment outcome(9). Ethiopia ranks seventh among the world's 22 high-burden TB countries(10, 11). In Ethiopia, 20% of all TB cases were in HIV patients in 2007,TB was the cause of 76 thousand deaths, out of which 30% were among HIV positive patients(1, 10). And only 20,723(16%) of total TB patients have Known HIV result, of which (30.6%) are co infected with HIV(1). The impact of HIV on TB is illustrated by detection of higher proportion of EPTB and sputum smear negative TB than sputum smear positive TB since 2002(7).

1.1.Rationale of the Study

The goal of TB/HIV collaborative activities is to reduce mortality, default, and relapse and to prevent drug resistance (6, 7, 12, 13). However, Ethiopia suffers from shortage of data on treatment outcome of TB in HIV positive patients (1, 10, 14). Therefore availing scientifically sound data on the aforementioned gaps will have paramount importance for evaluation of the program and differentiated approach to TB in HIV positive patients. The present study was designed to assess the impact of HIV infection on the survival, treatment outcome and clinical presentation of TB while bridging the aforementioned gaps.

2. LITRATURE REVIEW

About a third of world population is infected latently by Mycobacterium Tuberculosis (6, 15). Globally, the latest data suggests that there were 1.4 million new HIV-positive TB cases in 2007 (out of a total of 9.27. million). Of the 9.27 million incident TB cases in 2007, an estimated 1.37 million (15%) were HIV-positive; 79% of these HIV-positive cases were in the African Region and 11% were in the South-East Asia Region(1). The synergy between HIV and TB is strong; in high HIV prevalence populations TB is the leading cause of morbidity and mortality, and HIV is fueling the tuberculosis epidemics. The HIV epidemic worsens the TB situations by: accelerating the progression from primary infection to disease and increasing the reactivation. The life time risk of developing tuberculosis in HIV positive patients is estimated to be between 50% to 60%, in contrast to the life time risk of only 5 to 10% in HIV negative patients(6)**.**

To address TB/HIV co infection, WHO has adopted TB/HIV collaborative activities to be implemented by high priority countries which collectively comprise 97% of world HIV infection(1). Collaborative TB/HIV activities are meant to ensure that HIV-positive TB patients are identified and treated appropriately, and to prevent TB in HIV-positive people. These activities include establishing mechanisms for collaboration between TB and HIV programmes (coordinating bodies, joint TB/HIV planning, monitoring and evaluation, HIV surveillance); infection control in health-care and congregate settings; HIV testing of TB patients and, for those TB patients infected with HIV,CPT and ART; and intensified TB case finding among people living with HIV followed by IPT for those without active TB(1, 16).

Many countries including Ethiopia kicked off with TB/HIV collaborative activities around 2002(16). However, the desired targets such as case detection rate and cure rates etc have not been attained except for treatment success rate. Why do most counties, do not attain the stated

TB control goals? Ranges of possible answers can be stated but infection with HIV is the primary reason for most to fail to attain the stated goals(7). Different studies illustrate this impact of HIV on TB as follows:

In immuno-competent patients, pulmonary tuberculosis is the most common form of tuberculosis encountered and accounts for about 80% of the cases, while extra pulmonary tuberculosis accounts for 20% and 53-62% of cases of tuberculosis in HIV-negative and -positive patients respectively, which places diagnostic challenges because of its overlapping clinical presentation with other opportunistic infections. Moreover, HIV-infected, smear positive TB patients tend to excrete significantly fewer organisms per ml of sputum than HIV- negative patients, which can lead to AFB being missed if the appropriate number of sputum samples as well as high power fields is not examined by microscopy. The sputum negativity tends to increase as the HIV disease and immuno-suppression progress. As a consequence of all these, treatment outcome of tuberculosis is affected by HIV infection especially in patients with advanced AIDs(9, 17)

According to different studies, the proportion of TB/HIV co-infected dying while being on TB treatment is higher on patients who sought care for TB symptoms than those identified by routine screening for TB(17). An estimated 37% of cases of smear-positive TB are not being treated in DOTS programs. The majority of HIV-positive TB cases do not know their HIV status, and those who know, are not yet accessing anti-retroviral therapy(18, 19). Therefore, undetected and un managed HIV in the vast majority of TB/HIV patients may also be the reason for low cure rate, high default ,treatment failure and relapse rates globally and nationally, calling attention to be paid on both epidemics management basing on appropriate and scientifically sound information.

Reports show that HIV infection increases progression of latent TB to TB disease by 50-100 fold, HIV infected people are more likely to have sever forms of TB(disseminated and EPTB),as a consequence of which TB is the leading cause of mortality and morbidity in HIV infected people with up to one in three dying from TB(15). From another report by MSF, up to half of all deaths of HIV patients are due to TB(20).Unlike, similar TB treatment outcome irrespective of ones sero status(8), WHO global TB report 2009, from 55 countries (mainly from developed) showed low cure rate(48% vs 82%), high death, default and transfer out rates in HIV positive new smear positive TB patients. The same report also indicates low treatment completion rate, high death rate and default rate in HIV positive new smear negative and EPTB TB patients(from 48 countries)(1).Another prospective cohort study conducted in Nigeria in 2006, is in agreement with the above WHO report. It showed low cure rate in HIV positive compared to HIV negative (60.3% v 80.0%; p = 0.0001) and high death rate in HIV positive than negative TB patients (15.5% v 3.1%; p = 0.00007)(21, 22).

Regarding death as a treatment outcome of TB, a patient with both diseases can be four times more likely to die during TB treatment than someone being treated for TB alone**(20).** Simple addition of co trimoxazole was found to reduce death rate during TB treatment by up to 40%(20) A multi-center observational study of HIV-infected patients newly diagnosed with TB in Thailand, showed statistically reduced risk of death with the use of ART, fluconazole and cotrimoxazole(23).

Regarding the survival rate, HIV negative TB patients have better survival after treatment than HIV infected TB patients. A controlled clinical trial conducted in Brazil demonstrated that the probability of 12 and 24 months survival rates as 77 and 69 respectively in HIV sero- positive

TB patients and 100 and 98 in HIV sero-negative TB patients (24). In the same study, the six months treatment completion rate was significantly different in the two groups, highest (99%) in HIV negative and 77.6% in HIV positive TB patients. This difference may be due to high rate of adverse effects of TB treatment in HIV positive patients (24).

Similarly a comparative study which compared 247 HIV-infective patients with smear positive pulmonary or clinically confirmed EPTB with 312 HIV-negative TB patients showed higher mortality in HIV-infected patients (6% vs 0.4%) during treatment(25). According to the same study, treatment outcome of TB depends on the HIV status, type of TB and age group which is illustrated by the death of one third of all HIV-positive patients and half of the new HIV-positive smear-negative pulmonary patients during treatment. The postulated reasons for high death rates among smear-negative patients being incorrect diagnosis, as there are many operational difficulties in resource-poor settings in Sub-Saharan Africa(8, 25).

Data on the outcomes of treatment for HIV-positive and HIV negative TB patients reported mostly from Region of the Americas and the European and fewer data for African countries even though Africa accounts for 79% of estimated HIV-positive cases show lower treatment success rates among HIV-positive patients, due mainly to higher death rates and, to a lesser extent, higher default rates(1).

HIV infection not only affects treatment outcome of TB but also its clinical presentation. A retrospective cohort study conducted in the San Francisco showed that HIV-infected cohort was significantly more likely to have EPTB in addition to pulmonary involvement at the time of diagnosis but significantly less likely to have cavitary disease on initial chest radiograph as

compared with the HIV-uninfected cohort (all $p < 0.001$) (26, 27).This finding is illustrated by another study, where, extra pulmonary TB is higher in patients with HIV than those without it (18.4% in the former vs 11.6% in the latter)(28). Similarly, another study conducted in Tanzania illustrates more EPTB in HIV infected people by diagnosing 30% of HIV/TB co infected patients in WHO stage III and 70 % in stage IV (29)

As postulated by many researchers, relapse rate of TB was significantly higher in those with HIV infection. 6% of 196 HIV infected and 0.8% of 362 non HIV infected TB patients had relapse (true relapse as confirmed by molecular genotyping) after completing therapy with relapse rates of 9.31 and 0.97 per 100 person-years respectively ($p < 0.001$).

Potential risk factors for relapse were also assessed. HIV status ($p = 0.003$), and receiving a regimen that was intermittently dosed ($p = 0.004$ were found to be independent predictors of relapse. It also showed association to duration of treatment, with higher relapse rate among those who completed tuberculosis treatment within a 6-month period (23.4 per 100 person-years [5 of 33 cases] vs. 7.0 per 100 person-years [8 of 163 cases] for patients treated longer; $p = 0.04$)(26),and patients who received 6 months of tuberculosis treatment were four times more likely to relapse than those treated , longer than 6 months, and patients who received intermittent dosing were four times more likely to relapse than those who had daily dosing, however extension of intensive phase of TB treatment was associated with reduced relapse rate(26).

2.1. Factors related to unfavorable TB treatment outcomes

A prospective cohort study conducted in Brazil, investigated risk factors for unsuccessful TB treatment outcomes. Variables significantly and independently associated with unsuccessful TB

treatment (treatment failure, death, and default) were the 20-34 and 35-49-year age groups, prior TB treatment, illiteracy, HIV infection, alcoholism, and health district. The attributable risks of these factors were as follows: age 20-34 years, 51%, and 35-49 years, 48.4%; prior TB treatment, 41.2%; illiteracy, 35.5%; HIV infection, 68.3%; and alcoholism, 51%. It is clear from the findings that highest population-attributable risk percentages were related to HIV infection and alcohol consumption (30).Treatment delay of more than 60 days was associated with treatment failure and death. Treatment delay allows progression of the disease to a more severe clinical phase in which cure becomes more difficult.

Completion of TB treatment was most affected by medication intolerance (side effects especially to INH) and commuting difficulties for follow-up visits (distance travelled). Defaulting from TB treatment was therefore associated to these factors (31). Studies also identified risk factors for death due to TB, among which were, older age, male sex, absence of cough, more than one site of TB, bacteriologically confirmed laboratory results and resistance to at least INH and Rifampicin or to at least INH but not rifampicin (32).

3. OBJECTIVES

3.1 General Objectives

- To compare the clinical presentation and treatment outcome of TB and on treatment Survival between HIV positive and negative TB patients treated for TB under short course chemotherapy (DOTs) in Hawassa Health Center.

3.2 Specific Objectives

- To examine differences in clinical presentation of TB between HIV positive and negative TB patients.
- To compare treatment outcome of TB between HIV positive and negative TB patients on short course DOTs.
- To compare Survival between HIV positive and negative TB patients on DOTs.
- To identify factors for Survival in TB/HIV co-infected patients.

4. METHODOLOGY

4.1. Setting

A retrospective observational study was conducted in February 2010 at Hawassa Health Center which is found in the capital of SNNPR, Hawassa. Hawassa health center is the only governmental health center till the beginning of 2009.The health center provides services to more than 124,266 populations. TB/HIV collaborative activities have been launched in the health center since 2006/07. A TB patient who comes to the health center for TB treatment undergoes a process called PIHCT, where the TB care provider councils the patient for HIV test. The patient's HIV status and other relevant information including treatment outcome is recorded on the TB log book prescribed by Ministry of Health of Ethiopia. The national tuberculosis programme manages new tuberculosis cases with 8 months course of treatment with a combination of drugs such as (Isoniazid, Rifampin, Pyrazinamide, and Ethambutol for 2 months (intensive phase) followed by EH for 6 months (continuation phase), [2HRZE/6EH]) is administered for a new TB patient free of charge.

N.B The study was planned at the proposal stage to be conducted at two centers; Hawassa referral hospital and Hawassa health center. However, when it was learned immediately before the time of data collection that most of patients in the hospital were smear negative PTB, which cannot be representative of the reality and most are referred to centers outside, it was determined to limit the scope of this study to the health center.

4.2 Study Design

A retrospective cohort study design was employed to compare the clinical presentation of TB and its respective treatment outcome between HIV positive and negative patients who were through short course DOTs. Patient's HIV status during the diagnosis of TB or time of initiation

of DOTs was considered a main exposure variable, and TB treatment outcome (cure, treatment failure, treatment completion, and death), clinical presentation of TB and time until on treatment death were considered as outcome variables.

4.3 Study Population

4.3.1 Source Population: All TB patients who are on DOTs and aged 15years or more.

4.3.2 Study Subjects: All TB patients, whose HIV status was determined, started DOTS and ended up with any one of TB treatment outcomes.

4.4 Starting and End points of the follow up

Both the exposed (HIV positive) and non exposed (HIV negative) TB patients were followed at least on the register starting the date they started DOTs until any one of the aforementioned TB treatment outcomes were observed in the course of DOTS therapy. The duration of the follow up period is defined as 8 months from the beginning of the TB treatment to the date the first outcome was registered as final.

4.5 Inclusion and Exclusion Criteria

4.5.1 Inclusion Criteria: Any TB patient with a known HIV status, 15 or more years of age that had initiated TB treatment and ended up with any one of TB treatment outcomes.

4.5.2 Exclusion Criteria: Cases with initial drug resistance and age younger than 15 years were not part of the study.

4.6 Sampling procedures

Different sampling scheme was employed for the exposed and non exposed groups to have reasonably comparable groups. All TB patients with HIV infection who fulfill the inclusion criteria were included in the study for their relative small number. Because HIV negative TB patients were adequate enough to be sampled, they were selected using simple random sampling scheme.

4.7 Sample size determination

Sample size was determined using two-population proportion formula, taking type one error to be 5%, and 80 % power.

$$n_1 = \frac{\left[z_{\alpha/2}\sqrt{(r+1)\bar{p}\bar{q}} + z_{1-\beta}\sqrt{rp_1q_1 + p_2q_2} \right]^2}{r(p_1 - p_2)^2}, \; n_2 = r \times n_1$$ Where;

- n_1= number of TB patients with HIV infection (Exposed)
- n_2= number of TB patients without HIV infection(non expose
- r= the ratio of exposed to non exposed TB patients=1
- $\bar{p} = \frac{p_1 + r \times p_2}{r+1}$; $\bar{q} = 1 - \bar{p}$
- P_1= proportion of treatment outcome in HIV positive TB patients
- P_2=proportion of treatment outcome (cure) in HIV negative TB patients
- $z_{\alpha/2}$= Critical value at 95 % level of significance
- $z_{1-\beta}$= standard normal distribution value corresponding to power

Sample size was calculated for different TB treatment outcome variables (cure, death, defaulting, and treatment completion). Since there was no study conducted in Ethiopia addressing these issues, proportion of treatment outcomes from different studies conducted elsewhere and WHO 2009 reports were considered (1, 21, 22, 24, 25)(Table 1).

Table 1: Sample size determination procedure, 2009

Treatment outcome	Proportion(%) in		Sample Size for		Total Sample size
	Exposed	Non Exposed	Exposed	Non Exposed	
Cure	60.3	80	93	93	186/0.3=620*
	48	82	35	35	70/0.3=233
Death	15.5	3.1	100	100	200
	6	0.4	188	188	376
	13.7	0.5	73	73	146
Completed	77.6	99	43	43	86
Treatment success	59.6	75	157	157	314
EPTB	52	20	40	40	80

Unlike the denominator for death, treatment complete and success which is all types of TB, cure rate was calculated from smear positive PTB cases only. According to the 2008 MOHE TB report, 30% of all forms of detected TB was sputum smear positive cases**(7)**.Therefore, the calculated total sample size from this view was 186/0.3= 620. Taking the largest calculated sample size, 620 and considering 10% contingency for incomplete and inconsistent data, the resulting minimum sample size was 682(341 HIV positive and 341 HIV negative TB patients). However when it was learned in the field during data collection that it was possible to get extra

cases beyond the previous expectation, the sample size was increased to 740(**$n_1=n_2=370$**). In this case the power of the study has increased to **87%**.

4.8 Data Collection tools and procedures

Data collection format which helps to abstract necessary information from TB registration log book (Annex I) was prepared by the principal investigator in line with TB logbook(ministry of health format). First, TB patients from the TB logbook were identified as exposed (HIV positive) or none exposed (HIV negative), and then the outcome of TB treatment was sought forward as presented in **annex II**.

4.9 Data Quality Management

To ensure the quality of data, nurses who have been providing TB medications and recording patient information on TB/HIV register, were recruited and trained as data collectors. The principal investigator and supervisor frequently supervised the data abstraction process by checking completeness of the required type of data to correct faults if any on the spot. The investigator has entered coded questionnaires into EPI info version 3.3.2 statistical package. Once, data entry was through, data clean up was performed by running frequencies of each variable to check for accuracy, outliers, and consistencies. Regarding data, the diagnosis of pulmonary TB (smear positive and negative PTB) was carried out in the health center. The diagnosis was solely by microscope. A patient was regarded as smear positive if at least two smear results are positive; and negative if the patient with the clinical symptoms and signs suggestive of TB shows no progress for antibiotics and has negative smear result. EPTB was not diagnosed in the health center but at hospitals. HIV infection was determined by rapid test.

4.10. Data (Statistical) Analysis

Data were entered into **EPI info version 3.3.2** for exploration and cleaning and exported to **STATA version 9.2 for windows, Texas, USA** for statistical analysis. Rates were calculated for each TB treatment outcomes in both groups (HIV positive and negative TB patients).Incidence rates with Person-months and cumulative incidence were calculated for unsuccessful TB treatment outcome.

Independent two sample t-test with equal variance was used to compare mean difference in continuous variables among HIV positive and negative samples. **Paired t- test** was used to compare mean change of weight from the baseline to weight after two months of treatment. A two sample test of proportion was used to test difference in proportion of different TB types and treatment outcomes between HIV positive and negative study subjects.

Normality of continuous variables was checked using **Kolmogorov-Smirnov test**, **kernel density** and different normality plots. Variables, which were found to refute normality assumption, were treated using a non parametric test; **Mann-Whitney U test** and **Kruskal Wallis test**. A one way **ANOVA** was used to test differences in weight among TB types after checking for normality and homogeneity of variance. P values of less than 0.05 and a confidence level of 95% by a two-sided test was considered to indicate statistical significance.

Cox proportional hazard model was used to determine the relative risk (hazard ratio) of death for each main baseline predictor of survival. To assess the association between baseline variable and mortality two strategies were used; first each baseline variables which do have at least 10 events (deaths) were entered into a separate Cox proportional hazards models. Second multivariate adjusted model was fitted with the predictors that were statistically significant at $p \leq 0.3$ in the

bivariate analysis; however only those that remained significant at $p \leq 0.05$ were retained in the final model. Life table survival analysis method was used to estimate on DOTs survival probability of TB patients.

Kaplan Meier survival curve was also used to estimate graphically the survival probabilities.

Observed differences in survival times among strata of different predictor variables were compared with Log rank test. Violation of proportional hazard assumption was checked by procedures: Log (-log (st) plots**,** Schoenfeld residual plots and by regressing Schoenfeld residuals against time to test for independence between time and residuals. Variables which were not found to refute the assumption were fitted into the Cox Model.

4.11 Study Variables

4.11.1 Dependent(Outcome) Variables: include Clinical presentation of TB, TB treatment out comes and survival time.

4.11.2 Independent Variables

- **Exposure variable:** HIV status
- **Background and other baseline variables:** include age, sex, residence, baseline weight, marital status, prophylaxis and ART history, treatment category, smear result, TB regimens(Annex III)

The outcome variable for survival analysis was time until death, defined as time in months which is from the date of initial diagnosis to death or, in the case of individuals who did not die, the last follow-up recorded by the health service. Individuals who died were considered failures and those who remained alive until the end of the study were considered censored

4.12 Operational Definitions

Standard WHO definitions were used to classify tuberculosis cases and TB treatment outcomes.

- **New case:** A patient who has never had treatment for tuberculosis
- **Cured** A patient who was initially smear-positive and who was smear negative in the last month of treatment and on at least one previous occasion.
- **Treatment completed:** A patient who completed treatment but did not meet the criteria for cure or failure.
- **Died:** A patient, who died from any cause during treatment.
- **Relapse:** a patient declared cured or treatment completed of any form of TB in the past, but who reports back to health service and is now found to be AFB smear positive or culture positive.
- **Treatment Failure:** A patient who was initially smear-positive and who remained smear-positive at month 5 or later during treatment. Also includes a patient who was initially sputum smear negative but who becomes smear positive during treatment.
- **Defaulter:** A patient who has been on treatment for at least 4 weeks and whose treatment was interrupted for 2 consecutive months or more.
- **Treatment Success:** The sum of patients who are declared "cure" and who have "completed" treatment. includes cured or completed
- **Un favorable** treatment outcome: includes failure, death, or default and transfer out
- **Favorable treatment outcome**: in cases of cure and treatment completed,
- **Treatment category**
    - **I-** includes new smear positive PTB, seriously ill smear negative PTB and EPTB
    - **II-**includes smear positive relapse, failure, and return after default; PTB patients who become smear positive after 2 months of treatment
    - **III-** includes new smear negative and EPTB, who are not seriously ill.
- **Clinical presentation of TB** – Type(form) of TB at presentation to the health facility or form of TB the patient is diagnosed with.

4.13 Ethical Consideration

The proposal was submitted to the Institutional Review Board (IRB) of Addis Ababa University, Faculty of Medicine for approval. Following the endorsement by IRB, Hawassa City administration health office and Hawassa health center were informed about the objective of the study through a support letter from the School of Public Health, AAU. Moreover, the administrators of the organizations were briefed verbally that the study subject will not be subjected to any harm as the study will be conducted through review of medical records alone as far as the confidentiality is guaranteed and that informed consent is also planned to be obtained from study subjects who might happen to be in the health center for any reason during record review. Subsequently a written permission was obtained from the city health office to the health center and oral permission from the health center administration.

To preserve the confidentiality, nurses working in TB/ART clinic, Hawassa health center were recruited to extract the data from the medical records. Moreover, no personal identifiers were recorded on data abstraction format. The recorded data were never accessed by a third person except the principal investigator, and is kept with a firm confidentiality.

5. RESULTS

5.1. Description of the Cohort

Among TB patients registered for DOTs program from 2006 –2010, the data of 740(370 HIV positive and 370 HIV negative) patients were retrieved from TB logbook for the study. Nearly all of the study subjects 723(97.7%); 99.2% of HIV positives and 96.2% of HIV negative TB patients were residing in the urban area(Hawassa City Administration). The median and inter quartile range(IQR) for the age of HIV positive TB patients were 30 and 25-36 years respectively while the corresponding values for HIV negative study subjects were 25 and 20-36 years. Males were predominant in both groups especially among HIV negative TB patients; 189(51.1%) in HIV positives and 228 (61.6%) in HIV negatives. Almost equal proportion of TB patients were treated for TB for the first time in both HIV positive 351(94.9%) and negative 345(93.2%) TB patients. Higher proportion of HIV positive 351(94.9%) than negative 322(87%) TB patients were treated as category one. But lower proportion of HIV positive 4(1.1%) than negative 25(6.8%)TB patients were treated as category three. CPT and ART initiation was appropriately recorded for 133(36%) and 91(24.6%) HIV positive TB patients respectively. Accordingly, among HIV positive TB patients, 124(33.24%) were known to have started CPT, but the majority 237(64.2%) had unknown CPT status. Regarding ART initiation, out of 370 HIV positive TB patients; 52(14.1%) were known to have started, 39(10.5%) were known not to have started, and the rest 279(75.4%) have no known history of ART initiation. Information on marital status was recorded for only 130 (35.1%) HIV positive patients, of whom 56(43.1%) were single and 225(60.8%) HIV negative TB patients, of whom 138(61.3%)were single (Table 2).

Table 2: Baseline characteristics TB patients treated under HHC from 2006- 10.

Baseline Variables	HIV Positive(n=370)	HIV negative(n=370)	Total
Residence			
Urban	367(99.2)	356(96.2)	723(97.7)
Rural	3(0.8)	14(3.8)	17(2.3)
Sex			
Male	189(51.1)	228(61.6)	417(56.4)
Female	181(48.9)	142(38.4)	323(43.6)
Age (years)			
15- 20	39(10.5)	101(27.3)	140(18.9)
21-40	279(75.4)	197(53.2)	476(64.3)
41-60	48(13)	58(15.7)	106(14.3)
60-90	4(1.1)	14(3.8)	18(2.4)
Marital Status(n=355)			
Single	56(43.1)	138(61.3)	194(54.6)
Married	64(49.2)	84(37.3)	148(41.7)
Divorced	9(6.9)	2(0.9)	119(33.5)
Widowed	1(0.8)	1(0.5)	2(0.6)
no mention**	240(64.9)	145(39.2)	385(52)
Case definition			
New	351(94.9)	345(93.2)	696(94)
Relapse	17(5)	22(6)	39(5.3)
Return after default	2 (0.5)	10.3)	3(0.4)
Failure	0	2(0.5)	2(0.3)
TB Type			
Pulmonary positive	80(21.6)	177(47.8)	257(34.7)
Pulmonary negative	234(63.2)	115(31.1)	349(47.2)
EPTB	56(15.1)	78(21.1)	134(18.1)
Rx Category			
I	351(94.9)	322(87)	673(91)
II	15(4.1)	23(6.2)	38(5.1)
III	4(1.1)	25(6.8)	29(3.9)
Diagnosis Center			
Hawassa Health center	275(74.3)	263(71.1)	538(72.7)
Hospital	88(23.8)	103(27.8)	191(25.8)
Others*	7(1.9)	4(1.1)	11(1.5)
CPT Initiated(n=133)			
Yes	123(92.5)		123(92.5)
No	10(7.5)		10(7.5)
No mention***	237(64.1)		237(64.1)
ART Initiated(n=91)			
Yes	52(14.1)		52(14.1)
No	39(10.5)		39(10.5)
No mention***	279(75.4)		279(75.4)

*The denominator for ** is 740, but for *** is 370(HIV positive). * includes other HCs & private health institutions*

5.2. Clinical presentation(Forms) of TB by HIV status

The commonest presentation of tuberculosis among HIV positive TB patients was Sputum smear negative Pulmonary TB 234 (63.4%). But, in HIV negative TB patients, the most frequently observed clinical form of TB was smear positive PTB 177 (47.8%), (Fig 1).

The observed difference in proportion of different TB types between HIV positive and negative study subjects, (Figure2**)** was tested using a **two sample test of proportion**. In accord with the graphically observed difference, the proportion of all TB types was significantly different between the two groups.

The significant difference in proportion; (-0.26; 95%CI (-0.33 -0.19; Z=-6.25, P=0.000) of Smear positive pulmonary TB was in favor of HIV negative individuals. Unlike, the case for Smear positive PTB, smear negative PTB was significantly higher 0.32, 95%CI (0.25, 0.39; Z=8.76, P=0.000) in HIV positive study subjects. Similarly, though the level of significance is of borderline, the proportion of EPTB was higher among HIV negative TB patients -0.06, 95% CI (-0.11 -0.004, Z=-2.10, P=0.045).

In addition TB was significantly predominant in males (P=0.0000).

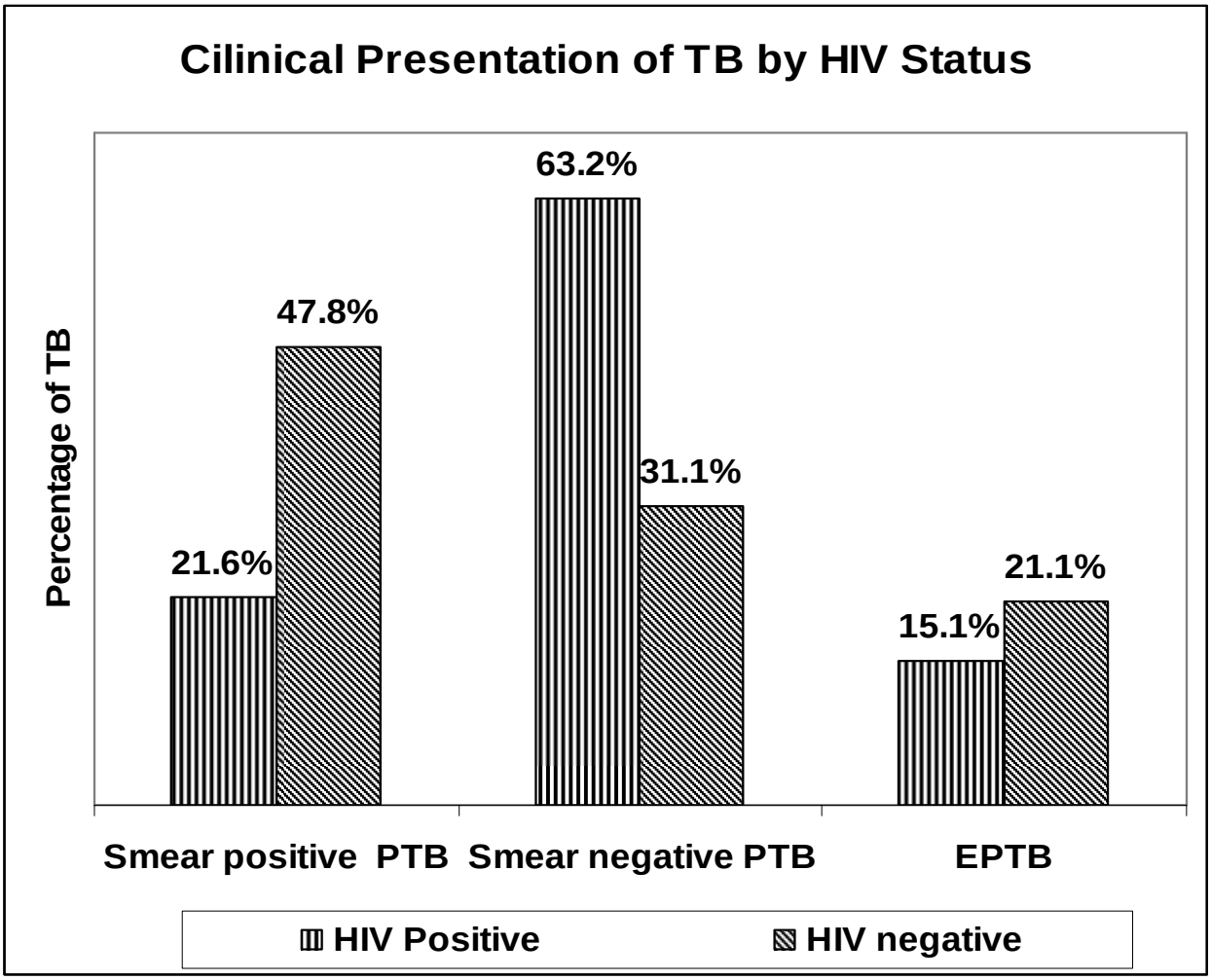

Fig.1: Clinical presentation of TB by HIV status, Hawassa Health Center, 2006- 2010

In an attempt to answer the basic epidemiologic question; **"What determines distribution of the three TB types** as observed above?, the role of ranges of variables if any was examined using different statistical methods.

To evaluate whether the population is the same in terms of age during the diagnosis of TB among the three types of TB (Smear positive PTB, Smear negative PTB and EPTB), a non parametric test; **Kruskal-Wallis test** was employed because age was not normally distributed as examined by kernel density, Kolmogorov-Smirnov test and other different graphical plots. There

was statistically significant difference in age at least among two TB types at diagnosis of TB **(Kruskal-Wallis test= 43.8, df =2, P= 0.0001).** The mean and median age were 27.6 and 25; 33.4 and 30; 30.4 and 28 years in smear positive PTB, negative PTB and EPTB respectively. The observed difference in age among TB types was further scrutinized using **Mann-Whitney U test as** a multiple comparison test to know which TB types differ. Accordingly, smear positive TB patients tend to be commonly diagnosed on average in relatively earlier age than smear negative TB patients **(Mann-Whitney U test, z=-6.6, P=0.000),** and EPTB patients (**Mann-Whitney U test,** z=-2.9, P=0.004). Similarly smear negative pulmonary TB patients in their turn are diagnosed in later ages than EPTB patients (**Mann-Whitney U test,** z= 2.35, P=0.02). More simply, among the study subjects, smear negative pulmonary TB was diagnosed in patients with relatively higher age, followed by EPTB and finally by smear positive TB.

In a similar manner, HIV negative TB patients were diagnosed of their TB at the median age of 25 years, while HIV positives at the median age of 30 years. This difference was statistically significant **(Mann-Whitney U test**, z = 4.89, P= 0.0000)

Although, it is difficult to ascertain that the study population was free from TB at the time they become HIV infected; for the intrinsic limitation of the study design employed, the cumulative incidence rate and or RR was calculated with the assumption that exposure to HIV precedes development of TB. Or more simply, TB in HIV positive patients was considered as an opportunistic infection coming late in the course of HIV/AIDs as in WHO clinical staging.

Majority of HIV positive patients 209(56.5%) developed TB after median age (>28 years) while majority of HIV negative patients 225(60.8 %) developed before the median age. Regarding the association between age at onset of TB and HIV status, risk of getting TB before age 28 was

found to be lower in HIV positive as compared to HIV negative study subjects (RR=0.72,:95%CI: 0.62-0.82, p=0.000), accordingly **the cumulative incidence** of developing TB before age 28 years was 43.5 and 60.8 per 100 when HIV positive and negative respectively. The risk of developing smear positive TB before median age was significantly higher among smear positive TB patients when compared to smear negative TB patients, (Table 3)

In consistence with table 3, the age at which females show up to seek care for TB was significantly lower (mean =29 years) than males (mean=32years) (**Mann-Whitney U test** = 3.346, P=.0008). The median age (in years), at which study subjects show up for care in the order of Median (IQR) was 27 (22-33) for females and 30(22-40) for males.

Table 3: Association of TB type, Sex and HIV status with age of getting TB among TB patients treated under Hawassa health center from 2006-2010.

		Developed TB before Median Age (28yrs)		Risk	RR(95% CI)
		Yes	No		
HIV Status	Positive	161	209	0.42	0.71(0.61-0.82)
	Negative	225	145	0.59	1
Sex	Male	196	221	0.47	1
	Female	190	133	0.59	1.25(1.1- 1.4)
TB type	P/positive	175	82	0.68	1.66(1.4-1.9)
	P/negative	143	206	0.41	1
	EPTB	68	66	0.51	1.23(1.0-1.5)

The median age under analysis is the global median age for the whole study subjects.

5.2.1. Weight difference among different categories

Weight of TB patients is taken to determine the dose of anti TB drugs at the base line and after intensive phase. These two weights (weight at the base line and after two months of anti TB treatment) are normally distributed. An independent **two sample t-test with equal variances**

was used to compare baseline weights between HIV positive and negative TB patients. The mean baseline weight was significantly lower among HIV positive TB patients (48.3 kg) than in HIV negative TB patients (51.6kg), t = -4.8, df= 738, P=0.000).

Similarly, **a one way ANOVA** was employed to ascertain, mean weight differences among types of TB. Accordingly, there was significant difference in mean weights by TB type both at the base line (F= 6.87, df =739, P= 0.001) and after two months of anti TB treatment (F=4.7, df=664 P=0.0096**),** (Table 4)

Table 4: Association of weight and different levels of variables using t-test and ANOVA for TB patients treated in Hawassa Health Center from 2006-2010.

Variables	Category	Mean weight(kg) Base line/after 2 months	Test Type	Test statistic baseline/after IP & df	P-value baseline/ after IP
HIV status	HIV positive	48.3/50.4	t-test	t=-4.8/ -3.9	0.000/0.0001
	HIV negative	51.6/53.3		df=738/663	
TB Type	Smear Positive PTB	50.5/52.7	ANOVA	F= 6.87/4.7	
	Smear negative PTB	48.7/50.7		df=739/664	0.0011/0.0096
	EPTB	52.1/53.1			

IP- intensive phase

To further, scrutinize the differences among different TB types, **Bonferroni** test was used. The mean weight difference was between sputum smear negative pulmonary TB and EPTB (Bonferroni, t= 3.3, P= 0.001) at the base line. But in the later (weight after 2 months), significant mean weight difference was observed between sputum smear negative and sputum smear positive TB patients (Bonferroni, t= -2.08, P= 0.032). Both the baseline and after two months weight were statistically lower in HIV positive and smear negative PTB patients (Table 4**)**

5.3. Treatment Outcome of TB

5.3.1. Treatment Outcome by TB Type

Treatment outcome indicators: cure, treatment complete, default, transfer to another center and death were assessed in relation to the HIV status and TB type of the patients.

Analysis of the outcome of TB treatment was computed for only 697 patients after excluding 43 patients whose treatment outcome was not known.

Cure rate was calculated in the same manner it has been worked up by MOH and WHO using the formula below, which might have importance in the program evaluation.

$$\text{Cure Rate} = \frac{\text{Number of New smear positive Cases "Cured"}}{\text{Total number of smear positive cases put under treatment}}$$

To have a better clue informative than the above, as the information is diluted because of inclusion of patients whose treatment end is unknown, cure rate was recalculated after excluding transfer outs from the denominator; and was found to be 85.5%.

Among the 697 study subjects, who come to the end of any one of the treatment outcomes, only 96(12.9%) have an unknown status (defaulted, and transferred out). Treatment completion rate was higher in EPTB patients 104(83.2%) than in Smear negative pulmonary TB patients 262(77.7%), but not statistically significant with two population proportion test (Z=1.28 P=0.2). Death was statistically higher (Z= 1.9**, P=0.047**) in Smear negative pulmonary TB patients; 47(13.9%) when compared to smear positive pulmonary TB; 20(8.5%). But there was no statistically significant difference in death rates between EPTB and both Smear negative and positive pulmonary TB patients (Z=1.48, P= 0.138 and Z=-0.09, P=0.9 respectively). Default rate was not statistically different among TB types (P>0.05).

5.3.2 Treatment Outcome by HIV Status

The proportion of each treatment outcome was compared between HIV positive and negative TB patients using two-sample test of proportion at 95 %CI to determine the impact of HIV infection.

Table 5: Comparison of treatment outcomes of Tuberculosis between HIV positive and negative study subjects, treated in Hawassa health center, from 2006-2010**.**

Treatment Outcome	HIV Status	Patients Registered (baseline)	Treatment outcome (proportion)	Proportion difference (95%CI)	Z value	P value
Cure	Positive	73	54(.739)	-0.13 (-0.24 ,-0.02)	-2.5	0.014
	Negative	162	141(.87)			
Completed	Positive	272	211(.775)	-0.04(-0.114,0.034)	-1.04	0.29
	Negative	190	155(.816)			
Died	Positive	345	50(.145)	0.065(0.02 - 0.11)	2.74	0.006
	Negative	352	28(0 .0795)			
Defaulted	Positive	345	19(0 .055)	.012(-0.02,0.044)	0.76	0.445
	Negative	352	15(.043)			
Transferred	Positive	345	8(.023)	-0.008(-0.03,0.02)	-0.65	0.513
	Negative	352	11(.031)			

Unlike for cure (calculated for smear PTB) and treatment completion rate (for smear negative PTB and EPTB), calculation of death, failure and default rates were from all TB patients who were through the DOT (n=697).

Cure rate was statistically lower in HIV positive than negative TB patients (73.9% vs. 87.0%, Z= -2.5, P= 0.014).But, treatment completion rate was not statistically different between HIV positive and negative TB patients; with a two population proportion test of difference and 95% CI:- -0.04(-0.114,0.034), (Table 5)

5.3.3 Death as a TB treatment outcome

All the 740 study subjects have contributed to a total of 5012.867 months of follow up by the time they ended up with one of the aforementioned treatment endpoints; outcomes, and a total of 78 deaths have been recorded during the course of DOTs. Accordingly, the overall incidence rate of death

among all the study subjects was 15.6 deaths per 1000 person- months of follow up. The incidence rate of death among HIV positive TB patients was 20.6 per1000 person-months of follow up; whereas it was 10.8 per 1000 person - months of follow up in HIV negative TB patients. HIV positive TB patients had significantly higher risk of death when compared to HIV negative TB patients. (RR=1.89, 95% CI: 1.2- 3.1). In agreement with this is the finding in table 2 above, that there was significantly higher death in HIV positive TB patients (Z=2.74, P=0.006)

HIV positive TB patients were more likely to die while on DOTs if they have also smear positive PTB, (**Table 7)**

Table 7: Association of death and TB type by HIV status, Hawassa Health center, 2006-10.

	Smear Positive PTB		**Smear Negative PTB**		**EPTB**	
	Total TB	**No Died**	**Total TB**	**No Died**	**Total TB**	**No Died**
HIV Positive	73	11	224	33	48	6
HIV Negative	162	9	113	14	77	5
Proportion difference(95%CI)	0.095(0.005, 0.18)		0.023(-0.05,0.1)		0.06(-0.05-0.17)	
P-Value	0.016		0.56		0.249	

Other TB treatment outcomes; failure, default and transfer out were not statistically different among the two groups; HIV positive and negative, i.e. Failure; RR= 1.5, 95 %CI: 0.25-8.90); Transfer out, RR=0.73 95%CI:0.3- 1.80, and default, RR =1.3, 95%CI: 0.65-2.5.

The treatment outcomes were re-categorized into favorable (cured and treatment complete) and unfavorable (death, failure, default and transfer out) to determine strength of association. The overall risk of developing unfavorable treatment outcomes in the study cohort was 27.1 events per 1000 person-months of follow up during the course of DOTs. Risk of developing

unsuccessful treatment outcome was significantly higher among HIV positive (Incidence rate=32.9 per 1000 person-months of observation) than negative TB patients (21.7 per 1000 person-months of follow up) during the course of DOTs (RR=1.52, 95% (1.1 - 2.2). About 11.2 unfavorable treatment outcomes in HIV positive TB patients per 1000 person months of follow up in this study was attributed to their exposure to HIV infection (AR= 11.2, 95%CI (2 to 20 per 1000 person- months of follow up).

Default rate was not statistically higher in HIV positive TB patients (RR=1.3, 95%CI: 0.68- 2.5) among the study subjects. In the same manner, there was no statistically significant difference in default rate among any one of the TB types, and among males and females (P- value for the proportion difference of two populations >0.1).

5.3.4 Time of occurrence for Unfavorable Treatment Outcomes

The timing of occurrence unfavorable treatment outcomes was one of the interests of the investigator. The study revealed that, most of the death 46(58.9%) and default 21(61.7%) occurred during the intensive phase of treatment while majority the patients 12(63.2) were transferred out in the continuation phase. In accord with the above finding, the mean and median time of death for those who died in the intensive phase was 0.93 and 0.97 months respectively. Generally most of the deaths occurred at the end of first month of intensive phase. Similarly, majority of the default occurred in the mid of intensive phase with a mean and median of .99 and 1.1 months after initiation of treatment. Concerning the association between HIV status; and death and default during the intensive phase, the risk appears to be higher among HIV negative TB patients, however not significantly(Risk=0.48 for HIV positive and 0.78 in HIV negative,

RR=1.15, 95%, 0.7,1.9,P= 0.50 for death) and (Risk =0.046 and 0.348 for HIV positive and negative respectively, RR=1.16, 95%CI: 0.58, 2.34 for default)

The role of sex in the treatment outcome of tuberculosis was assessed using **a two population proportion comparison test**. No one of the treatment outcomes had significant difference across the strata of sex (P>0.1.

The presence of difference in treatment outcome among the three treatment categories is not determined because, disproportionately higher proportion of TB patients 633(90.8%) were in TB treatment category one. The rest 35(5.02%) and 19(4.2%) TB patients were in category two and three respectively.

5. 3.5. Sputum Conversion Rate as a Treatment Outcome

The sputum conversion rate of smear positive pulmonary TB patients was determined. Among 257new sputum smear positive pulmonary TB patients evaluated at the base line, 17 patients failed to survive to the end of intensive phase. The sputum smear evaluation at two months of DOTs was documented for 231 patients only. Of those evaluated at the end of intensive phase, 226(97.8%) had their sputum smear converted to negative. Sputum smear conversion rate was also determined between HIV positive and negative TB patients to have an insight of HIV effect on smear positive pulmonary TB. Accordingly, among 68 new smear positive TB patients evaluated at the time of diagnosis, 8 failed to reach to the end of intensive phase and 1 remained to be sputum smear positive at the end of intensive phase among HIV positive patients. This makes the sputum smear conversion rate to be about 99.3% in HIV positives; and among158 new sputum smear positive TB in HIV negative patients, 149(93.7%) patients were evaluated at the

end of intensive phase. None had smear result positive at the second month. Sputum smear conversion rate in this group was 100%**.**

Smear positive TB patients who defaulted, died and who were transferred out before the second month were excluded from the denominator)

5.3.6. Weight gain as an indicator of improvement

To determine the presence of significant weight gain at the end of intensive phase by HIV status, TB type and treatment category, **a paired sample t- test** was used. The study revealed that the global (un stratified) weight gain was statistically significant (t = -10.4, df= 664, P= 0.0000). The observed weight gain was further analyzed among different strata to determine the presence of any difference. There has been statistically significant weight gain irrespective of one's HIV status (in HIV positive: t =-6.9, df =328 p=0.000 and in HIV negative: t =-8.2, df=335, P=0.000) during the period of intensive Phase. Similarly, weight gain was statistically significantly higher in later measurements at two months as compared to the base line, in all types of TB patients using paired**,** t-test($p<0.0001$).Except for treatment category one, weight gain was not statistically significant in categories two and three($P>0.05$).

The difference in weight gain (the magnitude of the difference) between HIV positive and negative TB patients was tested to be non significant statistically using two-sample Mann-Whitney U test($z = 0.459$, $P = 0.65$). The median weight gain between the two groups was the same (1kg). Similarly, there was no statistically significant evidence to support that weight gain was associated to any one of TB types (Pearson $X^2= 1.66$,df=2 $P = 0.437$)

5.4. Survival Status of the Study Subjects

Of 740 study subjects followed for 8 months, 78(10.5%) died and the rest 662(89.5%) became censored during the follow up period. The minimum follow up period was 10 days and the maximum being 8 months. The majority of death; 46(58.97%) occurred in the intensive phase, while the rest 32(41.03%) occurred during the intensive phase.

Life table method was used to estimate survival and hazard probabilities of TB patients. As by the life table analysis, the probability of survival at the end of the intensive phase was almost the same in HIV positive and negative TB patients (93.7% and 93.97% respectively). After intensive phase, the survival probability in HIV positive TB patients declined sharply to 85.7% within seven months of treatment, and then remained at 85.7% until all patients become censored at month eight. But in HIV negative TB patients, at the end of the 8^{th} month, by which time all patients were censored, the survival probability was 92.2%, (Table 7)

In agreement with the life table estimation, the **Kaplan Meier survival curve**, (Figure3) shows statistically lower survival in HIV positive TB patients (log rank statistic= 6.90, df= 2, ***P***= 0.0086). Females survival was slightly higher than males before 4^{th}month and becomes slightly lower after 6^{th} month of DOTs, but not statistically significant (**log rank=0.02, df=1, P=.9**). For the survival probability in relation to age, age greater than 60 years carries the lowest survival probability, as compared to other age categories; i.e. at the end of intensive phase, the survival probability in this age group was 82.7% and reduced to 64 % at the time of the treatment completion; at 8 months. But, the survival probability at the end of intensive and continuation phase was 97.1% and 92.6%; 94.2% and 89.9%, and 89.5 and 84.3 % in age categories: less than 20 years, 21-40 years and 41-60 years respectively. This carries a statistically significant difference in the survival curves (log rank=16.10,df=3,P= 0.0011)

Table 7: Life table Survival and Failure probabilities of TB patients by HIV status, Hawassa health center 2006- 2010.

	HIV Positive					HIV Negative				
Interval	N(j)	Death(j)	Censored(j)	Survival(j)	Failure(j)	N(j)	Death(j)	Censored(j)	Survival(j)	Failure(j)
(0- 1)	370	10	7	0.9727	0.0273	370	13	5	0.9646	0.0354
(1-2)	353	13	7	0.9365	0.0635	352	9	8	0.9397	0.0603
(2-3)	333	10	6	0.9082	0.0918	335	1	4	0.9369	0.0631
(3-4)	317	5	8	0.8936	0.1064	330	1	7	0.934	0.066
(4-5)	304	8	14	0.8696	0.1304	322	2	7	0.9281	0.0719
(5-6)	282	2	9	0.8633	0.1367	313	2	6	0.9221	0.0779
(6-7)	271	2	3	0.8569	0.1431	305	0	7	0.9221	0.0779
(7-8)	266	0	1	0.8569	0.1431	298	0	2	0.9221	0.0779
(8-9)	265	0	265	0.8569	0.1431	296	0	296	0.9221	0.0779

j used to specify the occurrences of failures and censored cases in different intervals(e.g. death in j^{th} interval)

The survival curve was also plotted by HIV status after adjusting for age, weight and TB type. In the adjusted survival curve, the survival probability of HIV negative TB patients was above 85% at the end of eighth month. But for HIV positive TB patients, the median survival was at about the end of intensive phase, and reaches to below 15% at the end of the study period (at eighth month) where all the remaining TB patients become censored.

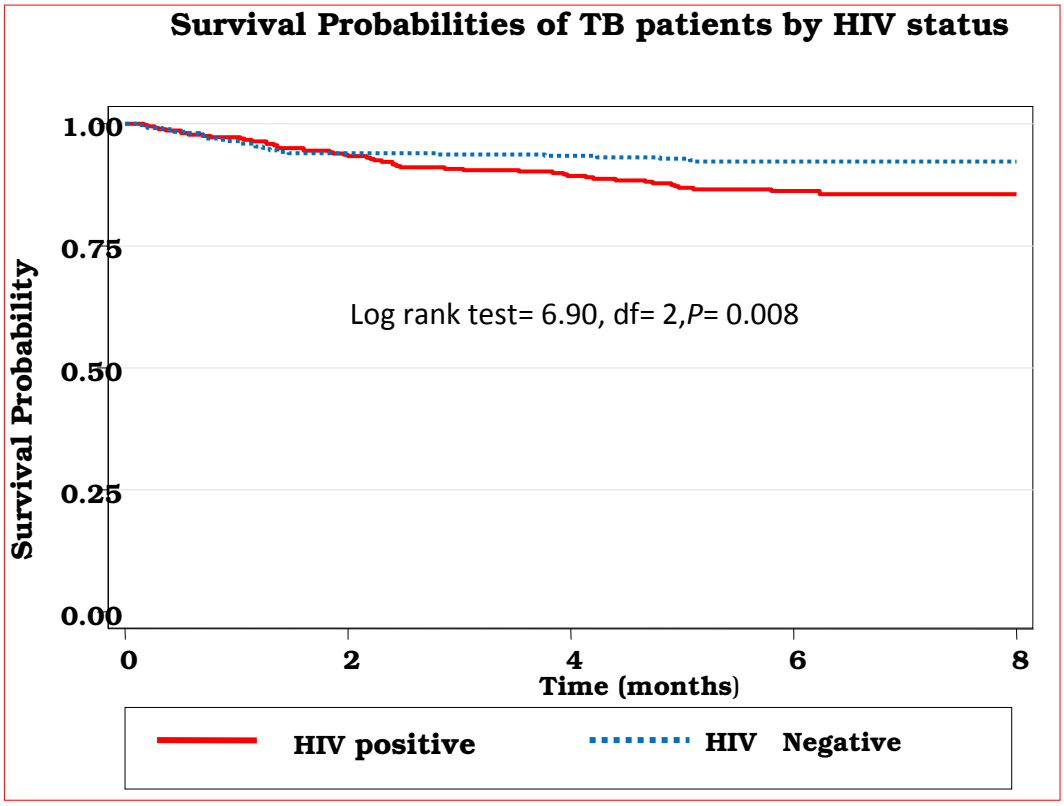

Figure 2: Survival Probabilities by HIV status of TB patients treated in Hawassa health center, 2006-2010

There was also significant difference among survival curves of the different types of TB disease (log rank statistic= 6.7, df= 2, *P*= 0.0349)

The survival rates at the end of the intensive phase were 95.7%, 91.5% and 96.2% in the smear positive pulmonary, smear negative pulmonary, and EPTB patients, respectively. The survival rate was lower for smear negative pulmonary TB patients, throughout the study period, reaching to 85.9% after 6th month and up until the time during which study subjects all become censored (Table 9)

Table 8: Life table for Survival and Failure probabilities of the study subjects by TB type 2006-10

Interval	N(j)	Deaths(j)	Censored(j)	Survival(j)	Failure(j)
Smear Positive Pulmonary TB					
(0 - 2)	257	11	6	0.9567	0.0433
(2 - 4)	240	4	10	0.9404	0.0596
(4 - 6)	226	4	17	0.9231	0.0769
(6 - 8)	205	1	9	0.9185	0.0815
(8 -10)	195	0	195	0.9185	0.0815
Smear Negative Pulmonary TB					
0 -2)	349	29	15	0.9151	0.0849
(2- 4)	305	8	12	0.8906	0.1094
(4 - 6)	285	9	11	0.8619	0.1381
(6 - 8)	265	1	2	0.8587	0.1413
(8 -10)	262	0	262	0.8587	0.1413
EPTB					
(0 - 2)	134	5	6	0.9618	0.0382
(2 -4)	123	5	3	0.9223	0.0777
(4 - 6)	115	1	8	0.9139	0.0861
(6-8)	106	0	2	0.9139	0.0861
(8-10)	104	0	104	0.9139	0.0861

When adjusted for age weight sex and TB treatment category, the survival probability of EPTB would have been worst declining to zero at month four; the median survival time would be 1 month for smear negative PTB and EPTB; and 3 months for smear positive PTB. At the end of the study period (8^{th} month) the survival probability of smear positive PTB patients would be 40% and 15% for HIV negative TB Patients.

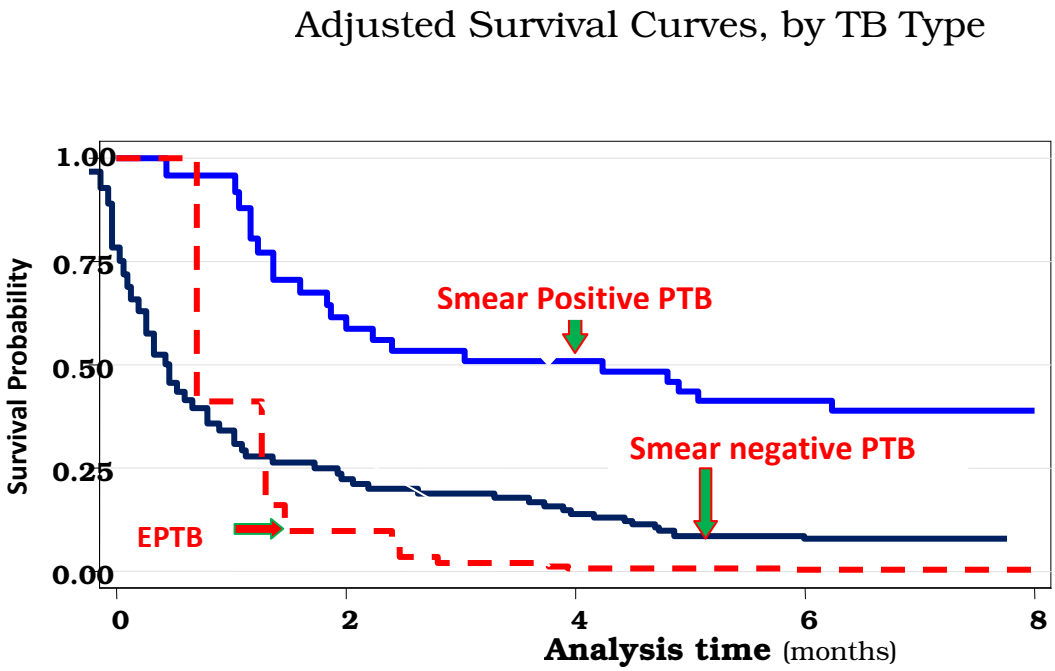

Figure 3. Adjusted survival Curve by TB type, of patients treated in HHC, 2006-2010

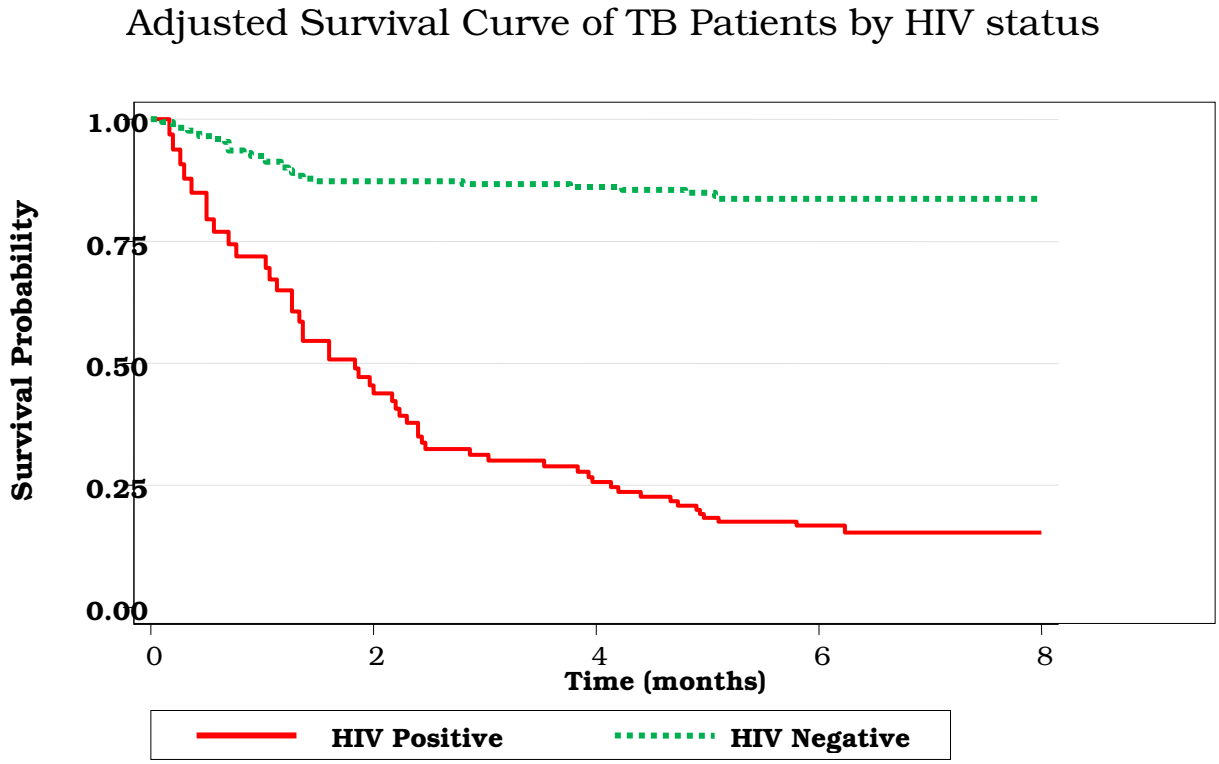

Figure 4: Adjusted Survival curve of the study subjects by HIV status, Hawassa Health Center, 2010

5.5. Prognostic Factors for the Survival of TB patients on DOTs

The relationship between the main baseline variables and the risk of death was analyzed using Bivariate Cox proportional Model. Before fitting the covariates into the model, Proportional hazard assumption was checked by plotting “Schoenfeld residual, regressing Schoenfeld residuals against time to test for independence between time and residuals and by examining log (log (st) plots. The Covariates which refuted the assumption were not treated with the Cox model. The result showed: age, weight, smear negative pulmonary TB, dose of anti TB drugs and HIV status were all significantly associated with death of TB patients during the period of DOTs.

Compared to the reference, bivariate analysis showed that the HR of dying from TB increased significantly by 84% in HIV positive TB patients on DOTs. Mortality risk among TB patients increases about 2.8% for every year increase in age. Similarly, for every five and 10 years increase in age, the risk of death increases by 14.7% and 31.5% respectively. But decreases by about 5.5% for every kg increase in weight. This risk further decreases by 15% and 43.6% for every five or ten kg increase in weight respectively. The risk of death among the study subjects with negative smear result at the baseline increased by 80% over smear positives significantly(HR=1.8, P=.022)

Table 9: Univariate Predictors of death among TB patients on DOTs in HHC, 2006-10

Covariates	Number at risk	Number of death	Crude Hazard Ratio	95% CI	P-value
Residence					
Urban	723	75	1		
Rural	17	3	1.9	(.59,5.9)	0.28
Gender					
Male	417	43	1		
Female	323	35	1.03	(.66-1.6)	0.14
Age(years)	740	78	1.028	(1.01,1.04)	0.000
Weight(kg)	740	78	.944	(.92, .97)	0.000
Marital Status(n=342)					
Single	194	16	1		
Married	148	22	1.9	(.99-3.6)	0.053
Center TB Diagnosed					
Health Center	549	59	1		
Hospital	191	19	0.92	(.55-1.54)	0.74
TB treatment history					
New	696	73	1		
Re-treatment	44	5	1.1	(.43-2.6)	0.9
Treatment Category					
I	673	72	1		
II	38	4	0.97	(.35-2.6)	0.9
III	29	2	0.61	(.15-2.5)	0.5
Smear(baseline)n=606					
Positive	257	20	1		
Negative	349	47	1.8	(1.1-3.1)	0.022*
Regimen					
ERHZ	673	72	1		
RHZ	31	3	0.88	(.28-2.8)	0.822
STM+ERHZ	36	3	0.74	(.23-2.4)	0.614
HIV Status					
Negative	370	28	1		
Positive	370	50	1.84	(1.2-2.9)	0.01*
CPT(n=133)					
No	10	2	1		
yes	123	14	0.38	(.09-1.7)	0.21
ART(n=91)					
No	39	7	1		
yes	52	9	0.88	(.33-2.4)	0.8

To be diagnosed at hospital reduced the risk of death by 8% but not significantly, when compared to those diagnosed at Health center. ART and CPT use was found to be protective but not significantly (HR=0.88, P=.8 and HR=.38, P=.21 respectively) (Table 9).

A multivariate Cox proportional hazard adjusted model was fitted with variables having a p-value < 0.3 in the Bivariate Cox proportional model. However, cases with missing values were excluded from the multivariate analysis. Besides smear result at the baseline was dropped because of its co linearity. In the final model, variables with P-value less than 0.05 were retained as independent predictors of death. Accordingly, only three covariates, namely being HIV positive (positively), age (positively), and baseline weight (negatively) remained to be independent predictors of death, (Table 11)

Table 10: Multivariate Cox Proportional Hazard Model for baseline characteristics associated with death of TB patients treated under Hawassa health center from 2006-2010.

Covariates	Number at Risk	Number of death	Adjusted Hazard Ratio	95% CI	P-value
Residence					
Urban	723	75	1		
Rural	17	3	1.96	(0 .6, 6.4)	0.26
Gender					
Male	417	43	1		
Female	323	35	0.87	(0.51, 1.5)	0.61
Age(years)	740	78	1.03	(1.02,1.05)	0.000*
Weight(kg)	740	78	0.94	(.92, .97)	0.000*
TB Type					
Smear positive PTB	257	20	1		
Smear positive PTB	349	47	1.2	(0.68,2.1)	0.53
EPTB	134	11	0.9	(0.44, 1.95)	0.84
HIV Status					
Negative	370	28	1		
Positive	370	50	1.6	(1.01, 2.6)	0.04*

** Significant at α=0.05; ** significant at α=0.01*

6. DISCUSSION

According to the WHO latest report on TB for 2009(1), Ethiopia is one of the African countries, which lacks data on treatment outcome of TB among HIV/TB patients, yet the TB/HIV co infection is among the highest in Africa. To the best of my knowledge, this study is the first of its kind to come up with comparison of treatment outcome of TB and the survival of TB patients between HIV positive and negative TB patients on DOTs in Ethiopia.

To come up with the impact of HIV infection on TB treatment outcome and survival of TB patients, a retrospective cohort study design was employed. The bottom line assumption is that TB and TB treatment outcomes were considered to have occurred as a consequence of HIV infection and; exposure to HIV as an exposure variable to have occurred before TB. This assumption is in line with a finding from Tanzania(29) that all TB in HIV positive occurred as a consequence of progression HIV to AIDS(30% and 70% of TB occurred during HIV clinical stage three and four respectively signifying the current underlining assumption). Similarly, because the rapid HIV test in use by country, cannot diagnose recent HIV infections(less than 3 months), we can be sure that HIV positive TB patients diagnosed in the study area were infected by HIV at least three months ago. However, as for the natural history of TB, there are still possibilities (25 per 100 untreated cases) for a TB patient to be chronically ill (6). In this case a chronic TB patient might have become HIV infected later on; in such situation the design might not be appropriate in discriminating as to which has occurred first (exposure or outcome?).

For the reason that study was conducted on data solely from patient's clinical records, some of the findings of this study might have suffered from lack of relevant variables wholly (CD4 count, some of socioeconomic variables, history of alcoholism and cigar smoking) and when present with a questionable accuracy. Some of the recorded variables were incomplete and

inconsistent (e.g. marital status, ART and CPT administration). Not merely for the design, it is difficult to ascertain some of the causes of treatment outcomes of TB, especially of death as it is difficult whether it has occurred as a consequence of TB/HIV or of any other cause.

The aforementioned difficulties might partially have affected the study findings. Apart from the aforementioned seemingly limitations, this study is robust in that it has utilized higher power (about 87%). Contrary to other studies elsewhere (33), which have generated internal comparison groups from a single cohort, this study has allowed an adequate power from the very inception of the research 80%.

In addition, to have a reasonably comparable number of TB/HIV co infected patients, with HIV negative TB patients, all HIV positive TB patients who passed the inclusion criteria were included in study; where as in HIV negative TB patients, the selection was with the application of simple random sampling. Even if the strategy employed may run the risk of generating two incomparable groups somehow to certain extent, having comparison groups on the bases of 1 to 1 ratio in other hand might have tackled the problem allowing adequate power.

In agreement with other studies(17), the results of this study has demonstrated that people with HIV are significantly (P=0.000) much more likely than HIV-negative patients to have smear-negative pulmonary tuberculosis and HIV negative patients are significantly much more likely than HIV-positive patients to have smear-positive pulmonary tuberculosis.

The increase in epidemiology of smear negative PTB and decrease in smear positive PTB in HIV positive patients might possibly have resulted from over diagnosis of sputum smear negative

pulmonary TB due to diagnostic difficulties; as there are different TB mimicking diseases(34), and under diagnosis of sputum smear-positive PTB due to excess laboratory workload as they were mentioned in different sources (5, 7, 8). Moreover, sputum under a simple light microscope is the diagnostic tool in use by the resource poor settings including Ethiopia. There is an evidence that this test detects fewer than 60 percent of all new TB infections and as few as 20 to 35 percent of HIV/TB infections(35). Different studies have also documented fewer bacilli in the sputum of HIV positive than their counter part, HIV negative(6) due to reduced immune response(36) and even in the presence of high bacillary load, patients with heavy immunodeficiency will not often provide positive sputum smear(34).Like in other studies elsewhere (8, 37), in this study PTB is still the commonest form of TB in both HIV positive and negative study subjects.

Contrary to different studies (6, 17), the higher proportion of EPTB in favor of HIV negative, although of borderline statistical significance(p=.045), was a strange finding. This seemingly strange finding might have resulted from smaller number of EPTB compared with other TB types to detect real difference. Though difficult to detect, there might be careful diagnosis of EPTB in HIV positives once the clinicians become aware of the patient's being HIV positive.

There was significant evidence that Smear negative PTB patients tend to have their TB diagnosed at relatively later ages than that for smear positive PTB (P=0.000), and EPTB(P=0.02). Smear negative PTB patients were diagnosed late probably because they reported late, or the existing treatment algorism may, to some extent delay the diagnosis as there are ranges of delays from 80 days in local studies(38) to 240 days in Ghana(39),and or smear negative PTB might have occurred in later ages. It may also be that for the fact that about 63% of TB in HIV positives were smear

negative PTB, the diagnosis might have been delayed because of the similar and overlapping manifestations of possible other opportunistic infections, as in a previous study(9). One local study also has demonstrated that bacterial infections and pneumocystis Carni pneumonia more common than smear negative PTB in patients among registered smear negative patients(40).

The study also showed that the study population was different in its baseline weight among the three TB types(P=.0011). From Bonferroni test it was evident that smear negative PTB patients reported with the lowest base line weight than EPTB (P= 0.001). This might be in accord with the above explanation that most of smear negative PTB patients were with HIV infection; the known chronic cause of weight loss (37) and progression of the disease possibly due to delay in treatment initiation for reasons remarked above might have played a prominent role.

In accord with different sources elsewhere, (1, 8, 21, 33), cure rate was statistically lower in HIV positive than negative smear PTB patients. Cure rate is lower, particularly in this study because of occurrence significantly higher unfavorable treatment outcomes (death, default and transfer out) in HIV positive smear positive PTB patients when compared to HIV negative smear positive PTB patients (21.9% vs.11.7%, P=0.04),which diluted the denominator in the former.

In the study we found cure rate of 82.9% which is higher than the program cure rate (67.4% in 2008)(41), but still lower than the recommended 85%.This cure rate was statistically further lower than the WHO target, in HIV positive smear positive PTB patients(73.9%,P=0.000), while it was above the target for HIV negative smear positive PTB cohort(87%).The difference is statistically significant. This result may indicate that Infection with HIV is the reason among others not to attain the targets set by WHO. However, it must be noted that almost all; 723 (97.7%) of the study subjects were exceptionally from urban area. It is unknown what would happen, if proportional amounts from rural were included in the study.

In the current study there was no statistically significant difference when comparing treatment completion rate between HIV positive and negative patients, consistent with a study finding from Sudan(33); However, as opposed to these studies, a other studies have showed significantly lower treatment completion rate in HIV positive TB patients partly due to high rate of adverse effects of TB drugs (26, 42).

Similar to the current study, numbers of studies (13, 33) have reported higher death rates among HIV-positive TB patients; as high as four times increased risk of death(20) in a previous report during TB treatment. Besides to HIV as a factor above, another study in consistence with the current study has also attributed age as a cause of death(43). Besides to its association with HIV, risk of death was also significantly associated to TB type. Smear negative TB patients were much more likely to die than smear positive PTB patients in the current study as was shown in other studies(8). The same study postulated incorrect diagnosis as a possible reason.

As in a study from Sudan(33), HIV positive TB patients were much more likely to die while on treatment if they had also smear positive PTB.

Information about the time of occurrence of un favorable treatment outcomes among TB patients while on treatment could help provide the necessary care timely so that TB treatment outcome could be improved. In the current study, most of un favorable treatment outcomes particularly death and default occurred during the intensive phase. And generally, overall mortality rate and mortality among HIV positive TB patients was higher in the current study than in others. It needs a further job to be done in order to ascertain as to why it happened.

As in a previous study (21, 33), treatment outcomes other than cure and death; i.e. failure, default, transfer out and treatment complete were not statistically higher in HIV positive TB patients in the envisaged study.

Sputum smear conversion rate at month two was almost equal between HIV positive; 99.3% and negative; 100% smear positive PTB patients. Similarly a study from Sudan showed that in HIV-positive and negative TB patients who underwent through DOTs therapy, no difference in sputum conversion rate was observed. The result of the study may signify that if both HIV positive and negative smear positive TB patients adhere to anti TB treatment the conversion rate will not differ between the two. The global Sputum smear conversion rate in the current study was about 97.8%; which is above the theoretically recommended level (above 80%)(34).

In the present study, there is a significant predominance of tuberculosis in males than females as another study from Iran (44) can partly be explained by the higher rate HIV infection in male TB patients (51.1%).

In the current study, the survival probability is significantly lower in HIV positive TB patients; internally consistent with the earlier finding that significantly more deaths occurred in HIV positive TB patients. In addition if other factors such as age, sex, TB type, baseline weight and age were kept constant, the median survival probability of HIV positive TB patients would be within intensive phase and subsequently reaches to less than 15% at the end of continuation phase, while the survival for HIV negative TB patients remain above 80 throughout the course of DOTs.

Survival probability by treatment category is inconclusive. Different studies showed overlapping results

In contrast to a study from India(45), but in line with a study from south India(46) there was no adequate evidence to consider presence of difference in survival probabilities among the three TB treatment categories in the present study, partly due to occurrence of negligible amount of

events 2(2.6%) in category III and 4(5% in category III) when compared to 72(92.3% in category I). As with the former study(45),in the current study survival probability did not differ by sex. Similarly, survival of smear negative PTB was found to be lower in the current study in line with its highest share of HIV infection as indicated earlier. Had it not been masked by sex, weight, age and HIV status, the Survival probabilities of smear negative PTB and EPTB patients would have been worsened to less than 15 % and 5% respectively at the time of DOTs completion. This might be explained by effect of their overlapping clinical manifestations leading to delay in diagnosis and misdiagnosis. Similarly even if undetected by the current study, some other factors (alcoholism, smoking) were shown to decrease the survival of TB patient in other studies(46) might have might be prevalent in our study subjects.

In keeping with previous studies (33), age, baseline weight and HIV infection were found to be independent predictors of death among TB patients on DOTs in a multivariate adjusted Cox model. Studies show that risk of death from TB increases in individuals with weight loss. Weight loss is a very common phenomena in HIV (8)(to the extent of being considered as AIDs defining illness) and TB patients(47). Weight loss is much pronounced in patients with dual infection (TB/HIV co infected) compared to HIV negative TB patients(34). Consistent with the studies mentioned, and internally with Cox model, baseline weight was significantly lower in HIV positive TB patients. AIDs patients are likely to become malnourished from constantly being sick, from diarrhea that prevents absorption of nutrients, from loss of appetite and sores of mouth that make eating difficult and from opportunistic infections. Similarly, weight loss in TB patients might be explained partly by the loss of appetite and loss of energy by the disease itself(48). In the same manner, this study also finds out that significant reduction of risk of death, with reasonable weight gain

Various studies from abroad have indicated that the risk of dying from TB increases with the patient's age. Evidences show that TB is among five top killers of geriatric population. The studies also attributed mortality from TB in older individuals to the increased physiologic risk of death, to the vague symptoms in the elderly, diagnostic problems (the problem may be overlooked in elderly because of the association of other conditions that preoccupy the attention of physicians) and presence of co-morbidities and difficulties in accessing diagnosis in this group of patients, thereby delaying the onset of treatment (45, 46, 49, 50).

In congruence to the above studies, in the present study, the relative risk of dying from TB increased with the age of individuals in a dose-response manner in both the univariate and multivariate analysis.

Though CPT did not significantly reduce death among HIV positive TB patients in an Indian study (51); partly due to adherence problem, the significant death rate reduction effect of CPT and ART during TB treatment was demonstrated in other stud(20, 24, 26). The World Health Organization (WHO) TB/HIV clinical guideline for the management of HIV-infected persons with tuberculosis recommend the provision of cotrimoxazole prophylactic treatment (CPT) and antiretroviral treatment (ART) to tackle opportunistic infections and mortality(8). And the study from India indicated significant protective effect of ART.

Regarding the information about CPT and ART initiation in the current study, except a report of 100 % CPT coverage , there was no record for whom the CPT and ART was considered except; 133 for CPT and 91 for ART. The higher mortality rate(14.5%) in HIV positive TB patients in the current study than in others elsewhere(33, 37, 51) may reflect the fact that patients were not being given ART and CPT as high as the report of the health center. Other possible reasons remain to be investigated as well.

7. STRENGTHS AND LIMITATIONS

7.1 STRENGTHS

- ✓ Strong power
- ✓ Retrospective Cohort study design
- ✓ Different statistical analysis methods employed

7.2 LIMITATIONS

- ✓ Narrow scope of the study setting and population
- ✓ The study was retrospective. Therefore, despite the meticulous conduct, it is possible that not all factors such as co-morbid conditions, CD4 count and other important ones were recorded.
- ✓ Retrospective cohort study design
- ✓ Mycobacterium strain unknown(i.e. Resistant or new among newly presenting patients)
- ✓ Competing causes of death unknown
- ✓ Secondary data, where some of data were incomplete and inconsistent.

8. CONCLUSION

- People with HIV are much more likely than HIV-negative patients to present with smear-negative pulmonary tuberculosis; and less likely than HIV-negative patients to present with smear-positive pulmonary tuberculosis in this study.
- Sputum smear negative tuberculosis cases constituted the significant proportion, among HIV positive individuals.
- HIV positive TB patients are substantially more likely to die while on treatment
- Risk of not to be cured is highest among HIV positive TB patients(smear positive PTB)
- Unfavorable treatment outcomes particularly death and default occur mainly during the first two months of DOTs.
- Survival probability is substantially lower for HIV positive TB patients, and smear negative PTB patients during DOTs period.
- The most important determinants of survival during TB treatment period were HIV infection, older age and lower weight.

9. RECOMMENDATIONS

Based on the study findings the following recommendations are forwarded.

To Researchers

- The study consumed information registered (not exhaustive) in four consecutive years for the sake of sample size. Therefore it needs to conduct a multicenter study, so that reasonably comparable groups with necessary variables can be generated in the same year for both the exposed and non exposed individuals by the same sampling scheme.

To service providers

- Mandatory nutrition counseling should be part and parcel of TB management in patients with weight loss subsequent to investigating the possible causes of weight loss.
- Smear negative PTB was diagnosed most often in TB/HIV infected individuals. An endeavor effort should be exercised, not to overlook the mimicking other possible opportunistic infections, not to over diagnose smear negative PTB and not to under diagnose smear positive PTB.
- HIV positive TB patients need a more comprehensive and utmost care during the course of DOTs if their lives is to be saved.
- Targeted management of TB is required in the elderly patients; to prolong their lives.

To TB Program Managers

- Right information is the foundation for right planning and program evaluation. However, some of the data in the log book were incomplete, inconsistent and incorrect. The TB clinic service providers therefore need training and a subsequent and frequent supervision so that they would appropriately record patient information.

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11. ANNEXES

ANNEX I: DATA COLLECTION FORMAT

Data collection format for Addis Ababa University, MPH research project on clinical presentation and treatment outcome of Tuberculosis in HIV positive patients

Sr. no	Variables	Descriptions	Remark
Part I:Socio demographic Characteristics			
1	HIV status	1.Reactive 2.Non reactive	
2	Age (years).		
3	Sex	1. Male 2. Female	
4	Weight(Kg)		On diagnosis
5	Residence	1. Urban 2. Rural	
Part II: TB related Information			
1	Sputum result	1. Positive 2.negative	For PTB
2	Site of TB or TB Category	**1.** Pulmonary positive **2.** Pulmonary negative **3.** EPTB **4.** combined	
3	TB treatment category	1. I 2. .II 3. III 4. IV	
4	Intensive phase 1.Start date (DD/MM/YY)	_____/_____/_____ E.C	
	2.Drug and Dose	1. 2ERHZ(dose_____)	

		2. 2SRHZ**(**dose_____) 3. 2S(ERHZ)/1ERHZ_____ **4.** Other specify_____	
5	**Continuation Phase** Start date(DD/MM/YY)	_____/_____/_____ E.C	
	Drug and dose	1. 6EH daily(dose_____) 2. $5(RH)_3E_3$(dose_____) 3. other specify_____	Write gram in the combination
6	**Sputum result at the end of** a, 2nd month b,5th month c, 7th month	1. Positive, 2. Negative 2. Positive 2. Negative 3. Positive 2. Negative	
7	**Treatment outcome**(Circle)	**a, Cured** Date ___/___/___ E.C **b, Treatment completed** Date ___/___/___ E.C **c, Died** Date ___/___/___ E.C Duration on treatment_____ (days) **d, Failure** Date ___/___/___ E.C Duration on treatment_____ (days) **e. Defaulted** Date ___/___/___ E.C Duration on treatment_____ (days) **f, Transfer out** Date ___/___/___ E.C Duration on treatment_____ (days)	
Part II HIV related information			

7	HIV status	1. Positive 2. Negative	
8	Date of HIV test	_____/_____/_____E.C	**For HIV positive**
9	Base line CD4 count/Ml		
10	Co trimoxazole prophylaxis initiated?	1. Yes 2. No	For HIV positive *If yes go to ques, 11*
11.	If yes to question number 9, for how long has he/she been on it?	Date started_____/_____/_____E.C Duration_____(days, weeks)	
12	ART initiated?	1. Yes 2. No	
13	If yes to question number 11, for how long has he/she been on it?	Date started_____/_____/_____E.C	
14	Any OI?	**1.** Yes 2. No	
15	If yes specify?		

ANNEX II: ANALYSIS PLAN FRAME WORK

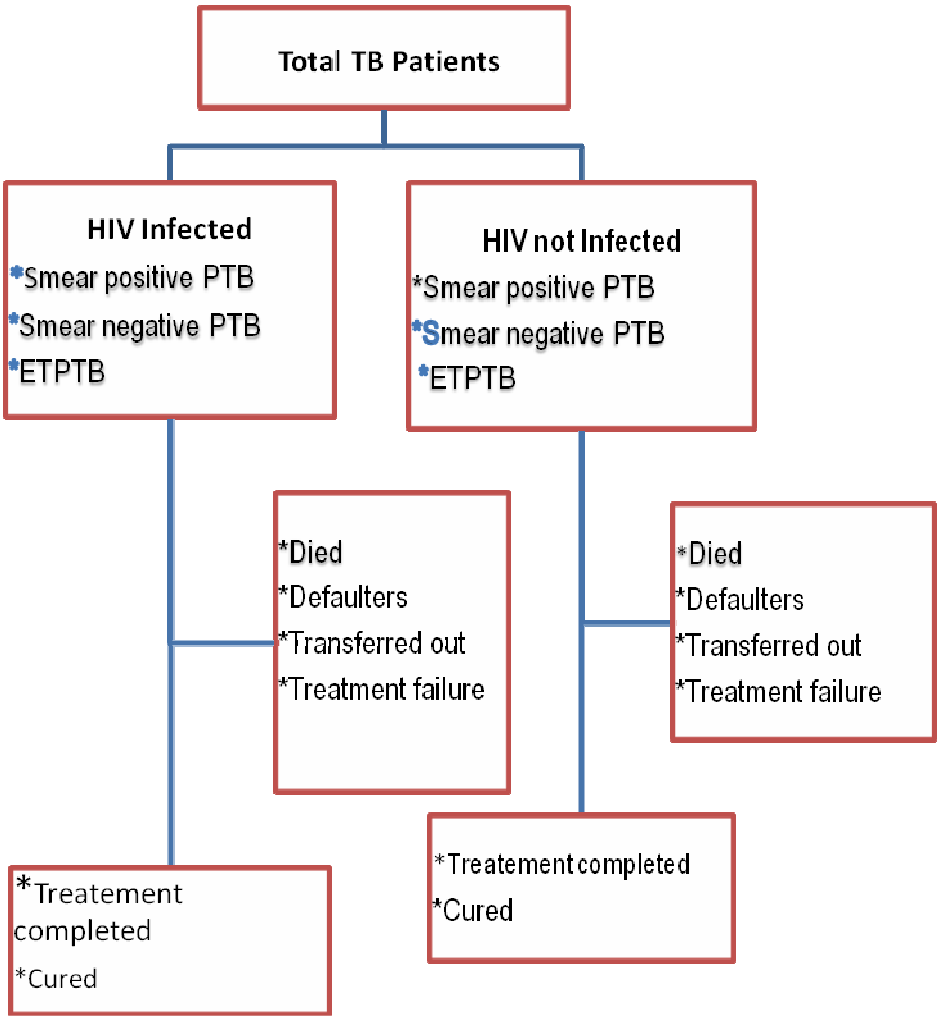
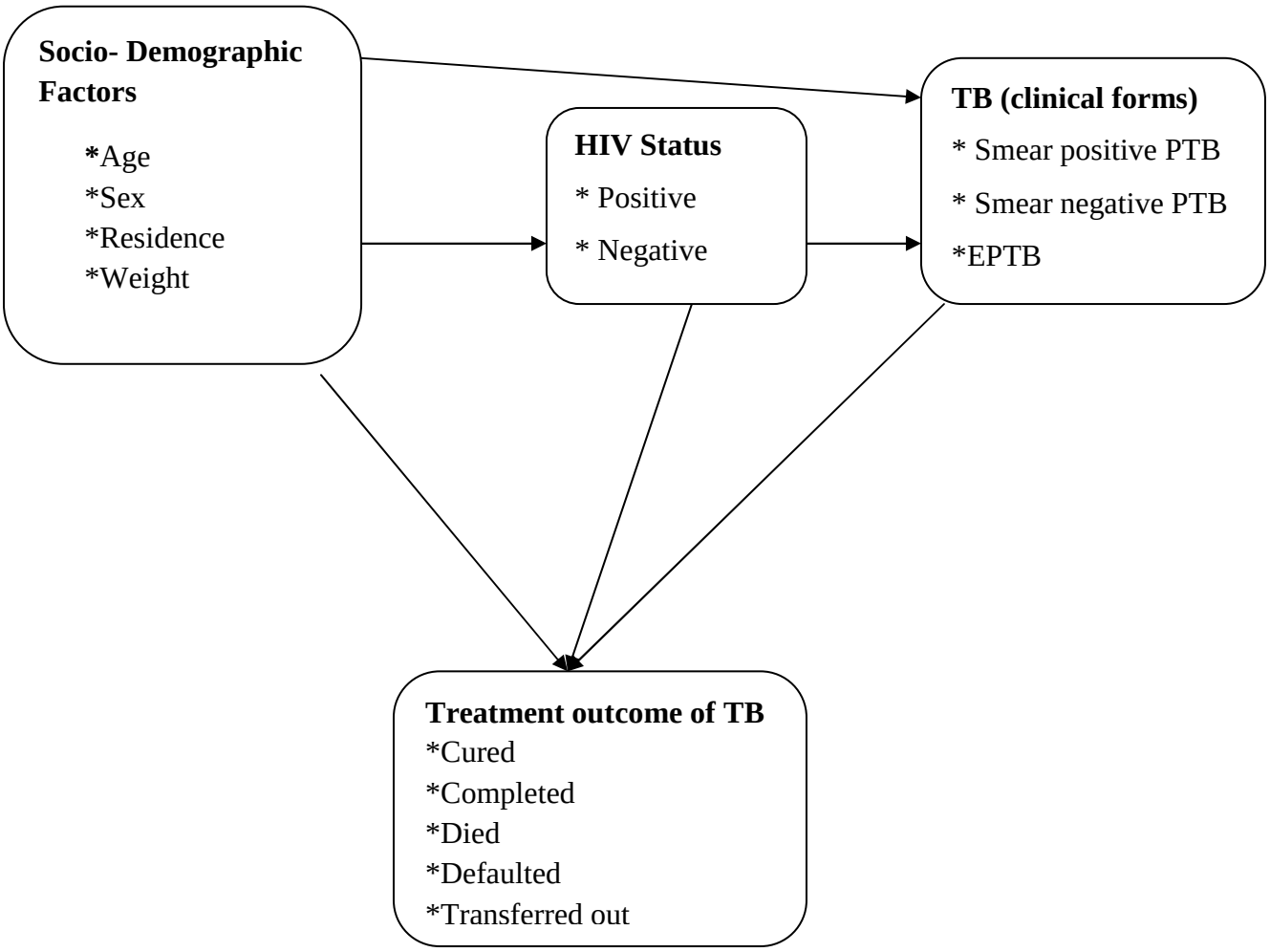


Figure1. Schematic presentation of the planned data collection process

ANNEX III: Conceptual Frame work for data Analysis, September 2009



ANNEX IV. English Patient Information Sheet

Participant Information Sheet

Description of the study

Title of the study: Clinical Presentation and Treatment Outcome of Tuberculosis among HIV positive TB patients on Short course DOTs in Hawassa Referral Hospital.
Objective of the study: To compare the frequency of clinical presentation and treatment outcome and Survival between HIV positive and negative TB patients treated for TB under DOTs
Introduction: Anti TB treatment is used to reduce morbidity, mortality, relapse, treatment failure and increase cure rate when appropriately addressed. However, TB control program target set by WHO is not attained by many countries, with high death, default and low cure rates, primarily due to HIV infection according to many studies conducted abroad.
Rationale of the Study and its benefits

In face of currently underway TB/HIV collaborative activities, Ethiopia suffers from shortage of data on clinical presentation and treatment outcome of TB in HIV positive patients. More over no study has assessed the independent impact of HIV infection on TB presentation and treatment outcomes except few prevalence studies. Therefore availing scientifically sound data on the aforementioned gaps will have paramount importance for evaluation of the program and differentiated approach to TB in HIV positive patients. The envisaged study is designed to assess the impact of HIV infection on the survival, treatment outcome and clinical presentation of TB while bridging the aforementioned gaps.

Information which is necessary for the study will be taken from TB log book. As the study will be conducted through review of medical records alone, the individual patients will not be subjected to any harm as far as the confidentiality is kept. To preserve the confidentiality, nurses working in TB clinic, Hawassa referral hospital will extract the data from the medical records. Moreover, no personal identifiers will be used on data collection form. The recorded data will never be accessed by a third person except the principal investigator, and will be kept with a firm confidentiality in much secured place plus it will not be used for other purposes.

ANNEX V: Amharic Patient information Sheet

<u>ለጥናቱ ተሳታፊዎች መረጃ የመስጫ ቅጽ</u>

<u>የጥናቱ መግለጫ</u>

የጥናቱ ርዕስ- የኤች.አይ.ቪ /ኤድስ ተጽእኖ በቲቢና በቲቢ ሕክምና ላይ

የጥናቱ ዓላማ- የቲቢ ዓይነቶችንና የቲቢ ሕክምና ዉጤቶችን ከኤች አይ ቪ ጋር በሚኖሩና ከኤች አይ ቪ ነጻ በሆኑ የሀዋሳ **ጤና ጣቢያ** ቲቢ ታካሚዎች መካከል ማነጻፀር፡፡

መግቢያ

ጸረ-ቲቢ መድሃንቶች በትክክል ከተሰጡ ሞትንና በሽታን በመቀነስ ትልቅ አስተዋጽኦ አላቸዉ፡፡ ሆኖም ግን የአለም ጠና ድርጅት ያስቀመጣቸዉን የቲቢ መቆጣጠሪያ ግቦች ብዙ አገሮች አላሳኩትም፡፡ ለዚህም ዋነኛዉ ምክንያት የኤች.አይ.ቪ/ኤድስ ተጽእኖ መሆኑን ከአገር ዉጭ የተሰሩ የተለያዩ ጥናቶች ያመለክታሉ፡፡

የጥናቱ አስፈላጊነት

ጥናቱ ካስፈለገባቸዉ ምክንያቶች መካከል ኢትዮጲያ ቲቢንና ኤች.አይ.ቪ/ኤድስን ለማከም ጥረት እያደረገች ባለችበት በአሁኑ ሰአት የኤች.አይ.ቪ/ኤድስ በቲቢ ና በቲቢ ሕክምና ላይ ያለዉን ተጽእኖ የሚያሳይ ምንም አይነት መረጃ ያለመኖርና ይህንን ጉዳይ የሚዳስስ ጥናት ያለመደረጉ ናቸዉ፡፡

እነዚህ ነገሮች ላይ ሳይንሳዊ ሂደትን የተከተለ መረጃ ማቅረብ የቲቢ ና የኤች አይ ቪ መከላከያና መቆጣጠሪያ ፕሮግራሞችን ለመገምገምና በኤች አይ ቪና ቲቢ ታካሚዎች የተለየ ጥንቃቄ እንዲደረግ አስተዋጽኦዉ የጎላ ነዉ፡፡

ስለለዚህ ለጥናቱ አስፈላጊ የሆኑ መረጃዎች ከሀዋሳ **ጤና ጣቢያ** ቲቢ ታካሚዎች ቲቢ ህክምና መዝገብ ላይ ይወሰዳሉ፡፡ ጥናቱ የሚደረገዉ የቲቢ ህክምናን የጨረሱ ያቋረጡ እና የሞቱ ሰዎች መረጃ ላይ ስለሆነ ግለሰቦቹን የሚጎዳ ምንም ነገር አይኖርም፡፡ ምስጥራዊነቱን ለመጠበቅ እዚያዉ የቲቢ ህክምና የሚሰጡ የጤና ባለሙያዎች መረጃ ከመዝገብ እንዲሰበስቡ ይደረጋል፡፡ በመረጃ ስብሰባ ወቅት ለሚመጡ ታካሚዎች ፈቃደኝነታቸውን በመጠየቅ መረጃ ይወሰዳል፡፡

በተጨማሪም የቲቢ ታካሚን ማንነት የሚገልጽ ምንም አይነት መረጃ መጠይቁ ላይ አይሞላም፡፡የተወሰደዉ መረጃ ሚስጥራዊነቱ ተጠብቆ ሙሉ በሙሉ ጠቀሜታዉ ለምርምር ሥራዉ ብቻ ይዉላል፡፡

ANNEX VI: English Consent Form

My name is _____, I am a TB clinic nurse working here in Hawassa health center TB clinic and now I am collecting data from our patients TB logbook for the research being conducted to determine the impact of HIV infection on clinical presentation and treatment outcome of TB, by Ato Debebe Shaweno who is the Master of public Health student in Addis Ababa University. You are selected as one of study subject by chance. The investigator employed me (from this TB clinic) for this data collection to maintain your data strictly confidential, i.e not to let others outside of this clinic to access your name and other identifiers. We believe that the findings of this study will have paramount importance for evaluation of TB/HIV programs and to initiate differentiated approach to TB in HIV positive patients.

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

Your willingness for your TB record information to be utilized in this study will help us achieve the stated benefits of the study. Your name and other personal identifiers will not be recorded on data collection form and the information that you give us will be kept confidential and will also be used for this study purpose alone. You have full right not to let your information on TB logbook to be consumed for this study. But the information that would be taken will be quite useful for the study. You will not face any problem if you do not allow the information to be taken from your records and you will not also be denied of getting any medical services from the hospital. If you have any questions about this study you may ask me or the principal investigator Debebe Shaweno (Tel: 0912 04 24 35 or E-mail: debebesh@gmail.com)

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

1. Yes 2. No

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

ANNEX VII : Amharic Consent Form

ለጥናቱ ተሳታፊዎች የፈቃደኝነት መጠየቂያ ቅጽ

ስሜ _____ ይባላል። በዚህ በሐዋሳ ጤና ጣቢያ ቲቢ ክሊኒክ ውስጥ የሚሠራ የጤና ባለሙያ ስሆን አሁን የኤች.አይ.ቪ/ኤድስ ተፅዕኖ በቲቢ ዓይነትና ሕክምናው ላይ በሚል ርዕስ በአዲስ አበባ ዩኒቨርሲቲ ድህረ ምረቃ ተማሪ የሆኑት አቶ ደበበ ሻወኖ ለሚሰሩት ጥናት መረጃ ከቲቢ ታካሚዎች መዝገብ ላይ እየሰበሰብኩ ነው። አንተ/ቺ የጥናቱ አካል በመሆን ተመርጠሃል/ሻል። አጥኚው እዚሁ ቲቢ መዝገብ ላይ የሚሠራውን እኔን ለመረጃ ሰብሳቢነት ሲመርጠኝ የመረጃውን ምስጢራዊነት ለመጠበቅ ብሎ ነው። ማለትም ከክሊኒኩ ውጪ ያሉት በመረጃ ስብሰባ ወቅት ስምዎንና ሌሎች መረጃዎትን እንዳያዩ ሲባል ነው።

የጥናቱ ውጤት ሳይንሳዊ ሂደትን የተከተለ መረጃ በማቅረብ የቲቢ/ኤች.አይ.ቪ መከላከያና መቆጣጠሪያ ፕሮግራሞችን ለመገምገምና ለኤች.አይ.ቪ እና ቲቢ ታካሚዎች የተለየ ጥንቃቄ እንዲደረግ አስተዋጽኦ የጐላ እንደሚሆን ይታመናል። በመሆኑም ለጥናቱ አስፈላጊ የሆኑ መረጃዎች ከእርስዎ ቲቢ መዝገብ ላይ ይወሰዳል። ጥናቱ የሚደረገው ከቲቢ ሕክምና መዝገብ ላይ ስለሆነ በእርስዎ ላይ ምንም ዓይነት ጉዳት አያመጣም። መረጃዎ ከመዝገብ ላይ የሚወሰደው እርስዎ ፈቃደኛ ሲሆኑ ብቻ ነው። የእርስዎ መረጃዎ እንዲወሰድ መፍቀድ ለተጠቀሰው የጥናቱ ዓላማ መሳካት የጐላ አስተዋጽኦ ይኖረዋል። ከሕክምና መዝገብዎ ላይ መረጃ ሲወሰድ የእርስዎን ማንነት የሚገልጽ ስም እና ሌላ ምንም ዓይነት ነገር ወደ መጠይቁ አይሞላም። የተወሰደውም መረጃ ምስጢራዊነቱ ተጠብቆ ሙሉ በሙሉ ለምርምር ሥራው ብቻ ይሆናል። የሕክምና መረጃዎ ለምርምር ሥራ እንዳይውል የማድረግ መብት አለዎት። ነገር ግን መረጃዎ ለምርምር ሥራው ቢውል ጠቀሜታው የጐላ ነው። በጥናቱ ለመሳተፍ ፈቃደኛ ባይሆኑ በሕክምናዎት ላይ ምንም ዓይነት ጉዳት አይፈጠርም። በሌላ በኩል መረጃዎን በመስጠትዎ የሚያገኙት የተለየ ጥቅም አይኖርም። ጥናቱን በተመለከተ ጥያቄ ካለዎት እኔን ወይም አጥኚውን አቶ ደበበ ሻወኖን በስልክ ቁጥር 0912 04 24 35 ወይም በኢሜል አድራሻ debebesh@gmail.com መጠየቅ ይችላሉ።

መረጃው ለምርምር ሥራ ቢውል ፈቃደኛ ነዎት?

1. **አዎ**
2. **አይደለም**

መረጃቸውን ለጥናቱ ሥራ እንዲውል ፈቅደዋል። የመረጃው ሰብሳቢ ስምና ፊርማ _____

_____

DECLARATION

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

Name: Debebe Shaweno

Signature: _____

Date _____

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

Name: Dr. Alemayehu Worku(PhD)

Signature:_____

Date:_____