TIME TO DEATH AND ASSOCIATED FACTORS AMONG TUBERCULOSIS PATIENTS IN DANGILA WOREDA, NORTHWEST ETHIOPIA

By:

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JUNE, 2014
JIMMA, ETHIOPIA

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ABSTRACT

***Background**: Tuberculosis is among the leading cause of morbidity and mortality worldwide. According to World Health Organization 2013 report the estimated prevalence and incidence rate of TB in Ethiopia was 224 and 247 per 100,000 populations respectively. The mortality rate was 18 per 100,000 populations. Among patients who died during TB treatment more than 70% occurred in the first two months of anti-TB medication. HIV positive, old age and re-treatment cases were found to be the major risk factors that increase early death of TB patients.*

***Objective**: To assess the time of reported death and associated factors in a cohort of patients with tuberculosis during anti-tuberculosis treatment in Dangila Woreda, Northwest Ethiopia, 2008-2012.*

***Methods**: Institution based retrospective cohort study was conducted in March 2014. All TB patients registered in DOTs clinic from 2008-2012 were included in to the study. The collected data was checked for completeness, coded, and then entered into Epi data software then edited, cleaned and exported to SPSS for analysis. Descriptive statistics was used to determine frequency, percentage, mean and median. The survival probability of patients who were on TB treatment was analyzed by Kaplan Meier method and KM plot was applied to see the survival curve among different categories of TB patients. Cox regression analysis was applied to assess the association between the outcome and explanatory variables.*

***Result**: From a total of 872 cases registered on TB log book 810 were used for the analysis and 60(7.4%) died during TB treatment. The mean and median survival time was 7.6 and 7.7 months respectively. The overall incidence rate of death was 12.8 per 1000 person months of observation. Majority of TB deaths 34(56.7%) occurred during intensive phase and the median time of death for patients who died during TB treatment was 2 months. The comparison of Kaplan Meier survival curve and log rank test revealed that there was a significant difference between patient categories. Age, HIV status and baseline body weight were independent predictors of death during anti-TB treatment regimen.*

***Conclusion**: This study showed that most patients died in the first two months of TB treatment initiation. Risk factors like old age, TB/HIV co-infection and weight <35kg during treatment initiation were significantly associated with increased rate of death during TB treatment. Therefore, screening for TB every patient who visits the ART clinic and provision of prophylaxis as necessary is needed to reduce the effect of TB/HIV co-infection. Additional nutritional support especially for underweight patients is needed reduce death during TB treatment.*

***Keywords**: TB death, Survival time and TB treatment*

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AFB	Acid fast bacilli
AHR	Adjusted hazard ratio
CHR	Crude hazard ratio
CI	Confidence interval
DOTs	Directly observed therapies
EPTB	Extra-Pulmonary tuberculosis
HBCs	High burden countries
IQR	Inter quartile range
IR	Incidence rate
PMO	Person months of observation
PTB	Pulmonary tuberculosis
PYO	person year of observation
SNPTB	Smear negative pulmonary tuberculosis
SPPTB	Smear positive pulmonary tuberculosis
SPSS	Statistical Package for Social Sciences
TB	Tuberculosis
WHO	World Health Organization

CHAPTER ONE

1. Introduction

1.1 Background

Tuberculosis (TB) is a chronic Mycobacterial infection present in all parts of the world (1) and remains an important public health problem, especially in developing Countries. It can affect any part of the body by which it is categorized as pulmonary and extra-pulmonary tuberculosis based on the organ it involves. Pulmonary tuberculosis (PTB) is an infectious disease of the lung with airborne transmission that is associated with high morbidity and mortality worldwide (2). Despite the advances in anti-tuberculosis (anti-TB) medication and the use of a Direct Observation Therapy/Short Course (DOTs) strategy, the tuberculosis mortality and morbidity rate remain high in many areas (3). To stop the spread of the disease, treatment of active PTB patients is the most effective strategy since a contagious person can infect up to 15 people every year if left untreated (4).

About a third of the world's population is estimated to be infected with tubercle bacilli and become a lifetime risk for development of active disease (5-7) with more than 95% of cases and deaths occurred in the developing world (7, 8). TB kills nearly 2 million persons per year worldwide and is still one of the leading causes of deaths in the world accounting for 2.5% of the global burden of disease and 25% of all avoidable deaths in developing countries (1). Mortality rate of TB is high if untreated; by the end of 5 year 50% will die, 25% recurs and 25% will have chronic TB (6).

People infected with Mycobacterium have 10% risk of developing active TB throughout lifetime. However, immune compromised individuals, such as people living with HIV, malnutrition, diabetes, people who use tobacco and alcohol have higher risk of developing active TB disease (7). Tuberculosis after the events of HIV is the most common killer disease in the world (6).

There were an estimated 8.6 million new cases of TB (122 cases per 100,000 populations) of which 1.1 million (13%) co-infected with HIV and 12 million prevalent cases (169 cases per 100,000 populations) of TB in 2012 globally (9) and only 5.7 million newly diagnosed cases were reported and about 3 million were missed, either because they were not diagnosed or they were diagnosed but not reported (10).

The burden of TB is highest in Asia and Africa. Asia accounts for 55% of global cases and the Africa for 31%. Among 15 countries with highest estimated TB incidence rates, 13 are in Africa, which is associated with high rates of HIV co-infection (11). Almost 80% of TB cases among HIV positive peoples reside in Africa (12).

According to the Ethiopian Ministry of Health 2008 report TB is the leading cause of morbidity, the third cause of hospital admission (after delivery and malaria) and the second cause of death (after malaria) in Ethiopia(13)

The national population based TB prevalence survey in 2010/11 revealed that the prevalence of bacteriologically confirmed and all forms of TB was 156 and 240 per 100,000 populations respectively (14). Based on WHO 2013 report, Ethiopia had an estimated of 247 and 224 per 100,000 population new and prevalence cases respectively in 2012 (9).

Ethiopia ranks 8th among 22 high burden countries (HBCs) worldwide and the 2nd in Africa next to South Africa in 2012. The mortality rate was 18 per 100,000 populations in 2012(9). According to a study in Felege Hiwot Referral Hospital 5.8% of TB cases died during TB treatment (15). So identifying the time when most death occur and associated factors during TB treatment and acting accordingly is useful in reducing the burden of death during TB treatment in the study area.

1.2 Statement of the problem

The aim of TB treatment is focused on curing patients, interrupting transmission of the disease and preventing emerging of drug resistant bacilli. This can be achieved by improving the treatment success rate in the DOTs program. Death of patients during TB treatment is among the possible reasons that have negative effect on treatment success rate (9).

The global TB mortality rate was 29/100,000 in 1990 and increased to 32/100,000 in 2000 before falling to 18/100,000 in 2012. WHO has set the goal to reduce TB mortality below 15 per 100,000 by 2015 (9, 16-18).

There were an estimated 1.3 million TB deaths in 2012. Around 75% of total TB deaths occurred in Africa and Southeast Asia regions. The mortality rate of TB was 13 deaths/100,000 populations and 17.6 deaths/100,000 populations when HIV positive patients are included. In Ethiopia there was an estimated 16,000 TB death with death rate of 18 per 100,000 populations of TB patients (9).

Studies showed that sex, age, type of TB, treatment category and TB/HIV co-infection of the patient were risk factors associated with death of patients during TB treatment (19-21). Though TB/HIV co-infection has been shown not to affect the failure rate of TB treatment, high mortality has been reported among HIV infected TB patients in sub-Saharan Africa (22). Age and death of patients during TB treatment has direct association, as the age of the patients increase death rate during TB treatment also increase (22). While another study conducted in Iran showed HIV infection and old age were not frequent risk factors for death where majority of deaths occurred in male TB patients when compared to females (64.8% Vs 35.2%). The mortality rate in males and females were 3.3% and 2.8% respectively (19).

A study in India with general case fatality rate of 6% both for new smear-positive and smear-negative PTB, showed higher mortality rate in previously treated TB patients. Age above 50 years and new TB patients had increased odds of early death. Those with category 1 and 3 were at increased risk of early death compared

to patients with previously treated TB. But previously treated patients had higher mortality rate compared to new pulmonary patients (20).

Majority of TB deaths occurred in the first 2 months of TB treatment. A study in Iran revealed that 73.6% deaths occurred during the first two months of TB treatment (19). Being HIV positive, old age and under treatment category II was found to be significant risk factors for early death. A study conducted in Northern Thailand showed that HIV status and old age group were significant risk factors of death in the first month of TB treatment (17). In contrast, death of TB patients during the course of treatment was evenly distributed and HIV status was not associated with early death as a study in south India (20) reported. There was a significant difference in the survival curve of the three treatment categories, where higher proportion of death in category I and III occur in the intensive phase (23) while another study in the rural area of South India revealed that there was no significant difference between the survival times of TB patients among the three categories ($p = 0.1$) (24).

As there is a gap in different study findings where some revealed early death of TB patients was highly associated with TB/HIV co-infection (17), others explained that TB/HIV co-infection was not associated with early death even though co-infection has higher mortality rate compared to others (25). There are also contradicting findings on survival time among TB treatment categories, where there was a study which revealed the presence of significant difference (23) while another showed no difference at all (24). In addition, there is a lack of study that investigated the time of death of TB patients in the study area. So there is a need to study the time of death and associated factors for patients who died while on TB treatment.

The purpose of this study was to assess the survival status and to identify factors associated with death during TB treatment. So that the finding of this study made available to show the type of intervention and when to intervene to reduce TB death by identifying characteristics of patients who died of TB during highest risk period in the course of TB treatment.

CHAPTER TWO

2. Literature review

2.1 Overview of TB

Tuberculous infection occurs when a person carries the tubercle bacilli inside the body but many people infected with tuberculous remain well for many years probable for life (26). In these asymptomatic individuals, the only evidence of infection is positive tuberculin skin test. (6).

The most important source of infection is SPPTB patients who produces infectious droplet nuclei which remain suspended in the air for long time to infect others (6, 27). Tuberculosis is a state where the tubercle bacilli start to multiply and overcome the body's defense (25).

2.2 TB treatment regimen, duration and outcomes

Patients diagnosed with TB will be referred to DOTs clinic and start TB treatment after classified to one of the treatment category to take combination of drugs for 6 to 8 months based on the national TB treatment guideline. The final treatment outcomes of TB treatment are classified as cured, treatment completed, failure, defaulter, died or transfer out and treatment success is the sum of cured and treatment completed cases (5, 25).

The treatment success rate is showing improvement following the introduction of DOTs program. According to WHO 2013 report, the global treatment success rate was 87% which is the fifth successive year for it to be above MDG (≥ 85%). TB treatment success rate in Africa was 82% with steady improvement since 1999 showing hope to achieve MDG goal (9). A register based cohort study conducted in China also showed the treatment success rate was gradually increasing from 75.7% to 84.1%, and it then reached and stayed at 90% for six years while both failure and defaulter rate were dropped during the same time (28).

A retrospective and cross-sectional study conducted in Tigray on PTB patients reported 89% treatment success rate (85.5% cured, 4.4% completed treatment). Of

unsuccessful treatment outcomes 3.7% were treatment failure, 3.2% defaulted and 3.9% died (29). Another study in Northwest Ethiopia on 827 TB patients revealed that 15.5% were cured, 70.1% completed treatment, 3.5% defaulted, 3.3% died, and 7.6% transferred out (30). A study in Addis Ababa showed the treatment failure, defaulter and death rate was 0.4%, 5.1% and 3.7% respectively (31). Out of 655 culture positive PTB cases in Norway 58 (9%) patients died and 39 (6%) occurred while on treatment (32). In shanghai, a study on culture positive PTB patients revealed 5.5% cases died prior to completion of therapy (33).

2.3 Time of occurrence of death and survival status of TB patients

Studies indicated that majority of deaths of TB cases occurred during the first two months of TB treatment. A study conducted in Iran showed from 125 deaths during TB treatment 73.6% occurred in the first two months of treatment regimen (19). Similar result was obtained from a study in Malawi on patients with all form of TB which reported that there was a high early death with 19% of deaths occurred by day 7, 41% by month 1 and 59% by month 2 (34). A study from Thailand revealed higher probability of TB death occurred in the first month of anti-TB treatment and it was found to be higher with advanced age (17). The median time of death was two months as shown from a study in India (23).

A study in Recife, Brazil showed the TB case fatality rate of 7.7 per 1000 PYO (35). The TB mortality rate per 100 PYO was 2.5% per annum (21). Another study in Addis Ababa showed TB mortality rate of 6.3/100 PYO (6.3%) per annum during TB treatment (36). Survival at 2, 6 and 12 months following initiation of TB treatment was 90.7%, 82.8% and 78.8% respectively and the survival curve turn into much flatter after 6-months of TB treatment which was reflected from a follow up study in Malaysia (37).

There was no difference in survival rate among male and female TB patients during anti-TB treatment according to one study in Malawi and two studies in India revealed that there was no significant difference between male and female survival curve (20, 23, 34). But a study in Shanghai, China reported that male culture positive TB patients had lower survival curve than female patients (33).

The survival probability of TB patients with advanced age during TB treatment was lower compared with young age patients (20, 32). The median age of death during TB treatment was 81 years and the average duration of treatment was 67 days (32). Similar study reported that there was increased odds of early death in patients with age above 50 years (20).

There were significantly more deaths in SNPTB and EPTB than SPPTB patients at the first and second months of TB treatment. EPTB patients died more significantly than SPPTB patients within the first 21 days of treatment (34).

The survival rate by the end of both intensive and continuous phase was lower in TB patients under treatment category II (re-treatment cases). Retrospective cohort study in India showed the survival rate by the end of intensive phase and at 6^{th} month of treatment for category I TB patients was 96%. The survival rate at the end of intensive phase and by the time all patients censored in treatment category II and III TB patients was 93% Vs 88% and 99% Vs 96% respectively. Significant difference was observed on survival curve for the three treatment category with (log rank statistics= 7.26, d.f= 2 and P= 0.02) (23). Another study showed new patients had an increased risk of early death compared with patients who had previously treated TB (20). However, another study reported that there was no significant difference between the survival time of TB patients among the three categories ($p = 0.1$) (24).

A study in Brazil showed TB/HIV co-infection was among factors that cause early death of TB patients (35). Another study in south India revealed that HIV status was not significantly associated with early death of TB patients (20). Even though, there was no significant difference in risk of death between HIV positive and HIV negative TB patients ($p=0.15$) during the intensive phase, the risk of death was higher among HIV positive TB patients during the continuation phase with 7.5/1000 compared to HIV negative TB patients 1.7/1000 according to a study in Hawassa Health Center (25). A study in Dahir Dar revealed that the general incidence rate (IR) of mortality of HIV positive TB patients was 4.09/100 per months of observation (PMO) and the survival probability in on ART patients was

significantly greater than in the non ART patients at time of TB treatment period (38).

2.4 Factors affecting the survival status of patients during TB treatment

Being male increased the risk of mortality by active TB. A study in Iran reflected that the mortality rate of males and females was 3.3% Vs 2.8% with total mortality rate of 3.15% (19). Another study in Shanghai showed male patients were 1.7 times at increased risk of death (33). But sex was found not statistically significant risk factor for death during TB treatment as shown from study in South India (24). Meanwhile higher death rate was reported for female patients as compared to male TB patients according to a retrospective study in Felege Hiwot Referral Hospital, Northwest Ethiopia(15).

Among factors associated with increased rate of death of patients during TB treatment was age of the patient as reflected in many studies. As the age of a patient increases the chance of dying during TB treatment also increases (33). For each year increase in age there was 4% increase risk of TB death (39). Another study also showed that patients aged 41-60 years and greater than 60 years were 7.8 and 21.3 times more at risk of death compared to patients less than 20 years of age respectively (23). Similar finding was found from a study conducted in Dembia and Gonder which showed the death rate during TB treatment increased as age of patients increased (22, 30). But a prospective study conducted in New York on 216 TB cases showed age was not independently associated with survival of TB patients (40).

Body weight at TB treatment initiation was the risk factors for increased risk of death during TB treatment according to a study in Addis Ababa which revealed TB patients weighting more than 34 kg at initiation of TB treatment were 10.1% less likely to die [AHR = 0.899] compared with those weighting less than 34 kg (36). A similar study in South India revealed that being <35kg at initiation of TB treatment was 3.7 time more likely to die of TB during treatment (24).

Type of TB is also among factors associated with mortality of patients who are on TB treatment. Being SNPTB case increased the risk of death compared to SPPTB

and EPTB cases as reported by a study in southern Ethiopia (21). But a similar study conducted in Addis Ababa presented with EPTB patients were more likely to die during TB treatment rather than SNPTB patients. The proportion of death from SPPTB, SNPTB and EPTB patients was 2.7%, 3.6%, and 4.3% respectively (36). Compared with new SPPTB, the case fatality rate was significantly lower at 1.6% in those with EPTB and significantly higher at 12% in those with previously treated TB cases (20). A study in South-Eastern Iran also reported that SPPTB was an independent associated risk factor for the death of TB patients (41). Analysis of European surveillance data revealed that the risk of death in SPPTB cases was not statistically different from SNPTB cases (42).

In terms of the treatment category, a study in Addis Ababa reported that TB patients under retreatment were 1.74 times [AHR = 1.74] more likely to die compared to new TB patients (36). The death rates in category I, II and III were 6.8%, 10.38% and 3.28% respectively where the death rate was high in patients under treatment category II (23). But a study in rural area of South India revealed treatment categories were not an independent risk factor for death of TB patients during TB chemotherapy (24).

TB/HIV co-infected patients have much higher case fatality rate compared to HIV negative patients (43). A retrospective cohort study in Kolla Diba Health Center indicated that TB/HIV co-infected cases were more likely to die (13.3% vs. 2.0%) than HIV uninfected cases (30). A study in Hawassa also showed TB/HIV co-infection had 2 times higher risk of death than HIV negative patients during TB treatment (25). A prospective cohort study in Spain reported that the risk of dying for TB/HIV co-infected patients was 7.08 times higher compared to HIV negative TB patients (44). Similarly another study also revealed that HIV infection had more than 5 times higher risk of mortality compared to HIV uninfected TB patients (39).

2.5 Conceptual frame work

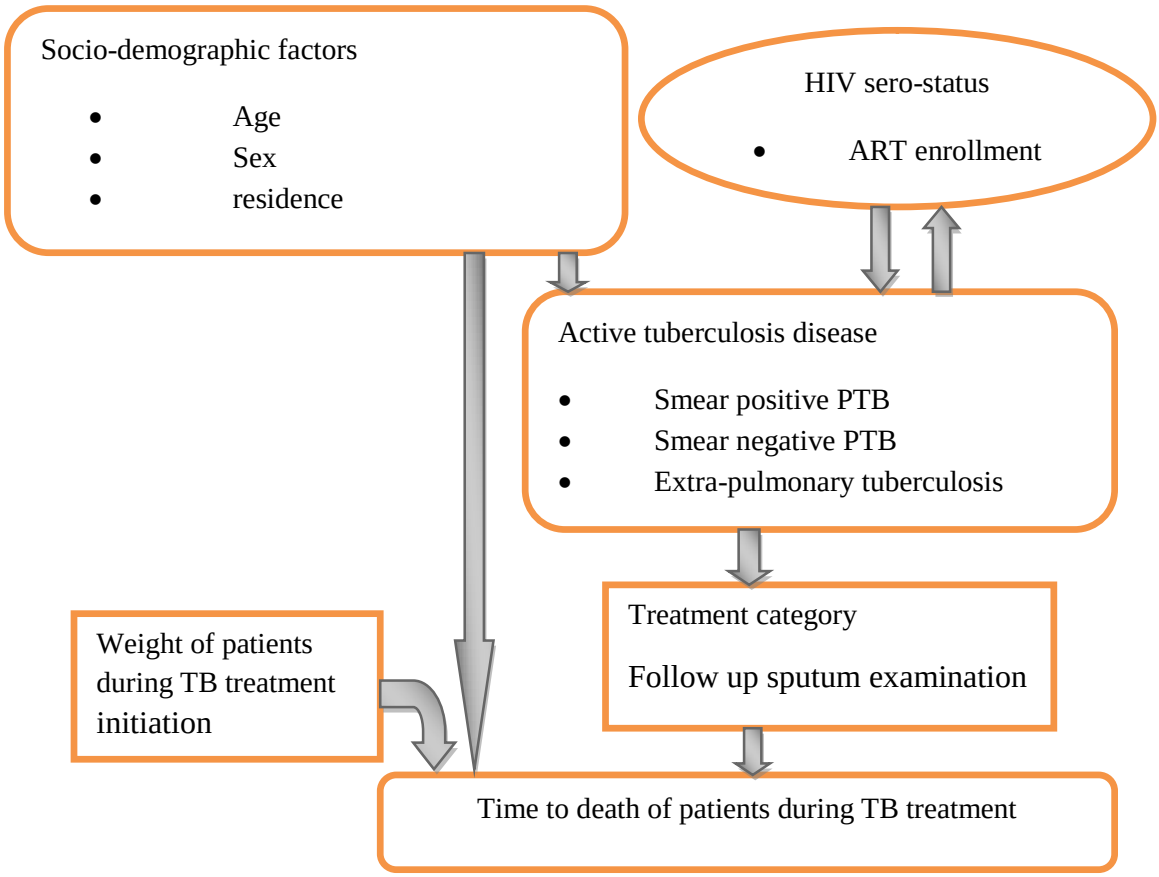

Figure 1: Conceptual frame work on time of death and associated factors during TB treatment in Dangla Woreda, Northwest Ethiopia, 2008-2012. (Developed after reviewing other similar studies)

2.6 Significance of the study

Despite the intense activities pertaining early detection of tuberculosis cases and treating of patients under DOTs program in curing the patient, interrupting transmission of tuberculosis to other persons and preventing bacilli from becoming drug resistant. There is a significant amount of death of patients during TB treatment. This outcome in turn affects the achievement of MDG which is greater than 85% treatment success rate. Again high proportion of death occurred in the intensive phase where there is a daily observed TB therapy according to DOTs program.

This study focused on the survival rate of TB patients at each treatment and identification of factors associated with increased rate of death of patients during the course of TB treatment.

Understanding the time most deaths occurred and identification of subgroup of TB patients who are at increased risk of death during TB treatment is important to show areas of health care service which needs improvement or to design additional health care measures. This is also useful to identify the time when and to whom interventions should be applied.

CHAPTER THREE

3. Objectives

3.1 General objective

- To assess the time of reported death and associated risk factors in a cohort of patients with tuberculosis during anti-tuberculosis treatment in Dangila Woreda, Northwest Ethiopia, 2008-2012.

3.2 Specific objectives

- To assess the time of occurrence of death of patients with tuberculosis during anti-tuberculosis treatment.
- To identify associated risk factors with the death of patients during the TB treatment regimen.
- To determine the TB treatment outcomes of patients who were on anti-tuberculosis treatment.

CHAPTER FOUR

4. Methods and Materials

4.1 Study area and period

The study was conducted in Dangila Woreda in March 2014. Dangila is located in the Northwest Ethiopia around 504km away from Addis Ababa and 64km from Bahir Dar. For administrative purpose the Woreda has divided to Dangila town administration and rural administration since 2001. The Woreda has a total of 5 urban and 16 rural Kebeles. Based on 2007 census Dangila Woreda had 157390 inhabitants where 79416 were males and 77974 were females. Concerning the health facilities, Dangila Woreda has six Health Centers, five private Clinics and 21 Health Posts. According to the Woreda health office authority report the DOTs program was started since 1996 with one Health Center. Know all (six) Health Centers are providing the service starting 2008.

4.2 Study design

Institutional- based retrospective cohort study design was applied.

4.3 Population

4.3.1 Source population

TB patients who had accessed health care service from Dangila Woreda public health facilities were taken as source population.

4.3.2 Study population

TB patients registered on TB log book and put on anti-tuberculosis treatment based on the national TB treatment guideline from 2008-2012 were the study population.

4.4 Inclusion and exclusion criteria

4.4.1 Inclusion criteria

- TB patients registered in all Health Centers in the Woreda for the specified time period.

4.4.2 Exclusion criteria

- TB patients with unregistered treatment outcome

4.5 Sample size and sampling procedure

All TB patients registered on TB log book and started anti-TB treatment in all Health Centers within the Woreda from 2008-2012 and fulfilled the inclusion criteria were included in the study.

4.6 Study variables

Dependent variable

Time to death in months

Independent variables

Age	Baseline body weight
Sex	Type of TB
Place of residence	ART enrollment
Treatment category	Follow up sputum result
HIV sero-status	

4.7 Data collection procedure and instrument

Secondary data was extracted from the registry using structured data sheet/data extraction format by trained health officers and nurses who are working in the DOTs clinic. The data sheet was adapted from other similar study (25) based on the local context of the study area.

4.8 Data analysis procedures

The data was checked for completeness, coded, and then entered into Epi data version3.1 software for edition, cleaning and then exported to SPSS version 16 Software for analysis. Patients were described using frequency with percentage, mean with standard deviation and median with inter quartile range (IQR).

Time to death during TB treatment was the outcome measure and the person-month of observation (PMO) was calculated by subtracting the date of TB treatment outcome occurred from date of treatment initiation for both cases with event of interest and censored cases then divided total days of follow up by thirty to obtain total months of follow up for all subjects under the study.

The survival probability of TB patients during anti-TB treatment with respect to socio-demographic and clinical variables was analyzed with Kaplan Meier (KM) method. KM plot was used to see the survival curve among different group of patients.

Log rank test was applied to test whether the difference in survival experience between each group of patients under different explanatory variable was a real difference.

Cox proportional hazard model was used to determine the hazard ratio (HR). Before fitting the covariates into the model, proportional hazard assumption were checked by plotting log-minus-log of the covariate against time and see whether the lines cross each other to test for independence of the covariate with time. On bivariate analysis variables with p value less than or equal to 0.25 and clinically important variables were candidate for multivariate analysis. Backward stepwise variable selection method was used in the multivariate analysis. Variables with P value less than 0.05 were considered as statistically significant predictors of TB death.

4.9 Data quality control

To ensure the quality of data two days training was provided to data extractors before data extraction. There was also a continuous daily monitoring and supervision of the data extraction by data extraction supervisors and principal investigator. The extracted data were examined for completeness and checked for consistency before entering it to Epi Data software. The data was double entered to Epi Data version3.1 software to control error during data entry.

4.10 Ethical consideration

Letter of ethical clearance was obtained from Ethical Review committee of Jimma University College of Public Health and Medical Sciences. A letter of support written to those health centers were also obtained from Dangila Woreda health office after discussion on the significance of the study. For confidentiality purpose the names of patients and their card number were not included in the data sheet.

4.11 Dissemination plan

The findings of this study will be presented to Jimma University scientific community in the thesis defense. Then the final report will be disseminated to relevant organizations and bodies who can use it for the prevention and control of death during TB treatment. Furthermore, great effort will be made to publish the finding of this study in a peer reviewed reputable journal.

4.12 Operational definitions and definition of terms

4.12.1 Definition of terms

Type of TB

Pulmonary tuberculosis (PB):- refers to TB involving the lung parenchyma. Patients having both pulmonary and extra-pulmonary TB will be classified as pulmonary TB (26).

Smear positive Pulmonary tuberculosis:- following 3 sputum smear examination (spot-morning-spot) for AFB by direct microscopy at least two smear results are positive or one smear positive for AFB and radiographic abnormalities consistent with active TB as determined by a clinician or one smear positive for AFB and HIV positive patients (26).

Smear negative Pulmonary tuberculosis:- patients having signs and symptoms suggestive of TB with three sputum smear examination negative for AFB and not responding to broad spectrum anti-biotic and suggestive radiological finding and clinician decision for full course of TB chemo-therapy (26).

Extra-pulmonary tuberculosis: refers to TB involving other than the lung like pleura, bone, lymph nodes etc. EPTB is not diagnosed at health center level where it needs at least one specimen with confirmed M. tuberculosis or histological or strong clinical evidence consistent with active EPTB, followed by a decision by a clinician to treat with a full course of tuberculosis chemotherapy (26).

Treatment category

When patients are entered to DOTs they categorized to one of the treatment category. According to the national TB/Leprosy control program guideline (5) this treatment categories are:-

- *New case*: A patient who never had treatment for TB, or has been on TB treatment for less than four weeks.
- *Return after defaulter*: A patient previously registered as defaulted from treatment and returns to the health facility with smear-positive sputum.
- *Treatment after failure*: A patient who, while on treatment, is smear positive at the end of the fifth month or later, after commencing.
- *Relapse*: A patient declared cured or treatment completed of any form of TB in the past, but who reports back to the health service and is now found to be AFB smear-positive.
- *Transfer in*: A patient who is transferred-in to continue treatment in a given treatment unit after starting treatment in another treatment unit.

Treatment outcome:

According to national TB and leprosy treatment guideline (5) the outcome of TB treatment are classified in to

- *Cure*: Patients smear positive at the beginning of treatment but smear negative for AFB in the last month of treatment.
- *Treatment completed*: Patients who complete full course of anti-TB treatment but do not have sputum smear negative result for AFB in the last month of treatment.

- *Defaulter*: Patients who take the treatment for at last one month and interrupt for two or more months.
- *Treatment failure*: A patient whose sputum smear is positive at 5 months or later during treatment.
- *Transferred out*: A patient who has been transferred to another recording and reporting unit and whose treatment outcome is unknown.
- *Successfully treated*: Is the sum of cured and treatment completed cases.

4.12.2 Operational definitions

TB death: Death during TB treatment irrespective of the cause of the death.

Early death: A patient who died within the first two months of anti-TB treatment.

Time to death: The time from anti-TB treatment initiation to death during anti-TB therapy.

Censored cases: Includes all cases end up with any of the TB treatment outcome except death during anti-TB treatment.

Re-treatment cases: Includes cases with treatment after default, treatment after failure and relapse cases.

Baseline body weight: The weight of the patients at time of anti-TB treatment initiation.

CHAPTER FIVE

5. Result

5.1 Description of the cohort

Among 872 TB patients registered in the DOTs program 62 were with unregistered treatment out come so they were excluded and a total of 810 TB cases were involved in the study. All public health facilities (six Health Centers) which are found in Dangila Woreda were involved in the study. Majority of subjects 437(54.0%) were from Dangila Health Center followed by Chara, Abadira, Gumdiri, Gissa and Afesa Health Centers respectively (Figure 2).

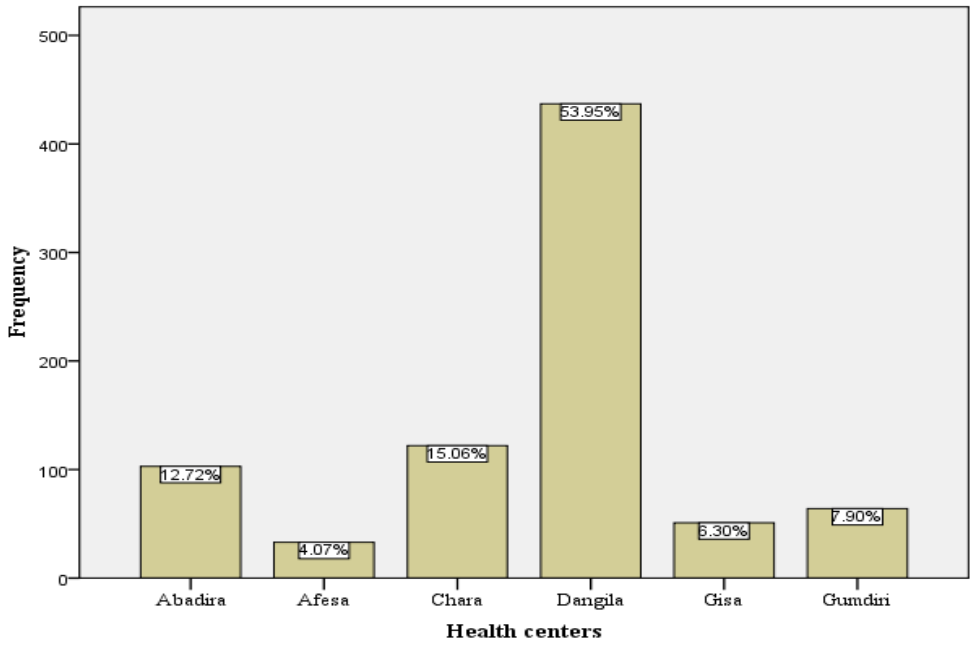

Figure 2: Health Centers involved in the study, Dangila Woreda, Northwest Ethiopia, 2008-2012

The age of study subjects range from 1 year to 86 years. The mean age of the patients was 32.4 years with standard deviation of 17 years and median age of 28 years with IQR 20 years to 44 years. Majority 447(55.2%) cases involved in the study were within the age range of 20 year to 44 years (Table 1).

As shown on table 1 below, majority of subjects 482(60.4%) came from the rural area. The baseline body weight of subjects range from 8kg to 81kg with mean weight of 44.8kg and standard deviation of 11.5kg. Most subjects 683(86.2%) had baseline body weight of greater than or equal to 35kg. Four hundred forty two (54.6%) of registered cases were females. The male to female ratio was 5:6.

Table 1: Socio-demographic characteristic and baseline body weight of study participants in Dangila Woreda, Northwest Ethiopia, 2008-2012.

Variables		**No**	**Percent**
Age	<20	163	20.1
	20-29	251	31.0
	30-44	196	24.2
	45-59	122	15.1
	60-74	63	7.8
	75+	15	1.9
	Total	810	100
Sex	Male	368	45.4
	Female	442	54.6
	Total	810	100
Residence	Urban	316	39.6
	Rural	482	60.4
	Total	798	100
Weight	<35kg	109	13.8
	≥35kg	683	86.2
	Total	792	100

Majority 494(61%) were EPTB cases followed by SNPTB and SPPTB cases with 176(21.7%) and 140(17.3%) respectively. From a total of 140 SPPTB cases 120(85.7%) patients had follow up sputum examination. Most 792(97.8%) of cases were new and 18(2.2%) were re-treatment cases (Table 2).

As shown on table 2 below, the prevalence of TB/HIV co-infection was 18.3%. Among 772(95.3%) TB patients under DOTs clinic who were tested for HIV

141(18.3%) tested HIV positive, 631(81.7%) tested HIV negative and the rest 38(4.7%) were not tested. Similarly from those who were tested positive for HIV 57(40.4%) were on ART, 72(51.1%) non ART and 12(8.5%) unknown ART status.

Table 2: Clinical characteristics of participants in Dangila Woreda, Northwest Ethiopia, 2008-2012.

Variables		**No**	**Percent**
Type of TB	SPPTB	140	17.3
	SNPTB	176	21.7
	EPTB	494	61.0
	Total	810	100
Follow up sputum examination	Yes	120	85.7
	No	20	14.3
	Total	140	100
Type of cases	New	792	97.8
	Re-treatment	18	2.2
	Total	810	100
Tested for HIV	Yes	772	95.3
	No	38	4.7
	Total	810	100
HIV status	Positive	141	18.3
	Negative	631	81.7
	Total	772	100
ART	Yes	57	40.4
	No	72	51.0
	Unknown	12	8.6
	Total	141	100

Concerning the treatment outcome 103(12.7%) and 582(71.9%) cases cured and completed their treatment respectively. So the treatment success rate was 84.6%. The death rate of TB patients was 60(7.4%) and others 57 (7%), 6(0.7%) and 2(0.2%) were transferred out, treatment failure and defaulters respectively. The prevalence of treatment completion rate was increased from 38.5% in 2008 to 78.6% in 2012. Similarly the treatment success rate also increased from 46.2% in 2008 to 92.9% in 2012 (Table 3).

Table 3: TB treatment outcomes of participants over time in Dangila Woreda, Northwest Ethiopia, 2008-2012.

Treatment outcome	**Year of treatment outcome**					**Total**
	2008	2009	2010	2011	2012	
	No (%)	No (%)	No (%)	No (%)	No (%)	No (%)
Cured	1(7.7%)	23(17.7%)	30(12.0%)	151(72.9%)	30(14.3%)	103(12.7%)
Treatment completed	5(38.5%)	75(57.7%)	186(74.4 %)	151(72.9%)	165(78.6 %)	582(71.9%)
Defaulter	-	-	1(0.4%)	1(0.5%)	-	2(0.2%)
Treatment failure	-	1(0.8%)	3(1.2%)	2(1.0%)	-	6(0.7%)
Transfer out	3(23.1%)	13(10.0%)	17(6.8%)	21(10.1%)	3(1.4%)	57(7.0%)
Death	4(30.8%)	18(13.8%)	13(5.2%)	13(6.3%)	12(5.7%)	60(7.4%)
Total	13(100.0 %)	130(100.0 %)	250(100.0 %)	207(100.0 %)	210(100.0 %)	810(100.0 %)

5.2 Time of occurrence of death and survival status of TB patients

Study subjects were followed for a total of 4672 months (140,160 days) with the minimum and maximum follow up time of 2 days and 563 days respectively. The mean follow up time was 5.8 months with standard deviation of 1.7 months and median follow up time of 6 months with IQR of 6 to 7 months. Of 810 TB patients followed for a total of 4672 months 60 cases died and treated as failure cases (event of interest) and the remaining 750 TB cases became censored cases during the analysis.

Of all TB deaths majority 34(56.7%) occurred during the intensive phase and the rest 26(44.3%) died during the continuation phase of TB treatment regimen. The survival rate at the end of intensive and continuation phase was 95.8% and 86% respectively (Table 4).

As shown on table 4 below, the survival rate decrease rapidly during the intensive phase and become slightly flatter in the continuation phase. Even though, there is sharp decrement in the last follow up month (eighth month).

Table 4: Death rate and survival probability of participants throughout the course of TB treatment in Dangila Woreda, Northwest Ethiopia, 2008-2012.

Interval (month)	**No at risk**	**Death**	**%**	**Censored**	**Survival probability**	**Cumulative S. probability**
(0-1]	810	17	28.3	16	0.979	0.979
(1-2]	777	17	28.3	25	0.958	0.938
(2-3]	735	6	10	16	0.95	0.891
(3-4]	713	8	13.3	17	0.939	0.837
(4-5]	688	1	1.7	63	0.938	0.785
(5-6]	624	5	8.3	352	0.93	0.730
(6-7]	267	2	3.3	207	0.923	0.674
(7-8]	58	4	6.7	54	0.86	0.580

The overall mean and median survival time of patients during TB treatment was 7.6 months and 7.7 months respectively. The mean and median time of death for patients who died during TB treatment was 3 months and 2 months respectively. Correspondingly, both the mean and median time of death during the intensive phase was 1.5 months. During the continuation phase the mean and median time of death was 4.9 months and 4 months respectively.

Majority 38(63.3%) of deaths occurred among male TB patients. Similarly during the intensive phase most deaths were from male TB patients than female 23(38.3%) and 11(18.45) respectively. In case of residence, there was slightly high percentage of TB death 37(62.7%) in patients who came from rural area during their TB treatment regimen. Patients from rural area had higher percentage of TB deaths 23(39.0%) than urban patients 10(16.9%) during intensive phase. Death among rural patients was 22% higher compared to urban during the intensive phase. Concerning baseline body weight, 47(83.9%) deaths occurred in patients with baseline body weight of greater than equal to 35kg and 9(16.1%) occurred with less than 35kg weight patients (Table 5).

Majority of deaths occurred in EPTB patients followed by SNPTB and SPPTB patients. Of all TB deaths 34(56.7%) occurred from EPTB patients and others 8 and 18(30%) deaths occurred from SPPTB and SNPTB patients respectively. Most deaths 55(91.7%) were from new TB patients and 5 deaths from re-treatment cases. During the intensive phase of TB treatment 32(53.4%) and 2 deaths occurred from new and re-treatment cases respectively (Table 5).

Four TB cases died with unknown HIV status while 56(93.3%) deaths tested for HIV. Among 56 TB deaths with known HIV status 37(66.1%) and 19(33.9%) were HIV negative and HIV positive TB cases respectively. From HIV positive TB deaths 3 cases were on ART, 14(82.3%) non ART and 2 cases with unknown ART status (Table 5).

Table 5: Death by socio-demographic and clinical characteristic of participants during TB treatment regimen in Dangila Woreda, Northwest Ethiopia, 2008-2012.

Variables		Number at risk	Death		Total No (%)
			Intensive phase No (%)	Continuation phase No (%)	
Sex	Male	368	23(38.3)	15(25)	38(63.3)
	Female	442	11(18.4)	11(18.3)	22(36.7)
	Total	810	34(56.7)	26(43.3)	60(100.0)
Residence	Urban	316	10(16.9)	12(20.4)	22(37.3)
	Rural	482	23(39.0)	14(23.7	37(62.7)
	Total	798	33(55.9)	26(44.1)	59(100.0)
Age	<20	163	1(1.7)	2(3.3)	3(5.0)
	20-29	251	5(8.3)	1(1.7)	6(10.0)
	30-44	196	8(13.3)	5(8.4)	13(21.7)
	45-59	122	8(13.3)	10(16.7)	18(30.0)
	60-74	63	9(15.0)	4(6.7)	13(21.7)
	75+	15	3(5.0)	4(6.7)	7(11.6)
	Total	810	34(56.7)	26(43.3)	60(100.0)
Weight	<35kg	109	4(7.1)	5(9.0)	9(16.1)
	35kg+	683	27(48.3)	20(35.6)	47(83.9)
	Total	792	31(55.4)	25(44.6)	56(100.0)
Type of TB	SPPTB	140	6(10.0)	2(3.3)	8(13.3)
	SNPTB	176	16(26.7)	2(3.3)	18(30.0)
	EPTB	494	16(26.7)	18(30.0)	34(56.7)
	Total	810	38(63.4)	22(36.6)	60(100.0)
Follow up sputum examination	Yes	120	1(12.5)	1(12.5)	2(25.0)
	No	20	5(62.5)	1(12.5)	6(75.0)
	Total	140	6(75.0)	2(25.0)	8(100.0)
Rx category	New	792	32(53.4)	23(38.3)	55(91.7)
	Repeat	18	2(3.3)	3(5.0)	5(8.3)
	Total	810	34(56.7)	26(43.3)	60(100.0)
HIV tested	Yes	772	30(50.0)	26(43.3)	56(93.3)
	No	38	4(6.7)	-	4(6.7)
	Total	810	34(56.7)	26(43.3)	60(100.0)
HIV status	Positive	141	19(33.9)	-	19(33.9)
	Negative	631	19(33.9)	18(32.2)	37(66.1)
	Total	772	38(67.8)	18(32.2)	56(100.0)
ART	Yes	57	2(11.8)	1(5.9)	3(17.7)
	No	72	8(47.0)	6(35.3)	14(82.3)
	Total	129	10(58.8)	7(41.2)	17(100.0)

The incidence rate (IR) of death by the end of intensive and continuation phase was 21.4 per 1000 PMO (34 TB cases died in 1587 months of follow up time) and 8.4 per 1000 PMO (26 TB cases died in 3085 months of follow up time) respectively. Therefore, general IR of TB deaths was 12.8 per 1000 PMO (60 deaths in 4672 months of follow up time).

The IR of TB death among male TB patients was 18.8 per 1000 PMO and it was 8.3 per 1000 PMO among female patients. The mean survival time among male and female patients was 7.4 and 7.8 months respectively. According to Kaplan Meier analysis the survival rate at the end of intensive phase in male and female patients was 93.7% and 97.5% respectively (Table 6) and the log rank test showed that there was a significant difference in the survival time between male and female TB patients [log rank= 10.0, d.f= 1, p= 0.002] (Figure 3A).

As shown on table 6 below, the IR of TB death among urban and rural patients was 11.9 and 13.4 per 1000 PMO respectively. The mean survival time of patients from urban and rural was 7.7 months and 7.6 months respectively. Patients from rural had lower survival rate both at the end of intensive phase and sixth month when compared to urban patient which was 95.1% vs. 96.7% and 92.4% vs. 93.0% respectively (Table 6). There was no significant difference in survival curve between urban and rural TB patients during their TB treatment regimen [log rank= 0.2, d.f= 1, p= 0.653] (Figure 3B).

More than 85% of TB deaths occurred among patients age greater than 30 years. The mean age of death among patients who died during their TB treatment was 48.9 years (±18.25 years) with a range of 11 years to 86 years. The IR of TB death in patients with age group of <20, 20-29, 30-44, 45-59, 60-74 and ≥75 year was 3.1, 4.2, 11.2, 26.2, 38.1 and 98.6 per 1000 person months of observation respectively (Table 6). There was a significant difference in survival time between those age groups [log rank= 83.677, d.f= 5, p< 0.001] (Figure 3C).

In case of baseline body weight, the IR of TB death in patients with baseline body weight of <35kg and ≥35kg was 14.5 and 11.8 per 1000 PMO respectively. The mean survival time for both patients with <35kg and ≥35kg baseline body weight was 7.7 and 7.6 months respectively. The survival rate by the end of intensive phase and sixth month of TB treatment for both patients with baseline body weight of <35kg and ≥35kg was 96.3% Vs 96.0% and 92.8% Vs 93.4% respectively; which reflected the survival rate was almost equivalent between the two groups during intensive phase but during the continuation phase the survival rate of patients weighed <35kg was lower than patients weighed ≥35kg (Table 6).

According to log rank test there was no significant difference in survival time between the two group of patients [log rank= 0.2, d.f= 1, p= 0.657] (Figure 3D).

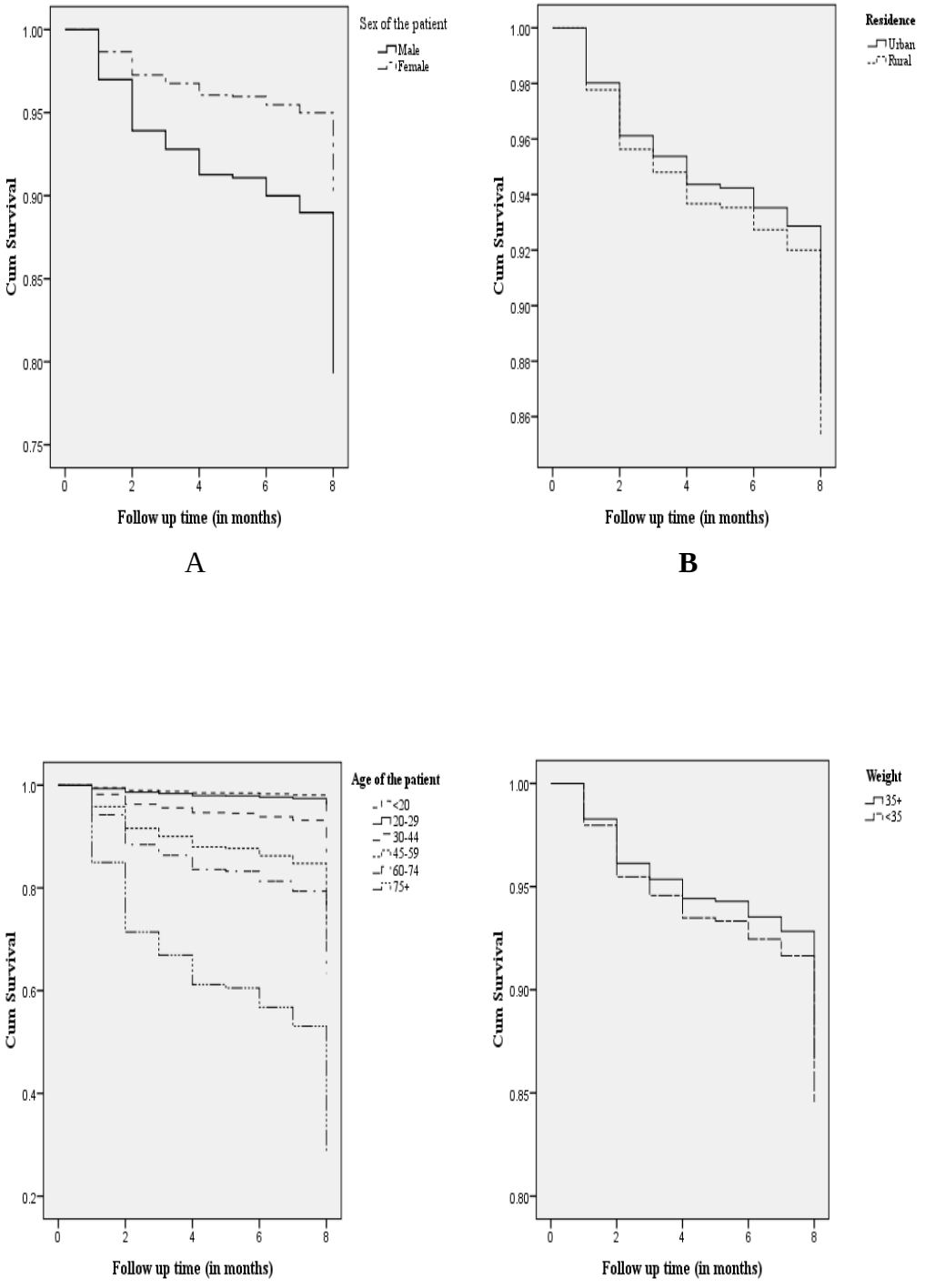

Figure 3: Survival curve of TB patients treated under DOTs program by baseline body weight and socio-demographic characteristics of participants in Dangila Woreda, Northwest Ethiopia, 2008-2012.

Regarding the type of TB, the IR of death among SPPTB, SNPTB and EPTB patients was 10.1, 18.8 and 11.7 per 1000 PMO respectively. The mean survival time of patients with SPPTB, SNPTB and EPTB was 7.7, 7.4 and 7.7 months respectively. SNPTB patients had lower survival rate compared to both SPPTB and EPTB patents at the end of intensive phase and sixth month of TB treatment [92.9% in SNPTB, 95.5% in SPPTB and 96.7% in EPTB patients] (Table 6). There was no statistically significant difference in survival time between SPPTB, SNPTB and EPTB patients during their TB treatment regimen [log rank= 3.364, d.f= 2, p= 0.186] (Figure 4A).

New and re-treatment TB patients had IR of TB death 12.1 and 47.2 per 1000 PMO respectively. The mean survival time for both new and re-treatment patients was 7.6 and 7.1 months respectively. The survival rate by the end of the first two months and sixth month of treatment for new TB patents was 95.9% and 93% respectively. The survival rate of patients who were on re-treatment during the intensive phase was 88.9% and by the end of sixth month 75.2% which kept constant till all cases censored (Table 6). According to log rank test, there was a significant difference in survival time between the two group of patients [log rank= 8.958, d.f= 1, p= 0.003] (Figure 4B).

The IR of TB death among HIV positive verses HIV negative and patients on ART verses non ART was 23.6 Vs 10.1 per 1000 PMO and 8.5 Vs 35.2 pre 1000 PMO respectively. The mean survival time for HIV positive verses HIV negative and patients on ART verses non ART was 7.3 Vs 7.7 months and 7.7 Vs 6.9 months respectively. The survival rate by the end of second and sixth month for TB/HIV co-infected patients was 92% and 86.7% respectively. Correspondingly, it was 96.9% and 94.1% for HIV negative TB patients (Table 6). There was statistically significant difference in survival curve between HIV positive and HIV negative TB patients [log rank= 9.1, d.f= 1, p= 0.003] (Figure 5C). Similarly there was statistically significant difference in survival time between TB patients who were on ART and non ART [log rank= 5.781, d.f= 1, p= 0.016] (Figure 4D).

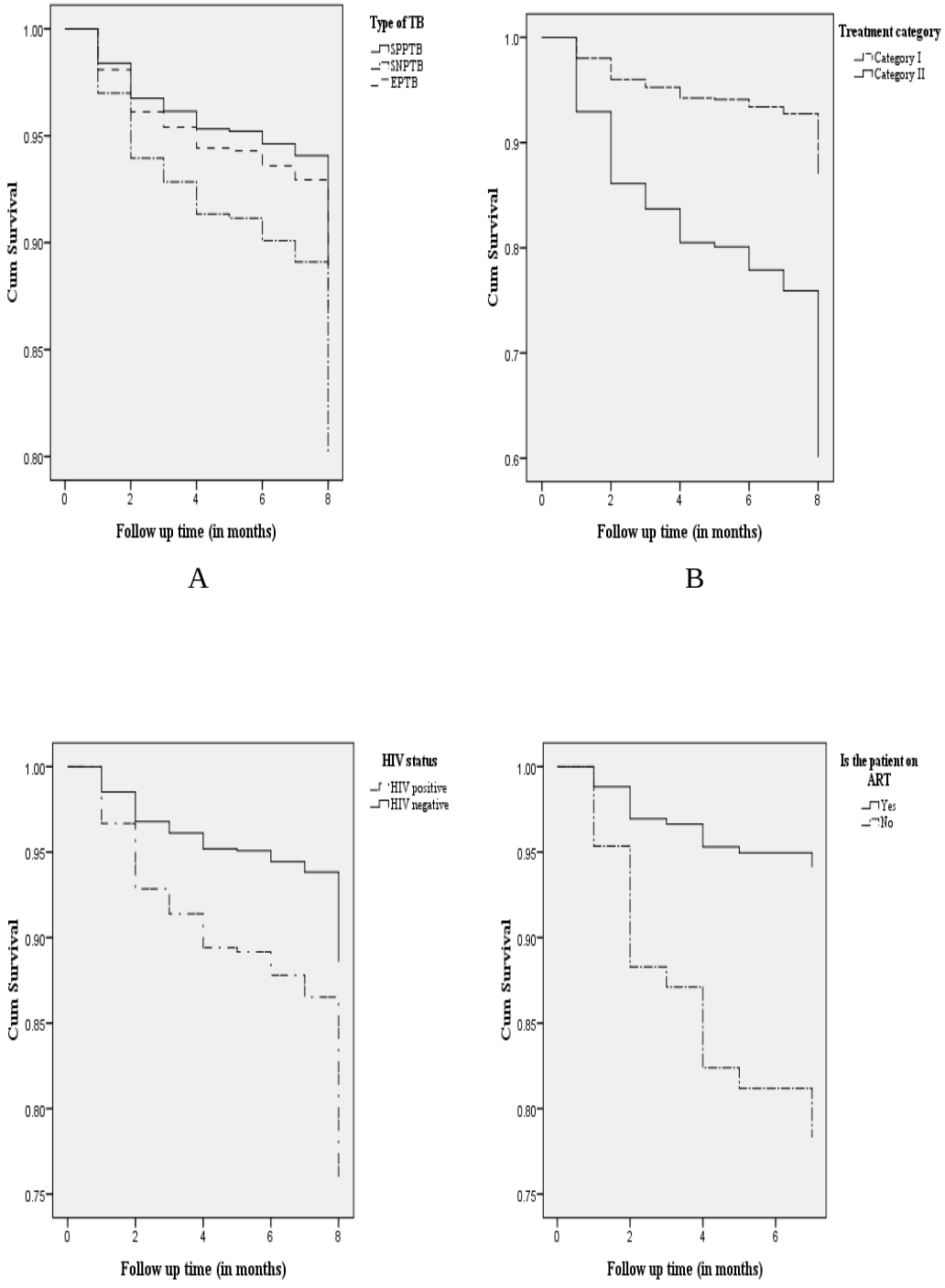

Figure 4: Survival curve by clinical characteristics of participants in Dangila Woreda, Northwest Ethiopia, 2008-2012.

Table 6: Incidence rate, mean survival time and survival rate by selected variables of participants in Dangila Woreda, Northwest Ethiopia, 2008-2012.

Variables		IR (per 1000 PMO)	Mean survival time (month)	Survival rate	
				2^{nd} month	6^{th} month
Sex	Male	18.8	7.4	93.8	89.1
	Female	8.3	7.8	97.5	95.4
Residence	Urban	11.9	7.7	96.7	93
	Rural	13.4	7.6	95.1	92.4
Age	<20	3.1	7.9	99.4	99.4
	20-29	4.2	7.8	98.0	97.5
	30-44	11.2	7.6	95.9	93.7
	45-59	26.2	7.3	93.4	86.1
	60-74	38.1	6.8	85.6	80.7
	75+	98.6	5.3	80.0	58.3
Weight	<35kg	14.5	7.7	96.2	90.9
	35kg+	11.8	7.6	95.9	93.2
Type of TB	SPPTB	10.1	7.7	95.5	92.9
	SNPTB	18.8	7.4	92.9	89
	EPTB	11.7	7.7	96.7	93.8
HIV status	Positive	23.6	7.3	92	86.7
	Negative	10.1	7.7	96.9	94.1
ART	Yes	8.5	7.7	96.5	94.7
	No	35.2	6.9	88.7	81.4
Category	New case	12.1	7.6	95.9	93
	Re-treatment	47.2	7.1	88.9	75.2

5.3 Factors affecting the survival status of TB patients

Based on bivariate analysis sex, age, type of TB, sputum follow up examination result, treatment category, HIV status and ART enrollment were found to have a significant relationship with increased rate of death of patients with p value of ≤ 0.25, so they were taken as candidate for multivariate Cox regression analysis. Even though, follow up sputum examination and ART enrollment were not included in the multivariate analysis since they had very small event of interest. Based on its clinical importance baseline body weight was included in the multivariate analysis

Accordingly to multivariate Cox regression analysis variables which were found to be an independent predictor for increased rate of death during TB treatment regimen were age, baseline body weight and HIV status of patients.

There was 5.2% increase in rate of death for every year increase in age of TB patients during their anti-TB treatment regimen; AHR= 1.052, 95%CI= [1.037, 1.067], p<0.001. Similarly for every 5 years and 10 years increase in the age of TB patient there was 26% and 52% increase in death rate during anti-TB treatment regimen respectively (Table 7).

Patients whose weight less than 35kg during TB treatment initiation were died at a rate 3.9 times greater than patients weighted greater than 35kg during TB treatment initiation; AHR= 3.904, 95% CI [1.634, 9.325], p= 0.002 (Table 7).

TB/HIV co-infected patients were died at a rate of 2.3 times higher during TB treatment period compared to HIV negative TB patients; AHR= 2.3, 95% CI [1.236, 4.244], p= 0.008 (Table 7).

Table 7: Predictors of death during TB treatment among patients on DOTs program in Dangila Woreda, Northwest, Ethiopia, 2008-2012.

Variables		Bivariate			Multivariate		
		CHR	95% CI	p-value	AHR	95% CI	p-value
Sex	Male	2.3	(1.342, 3.844)	0.002	1.673	(0.922, 3.035)	0.041
	Female	1			1		
Age		1.051	(1.037, 1.065)	0.000	1.052**	(1.037, 1.067)	0.000
Weight	<35kg	1.2	(0.575, 2.393)	0.66	3.904**	(1.634, 9.325)	0.002
	35kg+	1			1		
Type of TB	SPPTB	1			1		
	SNPTB	1.9	(0.808, 4.276)	0.145	1.717	(0.646, 4.565)	0.278
	EPTB	1.2	(0.542, 2.528)	0.682	1.993	(0.799, 4.97)	0.139
Rx category	New	1			1		
	Repeat	3.7	(1.459, 9.158)	0.006	1.979	(0.752, 5.206)	0.167
HIV status	Positive	2.3	(1.307, 3.956)	0.004	2.290**	(1.236, 4.244)	0.008
	Negative	1			1		
Residence	Urban	1					
	Rural	1.1	(0.665, 1.912)	0.656			
Follow up sputum examination	Yes	1					
	No	29.8	(5.808, 152.688)	0.000			
HIV tested	Yes	1					
	No	1.5	(0.557, 4.241)	0.406			
ART	Yes	1					
	No	4.0	(1.158, 14.034	0.028			

NB: ** indicates independently associated variables

CHAPTER SIX

6. Discussion

According to WHO 2013 report on global tuberculosis control (9), the global treatment success rate under the DOTs program was 87% worldwide and it was 82% in Africa with gradual improvement since 1999 showing hope to achieve MDG. Our study found that the treatment success rate of TB patients treated under DOTs program in Dangila Woreda was 84.6% (12.7% cure rate and 71.9% treatment completion rate). The observed result is higher than WHO report in Africa which was 82% in 2012. This can be due to the effect of Health extension program on tracing of TB patients during their follow up time. But lower than a study conducted in Tigray (29) which reported 89% treatment success rate (85.5% cured, 4.4% completed treatment) which showed a large difference on cure rate. This gap on cure rate may be due to study subject difference where the study in Tigray included SPPTB case only. This finding is consistent with a study in Kolla Diba Health Center (30) with treatment success rate of 85.7%.

Our study also showed that there is a significant increment in treatment success rate across the year which may implicate the positive effect of DOTs program on the improvement of treatment success rate in Dangila Woreda. This finding is consistent with WHO 2013 report (9) and with the finding of a study conducted in China (28). Similarly, there was a study which reflects the improvement in treatment success rate from 74.1% to 88.3% during the time period of 2008 to 2011(45).

Defaulter and treatment failure rates were 0.2% and 0.7% respectively and this showed low defaulter and treatment failure rate; which may reflect the contribution of health extension workers in supporting patients who are on TB treatment. This finding is inconsistent with a study in Tigray (29) with 3.2% defaulter and 3.7% treatment failure rate and Kolla Diba Health Center (30) which reported 3.5% defaulter rate. In case of the study in Tigray primary data was collected through

house to house visit. Regarding the treatment failure rate our study finding is supported by a study in Addis Ababa (31) with 0.4% treatment failure rate.

Regardless of the cause, the deaths of patients during their TB treatment period were taken as TB death according to the WHO definition. Based on this definition the mortality rate in our study was 7.4% which is higher than 3.9% reported from Tigray (29), 3.3% from Kolla Diba Health Center (30), 5.8% from Bahir Dar (15) and 6% from India (20). This study finding demonstrated slightly lower TB case mortality rate than the studies conducted in Azezo health center(45) with 8.5% and in Gonder university teaching hospital(22) with 10.1% mortality rate.

According to our study finding of lower treatment defaulter (0.2%) and failure (0.7%) rate and a substantial higher proportion of death rate (7.4%) might reflect the negative effect of death during TB treatment on farther improvement of TB treatment success rate in Dangila Woreda.

In our study, the overall incidence rate of mortality of patients during TB treatment was 12.8 per 1000 PMO. This result does not go in line with the study in Bahir Dar (38) on TB/HIV co-infected cases reported that the incidence rate of mortality during TB treatment was 40.9 per 1000 PMO. The observed difference in incidence rate of mortality of TB patients may be due to the fact that HIV infection increases TB mortality. Another study in Addis Ababa (36) and Brazil (35) also reflected that the general incidence rate of death was 63 per 1000 PYO and 7.7 per 1000 PYO respectively.

In our study, early death was the critical time where most TB patients died. Around 57% deaths occurred during the intensive phase of TB treatment. For patients who died during TB treatment the median time from treatment initiation to onset of death was 2 months. This could be due to the delayed presentation of patients to the health facility or late diagnosis of TB case which lead to advancement of the disease or it might also be because of drug intolerance. This finding is consistent with a study in Malawi (34) on all type of TB patients that showed early TB death rate of 59%. This finding also agrees with the finding of a study in India (23) where the median time to death for TB patients who died during the treatment regimen

was 2 months and with the finding of a study in Thailand (17) that reported higher probability of TB death occurred during the first month of treatment regimen. A study in Iran (19) showed higher early death rate of 73.6% compared to our study finding. Another study from South India (24) however revealed that TB death rate was evenly distributed throughout the course of anti-TB treatment. This difference might be attributed to geographical area difference.

Another factor that is significantly associated with death during anti-TB treatment regimen was baseline weight of the patient. Patients with body weight of less than 35kg during treatment initiation died 3.9 times at higher rate than patients with baseline weight of 35kg and above; (AHR= 3.904, 95% CI= 1.634-9.325) implicating the negative effect of under nutrition on the survival status of patients during TB treatment. This finding is consistent with study in Addis Ababa (36) which revealed that patients weighting more than 34 kg at initiation of treatment were 11.5% less likely to die compared to patients weighting less than 34 kg and a study in south India (24) which showed being less than 35kg at initiation of TB treatment was 3.7 time more likely to die during TB treatment.

In our study, HIV status was significantly associated with decrease in survival rate during the course of TB treatment. HIV positive TB patients had lower survival probability compared to HIV negative patients. This finding do not agree with the finding of a study in Hawassa (25) which revealed that there is no significant difference between HIV positive and HIV negative TB patients in survival rate at the end of intensive phase even though there is difference in the continuation phase of the treatment. This may be due to difference in study design where the study in Hawassa applied case control study. It is also inconsistent with a study in south India (20) which showed HIV status was not significantly associated with early death of TB patients which may be due to difference in socio-demographic characteristics of study subjects. In our study HIV positive patients were more at risk (about 2.294 times) of death compared to HIV negative TB patients. This finding is in agreement with a study in China (35) which reported that TB/HIV co-infection was the risk factor for early TB death. Similar finding was observed in Spain (44) and Tanzania (39) that the risk of dying for HIV positive TB patient was

7.08 and 5 times higher compared to HIV negative TB patients respectively. Even though, the risk is higher in both studies as compared to our study finding.

Age was another factor which was a significant risk for death of TB patients during the course of treatment. The survival probability of TB patients with advanced age was lower compared to young age patients. This finding is consistent with studies which reflected the survival rate of young TB patients was higher than old age patients (20, 32). In the present study there was 5.2% increase in death rate for every year increase in age of TB patients during their anti-TB treatment regimen. This finding is consistent with other studies which reported that the mortality rate of TB patients increases with their age (22, 30, 33). The study in India (23) also showed that patients aged 41-60 years and more than 60 years were 7.8 and 21.34 times more at risk of death as compared to patients less than 20 years of age respectively. Another study revealed that for every year increase in age the death rate increase by 4% (39) which agree with the present study finding.

Many studies both inside and outside of the country (23, 31, 36)showed that patients under re-treatment category were significantly more at risk of death during anti-TB treatment regimen. But a study in rural area of South India (24) revealed that treatment categories were not an independent risk factor for death of TB patients during chemotherapy. Similarly our study reflected that TB treatment category was not an independent risk factor for increased rate of TB death.

According to our study, type of TB was not associated with increased rate of death during anti-TB treatment. This finding is supported with the analysis of European surveillance data (42) which revealed that the risk of dying of SPPTB was not statistical significant different from SNPTB cases. But this study finding is inconsistent with studies in Southern Ethiopia (21) that reported SNPTB patients were at increased risk of death than SPPTB patients and in Addis Ababa (36) EPTB patients were more likely to die during anti-TB treatment rather than SNPTB patients.

Limitation of the study

- Incomplete registries to gather necessary variables like co-trimaxazole prophylaxis therapy (CPT).
- Absence of some important variables in the registry (behavioral factors, socio-economic factors, co-morbidities of the subjects).
- Deaths during TB treatment might have occurred due to multiple other reasons and this could cause misclassification.

CHAPTER SEVEN

7. Conclusions and Recommendations

7.1 Conclusions

The overall treatment success rate was 84.6% and there was a gradual improvement from 46.2% in 2008 to 92.9% in 2012. The general mortality rate of TB patients during anti-TB treatment in Dangila Woreda was 7.4% during the study period. Similarly the incidence rate of TB death was 12.8 per 1000 PMO. From unsuccessful treatment outcomes there was high proportion of death rate compared to treatment defaulter and failure rate so death during TB treatment has considerable negative effect on further improvement of TB treatment success rate in Dangila Woreda.

According to the present study most of TB deaths occurred in the first two months of treatment initiation. So the first two months of TB treatment follow up is critical time for the death of TB patients.

There was a substantial lower survival probability in older than younger patients, patients with baseline body weight of less than 35k than greater than and equal to 35kg and TB/HIV co-infected patients than HIV negative patients during TB treatment regimen.

Age, baseline body weight and HIV sero-status were independent predictor of death during the course of TB treatment. Elders, patients with baseline body weight of less than 35kg and TB/HIV co-infected patients were significantly at increased rate TB death compared to their corresponding subgroup of TB patients.

7.2 Recommendations

- Health professionals should strengthen the DOTs program and follow the prognosis of patients with regard to disease progress, drug side effect and tolerance especially in the intensive phase of the treatment, since most TB deaths occurred during this treatment period.
- Regional health bureau and other stakeholders should provide additional nutritional support for TB patients especially patients with baseline body weight <35kg to improve TB treatment outcomes.
- TB clinics should given emphases for elder patients during TB treatment follow up time to reduce the effect of age on TB death.
- Researchers should conduct study on survival status of patients during TB treatment by incorporating important variables like behavioral and socio-economic factors, co-morbidities.

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ANNEXE II: Datasheet (English version)

Instructions: data collectors must circle or write on the space provided based on the appropriate answer recorded on TB log book.

Datasheet number _____ health center_____

Name of data extractor _____ date of data extraction ___/____/____

S. No	Question	Response	Skip
Part I: *Socio-Demographic characteristics*			
101	Age (in years)	_____	
102	Sex	1. Male 2. Female	
103	Weight during TB treatment initiation (in Kg)	_____.	
104	Residence	1. Urban 2. Rural	
Part II: Survival time and factors associated with patient death during TB treatment			
201	Type of TB	1. Smear positive pulmonary tuberculosis 2. Smear negative pulmonary tuberculosis 3. Extra pulmonary tuberculosis	
202	Treatment category	1. New 2. Re-treatment	
203	Did the patient tested for HIV?	1. Yes 2. No	
204	If the answer is yes to question no 203, what was the result?	1. HIV positive 2. HIV negative	
205	If the answer is 1 to question no 204, Is the patient on ART?	1. Yes 2. No	
206	Date of TB treatment initiated?	___/____/_____ dd/mm/yyyy	
207	What was the treatment out come?	1. Cured 2. Treatment completed 3. Defaulter	

		4. Treatment failure 5. Transfer out 6. Death	
208	Date of treatment out come?	___/____/_____ dd/mm/yyyy	

ASSURANCE OF PRINCIPAL INVESTIGATOR

The undersigned agrees to accept responsibility for the scientific ethical and technical conduct of the research project and for provision of required progress reports as per terms and conditions of the College of Public Health and Medical Sciences in effect at the time of grant is forwarded as the result of this application.

Name of the student: _____

Date._____ Signature _____

APPROVAL OF THE ADVISORS

Name of the first advisor: _____

Date._____ Signature _____

Name of the second advisor: _____

Date._____ Signature _____