PREDICTORS OF POOR TUBERCULOSIS TREATMENT OUTCOME AT ARBA MINCH GENERAL HOSPITAL, SOUTHERN ETHIOPIA: A CASE-CONTROL STUDY

BY

DEBALKE DALE(B.PHARM)

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JIMMA, ETHIOPIA

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DEBALKE DALE(B.PHARM)

ADVISORS:

BELAY YIMAM, B.PHARM, MSC

ELIAS ALI, MD, MPH

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ABSTRACT

Back ground: *Tuberculosis (TB) is the leading cause of death in the world. Ethiopia ranks seventh among the world's 22 countries with a high burden of TB. Currently, Ethiopia reports treatment success rate of 83%. Even where free medication is available, many patients are not successfully treated for TB. Therefore, this study is aimed at assessing predictors of poor TB treatment outcome at Arba Minch General Hospital (AMGH), Southern Ethiopia.*

Methods: *A case- control study comprising simple random sampling was conducted at AMGH from January 30 to February 28, 2014. Cases were patients who were registered as failed treatment, defaulted or died during TB treatment and controls were patients who were registered as cured or completed treatment in the period 1st January 2009- 30th December 2013 in AMGH. A prepared standard checklist which is adapted from WHO and according to the objectives of the study was used to assess the predictors of poor treatment outcome, a chi-square test and a T-test were used to compare categorical and continuous variables between the two groups, respectively. P- Value of less than 0.05 was considered statistically significant in the final model.*

Result: *The case group was composed of 224 patients with poor outcome while the control group was composed of 448 patients with successful outcome. Male sex (AOR=1.600 (95%CI=1.104, 2.317), age older than 35 years (AOR=2.381 (95%CI=1.643, 3.448), rural residence (AOR=1.496 (95%CI=1.037, 2.159), retreatment category(AOR=3.305 (95%CI=1.298, 8.415), smear negative PTB (AOR=*2.4 *(CI=1.4,4.1), EPTB (AOR=*2.5*(CI=*(1.3, 4.6)*), positive smear at 2nd/3rdmonth (AOR=53.3 (95%CI= 9.6, 296.1),HIV positive (AOR=2.364 (95%CI=1.574, 3.552) and not tested for HIV(AOR=2.553 (95%CI=1.283, 5.081), treatment of TB in the year before 2011 G.C were predictors of poor TB treatment outcome.*

Conclusion: *Male patients, those resided in rural area, older age, previously treated patients, patients with smear negative PTB and EPTB, having positive smear at 2nd/3rdmonth follow up, HIV co-infected patients, those not tested for HIV and treated for TB before 2011 G.C were at significantly increased risk of developing poor outcome. Targeted measures should be considered to reduce the rate of poor outcome among high-risk groups; careful monitoring, making DOTS program more accessible for the rural population, sputum smear examinations during follow up, counseling patients with TB on the need for HIV testing, linking the HIV positive patients to support groups, Drug susceptibility test (DST) is also highly recommended for all previously treated patients before they are treated with the retreatment regimen.*

Key words: *Tuberculosis, poor treatment outcome, predictors, Arba Minch General Hospital, Southern Ethiopia*

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List of Abbreviations and acronyms

AIDS	Acquired Immune Deficiency Syndrome
AMGH	Arba Minch General Hospital
HAART	Highly Active Anti-Retroviral Treatment
CPT	Cotrimoxazole Preventive Treatment
DOTS	Directly Observed Treatment, Short Course
E	Ethambutol
EPTB	Extra pulmonary Tuberculosis
FMOH	Federal Ministry of Health
G.C	Gregorian calendar
H	Isoniazid
HBC	High-Burden Country
HIV	Human Immunodeficiency Virus
JU	Jimma University
MDR-TB	Multi Drug Resistant Tuberculosis
M.TB	Mycobacterium Tuberculosis
NTLCP	National Tuberculosis & Leprosy Control Program
PTB	Pulmonary Tuberculosis
PTB-	Smear Negative pulmonary Tuberculosis
PTB+	Smear Positive Pulmonary Tuberculosis
R	Rifampicin
S	Streptomycin
SCC	Short-Course Chemotherapy
SNNPR	South Nations Nationalities and Peoples Region
SPSS	Statistical Package for Social Sciences
TB	Tuberculosis
WHO	World Health Organization
Z	Pyrazinamide

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CHAPTER ONE: INTRODUCTION

1.1 Back ground

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis.* Occasionally the disease can also be caused by *Mycobacterium bovis and Mycobacterium africanum*. It typically affects the lungs (pulmonary TB) but can affect other sites as well (extra pulmonary TB). The disease is spread in the air when people who are sick with pulmonary TB expel bacteria, for example by coughing. In general, a relatively small proportion of people infected with *M. tuberculosis* will develop TB disease; however, the probability of developing TB is much higher among people infected with HIV. TB is also more common among men than women, and affects mostly adults in the economically productive age groups(1).

TB is a major public health problem throughout the world. About a third of the world's population is estimated to be infected with tubercle bacilli and hence at risk of developing active disease. According to the WHO Global TB Report 2013, there were an estimated 8.7 million incident cases and 12 million prevalent cases of TB globally, in 2011, of which 1.1 million (13%) were among people living with HIV. About 26% of the incident TB cases occurred in Africa in 2011. The proportion of TB cases co-infected with HIV is highest in countries in the African region; overall, the African region accounted for 79% of TB cases among people living with HIV. The majority of cases worldwide in 2012 were in the South-East Asia (29%), African (27%) and Western Pacific (19%) regions. India and China alone accounted for 26% and 12% of total cases, respectively (1, 2).

The World Health Organization (WHO) – recommended treatment strategy, directly observed treatment (DOT), which forms the basis of the Stop TB Strategy. The essential anti-TB drugs are isoniazide, rifampicin, Pyrazinamide, Ethambutol and Streptomycin(1).

The treatment of TB has two phases: Intensive (initial) phase. This phase consists of three or more drugs for the first 8 weeks for new cases, and 12 weeks for re-treatment cases. During the intensive phase, the drugs must be collected daily by the patient and must be swallowed under the direct observation of a health worker. Continuation phase requires at least two drugs, to be taken for 4 – 6months. During the continuation phase, the drugs must be collected every month and self-administered by the patient, except for retreatment cases and for regimens containing Rifampicin(1)

The 22 High Burden Countries (HBCs) that have been given highest priority at the global level since 2000 accounted for 82% of all estimated cases worldwide. These countries have been the focus of intensified efforts in DOTS expansion. Ethiopia ranks seventh among the world's 22 countries with high TB burden. At present, TB (all cases) is ranked fourth among leading causes of hospital admission and second in causes of hospital death in Ethiopia. The national population based TB prevalence survey conducted in 2010/11 revealed that the prevalence of all forms of TB in Ethiopia is estimated to be 240/100,000 populations. The proportion of new smear-positive, smear negative and EPTB among all new cases is 32.7%, 34.8%, and 32.5% respectively. Re-treatment cases represent about 2.9% of all TB cases notified (1, 3)

According to the guidelines for clinical and programmatic management of TB, TB/HIV and Leprosy in Ethiopia, among 804 newly diagnosed TB cases 1.6% were found to be infected with MDR TB. The rate of MDR TB among specimens from 76 previously treated TB cases was 11.8%. There were an estimated 1700 and 550 MDR TB cases among notified new and re-treatment pulmonary TB cases in 2011, respectively in Ethiopia(3).

In Ethiopia, a standardized TB prevention and control program, incorporating Directly Observed Treatment Short Course (DOTS), was started in 1992 as a pilot in Arsi and Bale zone, Oromia Region. The DOTS strategy has been subsequently scaled up in the country and implemented at national level. Currently, the DOTS geographic coverage reaches 90%, whereas the health facility coverage is 75%. First line drugs for treatment of TB in Ethiopia are Rifampicin(R);Ethambutol (E); Isoniazid (H); Pyrazinamide (Z); Streptomycin (S).The drugs are available in fixed dose combination and available as single drug(3).

Southern Nations Nationalities and Peoples Regional State (SNNPRS), TB is among the leading causes for sickness and death. As in many other resource-constrained settings, Directly Observed Treatment Short-course (DOTS) was introduced in the region in 1996; however, treatment outcomes for tuberculosis have not been satisfactory, mainly due to poor treatment compliance and low coverage of short course chemotherapy (SCC). Delays in the diagnosis and treatment initiation, the devastating HIV/AIDS epidemic and the potential threat of anti-tuberculosis drug resistance represent serious threats to the TB control effort in the region. A better understanding of the predictors and prognostic factors would allow closer follow-up and more targeted interventions to improve TB treatment outcome, thus reducing TB associated morbidity and mortality(4).

1.2 Statement of the Problem

Even though the objectives of TB treatment are curing the patient, preventing the spread of tuberculosis infection, and preventing the emergence of new drug resistant strains, these plans are not achieved in many regions of the world due to several factors that affect treatment success (5). Studies showed that TB treatment success rate ranged from 29.5% in Ethiopia(6) to 88.4% in Pakistan(7). Results from systematic review and meta –analysis of literatures also showed that treatment success rates varied widely from 49.6% to 92.8% and only 1 in 5 of them documented success rates above the 85% WHO recommended threshold(8).

In Africa, the treatment success rate was 82%, the overall cure rate for smear-positive TB was 74% and as low as 54% in some areas(9). Studies in Africa (10-12) showed that success rate was below the 85% WHO recommended threshold. Several reasons were mentioned among which the growing HIV epidemic, as the treatment success rate for all new HIV positive TB patients was low as 73% compared with 87% among HIV-negative TB patients, and increasing degrees of malnutrition represents a great challenge in the region (1).

The expected therapeutic success target of 85% among newly diagnosed individuals with positive smears is largely unachieved in many settings in sub-Saharan Africa(2). Currently, Ethiopia reports treatment success rate of 83% of all forms of TB. Even where free medication is available, many patients are not successfully treated for TB(3). Incomplete treatment may result in prolonged excretion of bacteria which causes disease and lead to increased morbidity/mortality and the spread of the disease(13). Studies in Southern region(14), Gondar area(6) and Gambella Region(15) of Ethiopia reported 74.8%, 29.5% and 63.4% treatment success rates in TB patients respectively; the overall treatment success rate was lower than the WHO target of 85%(16) and even was not homogeneous among the regions due to several factors that were mentioned by this studies.

Further, multi-drug resistant TB is now diagnosed in an estimated 12% of previously treated TB cases in Ethiopia. Drug-resistant TB is a man-made problem, largely being the consequence of improper treatment of drug-susceptible TB. Specific elements that suggest an increased risk for drug resistance are: Previous exposure to anti-TB treatment, exposure to a known MDR-TB case, history of using poor or unknown quality TB drugs, treatment in poorly-performing control program, co-morbid conditions associated with mal-absorption, HIV/AIDS(3). A major contributor to both treatment failure and the rise of multidrug-resistant TB is inadequate and incomplete treatment. While structural factors such as interruptions in drug supply play a role, patient default or drop-out from TB treatment

is one of the most important reasons for not completing treatment(17). Studies also showed that Patients who were not in strict DOTS programs and did not adhere to first-line TB treatment, and Category II retreatment were at significantly increased risk of developing MDR-TB(18, 19). The emergence of MDR-TB is a threat for the populations of resource-limited countries. To make things worse, in these TB and MDR-TB high burden countries patients stay in their communities for longer periods without being diagnosed or getting proper treatment. Even after diagnosis, because there are few diagnostic and treatment facilities and a lack of trained health professionals and drugs, patients do not start treatment immediately. This delay potentially allows easy spread of the disease to a large number of individuals within a short time. In Ethiopia, the low socioeconomic status of the people, high prevalence of infectious diseases and limited access to well-equipped health care facilities worsens the effect of MDR-TB. Furthermore, poor treatment outcomes, longer treatment time (about two years), higher treatment costs, and many more complications make MDR-TB a more complex disease than TB(17, 20).

Hence, WHO recommend monitoring the outcome of first-line TB treatment in order to evaluate the effectiveness of the DOTS program, patient adherence, risk of future relapse, treatment failures and drug resistance so as to take early measures for at high risk patients (1).

Several reasons and risk factors for poor TB treatment outcome have been reported by previous studies in other settings. Male sex, lack of education, elderly age, multidrug resistance, human immunodeficiency virus (HIV) co-infection, accessibility of health facilities, low socio-economic status, limited interest in information about the disease and its treatment and the side effects of anti-tuberculosis treatment(6, 19, 21, 22). Studies in southern Ethiopia (14, 23-25) identified: retreatment, positive smear at 2nd month of follow-up, having smear-negative pulmonary TB and being male as an independent risk factors for poor outcome. However, the previous studies in the region lacks information on HIV co-infection, initiation of HAART and CPT for TB/HIV co-infected patients, and drug use related factors on the treatment outcome. In addition to this, risk factors associated with poor outcome are likely to be different in different settings (5). In this context, therefore, updated information is needed on predictors of poor treatment outcome that can help to identify those patients that are at a higher risk of poor treatment outcome while being treated with anti-TB drugs. Therefore, the aim of present study was to assess predictors of poor TB treatment outcome at Arba Minch General Hospital, Southern Ethiopia.

CHAPTER TWO: LITERATURE REVIEW

2.1. Literature Review

The following literatures were reviewed to assess factors associated with TB treatment outcome:

A cohort of cases initiating tuberculosis treatment from May 2001 to July 2003 was followed in Recife, Pernambuco State, Brazil, to investigate biological, clinical, social, lifestyle, and healthcare access factors associated with three negative tuberculosis treatment outcomes (treatment failure, dropout, and death) separately and as a group showed that treatment failure was associated with treatment delay, illiteracy, and alcohol consumption. Factors associated with dropout were age, prior TB treatment, and illiteracy. Death was associated with age, treatment delay, HIV co-infection, and head of family's income. Main factors associated with negative treatment outcomes as a whole were age, HIV co-infection, illiteracy, alcoholism, and prior TB treatment(26).

Again prospective study conducted in Brazil in 2010 on tuberculosis treatment outcomes and socio-economic status showed that unsuccessful treatment was associated with socio economic status according to any criteria used, except for the definition of poverty line. The only clinical variable associated with unsuccessful outcome was a history of previous treatment default. Proxy variables for socio economic status such as schooling and distance to the health care unit were also associated with unsuccessful outcomes. Educational background is amongst the most important determinants of socio economic status, and it is worthy of note that all deaths occurred in the group with lower educational level. Previous default was also a significant predictor of default. Other previously identified risk factors for unsuccessful treatment, such as body mass index, drug resistance, alcohol abuse and HIV infection, were not analyzed in this study, but demographic and clinical characteristics were not important determinants of outcome(27).

Another prospective cohort study conducted in Brazil in 2011 on the Risk factors for default from tuberculosis treatment in HIV-infected subjects older than 18 years who had started treatment after a diagnosis of TB in two referral hospitals for HIV/AIDS showed that the default rate from tuberculosis treatment was 21.7% and the risk factors identified were: male gender, smoking and CD4 T-cell count less than 200cells/mm3. Age over 29 years, complete or incomplete secondary or university education and the use of highly active antiretroviral therapy (HAART) were identified as protective factors for the outcome. The default rate was higher when compared with the previous study (28).

A study conducted in Finland in 2007, which investigated the patient- and treatment-system dependent factors affecting treatment outcome in a two-year cohort of all treated culture-verified 629 pulmonary tuberculosis (TB) cases to establish a basis for improving outcomes showed that a favorable outcome was achieved in 441 (70.1%), 17.2% (108) died and other unfavorable outcome took place in 12.7% (80). Significant independent risk factors for death identified were being male sex, high age, non-HIV -related immune suppression and any other than a pulmonary specialty being responsible for stopping treatment. For other unfavorable treatment outcomes, significant risk factors were pause(s) in treatment, treatment with HRE/S, and internal medicine specialty being responsible at the end of the treatment. (29).

A Retrospective Case-Control Study done on Factors Affecting Treatment Outcomes for Pulmonary Tuberculosis in Istanbul, Turkey, in which the case group was composed of 464 patients with adverse outcome, while the control group was composed of 441 patients who had been cured of disease. Factors associated with adverse treatment outcome were >65 years of age (OR: 3.39 (1.99-5.76)) ; male gender (OR:2.11 (1.49-2.99)); born outside Turkey (OR: 5.48 (2.13-14.04)); co-morbidity (OR: 1.85 (1.29-2.65)); bilateral radiologic lesions (OR: 2.07 (1.41-3.00); previous treatment history (OR: 3.99 (2.78-5.74)); 3rd month positive microscopy (OR: 4.96 (3.04-8.09)) and any H&R +/- others multidrug resistant (MDR) resistance (OR: 22.64 (6.92-74.08)). There was no association between the adverse treatment outcome and the application site of direct observation treatment, short course (DOTS) delivery and the supervisors(30).

Study conducted on factors related to diagnostic delay and unsuccessful treatment of tuberculosis in the mountainous area of Yemen showed that Illiterate patients had a longer diagnostic delay than literate patients (P = 0.006). They also maintained their traditional view of illness, not the illness 'TB'. More females than males completed treatment (P = 0.046). Supervision by male relatives contributed to completion of treatment among female patients(31).

According to study conducted in New York City in 2001 the optimal duration of tuberculosis treatment for persons infected with human immunodeficiency virus (HIV) has been debated. A cohort of 4571 culture-positive drug-susceptible patients who received >=24 weeks of standard 4-drug tuberculosis treatment were assessed to determine the incidence of tuberculosis relapse. Tuberculosis "recurrence" was defined as having a positive culture <30 days after the last treatment date and "relapse" as having a positive culture >=30 days after the last treatment. Patients infected with HIV were more likely than those who were uninfected to have recurrence or relapse (2.0 vs. 0.4 per 100

person-years, *P*=.*001*). Patients infected with HIV who received <=36 weeks of treatment were more likely than those who received >36 weeks to have a recurrence (7.9% vs. 1.4%, *P*=.001)(32).

According to a study conducted in Malawi in 2002 on moderate to severe malnutrition in patients with tuberculosis is a risk factor associated with early death showed that significant risk factors for early mortality included increasing degrees of malnutrition (BMI<17.0kg/m2), age >35years, and HIV sero-positivity(10).

A cohort study conducted in Nigeria in 2009 to assess treatment outcomes and determinants of outcomes among tuberculosis patients in which the result showed that cure rate was 76.6%, failure 8.1%, default 6.6% and death 1.9%. The cure rate varied significantly treatment centers from 40 to 94.4 %(p<0.05). The treatment centers located within the specialist health centers at Jericho and university college hospital had 50 and 75% cure rates, respectively. The mean age of cured patients was 31.2+/- 3.1 years which was significantly lower than the mean age of those with poor treatment outcomes 36.7+/-3.5 years (p<0.05). Males had higher risk of having poor treatment outcome than females(11).

A retrospective hospital register-based cohort study conducted in Cameroon in 2013 to determine the rate, time to and determinants of ant tuberculosis treatment default. Socio demographic and clinical predictors of treatment discontinuation were investigated with the use of Cox regressions models. Of the 1688 included patients, 337 (20%) defaulted from treatment, 86 (5.1%) died, treatment failed in 6 (0.4%) and 104 (6.2%) were transferred. Treatment was successfully completed in 1154 (68.4%) patients. Median duration to treatment discontinuation was 90 days (IQR 30e150), and 62% of treatment discontinuation occurred during the continuation phase. Hospitalization during the intensive phase and non-consenting for HIV screening were the main determinants of defaulting from treatment in multivariable analysis(12).

A study conducted on treatment outcome of smear-positive pulmonary tuberculosis patients in Tigray Region, Northern Ethiopia in 2012 showed that out of the 407 PTB patients (221 males and 186 females) aged 15 years and above, 89.2% had successful and 10.8% had unsuccessful treatment outcome and identified the following risk factors as predictors of unsuccessful treatment outcome: older age, family sizes greater than 5 persons, unemployed and retreatment cases and in the final multivariate logistic model, the odds of unsuccessful treatment outcome was higher among patients older than 40 years of age, family size greater than 5 persons , unemployed and among retreatment cases as compared to their respective comparison groups. The strength of the study is collected data

directly from the patients and from medical records. But this study considered only smear-positive pulmonary tuberculosis patients (19).

A five - year retrospective study conducted on Treatment outcome of tuberculosis patients at Gondar University Teaching Hospital in 2009 showed that from the total of 4000 patients treatment outcome was classified as successfully treated in 1181(29.5%), defaulted in 730 (18.3%), died in 403 (10.1%), treatment failed in six (0.2%) and transferred out in 1680 (42.0%) patients. Males had the trend to be more likely to experience death or default than females, and the elderly were more likely to die than younger. The proportion of default rate was increased across the years from 97(9.2%) to 228(42.9%). Being female, age group 15-24 years, smear positive pulmonary tuberculosis and being urban resident were associated with higher treatment success rate. According to this study the treatment success rate of tuberculosis patients was unsatisfactorily low (29.5%) for one reason they considered transfer out as poor treatment outcome. A high proportion of patients died (10.1%) or defaulted (18.3%) (6).

A retrospective study conducted on the outcomes of tuberculosis treatment and risk factors of 756 TB patients registered from January, 2010 to 2012 in Felege Hiwot Referral Hospital showed that treatment outcome was classified as successfully treated 193 (26%), defaulted in 19 (2.5%), died in 44 (5.8%), treatment failed in 4 (0.5%) and transferred out in 496 (68.6%) patients. The percentage of deaths and defaulters was higher in females than in males. Being an older age group, a rural resident and EPTB patients were associated with a lower treatment success rate(21).

A retrospective cohort study conducted in Addis Ababa in 2011 on Mortality and associated risk factors in a cohort of tuberculosis patients treated under DOTS program showed that the survival status was significantly different between patient categories as well as across treatment centers ($P < 0.05$). The death rate of pulmonary positive, pulmonary negative and extra pulmonary TB patients were 2.7%, 3.6%, and 4.3%, respectively. Body weight at initiation of anti-TB treatment (<35 kg), patient category, year of enrollment and treatment center were independent predictors for time to death. But this study did not address other poor outcomes of TB treatment (default and failure) and associated factors(33).

A case- control study conducted on determinants of multidrug-resistant tuberculosis in patients who underwent first-line treatment at St. Peter Hospital and five health centers in Addis Ababa from 1 November 2011 to February 30, 2012 published in 2013 showed that drug side effects during first-line treatment; treatment not directly observed by a health worker; interruption of treatment of at least a day; duration of 1st course TB treatment between 2 and 7 months; and retreatment with the Category

II regimen (P = 0.000) were significantly associated factors with MDR-TB. In this study, HIV infection was not significantly associated with the occurrence of MDR-TB(18).

A retrospective study conducted in Azezo health center analyzing the data of 482 tuberculosis patients registered from September, 2008 up to August, 2011 included among whom 50.4% were males and the mean (SD) age was 32.8 (1.6) years. The HIV status of 323 patients was known out of which 38.1% were HIV positive. The trend of tuberculosis over the years studied was steadily increasing. Out of the study subjects 67.8% and 32.2% were pulmonary tuberculosis and extra pulmonary tuberculosis cases, respectively. Successful treatment outcome for all types of tuberculosis cases was 80.5%, being higher for females, smear positive pulmonary cases and HIV negative patients. Sex and HIV status of the patients showed statistically significant association with successful treatment outcome(34).

A retrospective trend analysis in Southern Region of Ethiopia on 19,971 tuberculosis patients registered for treatment in 41 treatment centers in Hadiya zone between 1994 and 2001 published in 2005 showed that treatment success for smear-positive tuberculosis rose from 38% to 73% in 2000, default rate declined from 38% to 18%, and treatment failure declined from 5% to 1%. Being female patient, age 15–24 years, smear positive pulmonary tuberculosis, treatment with short course chemotherapy, and treatment at peripheral centers were associated with higher treatment success and lower defaulter rates. The treatment success rate set by WHO was achieved but this study only considered smear-positive tuberculosis patients, it is more difficult for smear negative and extra pulmonary TB patients to achieve treatment success rate set by WHO (35).

Retrospective cohort study conducted in Southern Ethiopia in 2009 followed 368 cured smear-positive TB patients for 1463 person-years of these, 187 patients (50.8%) were men, 277 patients (75.5%) were married, 157 (44.2%) were illiterate, and 152 patients (41.3%) were farmers. 15 of 368 smear-positive patients had recurrence. The rate of recurrence was 1 per 100 PYO (0.01 per annum). Recurrence was not associated with age, sex, occupation, marital status and level of education(25)

A retrospective study conducted in the region in 2010 on the factors associated with poor tuberculosis treatment outcome showed that 74.8% had a successful and 16.7% a poor treatment outcome and being on retreatment, having a positive smear at the second month follow-up, having PTB-, age >55 years and being male were independent risk factors for poor outcome (14).

Another retrospective cohort study conducted in the region on mortality in successfully treated tuberculosis patients and pulished in the same year as the privious study followed a total of 725 TB

patients for 2602 person-years: 91.1% (659/723) were alive and 8.9% (64/723) had died. The mortality rate was 2.5% per annum. Sex, age and occupation were associated with high mortality. More deaths(SMR " 9.95, 95%CI 7.17–12.73) occurred in non-farmers (24).

A recent study conducted in Sidama zone of the region in 2013 on effect of innovative community-based approaches on tuberculosis case notification and treatment outcome showed that HEWs screened 49,857 symptomatic individuals (60% women) from October 2010 to December 2011. 2,262 (4?5%) had smear-positive TB (53% women). Case notification increased from 64 to 127/100,000 population/year resulting in 5,090 PTB+ and 7,071 cases of all forms of TB. Of 8,005 contacts visited, 1,949 were symptomatic, 1,290 symptomatic were tested and 69 diagnosed with TB. 1,080 children received IPT. Treatment success for smear-positive TB increased from 77% to 93% and treatment default decreased from 11% to 3%. Service users and providers found the intervention package highly acceptable (23)

However, the previous studies in the region lacks information on HIV co-infection, initiation of HAART and CPT for TB/HIV co-infected patients, and drug use related factors on the treatment outcome. Therefore, the aim of present study is to assess predictors of poor TB treatment outcome at Arba Minch General Hospital, Southern Ethiopia.

2.2. Conceptual frame work

Based on the review of literatures from previous studies in other settings: co-morbidity, socio-demographic factors, year of treatment, category of patients, type of TB, smear result and treatment regimen affect treatment outcome. From the socio demographic factors being male, old age, low body weight and living in rural area contribute to poor outcome of TB. TB/HIV co-infection associated with poor outcome than patients who have TB alone. On the other hand smear positive PTB had better outcome than smear negative PTB, EPTB and disseminated TB.

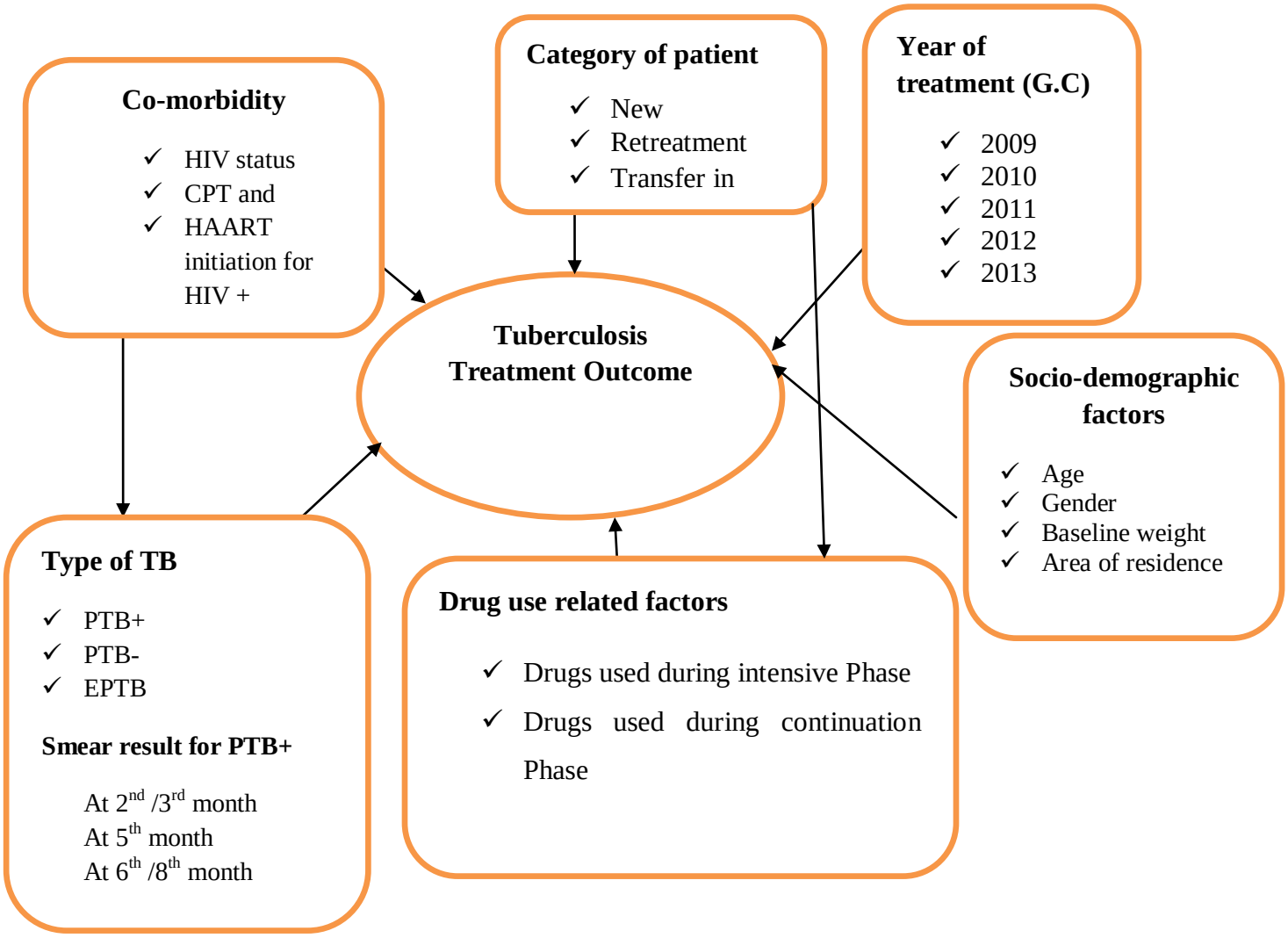

Figure1: Conceptual frame work for factors associated with TB treatment outcome

2.3. Significance of the study

The finding of this study will help in uderstanding predictors of poor TB treatment outcome in the current study area. Hence, the results could primarily help clinicians practicing in the area to give such patients special attention during their follow-up in order to prevent occurrence of negative consequences following poor treatment outcome. Health policy makers including the Regional Health Bureau, Zonal health department, hospital and health center staffs could also utilise the findings to develop treatment plans that emphasize directly observed treatments (DOTS) for at-risk patients.

In addition, understanding of predictors of poor TB treatment outcome plays important role in disease specific health promotion and education in hospitals and support in prevention of TB related morbidity and mortality in Ethiopia particularly in Arba Minch General Hospital.

This study finding is also expected to fill gaps in this area of research. By being added to the existing body of knowledge, it will help other researchers as reference for their work.

CHAPTER THREE: OBJECTIVE

3.1. General Objective

To assess predictors of poor tuberculosis treatment outcome at Arba Minch General Hospital, Southern Ethiopia

3.2. Specific Objectives

- To assess socio demographic predictors of poor treatment outcome among patients treated for tuberculosis at Arba Minch General Hospital, Southern Ethiopia.
- To assess clinical, drug use and year of treatment related predictors of poor treatment outcome among patients treated for tuberculosis at Arba Minch General Hospital, Southern Ethiopia.

3.3. Research question

- What are the socio demographic predictors of poor treatment outcome among patients treated for tuberculosis at Arba Minch General Hospital?
- What are the clinical, drug use and year of treatment related predictors of poor treatment outcome among patients treated for tuberculosis at Arba Minch General Hospital?

CHAPTER FOUR: METHODS AND PARTICIPANTS

4.1. Study Area and period

The study was conducted at Arba Minch General Hospital, Southern Ethiopia from January 30 to February 28, 2014. Arba Minch is the capital of Gamo Gofa Zone, located approximately 500 km to the South of Addis Ababa and 275 Kms away from the Regional capital, Hawassa. Arba Minch General Hospital is located in Arba Minch town, and has 158 beds and serves 1.5 million people. The hospital provides TB, HIV/AIDS, laboratory, health facility based medical care, information, education and communication services to the population of Arba Minch town and to the surrounding community. The treatment of TB in Arba Minch General Hospital follows the guidelines from the National TB and Leprosy Control Program of Ethiopia (NTLCP). If TB is confirmed, patient is registered in the DOTS clinic where they are given drugs for 6-8 months. First 8 weeks for new cases, and 12 weeks for re-treatment cases (intensive phase), patients take their medication on a daily basis in the DOTS centre in the presence of a designated health worker after which they collect their medication once monthly for 4 – 6months except for retreatment cases and for regimens containing Rifampicin (continuation phase). The recommended drug regimen for the intensive phase is isoniazid, rifampicin, Ethambutol and Pyrazinamide. In the continuation phase rifampicin and isoniazid are given. For retreatment cases, streptomycin is given for 3 months in the intensive phase in addition to isoniazid, Pyrazinamide, Ethambutol and rifampicin(36).

4.2. Study design

Hospital based retrospective case- control study was employed.

4.3. Population

4.3.1 Source population

The source population was all patients registered for treatment of TB from 1st January 2009- 30th December 2013 at Arba Minch General Hospital.

4.3.2 Study population

Selected tuberculosis patients having successful outcome (controls) and poor outcome (cases) fulfilling the inclusion criteria and selected to be included in the study.

4.4. Eligibility criteria

4.4.1 Inclusion criteria

- All TB patients registered in the DOTS from 1st January 2009- 30th December 2013

4.4.2 Exclusion criteria

- patients with no documented treatment outcome, illigble records and no full patient data
- patients transferred out to other facility

4.5 Sample size and sampling technique/procedure

4.5.1 Sample size determination

Sample size was determined using a formula for difference in proportions(37): according to a case control study done at Addis Ababa, the proportion exposed in the control group (successfully treated) is 61.2%(18). Moreover, in order to detect an OR of 1.8(38), 90% power, 5% significance level, and the size of the controls being 2 fold compared with the cases

$$n = \left(\frac{r+1}{r}\right)\frac{(\bar{p})(1-\bar{p})(Z_{\beta}+Z_{\alpha/2})^2}{(p_1-p_2)^2}$$

Where

- ✓ n= Sample size in the case group
- ✓ r= ratio of controls to cases (r=2)
- ✓ ṕ= A measure of variability (ṕ=65%)
- ✓ *Z α/2*= desired level of statistical significance (typically **1.96** at 95% significance)
- ✓ Zβ= desired power (typically 1.28 for 90% power)
- ✓ P1=the proportion exposed in the control group (p1=61.2%)
- ✓ For 90% power and 0.05 significance level, $\left(Z_{\alpha}+Z_{\beta}\right)^2$ =$(1.96+1.28)^2$=10.507

To get proportion of exposed in the case group (p2):

$$\text{P2=}\quad p_{case\exp} = \frac{ORp_{controls\exp}}{p_{controls\exp}(OR-1)+1}$$

$$p2 = \frac{1.8(0.612)}{0.612(1.8-1)+1} = 0.74=74\%$$

To get sample size in the case group (n):

$$n = (\frac{r+1}{r})\frac{(\bar{p})(1-\bar{p})(Z_{\beta} + \mathrm{Z}_{\alpha/2})^2}{(\mathrm{p}_1 - p_2)^2}$$

$$n = (\frac{2+1}{2})\frac{(0.65)(1-0.65)(10.507)}{(0.612-0.74)^2}$$

$$n = 1.5(\frac{(0.65)(0.35)(10.507)}{0.016})$$

$\boldsymbol{n = \frac{3.58}{0.016} = 224}$ =sample size in the case group

Sample size in the control group**= 2xn=2x224**= **448** and

Total sample size equal to **224+448=<u>672</u>**

4.5.2 Sampling procedure

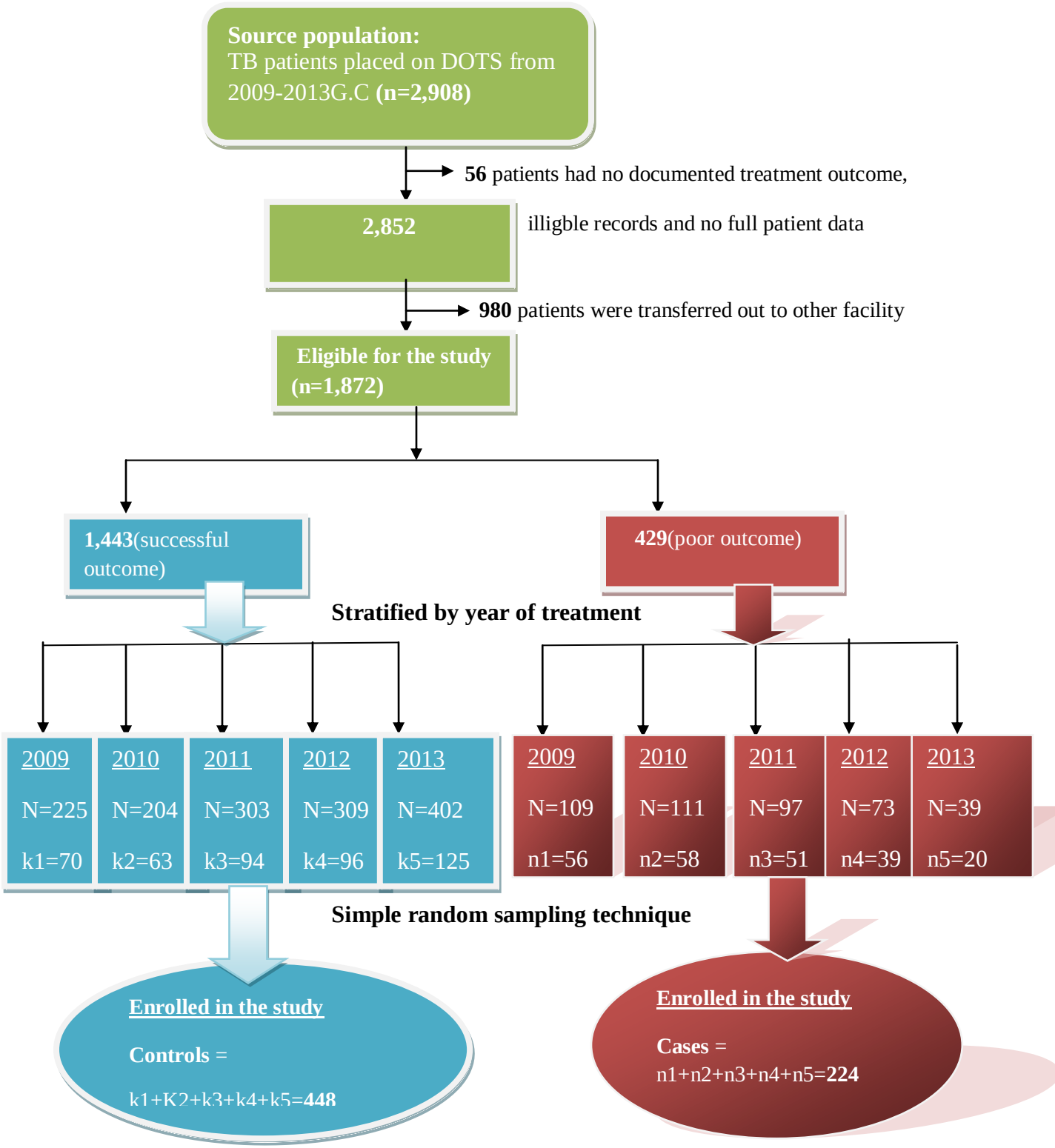

Fig 2: Schematic presentation of sampling procedure for TB patients placed on DOTS from 1st January 2009- 30th December 2013, Arba Minch general hospital, Southern Ethiopia

4.5.3 Sampling technique

Patients were categorized as having a successful treatment outcome (controls) if cured or if they had completed treatment with resolution of symptoms, or a poor treatment outcome (cases) if they had failed treatment, or had defaulted or died during treatment. Then cases and controls were stratified according to year of treatment and proportionate allocation for each year was done and SRS technique (Computer generated random numbers method using excel function of RANDBETWEEN) was used to select cases and controls from each year.

4.6. Variables

4.6.1 Dependent variable

Tuberculosis treatment outcome

4.6.2 Independent variables

- Socio-demographic factors
    - Age in years
    - Gender
    - Area of residence
    - Baseline weight in kilogram
- Co-morbidity related factors
    - HIV status
    - HAART initiation for HIV positive
    - CPT initiation for HIV positive
- Tuberculosis type
    - Smear-positive pulmonary TB
    - Smear-negative pulmonary TB
    - Extra-pulmonary TB
- Smear result for PTB+(at 2^{nd} /3^{rd} , 5^{th} and 6^{th} /8^{th} month follow up)
- Category of patient
    - New case
    - Re-treatment case
    - Transfer in

- Year of treatment (G.C)(2009, 2010, 2011, 2012, and 2013)
- Drug use related factors
    - Drugs used during intensive Phase and continuation Phase

4.7. Data collection instrument and procedure

Data collection was undertaken from January 30 to February 28, 2014. Data was collected through medical record reviews of patients using a prepared standard checklist which is adapted from WHO and according to local context and the objectives of the study. The checklist consists of socio-demographic factors, category of patients, TB type, smear result during follow up, treatment outcome, co morbidity, drug use related factors and year of TB treatment.

4.8. Data quality assurance

To ensure data quality, the following measures were taken: (a) Pre-test of the instrument was done at Chencha District Hospital TB clinic on 10 cases before the actual data collection time (b) one-day training was given for data collectors (4 nurses and 1 pharmacist working for the hospital) before the start of data collection, (c) the overall activities of data extraction was monitored by the principal investigator, and there was strict supervision during data collection, (d) all completed data sets were examined by the principal investigator for completeness during data collection, and (e) from the data extracted, 5% (34 cheklist) of the sample was randomly selected and validated against the registration book by the principal investigator.

4.9. Data analysis

Data was entered into SPSS 21 version, mean (with standard deviation) and frequencies (as percentages) were used to describe patients' characteristics among cases and controls. A chi-square test (for variables of 2X2 table format chi-square (X^2) under the continuity correction was used, 2X (>2) table format X^2 under the Pearson chi-Square was used and for cell in the table having < 5 expected count, likelihood ratio Fisher's Exact test was used) and a T-test were used to compare categorical and continuous variables between the cases and controls, respectively. All statistically significant ($p < 0.25$) factors in the bivariate analysis were included in the final model. We also carried out collinearity test to check for correlation between the independent variables before inclusion in the multivariate regression model.

Thus combination of the following criteria was used in selecting our exposure variables: P value less than 0.25 and collinearity coefficient of variables less than 0.6 was considered an acceptable value. Multivariate logistic regression model was used to determine predictors of poor outcome. P- Value of less than 0.05 was considered statistically significant in the final model. The crude and adjusted odds ratio (OR) and its 95% confidence interval (CI) were estimated.

4.10 Ethical consideration

Letter of ethical clearance was obtained from Ethical Review Board of Jimma University. The patient data was accessed upon the approval of clinical director of Arba Minch General Hospital. Confidentiality was ensured during the data collection, thus name and address of the patient was not recorded in the data collection check list.

4.11 Dissemination plan

The result of this study will be presented to Jimma university department of Pharmacy

The dissemination of the study will be SNNPR health bureau, Arba Minch zonal health office and Arba Minch General Hospital.

The study finding will also be submitted to professional journal for publication so as to serve as base line for further studies.

4.12 Definitions of terms and operational definitions

According to the standard definitions of the National Tuberculosis and Leprosy Control Program guideline (NTLCP)(3) adopted from WHO, the following clinical case and treatment outcome definitions were used:

Disseminated TB: A state in which the infectious disease TB has spread from the site of the original infection to affect several other parts of the body, either via the lymphatic system or in the blood stream.

Extra-pulmonary TB (EPTB): This included tuberculosis of organs other than the lungs, such as lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges, etc.

Smear-negative pulmonary TB : A patient with symptoms suggestive of TB, with at least two sputum specimens which were negative for AFB by microscopy, and with chest radiographic abnormalities consistent with active pulmonary TB (including interstitial or miliary abnormal

images), or a patient with two sets of at least two sputum specimens taken at least two weeks apart, and which were negative for AFB by microscopy, and radiographic abnormalities consistent with pulmonary TB and lack of clinical response to one week of broad spectrum antibiotic therapy.

Smear-positive pulmonary TB: A patient with at least two sputum specimens which were positive for acid-fast bacilli (AFB) by microscopy, or a patient with only one sputum specimen which was positive for AFB by microscopy, and chest radiographic abnormalities consistent with active pulmonary TB.

A case of TB is a patient in whom tuberculosis has been confirmed bacteriologically or diagnosed by a clinician. The following are case definitions:

- **New case (N):** A patient who never had treatment for TB, or has been on previous anti-TB treatment for less than four weeks.
- **Relapse (R):** 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 or culture positive.
- **Treatment Failure (F):** A patient who, while on treatment, is smear-positive at the end of the fifth month or later, after commencing. Treatment failure also includes a patient who was initially sputum smear-negative but who becomes smear-positive during treatment.
- **Return after default (D):** A patient previously recorded as defaulted from treatment and returns to the health facility with smear-positive sputum.
- **Transfer out (T):** A patient who started treatment in one treatment unit and is transferred to another treatment unit to continue treatment.
- **Chronic (C):** A TB patient who remains smear-positive after completing a retreatment regimen.
- **Other (O):** A patient who does not fit in any of the above mentioned categories (e.g., a PTB smear negative who returns after treatment interruption).

Treatment Outcome

- **Cured:** Finished treatment with negative bacteriology result at the end of treatment.

- **Completed treatment:** Finished treatment, but without bacteriology result at the end of treatment.
- **Failure:** remaining smear positive at five months despite correct intake of medication.
- **Defaulted treatment:** Patients who interrupted their treatment for two consecutive months or more after registration.
- **Died:** Patients who died from any cause during the course of treatment.
- **Transferred out**: Patients whose treatment results are unknown due to transfer to another health facility and

In line with WHO criteria, patients were categorized into:

- **Controls**: if were cured (i.e., negative smear microscopy at the end of treatment and on at least one previous follow-up test) or completed treatment with resolution of symptoms.
- **Cases**: if treatment of TB resulted in treatment failure (i.e., remaining smear-positive after 5 months of treatment), default (i.e., patients who interrupted their treatment for two consecutive months or more after registration), or death.

CHAPTER FIVE: RESULTS

The present study including 672 sudy subjects overall, the case group was composed of 224 patients with poor outcome, while control group was composed of 448 patients with successful outcome.

5.1 Socio-demographic Characteristics of study subjects

Overall, 380(56.5%) of all study subjects were males. Males were significantly higher in the case group compared to control group (65.6% vs. 52.0%; X^2=8.9, P=0.001). The majority of study subjects in the control group 141 (31.5%) were in the age group of 25-34 years while majority in the case group 56(25.0%) were in the age group of 35-44 years. The mean± SD age of the study subjects in the control group was 28.96± 13.388 years while the mean± SD age in the case group was 37.92±14.411 years. Cases were significantly older than controls (28.96±13.388 Vs 37.92±14.411, T=7.779; P=0.000). Significantly higher proportion of sudy subjects in the case group were from rural area compared to the control group (51.8% vs. 39.3%; X^2=8.9, P= 0.003). The majority of sudy subjects in the control group 205(45.8%) were weight greater than 55kg while the majority in the case group 141 (62.9%) were weight between 41-54kg. There was no mean weight difference between cases and controls (50.850±9.3423 Vs 51.906±13.3885, T=1.188; P=.235) as shown in table 1 below.

Table 1: Socio-demographic characteristics of study subjects, Arba Minch General Hospital, Southern Ethiopia, 2014 (N=672)

Patient characteristics	Case group N (%)	Control group N (%)	Total N (%)	P-value	X^2 value(df)
Number of cases	224(100)	448(100)	672(100)		
Sex					
Male	147(65.6)	233(52.0)	380(56.5)	0.001*	8.9 Φ (1)
Female	77(34.4)	215(48.0)	292(43.5)		
Age (years)					
<= 14	5(2.2)	44(9.8)	49(7.3)		
15-24	38(17.0)	141(31.5)	179(26.6)		
25-34	52(23.2)	130(29.0)	182(27.1)		
35-44	56(25.0)	71(15.8)	127(18.9)		
45-54	38(17.0)	43(9.6)	81(12.1)		
55-64	23(10.3)	8(1.8)	31(4.6)		
>=65	12(5.4)	11(2.5)	23(3.4)		
Mean ± SD	37.92±14.411	28.96±13.38		0.000*	¶
Area of residence					
Urban	108(48.2)	272(60.7)	380(56.5)	0.003*	8.9 Φ (1)
Rural	116(51.8)	176(39.3)	292(43.5)		
Baseline weight(kg)					
5-30	7(3.1)	40(8.9)	47(7.0)		
31-54	141 (62.9)	203(45.3)	344 (51.2)		
>= 55	76(33.9)	205(45.8)	281(41.9)		
Mean ± SD	50.850±9.3	51.906±13.4		0.235	¶

NB: *****Significant $p < 0.05$, **SD**- Standard Deviation, **Φ -** chi-square, **¶** - T-test Statistic for independent sample test used

5.2 Clinical characteristics of study subjects

Out of the 672 study subjects, 608(90.5%) were new cases. Higher proportion of retreatment category was in case group compared to the control group (8.5% vs. 2.2%, X^2=14.6 p=0.001). Majority of sudy subjects in the control group 243(54.2%) and case group 151(67.4%) had smear-negative pulmonary TB. Only 78(17.4%) of sudy subjects in the control group had EPTB while 151(67.4%) of the case group had EPTB. Concerning with smear result during 2^{nd} /3^{rd} month follow up for smear positive PTB, majority in the control group 120(95.2%) were smear negative while majority in the case group 16(64.0%) were smear positive. Regard to HIV status, 169(25.1%) were HIV positive. HIV positivity was significantly higher in the case group than in the control group (38.8% vs. 18.3%; X^2=45.1, p=0.000) and significantly higher proportion of sudy subjects in the case group had no result for HIV compared to the control group (9.4% vs. 4.5%; p=0.000). Among the HIV positive, significantly higher proportion of sudy subjects in the case group compared to the control group did not initiated CPT (21.8% vs. 8.5%; X^2=4.76, p=0.019) and HAART (37.9% vs. 19.5%; X^2= 6.09, p=0.014) as shown in table 2 below.

Table 2: Clinical characteristics of study subjects, Arba Minch General Hospital, Southern Ethiopia, 2014

Clinical characteristics	Case group N (%)	Control group N (%)	Total N (%)	P-value	X^2 value(df)
Patient category					
New	192(85.7)	416(92.9)	608(90.5)	0.001*	14.6 Φ(2)
Retreatment	19(8.5)	10(2.2)	29(4.3)		
Transfer in	13(5.8)	22(4.9)	35(5.2)		
Type of TB					
PTB+	25(11.2)	127(28.3)	152(22.6)	0.000*	25.2 Φ(2)
PTB-	151(67.4)	243(54.2)	394(58.6)		
EPTB	151(67.4)	78(17.4)	126(18.8)		
Smear result at $2^{nd}/3^{rd}$ month (N=151)					
Negative	9(36.0)	120(95.2)	129(85.4)	0.000*	54.2 Φ (1)
Positive	16(64.0)	6(4.8)	22(14.6)		
Smear at 5^{th} month					
Negative	0(0)	124(100)	124(96.1)	NA	NA
Positive	5(100)	0(0)	5(3.9)		
Smear at 6^{th} /8^{th} month					
Negative	0(0)	107(100)	107(99.1)	NA	NA
Positive	1(100)	0(0)	1(0.9)		
HIV status					45.1 Φ(2)
Negative	116(51.8)	346(77.2)	462(68.8)	0.000*	
Positive	87(38.8)	82(18.3)	169(25.1)		
No result	21(9.4)	20(4.5)	41(6.1)		
CPT initiated for HIV+ (N=169)					
NO	19(21.8)	7(8.5)	26(15.4)	0.019*	4.76 Φ (1)
Yes	68(78.2)	75(91.5)	143(84.6)		
HAART initiated for HIV+ (N=169)					
No	33(37.9)	16(19.5)	49(29.0)	0.014*	6.09 Φ (1)
Yes	54(62.1)	66(80.5)	120(71.0)		

NB: ***Significant p < 0.05, **Φ -chi-square, **CPT**-Cotrimoxazole prophylactic therapy, **HAART**-Highly Active Anti Retroviral Therapy, **PTB**-: pulmonary tuberculosis, **EPTB**: Extra Pulmonary Tuberculosis, **NA**- Not Analyzed because of missing values

5.3 Drug use related factors of study subjects

From the total study subjects, 651(96.9%) took drug regimen for new patients. Significantly higher proportion of subjects in the case group compared to the control group took previously treated patient regimen (8.0% vs. 0.7%; X^2=24.4, p=.000), used the regimen ERHZS/ERHZ in the intensive phase (8.0% vs. 0.7%; X^2=24.4, p=.000) and used the regimen EH/ERH in the continuation phase (53.1% vs. 29.0%; X^2=48.5, p=.000) as shown in table 3 below.

Table 3: Drug use related factors of study subjects, Arba Minch General Hospital, Southern Ethiopia, 2014

Variable	Case group N (%)	Control group N (%)	Total N (%)	P-value	X^2 value(df)
Drugs used during intensive Phase					
ERHZ	206(92.0)	445(99.3)	651(96.9)	0.000*	24.4ǂ(1)
ERHZS/ERHZ	18(8.0)	3(.7)	21(3.1)		
Drugs used during continuation Phase					
EH	103(46.0)	127(28.3)	230(34.2)	0.000*	48.5 Φ(2)
RH	105(46.9)	318(71.0)	423(62.9)		
ERH	16(7.1)	3(.7)	19(2.8)		

NB: ***Significant p < 0.05, **Φ - chi-square, **ǂ -**Fishers exact test, **E**- Ethambutol, **H**- Isoniazid, **R**- Rifampicin, **S**- Streptomycin, **Z**- Pyrazinamide

5.4 Distribution of study subjects with year of tuberculosis treatment

Majority 125(27.9%) of study subjects in control group were treated for TB in the year 2013G.C while majority 58(25.9%) in case group were treated for TB in the year 2010 G.C. The proportion of poor outcome was decreased from year 2009G.C to 2013G.C (X^2=44.9, p=0.000) as shown in table 4 below.

Table 4: Distribution of study subjects with year of tuberculosis treatment, Arba Minch General Hospital, Southern Ethiopia, 2014

Year of treatment(G.C)	Case group N (%)	Control group N (%)	Total N (%)	P-value	X^2 value(df)
2009	56(25.0)	70(15.6)	126(18.8)	0.000*	44.9 Φ(4)
2010	58(25.9)	63(14.1)	121(18.0)		
2011	51(22.8)	94(21.0)	145(21.6)		
2012	39(17.4)	96(21.4)	135(20.1)		
2013	20(8.9)	125(27.9)	145(21.6)		

NB: ***Significant p < 0.05, **Φ - chi-square, **G.C**- Gregorian calendar

5.5 Treatment outcome of study subjects

Control group was composed of patients cured from TB 119 (17.7%) and completed treatment 329 (49.0%); case group was composed of those died 34 (5.1%), failed 5 (.7%), and defaulted 185 (27.5%).

Table 5: Treatment outcome of study subjects, Arba Minch Hospital, Southern Ethiopia, 2014 (N=672)

Treatment outcome	Frequency	Percent
Cured	119	17.7
Completed	329	49.0
Died	34	5.1
Failed	5	.7
Defaulted	185	27.5
Total	672	100.0

5.6 Bivariate analysis of socio-demographic factors

Bivariate analysis of the socio-demographic factors indicated that males were 1.7 times more likely to develop poor outcome (COR=1.762 (95% CI=1.264, 2.456, p=.001). Those older than 35 years of age were more than 3 times more likely to develop poor outcome (COR=3.158(95% CI=2.263, 4.407) p=0.000). Rural residents were 1.6 times more likely to develop poor outcome than those who resided in urban area (COR=1.660 (95%CI=1.201, 2.294). as shown in table 6 below.

Table 6: Bivariate analysis of socio-demographic characteristics of study subjects, Arba Minch General Hospital, Southern Ethiopia, 2014

Patient characteristics	Case group N (%)	Control group N (%)	Total N (%)	Sig	COR(95% CI)
Number of cases	224(100)	448(100)	672(100)		
Sex					
Male	147(65.6)	233(52.0)	380(56.5)	.001	1.762(1.264,2.456)
Female	77(34.4)	215(48.0)	292(43.5)		1.00
Age (years)					
<35	315(70.3)	96(42.9)	441(61.2)		1.00
>=35	133(29.7)	128(57.1)	261(38.8)	0.000	3.158(2.263, 4.407)
Mean ± SD	37.92±14.411	28.96±13.388			
Area of residence					
Urban	108(48.2%)	272(60.7)	380(56.5)		1.00
Rural	116(51.8)	176(39.3)	292(43.5)	.002	1.660(1.201, 2.294)

NB: 1.00-reference group, **CI**-Confidence Interval, **COR**- Crude Odds Ratio, **SD**-Standard Deviation

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5.7 Bivariate analysis of clinical characteristics

Bivariate analysis of the clinical factors indicated that subjects on retreatment category (COR=4.117 (95% CI=1.878, 9.022) p=.000), those having smear negative PTB (COR=3.157(95% CI=1.964, 5.074), p=.000) and EPTB (COR=3.126(95% CI=1.786, 5.471), p=.000), smear positive at $2^{nd}/3^{rd}$ month of follow up (COR=35.5(95% CI=11.1, 113.1), p=.001), HIV positive (COR= 3.165(95% CI=2.191, 4.571), p=.000), not result for HIV (COR=3.132(95% CI=1.639, 5.984), p=.001) and TB/HIV co-infected patients not initiated CPT (COR=2.994(95% CI=1.185, 7.562), p=.020) and HAART (COR=2.521(95% CI=1.256, 5.061), p=.009) were at increased risk of developing poor outcome as shown in table 7 below.

Table 7: Bivariate analysis of clinical characteristics of study subjects, Arba Minch General Hospital, Southern Ethiopia, 2014

Clinical characteristics	Case group N (%)	Control group N (%)	Total N (%)	Sig.	COR(95% CI)
Patient category					
New	192(85.7)	416(92.9)	608(90.5)		1.00
Retreatment	19(8.5)	10(2.2)	29(4.3)	.000	4.117(1.878, 9.022)
Transfer in	13(5.8)	22(4.9)	35(5.2)	.493	1.280(.632, 2.595)
Type of TB					
PTB+	25(11.2)	127(28.3)	152(22.6)		1.00
PTB-	151(67.4)	243(54.2)	394(58.6)	.000	3.157(1.964, 5.074)
EPTB	151(67.4)	78(17.4)	126(18.8)	.000	3.126(1.786, 5.471)
Smear at $2^{nd}/3^{rd}$ month (N=151)					
Negative	9(36.0)	120(95.2)	129(85.4)		1.00
Positive	16(64.0)	6(4.8)	22(14.6)	.000	35.5(11.1, 113.1)
HIV status					
Negative	116(51.8)	346(77.2)	462(68.8)		1.00
Positive	87(38.8)	82(18.3)	169(25.1)	.000	3.165(2.191, 4.571)
No result	21(9.4)	20(4.5)	41(6.1)	.001	3.132(1.639, 5.984)
CPT initiated for HIV+					
NO	19(21.8)	7(8.5)	26(15.4)	.020	2.994(1.185, 7.562)
Yes	68(78.2)	75(91.5)	143(84.6)		1.00
HAART initiated for HIV+					
No	33(37.9)	16(19.5)	49(29.0)	.009	2.521(1.256, 5.061)
Yes	54(62.1)	66(80.5)	120(71.0)		1.00

NB: 1.00-reference group, **CI**-Confidence Interval, **COR**- Crude Odds Ratio, **CPT**-Cotrimoxazole prophylactic therapy, **HIV**-Human Immunodeficiency Virus, **HAART**-Highly Active Anti Retroviral Therapy, **PTB**-: pulmonary tuberculosis, **EPTB**: Extra Pulmonary Tuberculosis

5.8 Bivariate analysis of drug use related factors

Bivariate analysis of the drug use related factors indicated odds of poor outcome was higher among subjects who took the regimen ERHZS/ERHZ in the intensive phase (COR=12.961(95% CI=3.776, 44.492), p=.000) and used the regimen EH/ERH in the continuation phase (COR=2.772(95% CI=1.988, 3.865), p=.000) as shown in table 8 below.

Table 8: Bivariate analysis of Drug use related factors of study subjects, Arba Minch General Hospital, Southern Ethiopia, 2014

Variable	Case group N (%)	Control group N (%)	Total N (%)	Sig.	COR(95.0% CI)
Drugs used during intensive Phase					
ERHZ	206(92.0)	445(99.3)	651(96.9)		1.00
ERHZS/ERHZ	18(8.0)	3(.7)	21(3.1)	.000	12.961(3.776,44.492)
Drugs used during continuation Phase					
EH/ERH	119(53.1)	130(29.0)	249(37.1)	.000	2.772(1.988, 3.865)
RH	105(46.9)	318(71.0)	423(62.9)		1.00

NB: 1.00-reference group, **CI**-Confidence Interval, **COR**=-Crude Odds Ratio, **E**- Ethambutol, **H**- Isoniazid, **R**-Rifampicin, **S**- Streptomycin, **Z**- Pyrazinamide

5.9 Bivariate analysis of year of treatment

Bivariate analysis indicated that the likelihood of poor outcome was significantly decreased with years from 2009G.C to 2013G.C as shown below in table 9.

Table 9: Bivariate analysis of year of treatment with treatment outcome, Arba Minch General Hospital, Southern Ethiopia, 2014

Year of diagnosis (G.C)	Case group N (%)	Control group N (%)	Total N (%)	Sig.	COR(95.0% CI**)**
2009	56(25.0)	70(15.6)	126(18.8)	.000	5.000(2.776, 9.006)
2010	58(25.9)	63(14.1)	121(18.0)	.000	5.754(3.184, 10.397)
2011	51(22.8)	94(21.0)	145(21.6)	.000	3.391(1.894, 6.070)
2012	39(17.4)	96(21.4)	135(20.1)	.002	2.539(1.392, 4.632)
2013	20(8.9)	125(27.9)	145(21.6)		1.00

NB: 1.00-reference group, **COR**-Crude Odds Ratio, **CI**- Confidence Interval, **G.C**- Gregorian calendar

5.10 Predictors of poor TB treatment outcome

Variables having a P-value of less than 0.25 in the bivariate analysis and collinearity coefficient of less than 0.6 were selected and entered in to multivariate analysis on logistic regression Model.

From the variables that were included in the multivariate analysis development of poor outcome was significantly associated with male sex, age older than 35 years, rural residence, retreatment category, type of TB, smear positivity at 2^{nd} /3^{rd} month of follow up, HIV positive, no result for HIV and treatment of TB in the years before 2011G.C while use of the regimen RH or EH/ERH in the continuation phase (AOR=1.402; p=.145), initiation of CPT (AOR=.931; p=.917) and HAART(AOR=2.781; p=.056) for HIV+ were not found to be significantly associated with poor treatment outcome at P-value of < 0.05.

Males were 1.6 times more likely to develop poor treatment outcome (AOR=1.600 (95%CI=1.104, 2.317) when compared to females keeping other variables in the model constant. Rural residents were 1.5 times more likely to develop poor outcome than those who resided in urban area (AOR=1.496 (95%CI=1.037, 2.159). The odds for poor treatment outcome was higher among subjects older than 35 years of age (AOR=2.381 (95%CI=1.643, 3.448). Cases were 3.3 times more likely to have previous treatment history than the controls (AOR=3.305 (95%CI=1.298, 8.415). Regarding to type of TB, it was observed that subjects who had smear negative pulmonary TB and EPTB were 2.4 and 2.5 times more likely to develop poor outcome respectively when compared to subjects who had smear positive pulmonary TB. Smear positivity at end of 2^{nd}/3^{rd} month of follow up is risk factor for poor outcome. HIV positive (AOR=2.364 (95%CI=1.574, 3.552) and no result for HIV (AOR=2.553 (95%CI=1.283, 5.081) were associated with more than two- fold increase in odds for poor treatment outcome. Treatment of TB before the year 2011G.C was associated with over 2 fold increase in odds for poor outcome (AOR=2.097 (95%CI=1.298, 3.388). Table 10 below presents the results of the multivariate logistic regression analysis.

Table 10: Multivariate logistic regression analysis of predictors of poor tuberculosis treatment outcome, Arba Minch General Hospital, Southern Ethiopia, 2014

Variables	Category	Case group N (%)	Control group N (%)	Sig.	AOR (95% CI)
Sex					
	Male	147(65.6)	233(52.0)	.013*	1.6 (1.1, 2.3)
	Female	77(37.4)	215(48.0)		1.00
Age(years)					
	<35	96(42.9)	315(70.3)		1.00
	>=35	128(57.1)	133(29.7)	.000*	2.4 (1.6, 3.4)
Area of residence					
	Urban	108(48.2)	272(60.7)		1.00
	Rural	116(51.8)	176(39.3)	.031*	1.5 (1.0, 2.2)
Patient category					
	New	192(85.7)	416(92.9)		1.00
	Retreatment	19(8.5)	10(2.2)	.012*	3.3 (1.3, 8.4)
	Transfer in	13(5.8)	22(4.9)	.990	1.0(.4, 2.2)
Type of TB					
	PTB+	25(11.2)	127(28.3)		1.00
	PTB-	151(67.4)	243(54.2)	.001*	2.4 (1.4, 4.1)
	EPTB	151(67.4)	78(17.4)	.005*	2.5(1.3, 4.6)
Smear at 2^{nd} /3^{rd} month follow up (N=151)	Positive	9(36.0)	120(95.2)	.000*	53.3(9.6, 296.1)
	Negative	16(64.0)	6(4.8)		1.00
HIV status					
	Negative	116(51.8)	346(77.2)		1.00
	Positive	87(38.8)	82(18.3)	000*	2.4 (1.6, 3.5)
	No result	21(9.4)	20(4.5)	.008*	2.5 (1.3, 5.1)
CPT prescribed (N=169)	Yes	19(21.8)	7(8.5)		1.00
	No	68(78.2)	75(91.5)	.917	.9 (.2, 3.6)
HAART initiated (N=169)	Yes	33(37.9)	16(19.5)		1.00
	No	54(62.1)	66(80.5)	.056	2.8(.9, 7.9)
Drug used during continuation Phase					
	EH/ERH	119(53.1)	130(29.0)	.145	1.4(.890, 2.2)
	RH	105(46.9)	318(71.0)		1.00
Year of treatment(G.C)					
	Before 2011	165(73.7)	227(50.7)	.002*	2.0 (1.3, 3.4)
	After 2011	59(26.3)	221(49.3)		1.00

NB: "**1.00**"- reference group; **AOR**- Adjusted Odds Ratio, **E**- Ethambutol, **H**- Isoniazid, **R**- Rifampicin *****- significant P < 0.05; **PTB+**: Smear Positive Pulmonary Tuberculosis, **PTB-**: Smear Negative Pulmonary Tuberculosis, **EPTB**: Extra Pulmonary Tuberculosis, **G.C**- Gregorian calendar

CHAPTER SIX: DISCUSSION

A case control study with one to two ratio of case to control was conducted by recruiting a total of 672 subjects to determine predictors of poor TB treatment outcome at Arba Minch General hospital, Southern Ethiopia. Multivariate analysis showed that male sex, age older than 35 years, rural residence, retreatment category, type of TB, smear positivity at 2^{nd} /3^{rd} month of follow up, HIV positive, no result for HIV and treatment of TB in the years before 2011G.C, were the predictors of poor treatment outcome.

The present study showed that males were 1.6 times more likely to develop poor treatment outcome (AOR=1.600 (95%CI=1.104, 2.317) when compared to females. Similar findings were reported from other studies in Southern Region of Ethiopia (AOR 1.24, (95%CI 1.09–1.42) (14), Brazil (AOR=2.28 (95%CI=1.06 - 4.94)(28) and Turkey (AOR= 2.11 (1.49-2.99))(30). A study in Nigeria also showed that being male was a risk factor for defaulting from anti-TB medication(39). One reason for these could be attributed to the fact that in most societies, men are the bread winners in the family, highly exposed to cigarette smoking, alcohol consumption and thus find it difficult to comply with daily clinic attendance (40). On the contrary, different result was reported from Bahir Dar Felege Hiwot Referral Hospital in which the percentage of deaths, failures and defaulters was higher in females than in males. This might be due to differences in accessibility to health information & health care services, and community-based interventions (21). This is also supported by study conducted in South Ethiopia which showed that community-based interventions made TB diagnostic and treatment services more accessible to the poor women, thus, doubling the notification rate and improving treatment outcome (19, 23).

In this study, the odds for poor treatment outcome was higher among subjects older than 35 years of age (AOR=2.381 (95%CI=1.643, 3.448). Similar results from study conducted in Tigray region of Ethiopia, the odds of unsuccessful treatment outcome was higher among patients older than 40 years of age (AOR = 2.50, 95% CI: 1.12-5.59)(19), in Malawi age >35years(10), in Nigeria(11) the mean age of cured patients was 31.2+/- 3.1 years which was significantly lower than the mean age of those with poor treatment outcomes 36.7+/-3.5 years ($p<0.05$) while a significant association between poor outcome and older age may be partly explained by older individuals often have concomitant diseases, general physiological deterioration with age, are less able to reach health facilities (30). However, study conducted in Brazil showed that age over 29 years was identified as protective factor for the outcome (AOR= 0.50(95% CI= 0.25 - 0.99) p-value 0.047 compared to age 18 to 29 years. This

might be due to differences in assessed risk factors in which they assessed risk factors for only default from tuberculosis treatment while the current study assessed risk factors for failure and death in addition to default from TB treatment. Increased risk of death during TB treatment with age was evidenced by different studies (10, 11, 19, 41)

The present study showed that study subjects from rural area were 1.5 times more likely to develop poor outcome than those who resided in urban area (AOR= 1.496 (95% CI=1.037, 2.159)) p-value 0.031. The study conducted in Bahir Dar Felege Hiwot Referral Hospital showed similar results being a rural resident was associated with a lower treatment success rate(21). The lower treatment success rate in rural patients is probably due to lower awareness of TB treatment and the long distance between their homes and the treatment center(27). This is supported by other studies in India (42), Uganda(43) ,Gambia(44) and Brazil(27) which indicated that difficulty in accessing health facility was associated with lower treatment success rate, distance from home to clinic was associated with defaulting from TB treatment (OR 2.22; 1.21–4.06, defaulting rate was higher among those who incurred significant time or money costs travelling to receive treatment (HR 2.67; 95%CI 1.05–6.81; *P* _0.04), and proxy variables for socio economic status such as schooling and distance to the health care unit were associated with unsuccessful outcomes, respectively.

In this study cases were 3.3 times more likely to have previous treatment history than the controls (AOR=3.305 (95%CI=1.298, 8.415). A case- control study conducted on determinants of multidrug-resistant tuberculosis in Addis Ababa showed that being retreatment was found to be a significant risk factor for poor treatment outcome(18). Other studies conducted in Tigray region of Ethiopia, Brazil and Taiwan showed that retreatment cases were associated with poor outcome (adj. OR = 2.00, 95% CI: 1.37-2.92) as compared to their respective comparison groups(19), prior TB treatment was associated with dropout(26), and treatment success was significantly higher in new smear-positive cases and lower in retreatment cases(7), respectively. Globally, the treatment success rate for retreatment cases was low (72%), in comparison to new cases (87%) more so for treatment-after-failure (since previous failure may have been due to drug resistance) and treatment-after-default cases (since cases that defaulted previously are likely to have poor compliance and/or drug resistance) than for relapse cases(45). Individuals who were treated by the retreatment regimen had increased risk for MDRTB**.** An individual's treatment may fail because they have already had MDR-TB or because drug resistance was caused by the retreatment regimen (46). Hence, WHO recommends DST for all previously treated patients before they are treated with the retreatment regimen and in conditions

where DST is not available, the retreatment regimen can be used for relapse, default, and treatment failure for low- or medium-MDR-TB-burden countries (1).

Regarding to type of TB, it was observed that subjects who had smear negative pulmonary TB and EPTB were 2.4 and 2.5 times more likely to develop poor outcome respectively when compared to subjects who had smear positive pulmonary TB. Similar findings were reported from other studies in Southern region of Ethiopia, PTB+ cases had 1.8 (65% vs.37%) and 1.4 (65% vs. 48%) times higher rate of treatment success compared to PTB- and EPTB cases, respectively ($p < 0.001$)(35), Gondar University Teaching Hospital, Smear negative pulmonary tuberculosis patients had significantly low treatment success rate ($P < 0.001$; CI = 0.35 - 0.54) compared to smear positive and extra pulmonary tuberculosis patients(6), Felege Hiwot Referral Hospital, EPTB patients ($p = 0.004$) were associated with a lower treatment success rate (21) and Addis Ababa, the death rate of pulmonary positive, pulmonary negative and extra pulmonary TB patients were 2.7%, 3.6%, and 4.3%, respectively(22). This probably due to Low rate of identification of illness and delay to start treatment, long treatment duration, treatment outcome monitoring of smear-negative and extra pulmonary TB is only clinical condition and their diagnosis is difficult, often resulting in treatment delay and poor outcome(3). Hence, early diagnosis, aggressive treatment and careful monitoring to reduce the rate of poor treatment outcome in subjects who had smear-negative PTB and extra pulmonary TB have to be considered.

In this study Smear positivity at $2^{nd}/3^{rd}$ month follow up is risk factor for poor outcome. Similar results were reported from studies conducted in South Ethiopia and Turkey; having a positive smear at the second month follow-up (AOR 1.68, 95%CI 1.07–2.63) is independent risk factor for poor outcome(14) and 3^{rd} month microscopy positivity was associated with a five-fold increase in odds for adverse treatment outcome(46), respectively. Non-completion of treatment was associated with sputum smear positivity(47). Smears should be converted to negative in the majority of new smear-positive pulmonary TB patients after 2 or 3 months of anti-tuberculosis treatment. Sputum smear conversion after 2 or 3 months of treatment is a good predictor of eventual cure if treatment is completed. Negative predictive values (NPV) were high (at least 93%), indicating a negative sputum smear test result during any month of treatment makes relapse or failure unlikely(48). Because sputum smear conversion after 2 or 3 months of treatment is a good predictor of eventual cure, sputum smear examinations should be performed for smear positive PTB patients during follow up.

HIV positive (AOR=2.364 (95%CI=1.574, 3.552) and no result for HIV (AOR=2.553 (95%CI=1.283, 5.081) were associated with more than two-fold increase in odds for poor treatment outcome. Similarly study conducted in Azezo health center showed that HIV status (c2 = 12.33; P-value, < 0.001) was significantly associated with poor treatment outcome(34). The treatment success rate for HIV negative tuberculosis patients 24.6% (n = 139) was higher than for HIV positive patients 22.5% (n = 43), indicating that HIV testing before treatment is crucial(21). Study conducted in Uganda Hospital showed that the problem of TB is made worse by the concurrent infection with HIV(49). A retrospective hospital register-based cohort study conducted in Cameroon in 2013 showed that non-consenting for HIV screening (AOR= 1.65; (CI=1.24 to 2.21) was the main determinant of defaulting from treatment(12), Southwestern Nigeria(50) failure to give consent for HIV test affected the TB outcome negatively. One study conducted in New York showed that Patients infected with HIV were more likely than those who were uninfected to have recurrence or relapse (2.0 vs. 0.4 per 100 person-years, *P<0.001*)(32). Our finding is also inline with WHO 2013 and Federal Ministry of health report which showed that the treatment success rate for all new HIV positive TB patients 73% compared with 87% among HIV-negative TB patients(1) and HIV infection increases the likelihood of re-infections and relapses of TB(3), respectively. The current study showed that there was no statistically significant difference between cases and controls with initiation of HAART (AOR=2.8(95% CI=.9, 7.9, P=.056) and CPT (AOR=.9(95% CI=.2, 3.6, P=.917) for TB-HIV co-infected patients. However, different studies (26, 28, 41, 51) showed that TB-HIV co-infected patients who took HAART and CPT during TB treatment had a lower risk of hospital admissions and death that demonstrate the positive impact of HAART and CPT on the survival outcomes among TB-HIV co-infected patients, including successful immune restoration and reductions in morbidity and mortality. Guidelines also recommend for HIV-positive TB patients to initiate CPT and HAART(1, 3). The difference may be due to the fact that being TB patients alone might be with low pill burden, minimum adverse effects, mild drug-drug interaction and good immunity compared to TB/HIV co-infected patients, subjects received their TB medications as directly observed therapy while their prophylaxis and HIV medications were self-administered (3, 51).

In this study, subjects started their anti-TB medication before the year 2011G.C were more likely to have poor treatment outcome (AOR=2.097; 95%CI= (1.3, 3.4) p=.002) when compared to subjects started their medication after 2011G.C treatment year. This difference might be due to improvements in DOTS performance in the subsequent year of treatment, TB treatment regime changed from EH to

RH based treatment in the continuation phase, improvement in patient awareness about TB transmission and treatment as a result of health education and promotion, health extension workers involvement in the community. One study reports from South Ethiopia Hadiya zone showed that introduction and expansion of DOTS significantly increased treatment success rate and decreased in defaulters and failure rates(35). Study from Gondar also showed that death rate of tuberculosis patients was significantly decreased across the years from 13.9% in (September 2003 - August 2004) to 3.4% in (September 2006 - August 2007) ($p < 0.001$)(6). Another study conducted in Ghana showed that improvements in diagnosis, community TB care, stigma reduction among community and health workers towards TB patients, the public-private partnership, and the enablers' package contributed to the improved better treatment outcomes(52).

Strength and Limitation of the study

Strength of the study

- We collected data of TB patients' way back to the inception of DOTS program, thus a relatively large sample size was used in this study.
- We used a better sampling technique (computer generated random numbers) and procedure in screening the patients' hospital records

Limitation of the study

- Retrospective design of the study made it impossible to evaluate the contribution of other factors which might have impact on treatment outcome.
- No information about comorbid conditions other than HIV, concomitantly used medications, medication side effects from the TB register. It is imperative for the national tuberculosis and leprosy control program (NTLCP) to update the present form to include more information on the patients admitted in to the program.
- Major data were missing for the variables smear result at 5^{th} month follow up (15% missing) and $6^{th}/8^{th}$ month follow up (29% missing) for smear positive PTB, thus were excluded from the analysis

CHAPTER SEVEN: CONCLUSION AND RECOMMENDATIONS

7.1 Conclusion

The results showed that male patients, those resided in rural area, older age**,** previously treated patients, patients with smear negative PTB and EPTB, having positive smear at $2^{nd}/3^{rd}$month of follow up, HIV co-infected patients, those not tested for HIV and treated for TB in the year before 2011 G.C were at significantly increased risk of developing poor treatment outcome.

7.2 Recommendations

Based on the findings of this study, the following specific recommendations were forwarded:

- TB clinic of Arba Minch General Hospital
  - is expected to provide targeted measures (health education, careful treatment and monitoring) to reduce the rate of poor outcome among high-risk groups, such as: male, older age patients, patients who had smear negative PTB, EPTB, having a positive smear at the $2^{nd}/3^{rd}$ month of follow-up
  - Should take special care to make efforts to reduce re-treatment cases
  - Should consider counseling patients with TB on the need for HIV testing, linking the HIV positive patients to support groups
- SNNP Regional Health Bureau and Gamo Gofa Zone Health Department has to design strategies to improve access to services for the rural population
- National TB and Leprosy Control Program (NTLCP) of Ethiopia has to design strategies so as to conduct Drug Susceptibility Test (DST) for all previously treated patients before they are treated with the retreatment regimen.
- Finally, we recommend prospective studies to evaluate the contribution of other factors which might have impact on treatment outcome

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ANNEX: DATA COLLECTION CHECK LIST

General introduction: TB is the leading cause of death in the world. Even where free medication is available, many patients are not successfully treated for tuberculosis due to several factors that affect treatment outcome. Understanding the specific reasons for poor treatment outcome is important in evaluating the effectiveness of tuberculosis control program. The aim of this study is to assess risk factors for poor treatment outcome.

Instruction: Select your answer for the questions by marking "√" in the box provided

1.	Age(years)	----------	
2.	Sex	Male ☐ Female ☐	
3.	Baseline weight (Kg)	----------	
4.	Area of residence	Urban ☐ Rural ☐	
5.	Type of TB	Pulmonary TB ✓ Smear positive PTB ☐ ✓ Smear negative PTB ☐	Extra pulmonary TB ☐
6.	Category of patients	New ☐ Re treatment ☐ Transfer in ☐	

7.	Treatment outcome of TB	Cured ☐ Completed treatment ☐ Died ☐ Failure ☐ Defaulted ☐				
8.	HIV status of the patient	HIV positive ☐ HIV negative ☐ ART initiated Yes ☐ No ☐ CPT initiated? Not tested ☐ Yes ☐ No ☐				
9.	Smear result during follow up	At 2nd /3rd month Positive ☐ Negative ☐		At 5th month Positive ☐ Negative ☐		At 6th /8th month Positive ☐ Negativ ☐
10	Year of treatment(G.C)	2009 ☐	2010 ☐	2011 ☐	2012 ☐	2013 ☐
11	Drug use related factors	Drugs used during intensive Phase……..……. Drugs used during continuation Phase ……				