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TREATMENT OUTCOME OF TUBERCULOSIS IN HIV POSITIVE AND NEGATIVE PATIENTS IN SELECTED HOSPITALS IN THE ACCRA METROPOLIS.

BY

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DECLARATION

I, Ogyiri, Lily hereby declare that except for references made to other people's work which have been duly acknowledged, this dissertation is the result of my own research. This dissertation either in whole or part has not been presented for any degree elsewhere.

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DEDICATION

This work is dedicated to the Almighty God for His grace and mercies and to the Ogyiri family for their love and support.

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ABSTRACT

Introduction: Tuberculosis is currently causing more deaths than HIV. Approximately 1.8 million people died from TB; of which 0.4 million were HIV positive. Ghana is one of the 30 high burden TB/HIV countries with one of the highest TB/HIV incidence rates. The case fatality rates of tuberculosis in Ghana has stagnated at 10percent over the past few years and is unacceptably high. The prognosis of treatment in TB/HIV co-infected patients is poor compared to TB patients without HIV infection. This study investigated the outcomes of TB treatment and predictors of mortality among TB/HIV co-infected patients and TB patients without HIV infection.

Methods: A three-year (2013 to 2015) retrospective cohort study was conducted at La General Hospital and Achimota Hospital in the Greater Accra Region of Ghana. A pre-tested data extraction tool was used to extract relevant information. A total of 521 observations were analysed using STATA 14. Multinomial logistic regression was used to determine the difference in TB treatment outcome between HIV positive and negative patients. Survivor function and survival curves were estimated with Kaplan-Meier analysis. Cox proportional hazard regression model was used to determine predictors of mortality. All tests were two-tailed and statistical significance was set at 0.05.

Results: A significant increase in the risk (aRR 5.85, 95percentCI 2.83-12.09) of death relative to treatment success was observed among HIV positive patients compared to those without HIV infection. The cumulative probability of survival was 0.73 for TB/HIV patients and 0.93 for HIV negative patients (log rank test, p-value <0.001). More than half of deaths in the study population occurred in the initial phase of treatment. Predictors of

death among all TB cases were, baseline weight (adjusted HR = 0.96 95percent CI 0.192-0.99) and HIV negative status (adjusted HR= 0.29 95percentCI 0.16-0.53). Among TB/HIV co-infected patients, not taking CPT during treatment was associated with an adjusted hazard ratio of 3.39 (95percent CI 1.35-8.52). Only 3.9percent of TB/HIV co-infected patients were given ART during TB treatment.

Conclusions: These results suggest that interventions focussed on improving the outcomes of TB patients with low body weight and HIV infection could reduce TB mortality in our settings.

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LIST OF ABBREVIATIONS

AFB – Acid-Fast Bacilli

AIDS – Acquired Immune Deficiency Syndrome

ART – Anti Retroviral Therapy

CD4 – Cluster of Differenciation 4

CPT – Co-trimoxazole Preventive Therapy

DOTS – Directly Observed Treatment, Short course

EPTB – Extra Pulmonary Tuberculosis

GAR – Greater Accra Region

HAART – Highly Active Anti-Retroviral Therapy

HBCs – High Burden Countries

HIV – Human Immunodeficiency Virus

HSS – HIV Sentinel Survey

IRIS- Immune Reconstitution Inflammatory Syndrome

LTBI – Latent Tuberculosis Infection

LTFU – Lost-to-follow up

NTP – National Tuberculosis Control Programme

PLWH – People Living With HIV

PTB – Pulmonary Tuberculosis

SSM – Sputum Smear Microscopy

TB – Tuberculosis

WHO – World Health Organisation

DEFINITION OF TERMS

Bacteriologically confirmed TB case – a TB case from whom a biological specimen is positive by smear microscopy, culture or WHO-approved rapid diagnostics.

Clinically diagnosed TB case – a TB case that does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. This definition includes cases diagnosed on the basis of x-ray abnormalities or suggestive histology and extra-pulmonary cases without laboratory confirmation.

Pulmonary tuberculosis (PTB) – refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree.

Smear positive PTB – a patient with one or more initial sputum smear examinations as positive or one sputum examination as positive plus radiographic abnormalities consistent with active pulmonary TB as determined by a clinician or other medical practitioner.

Smear negative PTB – a case of TB not meeting the criteria for smear positive but with diagnosis criteria which include at least 2 sputum smear examinations negative for AFB and radiographic abnormalities consistent with active pulmonary tuberculosis.

Extra-pulmonary TB – refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs eg. Pleura, lymph nodes and spine.

Cured – a pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear or culture negative in the last month of treatment and on at least one previous occasion.

Treatment completed – a TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative either because tests were not done or because results are unavailable.

Treatment success – the sum of cured and treatment completed.

Treatment failed – a TB patient whose sputum smear or culture is positive at month 5 or later during treatment.

Died– a TB patient who dies for any reason before starting or during the course of treatment.

Lost-to-follow up – a TB patient for whom treatment was interrupted for 2 consecutive months or more.

Not evaluated – a TB patient for whom no treatment outcome is assigned. This includes cases 'transferred out' to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.

New patients – patients who have never been treated for TB or have taken anti-TB drugs for less than one month in the past.

Treatment after failure – patients who have previously been treated for TB and whose treatment failed at the end of their most recent course of treatment.

Treatment after loss to follow up – patients who have previously been treated for TB and were declared lost-to-follow up at the end their most recent course of treatment.

CHAPTER ONE
INTRODUCTION

1.1 Background

Mycobacterium tuberculosis is the causative organism of Tuberculosis (TB); a communicable disease which usually affects the lungs (Pulmonary Tuberculosis, PTB) (WHO, 2015) and also affects other sites of the human body like the bones, meninges, abdomen, skin, lymph nodes and genitourinary tract (Extra Pulmonary Tuberculosis, EPTB) (WHO, 2014). A person with PTB who coughs or sneezes can release bacteria into the air through aerosol. The organism may possibly end up in the lungs of another person who is in close contact with the infected person. The contact may develop latent or active TB depending on the host-agent relationship. The WHO (2015) defines latent tuberculosis infection (LTBI) as, *"a state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens without evidence of clinically manifested active TB"*. About 15 percent out of the 3 billion people worldwide infected with TB will develop an active disease during their lifetime (WHO, 2015). People with weakened immune systems are particularly susceptible to developing active TB disease (CDC, 2014). The signs and symptoms of TB include weight loss, fever, cough, diarrhea, night sweats and hepatomegaly.

There are two types of Human Immunodeficiency Virus (HIV) infection: HIV-1 and HIV-2. HIV-1 is more common and largely responsible for the global pandemic. HIV – 2 is less virulent and found mostly in West Africa (Campbell-Yesufu & Gandhi, 2011), Portugal and some former Portuguese colonies such as Aangola, Mozambique, Brazil and some parts of India (Carvalho, Valadas, Franca, Carvalho, Alexio, Mendez, Marques, Sarmento,

Doroana, Antunes, Branco, Aguas, Sarmento e Castro, Lazarus & Barros, 2012). The HIV pandemic remains one of the major public health challenges of our generation despite considerable achievements in containing it. The virus is transmitted through body fluids such as semen, blood, breast milk, pre-seminal fluid, vaginal fluid and rectal fluids from an infected person through sex, sharing of sharp objects like needles and breastfeeding.

Anti-retroviral therapy (ART) medications have been available since the 1990s and are effective in suppressing viral replication; transforming HIV infection from a highly fatal disease to a chronic disease that can be managed with a favourable prognosis (Maartens, Celum, & Lewin, 2014). There has been more than a two fold increase in the number of people receiving ART since 2010 in the world's most affected region, Eastern and Southern Africa. This made a large contribution to the reduction in Acquired Immune Deficiency Syndrome (AIDS) related deaths worldwide from 1.5 million in 2010 to 1.1 million in 2015 (UNAIDS, 2016). Thirty seven million people were estimated to be living with HIV in 2015 including 2.1 million new infections and sub-Saharan Africa alone accounted for about 70 percent of the global burden (UNAIDS, 2016).

1.2 TB/HIV co-infection

TB/HIV co-infection occurs when a person has both active TB disease and HIV infection. A synergistic relationship exists between TB and HIV infection. HIV is an important risk factor in the progression of LTBI to active TB disease. It increases the risk of active TB by 19 times in people living with HIV (PLWH) than people without HIV (WHO, 2016a). TB on the other hand speeds up the advancement of HIV infection to acquired immune

deficiency syndrome (AIDS) if left untreated (Mayer & Dukes Hamilton, 2010). TB is the leading cause of death in PLWH; 1 in 3 PLWH die from TB worldwide (WHO, 2016a).

1.3 Burden of TB

Globally, in 2015, about 11 percent of the 10.4 million incident TB cases worldwide were HIV positive. Approximately, 1.8 million people died from TB; of which 0.4 million were HIV positive. Deaths from TB have fallen by 22 percent from 2000 to 2015, yet, TB is still one of the top 10 causes of mortality in the world; now causing more deaths than HIV (WHO, 2016a).

Countries in the WHO African Region bear the brunt of the burden in terms of incident cases per population (281 per 100,000). About 75 percent of TB/HIV deaths that occurred in 2015 worldwide happened on the continent (WHO, 2016a). Case fatality ratios of TB varied from below 5 percent to over 20 percent among countries in the region.

The 2016 WHO global tuberculosis report lists Ghana as one of the 30 high burden TB/HIV countries with one of the highest TB/HIV incidence rates (36/100,000 population) (WHO, 2016a). An estimated 75,000 people had TB in 2014. About 44,000 new cases of TB were recorded that year with the rate of new infections at 165/100,000; an updated estimate which proved to be almost 3 times higher than previous estimates. The distribution of notified new and relapse TB cases in men and women above 15 years was 9129 and 4826 respectively (WHO, 2015).

According to the HIV Sentinel Survey (HSS), Ghana has experienced a steady decline in the prevalence of HIV from 3.6 percent to 1.6 percent in 2003 and 2014 respectively and

HIV remains as a generalized epidemic in the country (Ghana AIDS Commission, 2015). The estimated prevalence of HIV in adults aged 15 to 49 years for the year 2015 in Ghana was 1.6 percent (UNAIDS, 2016) and 22 percent of TB patients with known HIV status were HIV positive (WHO, 2016a).

The re-emergence of TB as a result of the HIV & AIDS pandemic in the 1990s attracted the interest of the world at large. The WHO in response declared TB as a global emergency and called upon nations to develop national control programs to contain the disease. Ghana established the National Tuberculosis Control Programme (NTP) in 1994 (Amo-Adjei & Awusabo-Asare, 2013).

The post 2015 agenda of the WHO for TB is to end TB by the year 2035. The End TB Strategy aims to eventually decrease the number of TB deaths by 95 percent and TB incidence rates by 90 percent compared to 2015 by the year 2035 (WHO, 2016a). Outcome of TB treatment is one of the key performance indicators in this agenda. An estimated 49 million deaths have been prevented by TB treatment globally between 2000 and 2015 (WHO, 2016a). The directly observed treatment, short course (DOTS) was first implemented in Ghana in 1994 and by the year 2000 reached a 100 percent coverage nationwide (GHS, 2008). The three years preceding 2016 have seen a steady decrease in reported cases of TB; from 15, 606 cases in 2013 to 14,999 cases in 2015 in Ghana (WHO, 2015).

1.4 Problem Statement

Mortality rate in TB in 2015 was 47 percent lower than in 1990 globally. This figure was a little short of the 50 percent reduction of TB mortality goal that was initially set by the WHO. Other regions of the world achieved this target with the exception of Africa, Europe and 11 of the TB High Burden Countries (HBCs) (WHO, 2015). Ghana's treatment success rate for new and relapse cases of TB has improved over the years; from less than 40 percent in 1997 to 85 percent in 2013. Also, out of a cohort of 2737 TB/HIV cases, 73 percent of them had successful treatment in 2013 (GHS, 2015a; WHO, 2015). These figures suggest that the prognosis of treatment in TB/HIV co-infected patients is poor compared to TB patients without HIV and it is a problem that needs to be investigated and addressed.

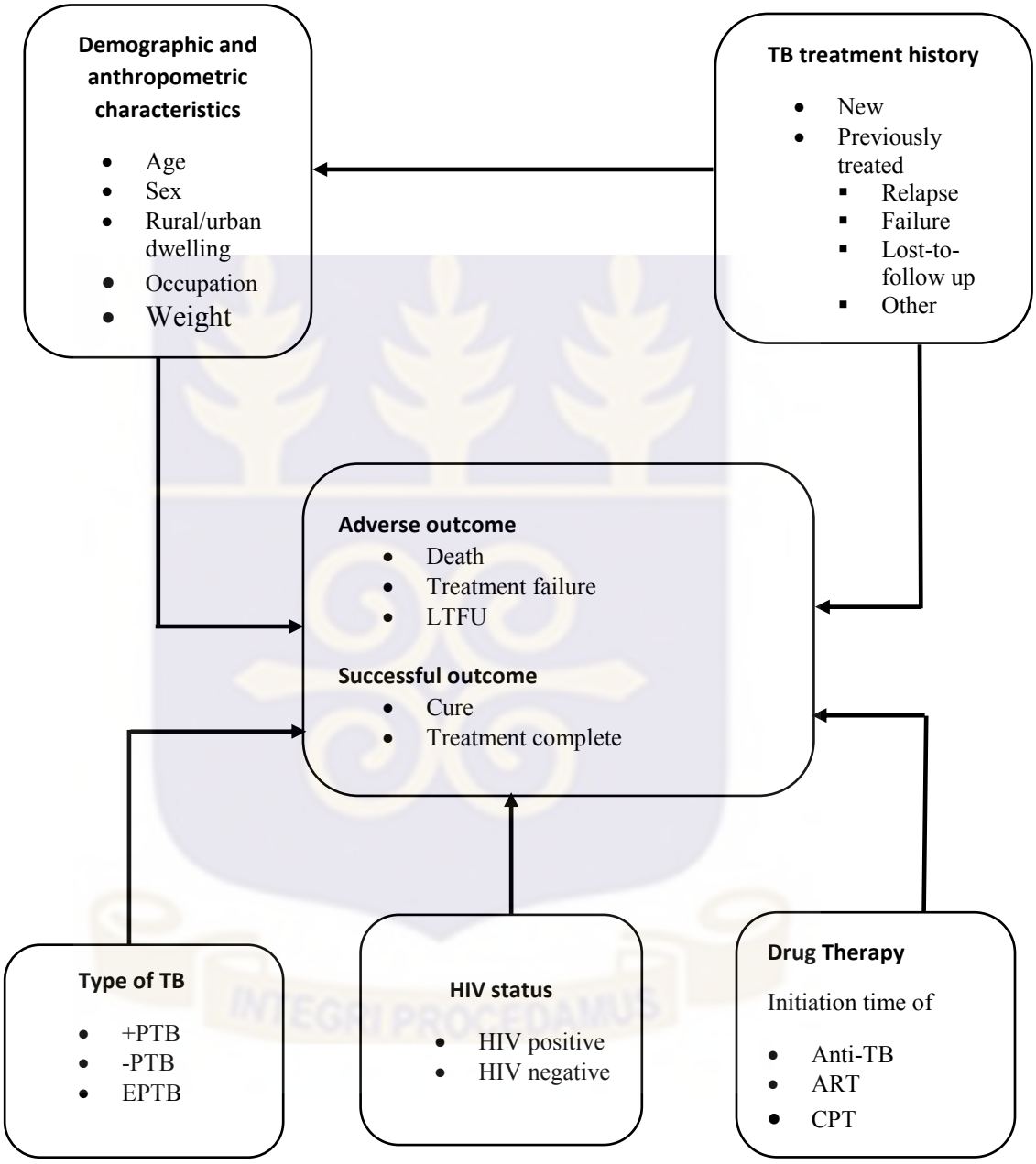
TB case-fatality rates have varied between 7.8 percent and 9 percent from 2001 to 2007 (GHS, 2008). The NTP, as part of its 2009-2013 TB strategic plan set out to achieve a target of less than 5 percent death rate by 2013 but this target could not be met; 10 percent of TB cases died during treatment that year (GHS, 2015a; WHO, 2015). The opposite can be said about the other components of adverse outcome. For instance, rates of lost-to-follow up (LTFU) previously categorized as defaults have decreased considerably. More than 20 percent of cases were lost-to-follow up in 1997 as compared to 3.1 percent in 2007. Failure rates have been consistently around 2 percent over the years (GHS, 2015a). Evidently more attention has to be drawn to the 10 percent of the patients who die during treatment in order to achieve the targets set in the End TB Strategy by 2035.

It has been reported that HIV positive TB patients are at a higher risk of dying (Burton, Forson, Lurie, Kudzawu, Kwarteng & Kwara., 2011; Shaweno & Worku, 2012), lost-to-

follow up or default treatment (Burton et al., 2011) and developing drug resistance to anti-tuberculosis treatment (Li, Munsiff, Driver, & Sackoff, 2005) than their HIV negative counterparts during TB treatment. However, few studies have reported on the mortality and default rates in TB patients (Burton et al., 2011; Dodor & Afenyadu, 2005; Norgbe, Smit, & du Toit, 2011) and one other study (Nassikas, Yang, Forson, Kwarteng, & Kwara, 2015) has reported on the predictors of death in extra pulmonary TB patients with HIV in Ghana. This study seeks to find out the differences in treatment outcomes of HIV positive and negative TB patients and the characteristics associated with mortality in TB/HIV co-infected patients attending two urban hospitals in Ghana.

1.5 Conceptual Framework

Figure 1: Conceptual framework of factors influencing treatment outcome of Tuberculosis



The conceptual framework describes the correlations or influences of demographic characteristics, clinical characteristics, treatment therapy, HIV status, type of TB and TB history on the type of treatment outcome a patient will have. Demographic and anthropometric characteristics such as being male, 55-64 years, living in a rural area and having low weight have been shown to be associated with adverse outcome (Dodor & Afenyadu, 2005; Gebremariam, Asmamaw, Hussen, Hailemariam, Asegu, Astatkie & Amsalu, 2016; Gebrezgabiher, Romha, Ejeta, Asebe, Zemene & Ameni, 2016; Kanungo, Khan, Ansari, & Abedi, 2015; Tabarsi, Chitsaz, Moradi, Baghaei, Marjani & Mansouri, 2012). Other demographic characteristics like socio-economic status and year of treatment have also been mentioned as having an influence on treatment outcome (Reddy Satti & Kondagunta, 2016). Having a history of TB treatment, either lost-to-follow up or treatment failure may reduce a patient's chance of successful outcome (Ambadekar, Zodpey, Soni, & Lanjewar, 2015; Biruk, Yimam, Abrha, Biruk, & Amdie, 2016). Furthermore, extra pulmonary TB patients have been reported to have a two fold higher success rate than patients with pulmonary TB. HIV positive patients also are more likely to die during TB treatment as compared to their HIV negative counterparts (El-Sony, Khamis, Enarson, Baraka, Mustafa & Bjune, 2002; Gebremariam et al., 2016; Nassikas et al., 2015). The initiation time of anti-TB treatment and prescription of co-trimoxazole preventive therapy (CPT) or ART have also been proven to be related to treatment outcome. If anti-TB treatment is not initiated early and HIV positive patients are not put on CPT or ART their chances of adverse outcomes increase (Khan, Minion, Pai, Royce, Burman, Harries & Menzies., 2010; Nassikas et al., 2015; Shaweno & Worku, 2012).

1.6 Justification

Information on the outcomes of TB treatment and the predictors of mortality may be useful in planning strategies aimed at reaching the WHO End TB Strategy by 2035. Such information can also be useful in planning disease control programs.

Determining the treatment success or treatment failure rates in the selected hospitals may help them know their stance in relation to the End TB goal and identify possible areas of improvement. This may subsequently lead quality improvement strategies to increase success rates, decrease deaths or default rates and prevent the development of drug resistance.

1.7 Objectives

1.7.1 Research questions

1) What are the treatment outcomes of tuberculosis in HIV positive and negative patients on DOTS?
2) What are the characteristics associated with deaths in HIV positive TB patients on DOTS?

1.7.2 General objective

To evaluate the treatment outcomes of tuberculosis in HIV positive and negative patients on DOTS in selected hospitals in the Greater Accra Region.

1.7.3 Specific objectives

a) To compare the outcomes of treatment between HIV positive and negative TB patients.
b) To compare survival of HIV positive and negative patients on TB treatment.
c) To identify predictors of mortality among all patients on TB treatment.
d) To identify predictors of mortality among TB/HIV co-infected patients on TB treatment.

CHAPTER TWO
LITERATURE REVIEW

2.1 Diagnosis and treatment of TB among adults in Ghana

Most cases of TB are found through passive case finding; where people experiencing symptoms report to the hospitals and health professionals carry out tests to make diagnoses. Other TB cases may also be found through active case finding; community health nurses visit communities to screen and educate people on tuberculosis. Diagnostic and treatment services are offered free of charge. Diagnosis is based on the guidelines for the clinical management of TB and HIV co-infection in Ghana: the decision to put a patient on anti-TB medication may rest on bacteriologically confirmed tests and/or clinical diagnosis. (GHS, 2007). The investigations used in diagnosing tuberculosis include firstly, sputum smear microscopy (SSM) for both HIV positive and negative patients. If SSM for acid-fast bacilli (AFB) is positive, it gives an indication of active tuberculosis. However, if the test is negative, follow up tests like chest x-ray and sputum culture are conducted. HIV counselling and testing services are offered to patients with unknown HIV status routinely with an option to opt out. Smear negative pulmonary TB and extra pulmonary TB are diagnosed based on clinical findings by experienced doctors. Diagnosis of TB in PLWH may sometimes be difficult because those with CD4 cell counts less than 250 cells per cubic millimetre may have atypical presentations of active TB disease.

Treatment is based on history of anti-TB treatment using a combination of isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E) and streptomycin (S). All new cases of TB, including HIV positive TB patients and extra pulmonary TB patients undergo an

initial/intensive phase of chemotherapy (HRZE) for 2 months followed by a continuation phase (HR) of 4 months, making a total of 6 months. Patients with smear positive PTB take SSM tests at the end of the initial phase and if they test positive, the initial phase is extended for another month. Patients with a previous history of anti-TB treatment undergo an initial phase (HRZE/S) of 3 months, then a continuation phase (HRE) of 5 months of chemotherapy. The duration of treatment can last longer (9 to12 months) usually based on doctors' recommendations. Drug resistant TB can occur if treatment regimen is not adhered to strictly.

2.2 Tuberculosis treatment outcome

The WHO has set standard definitions of key concepts for various NTPs across countries to enable comparisons to be made using data from different countries. Several classifications of the disease are made based on: anatomical site, history of previous TB treatment, HIV status and drug resistance. With respect to treatment outcomes, TB patients are divided into drug-susceptible TB and drug-resistant TB and definitions or reporting frameworks are set separately for them. These two groups are considered mutually exclusive since different treatment regimens are used for them. Seven different outcomes of treatment have been delineated by the WHO, and they can be further grouped into two: adverse outcome (death, lost-to-follow up and treatment failure) and successful outcome (cure and treatment complete). Those transferred out or not evaluated are not included in the two main outcomes because they are eventually assessed in other health facilities (WHO, 2014).

2.3 Demographic and anthropometric characteristics influencing treatment outcomes

2.3.1 Age

Many studies have acknowledged the role of demographic characteristics in the treatment outcome of tuberculosis. The influence of age on treatment outcome can be attributed to its correlation with immune function. The immune system is least developed at birth, gradually matures from childhood to adulthood and declines in function in old age (Simon, Hollander, & McMichael, 2015). Elmadhoun, Noor, Bushara, Ahmed, Mustafa, Sulaiman, Almobarak & Ahmed (2016), in describing the epidemiology of TB in the River Nile State in Sudan between 2011 and 2013, found that patients below 1 year and those above 50 years had a higher chance of death. Similarly, a prospective study conducted among 302 TB patients in India found people falling in the age groups of 15-30 and 31-45 years having better outcomes as compared to those who fell outside the mentioned age ranges (Kanungo et al., 2015). Sileshi, Deyessa, Girma, Melese, & Suarez, (2013) as well as do Prado, Rajan, Miranda, Dias, Cosme, Possuelo, Sanchez, Golub, Riley & Maciel (2017) also reported significant associations regarding older age and the likelihood of death whilst on TB treatment. This is contrary to the findings of Ambadekar et al., (2015), where in a retrospective cohort analysis of TB/HIV co-infected patients found that paediatric (less than 15 years) patients had better outcomes on anti-TB treatment than patients of adult age.

2.3.2 Residence

Tuberculosis has been linked with overcrowded living conditions such as prisons and slums. Housing quality and prevalence of TB in a community also have a role to play in the increased risk of TB (Schmidt, 2008). A descriptive analysis showed that almost 8 out

of 10 patients with successful outcome lived in urban areas (Firdie, Tariku, & Tewelde, 2016), which is not different from reports from another study in Ethiopia where the risk of adverse outcome was significantly increased in people living in rural areas (Gebrezgabiher et al., 2016). On the contrary, Kanungo et al., (2015), in determining the contribution of certain socio-demographic factors on TB treatment outcome found no association between residence and outcome of treatment.

2.3.3 Occupation

Poverty and TB are almost inseparable because of the symbiotic relationship that exists between them. TB fuels poverty by placing a huge economic burden on households affected by it. Poorer communities, due to lack of basic health services, inadequate nutrition and housing increase the chances of infection thereby spreading the disease quickly (WHO, 2002).

Even though Kanungo et al., (2015) found no association between occupation and treatment outcomes, other studies report otherwise. Income or socio-economic status is closely linked with occupation and has been found to greatly increase default rates in a study where defaulters and non-defaulters were traced to their homes and questionnaires administered on factors that affect treatment compliance (Dodor & Afenyadu, 2005). Inability to purchase supplementary medicines such as vitamins, pain killers and cough mixtures, travel to health facilities for treatment or afford adequate meals were found to be associated with lost-to-follow up or discontinuation of treatment regimen in a case control study where semi-structured questionnaires were used (Reddy Satti & Kondagunta, 2016).

2.3.4 Sex

Worldwide, more men fall ill with TB than women (WHO, 2015). The habit of smoking which is more common in men may put them at a greater risk of TB disease (Elmadhoun et al., 2016), and a number of studies agree on the higher rates of adverse outcomes among men as compared to women, although women are more affected in terms of stigma, discrimination, cultural and financial barriers to accessing health care in some settings (WHO, 2015). Kanungo et al., (2015) reported a higher proportion of adverse outcome among men, although this was not found to be statistically significant, Gebremariam et al., (2016), after analysing a six-year data from a retrospective review in Ethiopia reported that being male was significantly associated with deaths, defaults and treatment failure. The odds ratios of dying among males who had TB/HIV co-infection in three other studies were 2.6 (95% CI 1.5-4.5), 1.3 (95% CI 1.2-1.4) and 1.39 (95% CI 1.01-1.91) (Gadoev, Asadov, Tillashaykhov, Tayler-Smith, Issakidis, Dadu, de Colombani, Hinderaker, Parpieva, Ulmasova, Jalolov, Hamraev, Ali, van den Boom, Hammerich, Gozalov & Dara, 2015; García-Basteiro, Respeito, Augusto, Lopez-Varela, Sacoor, Sequera, Casellas, Bassat, Manhica, Macete, Cobelens & Alonso, 2016; Jacobson, Moll, Friedland, & Shenoi, 2015). Other studies by Ali, Mavundla, Fantu, & Awoke (2016) and Ismail & Bulgiba (2013) also support these findings.

2.3.5 Weight

Changes in weight during TB treatment may have an influence on the treatment outcome. A trial study among 1004 HIV-seronegative TB patients measured weight at diagnosis, after the initial phase of treatment and after the subsequent continuation phase of TB

treatment. After following study subjects for 2 years the authors reported a higher risk of relapse among subjects who were underweight at diagnosis and gained at most 5 percent of their baseline weight during the initial phase of treatment (Khan, Sterling, Reves, Vernon, & Horsburgh, 2006). Two different retrospective cohort studies reported similar findings: Bernabe-Ortiz, Carcamo, Sanchez, and Rios (2011) reported a higher risk of death in patients who lost weight in the first month of treatment and Hoa, Lauritsen, and Rieder (2012) even after finding that patients on average gained weight throughout treatment, those who failed to gain weight or lost weight in the initial phase of treatment had a higher risk of adverse outcome. In another study, a 6 percent decrease in the risk of mortality was observed per 1kg increase in weight among TB patients after adjusting for other demographic and clinical variables (Shaweno & Worku, 2012). Among hospitalized TB/HIV co-infected patients in Cameroun, the odds of dying was 2.38 times higher in patients with weight ≤50 kg whereas the odds of successful outcome among patients with baseline weight <43.7 kg was reduced by almost 50 percent in a University referral hospital in Ethiopia (Agbor, Bigna, Billong, Tejiokem, Ekali, Plottel, Noubiap, Abessolo, Toby & Koulla-Siro, 2014; Sinshaw, Alemu, Fekadu, & Gizachew, 2017).

2.4 Disease related factors influencing treatment outcomes

2.4.1 Type of TB/ TB disease classification

A retrospective study of 886 TB/HIV co-infected people reported that extra pulmonary TB patients had twice the risk of successful outcome than pulmonary TB patients and further asserted that pulmonary TB patients had 2 times the higher chance of deaths than extra pulmonary TB patients (Ambadekar et al., 2015). Both Ali et al. (2016) and Gadoev et al.,

(2015) reported reduced odds ratios of death in patients with extra pulmonary TB compared to smear positive pulmonary TB. Findings from Elmadhoun et al., (2016), similar to Shaweno and Worku, (2012) in studying TB patients also agree with this study. However, other studies contend this assertion; a study consisting of 422 TB/HIV co-infected patients in Ethiopia and another one in Nigeria reported that extra pulmonary TB patients had almost a threefold increase in risk of mortality (Alobu, Oshi, Oshi, & Ukwaja, 2014; Sileshi et al., 2013). Furthermore, two studies conducted in Ethiopia presented extra pulmonary TB patients and smear negative pulmonary TB patients as having higher probabilities of deaths and poor outcomes than patients with smear positive pulmonary TB (Biruk et al., 2016; Gebremariam et al., 2016; Gebrezgabiher et al., 2016). These studies further explained that such outcomes could be due to the high prevalence of HIV infection among extra pulmonary TB and smear negative pulmonary TB patients. Disseminated TB, TB meningitis, pleural effusion and abdominal TB were associated with higher risk of deaths in extra pulmonary TB patients at Korle Bu Chest Clinic in Accra, Ghana and PTB patients whose smear status was unknown also had higher risk of mortality in the same location (Burton et al., 2011; Nassikas et al., 2015).

2.4.2 History of exposure to anti-TB treatment

There are two categories of patients with respect to history of exposure to anti-TB treatment. New patients are defined as those who have never been treated for TB or patients who have received TB treatment for less than one month. The other category (retreatment) consists of patients with previous anti-TB treatment including patients being retreated after failure, lost-to-follow up and successful treatment (relapse or reinfection). These patients

may be more likely to have unsuccessful outcome or be transferred out to other treatment facilities compared to new patients (Ambadekar et al., 2015; Biruk et al., 2016; Gebremariam et al., 2016). A cross sectional study using the Brazilian national TB reporting system database from 2001 to 2011 reported that patients who were receiving treatment after lost-to-follow up and relapse had higher odds of adverse outcome; (1.69 and 3.67) respectively, compared to new patients (do Prado et al., 2017). Similar results have also been presented by Gadoev et al., (2015) and Ismail & Bulgiba (2013).

2.4.3 TB/HIV comorbidity

It is well known that HIV infection increases the risk of adverse outcome in TB patients. Cure rates in TB/HIV co-infected patients were significantly reduced (Ambadekar et al., 2015) and a 7-fold higher odds of death was reported among HIV infected TB patients in another study (Gebremariam et al., 2016). HIV co-infection and low levels of CD4 cell counts increased the chance of severe forms of extra pulmonary TB (meningeal and disseminated) in patients and this further increased the risk of death (Nassikas et al., 2015). Another study using only new cases of TB among 1797 patients in Sudan found no significant difference between the outcomes of treatment in HIV positive and negative patients except for risk of death, where the odds of death among HIV positive patients was 7.68 higher than HIV negative patients (El-Sony et al., 2002). Furthermore, a retrospective study in an Ethiopian University Hospital reported a higher probability of unsuccessful outcome in patients with unknown HIV status compared to patients who were HIV negative (Biruk et al., 2016). About 47.3 percent of deaths were found to be attributable to HIV infection and a risk ratio of 2 was reported among HIV positive patients compared to HIV

negative patients in another retrospective cohort analysis (Shaweno & Worku, 2012), consistent with other reports (Ali et al., 2016; Babatunde, Christiandolus, Bismarck, Emmanuel, Chike & Gabriel, 2016; Sileshi et al., 2013).

2.4.4 Presence of comorbidities or other opportunistic infections

Comorbidities include diseases that fall outside the scope of AIDS-defining illness; such as diabetes, hypertension, hypercholesterolemia, hepatitis and cancer. These diseases are usually age-related and occur mostly in older age (Rodriguez-Penney et al., 2013), although they can occur in young people too. Other opportunistic diseases or infections may also occur in the TB/HIV co-infected individual. Examples include Kaposi's sarcoma, *Pneumocyctis jirovecii* (previously known as *Pneumocystis carinii* pneumonia) and candidiasis (of the oesophagus, trachea, bronchi or lungs) (CDC, 2017). These diseases all add to the burden of morbidity and mortality in the TB/HIV co-infected person as reported in a study in Yaoundé Central Hospital, Cameroun; the presence of other AIDS related non-TB diseases and non-AIDS related comorbidities increased the odds of dying among TB/HIV co-infected patients by 2.73 (95% CI 1.27-5.86) and 3.35 (95% CI 1.37-8.21) respectively (Agbor et al., 2014).

2.4.5 CD4 cell count

Biological markers such as cluster of differentiation 4 (CD4) cell counts have not only been used by the WHO to define the categories of the severity of HIV infection and AIDS but they can also be used to predict the outcome of treatment of TB in people with TB/HIV co-infection. Many studies have cited the importance of CD4 cell counts in the prognosis of TB treatment. Pimchan, Suggaravetsiri, Tesana & Chaiklieng (2012) reported a risk ratio

of mortality of 2.81 among patients with CD4 counts below 25 cells/mm ^{3} compared to those with counts above 200 cells/mm ^{3}. Sileshi et al., (2013) similarly reported adjusted hazard ratio of 4.83 for those with counts less than 75 cells/mm ^{3} and Belayneh, Giday, & Lemma (2014) reported an odds of unfavourable outcome 6 times higher in patients with counts less than 200 cells/mm ^{3} .

2.5 Service related factors influencing treatment outcome

2.5.1 Anti-TB therapy and Antiretroviral Therapy

Treatment of TB is prioritized in people with HIV co-infection in order to halt transmission of TB. The 2014 guidelines recommend initiation of ART irrespective of CD4 cell count or as soon as possible; no later than 8 weeks of starting TB treatment. If TB diagnosis is made at a time where the patient is already on ART, adjustments may be made to ART regimen then anti TB treatment started as soon as possible. Co-trimoxazole preventive therapy (CPT) is also given to prevent the occurrence of other opportunistic infections (GHS & NACP, 2014).

A systematic review and meta-analysis of 6 randomized controlled trials and 21 cohort studies conducted by Khan et al., (2010) reported a significant association of ART during anti-TB treatment with lower rates of failure and relapse. Timing of initiation of ART is as important as giving ART to patients. Nassikas et al., (2015) found that early initiation of ART in EPTB patients with HIV reduced mortality among them. A multi-centre prospective study in Dar es Salaam, Tanzania also reported crude mortality risks among TB/HIV patients as follows: initiation of ART within 14 days after starting anti-TB treatment (1.4), initiation of ART more than 90 days prior to starting anti-TB treatment

(10.2), initiation of ART within 90 days after starting anti-TB treatment (10.3) and patients who were not on ART also had a crude mortality risk of 8.8 (Nagu, Aboud, Mwiru, Matee, Rao, Fawzi, Zumla, Maeurer & Magusi, 2017). Patients who were not given ART had adjusted hazard ratio of 4.83 (95% CI 1.98-11.78) and 3.21(95% CI 1.76-5.85) in two other studies (Ismail & Bulgiba, 2013; Sileshi et al., 2013) and Pimchan, et al., (2012) also reported relative risks of 0.04 and 0.03 of adverse outcome in patients initiating ART before TB treatment and patients initiating ART during TB treatment respectively.

2.5.2 Co-trimoxazole preventive therapy

Ambadekar et al., (2015) reported higher death rates among HIV co-infected patients who did not receive CPT and those who failed to start anti-TB treatment early, although findings were not statistically significant. Ali et al, (2016) and Pimchan et al., (2012) also reported results that indicate an increase in the risk of unfavourable outcome or death. The odds of dying was almost 4 times in patients who were not given CPT as compared to those who did otherwise during TB treatment (findings were statistically significant) (Agbor et al., 2014). Crude and adjusted hazards ratios reported by Sileshi et al., (2013) showed a threefold increase in risk of mortality for patients who were not given CPT during TB treatment.

2.6 Gaps in literature

Even though studies have reported that HIV increases the risk of adverse outcome of TB, there are a few gaps with respect to death as an outcome especially in Ghana. Questions regarding when patients are dying and what they have in common still need to be answered.

Some of the studies reviewed included paediatric patients in their studies and even compared their outcomes with that of adults. The flaw in their study design comes from the fact that it is difficult to diagnose TB in children since they cannot produce sputum for examination. Lack of bacterial confirmation in this case and even among adults in resource limited settings where more expensive diagnostic methods cannot be applied may lead to misdiagnosis. Also, the use of secondary data as observed from most of the studies poses issues of missing or incomplete data which sometimes affects the analysis of the data. The retrospective nature of the data collection also fails to explore other potential predictors of adverse outcome such as exposure to smoking and presence of other comorbidities such as diabetes. Prospective studies will have to be carried out to provide unquestionable diagnoses of TB among the study subjects and to explore other factors that influence outcome of treatment to bridge the gaps where retrospective studies fail. There is paucity of data in Ghana on the outcomes of TB treatment and the predictors of poor outcomes especially in non-teaching hospital settings. The purpose of this study is to investigate the factors that amount to the differences in treatment outcome of TB in people with and without HIV in the two selected hospitals. Results from this study will help in the design of future prospective studies to answer the questions that remain unanswered.

CHAPTER THREE
METHODS

3.1 Study design

A three-year retrospective cohort study was conducted in two hospitals in the Greater Accra Region of Ghana. A desk review of TB treatment cards and registers was carried out and relevant information pertaining to demographic and clinical characteristics recorded using a pre-tested data extraction tool.

3.2 Study location

The study included the La General Hospital and the Achimota Hospital in the Accra Metropolis. The Greater Accra Region (GAR) is one of the ten administrative regions of Ghana, and the region with the highest TB case notification rates (GHS, 2008). The region has six administrative districts: Accra Metropolis, Ga West, Ga East, Dangme East, Dangme West and Tema Municipality. La General Hospital and Achimota Hospital are located within the Accra Metropolis, being two out of four government hospitals in the district. The Accra Metropolis is the most densely populated part of the GAR with a population of about 1,665,086 as at 2010 (Ghana Statistical Service, 2014).

The La General Hospital and the Achimota Hospital both record about 70 to 110 TB cases yearly. They both have a DOTS centre for TB treatment and a general laboratory where bacterial confirmation of TB is carried out. These DOTS centres also offer HIV testing and counselling services.

3.3 Study Population

The study population included all TB patients who attended any of the two selected hospitals and were given anti-TB treatment.

3.4 Sample size determination

The minimum sample size was determined using the prevalence study formula

$$n = \frac{z^2 (pq)}{d^2}$$

Where z = value for confidence interval set at 1.96, d = margin of error set at 0.05, prevalence (p) of TB in Ghana, 2014 = 282/100,000 population

Hence, n = 432 (minimum sample size).

3.5 Inclusion Criteria

Folders of all TB patients 15 years and above who were given anti-TB treatment at any time from 1st January 2013 to 31st December 2015. The study period was restricted to the selected year period in order to achieve the minimum sample size. Patients who were registered from 2016 onwards were not included because of the possibility that some of them may still be undergoing treatment at the time of data collection.

3.6 Exclusion Criteria

Folders of patients who were transferred to other clinics to continue treatment were excluded from the study. Also folders with missing/incomplete data were excluded.

3.7 Variables

3.7.1 Dependent Variables

Treatment outcomes categorised into:

Successful outcome/treatment success: cured, treatment completed.

Adverse outcome: treatment failure, died and lost-to-follow up.

3.7.2 Independent Variables

Demographic and anthropometric characteristics: age, sex and weight.

Clinical characteristics:

TB type – smear positive pulmonary TB, smear negative pulmonary TB and extra pulmonary TB.

HIV status – HIV positive and HIV negative.

History of previous TB treatment – new patients, relapse patients, treatment after failure patients and treatment after lost-to-follow up patients.

Diagnostic and laboratory tests – sputum smear tests and chest x-ray.

Treatment – co-trimoxazole preventive therapy (CPT), anti-retroviral therapy (ART) and initiation time of anti – TB medication.

Other variable(s) – year of treatment and hospital.

Table 1: Description of variables

Category	Variable	Operational definition	Scale of measurement
Outcome	Successful outcome	Sum of patients cured and completed treatment	Categorical • Cured • Treatment completed
	Adverse outcome	Sum of patients who died, failed treatment or were lost-to-follow up	Categorical • Died • Treatment failed • Lost-to-follow up
	Death	Number of patients who died as a result of any cause during TB treatment.	Binary • Died • Survived
Independent	Sex	Sex of patient	Binary • Male • Female

	Age	Age ≥ 15 years at the time of initiation of TB treatment	Continuous
	Weight at baseline	Weight (kg) of patients at the initiation of treatment	Continuous
	HIV status	HIV serostatus of patient	Categorical • Positive • Negative • Unknown
	TB classification	The site of presentation of TB	Categorical • PTB+ • PTB – • EPTB
	Treatment history	New patients or patients on re-treatment	Categorical • New • Treatment after failure • Treatment after lost-to-follow up Binary • New • Retreatment
	CPT	CPT given to patient before or during TB treatment	Binary • Yes • No
	HAART	HAART given to patient before or during TB treatment	Binary • Yes • No
	Date of entry	Date of initiation of TB treatment	Numeric (interval)
	Date of exit	Date patient stopped taking TB treatment or date outcome was declared	Numeric (interval)

3.8 Pre-testing of tools

Pre-testing of tools was conducted at the Ridge Regional Hospital (another government hospital in the Accra Metropolis) using patient folders spanning the three-year period (2013 to 2015). This was done to ensure that the data extraction tool was complete and to identify

potential sources of errors in data collection. Pre-testing also served as training for the Research Assistants.

3.9 Data Extraction

Treatment cards of TB patients who were treated from January 1, 2013 to December 31, 2015 were collected and reviewed using a data extraction form (Appendix I). Information pertaining to socio-demographic, anthropometric and clinical characteristics were recorded in the form and then validated using the TB registers.

3.10 Data Quality Control

Two research assistants; one licensed pharmacist with experience in caring for TB and HIV patients and one nutritionist with extensive experience in data collection were recruited and trained on data collection processes involved in selecting relevant data from registers and patient folders. All data extraction forms were screened for consistency and correctness by the principal investigator daily and needed corrections were made the following day at the hospitals by cross checking from the registers or treatment cards. Data were validated, double checked to detect inconsistencies in Microsoft Excel and exported into STATA 14 for analysis. Data were also backed up with an external storage device.

3.11 Data Management and Analysis

Reviewing secondary data in the two hospitals over the three-year period yielded 542 observations out of which 4 records were found to be incomplete and hence excluded from the analysis. Also, 7 observations were transferred out to other hospitals to continue treatment and were excluded from the analysis. Observations containing missing values (9 in number) for variables such as duration of treatment, baseline weight and TB treatment

history were dropped from the analyses. One observation was dropped because it contained an outlier. The number of excluded observations formed less than 2% of the total number of observations, hence it was assumed that data were missing completely at random. A total of 521 observations were used in the analyses.

Frequency tables, cross tabulations and other descriptive analyses were used to study the data to identify missing information and remove observations containing outliers. Means and standard deviations were used to summarize continuous variables and proportions and frequencies were calculated for categorical variables. Chi square tests were used to determine the differences in proportions. Fisher's exact tests were used in place of Chi square when frequencies of variables were less than 5. Independent sample t-tests and ANOVA were used to test for differences in means. Multinomial logistic regression analysis was used to determine the impact of HIV positivity on treatment outcome among the patients. Successful treatment outcome (cured and treatment complete) was set as the base outcome and was the reference comparison with death as an outcome and treatment failure/lost-to-follow up.

Duration of survival was calculated from the date of initiation of TB treatment to the date of death or date patient discontinued treatment (as a result of lost-to-follow up) or date of last visit for patients who remained alive. The outcome of interest was death in the survival analysis and patients who were event free or were lost-to-follow up or remained living at the end of their treatment course were censored. Kaplan-Meier analysis was used to determine survivor function and plot survival curves. A Log-rank test was carried out to test for equality of survivor functions between the 2 groups (HIV positive and negative

patients). Cox proportional hazard regression model was used to determine the hazard ratio of death for each of the predictors. Crude associations were measured for variables that met the assumption of proportional hazards. The tests of proportional hazards assumption were conducted with the help of Schoenfeld's global test. The variable that represented the category of TB treatment did not fulfil the assumption of proportional hazards, hence, was excluded from the model. Also age in the HIV positive cohort did not meet the assumption of proportional hazards and was excluded in the model predicting deaths among TB/HIV co-infected patients. Variables that represented the category of TB history and uptake of HAART expressed multiple collinearity and hence were excluded from the model. Results were presented as bar graphs, survival curves and in tables as frequencies, percentages, crude and adjusted hazard ratios, 95 percent confidence intervals and p-values. All tests were two-tailed and statistical significance was set at 0.05.

3.12 Ethical Consideration

Ethical approval was obtained from the Ghana Health Service Ethics Review Committee and the University of Florida Institutional Review Board. Documented proof of ethical approval and an introductory letter from the School of Public Health, University of Ghana was delivered to the administrators or medical superintendents of the respective hospitals to seek for permission to carry out the study.

3.13 Privacy and Confidentiality

Data collected was handled as confidential. Names of patients were not recorded on the abstraction forms, rather patients' folder identification numbers were used for easy

identification in case corrections needed to be made. Data collected is only accessible to principal investigator and supervisor. The data will be destroyed after ten years.

3.14 Declaration of Conflict of Interest

The researcher has no conflict of interest to declare with respect to the study.

3.15 Funding

The study was funded by the NIH Fogarty International Centre through a partnership between the University of Ghana, College of Health Sciences and the University of Florida.

CHAPTER FOUR
RESULTS

4.1 Characteristics of study participants

A total of 521 observations were used in the analysis, 65.5 percent of whom were males. More than half were from the Achimota Hospital and 43.2 percent were from the La General Hospital. The ages of the patients ranged from 15 to 90 years with a mean and standard deviation of 41.3 ± 14.9 years. Those with HIV co-infection formed 20.0 percent of the population and those whose HIV status unknown (either indeterminate or status not tested) were 0.6 percent. Patients with unknown HIV status were not included in the subsequent analysis due to the nature of the research questions that were being answered. Almost two-thirds of the patients had smear positive pulmonary tuberculosis (65.1%) whilst smear negative pulmonary tuberculosis and extra pulmonary tuberculosis were 23.0 percent and 11 percent respectively. Table 2 shows the distribution of demographic and clinical characteristics between the two hospitals. The percentage distributions were similar across almost all the variables in both hospitals.

In Table 3, the distribution of demographic and clinical characteristics among HIV positive and negative patients is shown. The two cohorts had significant differences with respect to sex, type of TB and mean weight at baseline. There were more smear positive pulmonary TB patients in both cohorts and the mean baseline weight (48.88 ± 9.51 kg) of HIV positive patients was significantly lower than that of HIV negative individuals (52.73 ± 10.97). No statistical differences were observed between the two groups in the other variables; namely year, TB treatment history, hospital and age.

The mean age was about the same for both groups of patients and more than half of patients in each cohort came from the Achimota Hospital.

Table 2: Distribution of demographic and clinical characteristics of patients in La General and Achimota hospitals from 2013 to 2015.

Variable	Total N=521(%)	La General Hospital N=225 (%)	Achimota Hospital N=296 (%)
Year			
2013	188 (36.0)	72 (32.0)	116 (39.2)
2014	156 (29.9)	69 (30.7)	87 (29.4)
2015	177 (34.0)	84 (37.3)	93 (31.4)
Sex			
Male	341 (65.5)	146 (64.9)	195 (65.9)
Female	180 (34.5)	79 (35.1)	101 (34.1)
Age (years)			
Mean ± SD	41.30 ± 14.84	41.10 ± 14.24	41.45 ± 15.30
Weight at baseline (kg)			
Mean ± SD	52.91 ± 10.89	53.14 ± 11.80	52.73 ± 10.16
TB type			
PTB +	339 (65.1)	160 (71.1)	179 (60.5)
PTB -	120 (23.0)	35 (15.6)	85 (28.7)
EPTB	62 (11.9)	30 (13.3)	32 (10.8)
TB history			
New	500 (96.0)	211 (93.8)	289 (97.6)
Relapse	14 (2.7)	10 (4.4)	4 (1.4)
Treatment after failure	6 (1.1)	3 (1.3)	3 (1.0)
Treatment after LTFU	1 (0.2)	1 (0.4)	0 (0.0)
HIV status			
Positive	104 (20.0)	43 (19.1)	61 (20.6)
Negative	414 (79.4)	180 (80.0)	234 (79.1)
Unknown	3 (0.6)	2 (0.9)	1 (0.3)
Duration (days)			
Mean ± SD	166.43 ± 46.26	169.7 ± 45.9	163.4 ± 47.1

SD = standard deviation LTFU = lost-to-follow up EPTB= extra pulmonary TB

PTB + =smear positive pulmonary TB PTB – =smear negative pulmonary TB

Table 3: Distribution of demographic and clinical characteristics among HIV positive and negative patients.

Variable	HIV positive N=104 (%)	HIV negative N=414 (%)	p-value
Hospital			0.69$^{\infty}$
La General	43 (41.4)	180 (43.5)	
Achimota	61 (58.7)	234 (56.5)	
Year			0.57$^{\infty}$
2013	41 (39.4)	147 (35.5)	
2014	32 (30.8)	121 (29.2)	
2015	31 (29.8)	146 (35.3)	
Sex			<0.001$^{*\infty}$
Male	52 (50.0)	288 (69.6)	
Female	52 (50.0)	126 (30.4)	
Age (years)			0.78 $^{\alpha}$
Mean ± SD	41.66 ± 10.73	41.20 ± 15.71	
Baseline weight (kg)			
Mean ± SD	48.88 ± 9.51	53.94 ± 10.97	<0.001$^{*\alpha}$
30-39	15 (14.4)	22 (5.3)	<0.001$^{*\Omega}$
40-54	64 (61.5)	214 (51.7)	
55-70	24 (23.1)	146 (35.3)	
>70	1 (1.0)	32 (7.78)	
TB type			<0.001$^{*\infty}$
PTB+	46 (44.2)	292 (70.5)	
PTB –	43 (41.4)	76 (18.4)	
EPTB	15 (14.4)	46 (11.1)	
History			0.89$^{\Omega}$
New	101 (97.1)	396 (95.7)	
Relapse	2 (1.9)	12 (2.9)	
Treatment after failure	1 (1.0)	5 (1.2)	
Treatment after LTFU	0 (0.0)	1 (0.2)	
CPT			
Yes	91 (87.5)		
No	13 (12.5)		
ART			
Yes	4 (3.9)		
No	100 (96.1)		

SD= standard deviation ∞ = p-values derived from chi square tests *=Statistical significance

Ω = p-values derived from fisher's exact α = p-values derived form t-tests CPT=co-trimoxazole preventive therapy

ART=anti-retroviral therapy EPTB = extra pulmonary TB PTB + =smear positive pulmonary TB

PTB – =smear negative pulmonary TB

4.2 Outcomes TB treatment in HIV positive and negative patients

HIV positive patients had a treatment success rate of 77.0 percent compared to 91.3 percent in HIV negative patients and a case fatality rate of 22 percent compared to 5.3 percent in HIV negative patients. All ten patients who were lost-to-follow up were HIV negative TB patients. Table 4 shows the treatment outcomes for all patients, HIV positive and negative TB patients

In Table 5 Significant differences were observed in the treatment outcomes with respect to HIV status, mean baseline weight and the hospital the patient received treatment. The table presents the associations between treatment outcomes and demographic and clinical characteristics of the patients.

Table 4: Outcomes of TB treatment among HIV positive and negative patients.

Outcome	All patients N=518 (%)	HIV positive N=104 (%)	HIV negative N=414 (%)
Successful outcome	458 (88.4)	80 (77.0)	378 (91.3)
Cured	296 (57.1)	34 (32.7)	262 (63.3)
Treatment completed	162 (31.3)	46 (44.2)	116 (28.0)
Died	45 (8.7)	23 (22.1)	22 (5.3)
Treatment failed	5 (1.0)	1(1.0)	4 (1.0)
Lost-to-follow up	10(1.9)	0(0.0)	10 (2.4)

Successful Outcome = cured + treatment completed

Table 5: Treatment outcomes by and demographic and clinical profiles of TB patients.

	Treatment Outcome of TB among patients			
	Treatment Success N (%)	**Died N (%)**	**Treatment failure/LTFU N (%)**	**p-value**
Age (years)				0.11$^{\alpha}$
Mean ± SD	40.93 ±15.07	45.64 ± 11.85	39.4 ± 14.3	
Baseline weight (kg)				<0.01$^{\alpha*}$
Mean ± SD	53.44 ± 10.79	48.06 ± 10.89	51.94 ± 10.5	
Sex				0.97$^{\infty}$
Male	301 (88.5)	29 (8.5)	10 (2.9)	
Female	157 (88.2)	16 (9.0)	5 (2.8)	
Hospital				<0.01$^{*\Omega}$
La General	199 (89.2)	12 (5.4)	12 (5.4)	
Achimota	259 (87.8)	33 (11.2)	3 (1.0)	
Year				0.17$^{\Omega}$
2013	172 (91.5)	14 (7.4)	2 (1.1)	
2014	136 (88.9)	13 (8.5)	4 (2.6)	
2015	150 (84.8)	18 (10.2)	9 (5.1)	
TB type				0.82$^{\Omega}$
PTB +	297 (87.9)	29 (8.6)	12 (3.6)	
PTB –	105 (88.2)	12 (10.0)	2 (1.7)	
EPTB	56 (91.8)	4 (6.6)	1 (1.6)	
Treatment category				0.12$^{\Omega}$
New	442 (88.8)	43 (8.6)	13 (2.6)	
Retreatment	16 (80.0)	2 (10.0)	2 (10.0)	
HIV status				<0.001$^{*\Omega}$
Positive	80 (76.9)	23 (22.1)	1 (0.96)	
Negative	378 (91.3)	22 (5.3)	14 (3.4)	

*= Statistical significance SD= Standard deviation LTFU= lost-to-follow up

PTB+ =smear positive pulmonary TB PTB – =smear negative pulmonary TB EPTB= extra pulmonary TB

α=derived from ANOVA tests Ω = derived from fisher's exact tests ∞ = derived from chi square tests

In the unadjusted multinomial regression analysis illustrated in Table 6 HIV status and baseline weight were significantly associated with death. Being HIV positive increased the risk of death relative to successful treatment by a factor of 4.92. Also, if a patient's weight increased by one unit (kg), the risk of death relative to treatment success would be expected to decrease by a factor of 0.95. Being treated at the Achimota Hospital had a significant increase in the relative risk of death compared to treatment success and a decreased relative risk of treatment failure or lost-to-follow up compared to treatment success.

The magnitude and direction of the associations between treatment outcome and HIV status, baseline weight and the hospital of treatment were similar in the adjusted model as shown in Table 7.

Figure 2 shows the trend of treatment success over the years under review for all TB patients, TB/HIV co-infected patients and HIV negative patients. The proportions decrease from 2013 to 2015 for all the three categories of patients with HIV positive patients recording the lowest (80.5%, 75.0% and 74.2%) and HIV negative patients having the highest throughout the three years.

The proportions of patients who died in each of the years under review are presented in Figure 3 with comparisons among the total population, HIV positive and negative patients. HIV positive patients recorded the highest proportion of deaths in each of the 3 years and HIV negative patients recorded the lowest. The percentages increased with each year (2013 to 2015) for all the three categories of patients.

Table 6: Unadjusted multinomial logistic regression for factors associated wih TB treatment outcome.

Unadjusted Relative Risk of treatment outcomes of TB patients				
	Died	**p-value**	**Treatment failure/LTFU**	**p-value**
	uRR (95% CI)		**uRR (95% CI)**	
Age (years)	1.02 (1.0-1.04)	0.04	0.99 (0.96-1.03)	0.69
Baseline weight (kg)	0.95 (0.91-0.98)	<0.01*	0.99 (0.94-1.4)	0.60
Sex		0.86		0.94
Male	1		1	
Female	1.06 (0.56-2.0)		0.96 (0.32-2.85)	
Hospital		0.03*		0.01*
La General	1		1	
Achimota	2.11 (1.06-4.20)		0.19 (0.05-0.69)	
Year		0.30		0.03*
2013	1		1	
2014	1.17 (0.53-2.58)		2.53 (0.46-14.01)	
2015	1.47 (0.71-3.07)		5.16 (1.10-24.26)	
TB type		0.79		0.27
PTB +	1		1	
PTB –	1.17 (0.58-2.38)		0.47 (0.10-2.14)	
EPTB	0.73 (0.25-2.16)		0.44 (0.06-3.47)	
Treatment category		0.74		0.07
New	1		1	
Retreatment	1.28 (0.29-5.78)		4.25 (0.88-20.43)	
HIV status		<0.001*		0.30
Negative	1		1	
Positive	4.94 (2.62-9.30)		0.34 (0.04-2.60)	

Base outcome = Successful treatment | uRR = unadjusted relative risk | CI= confidence interval

LTFU= lost-to-follow up | Ref= Reference variable | *= Statistical significance

PTB+ =smear positive pulmonary TB | PTB – =smear negative pulmonary TB | EPTB= extra pulmonary TB

Table 7: Multivariate multinomial logistic regression for factors associated wih TB treatment outcome.

	Adjusted Relative Risk of treatment outcomes of TB patients			
	Died	**p-value**	**Treatment failure/LTFU**	**p-value**
	aRR (95percentCI)		**aRR (95percentCI)**	
Age (years)	1.02 (1.01-1.05)	0.04*	0.99 (0.96-1.03)	0.64
Baseline weight (kg)	0.95 (0.92-0.99)	0.02*	0.99 (0.94-1.04)	0.63
Sex		0.27		0.93
Male (Ref)	1		1	
Female	0.66 (0.32-1.38)		1.05 (0.32-3.43)	
Hospital		0.01*		0.02*
La General (Ref)	1		1	
Achimota	2.57 (1.23-5.37)		0.21 (0.06-0.78)	
Year		0.20		0.10
2013 (Ref)	1		1	
2014	1.18 (0.51-2.73)		2.4 (0.41-14.1)	
2015	1.63 (0.74-3.59)		4.71 (0.97-22.78)	
TB type		0.22		0.61
PTB + (Ref)	1		1	
PTB –	0.63 (0.28-1.42)		0.85 (0.17-4.32)	
EPTB	0.57 (0.18-1.84)		0.58 (0.07-5.03)	
Treatment category		0.41		0.16
New (Ref)	1		1	
Retreatment	1.96 (0.4-9.55)		3.34 (0.62-17.96)	
HIV status		<0.001*		0.34
Negative (Ref)	1		1	
Positive	5.85 (2.83-12.09)		0.36 (0.04-2.98)	

Base outcome = Successful treatment aRR = unadjusted relative risk CI= confidence interval

LTFU= lost-to-follow up Ref= Reference variable *= Statistical significance

PTB+ =smear positive pulmonary TB PTB – =smear negative pulmonary TB EPTB= extra pulmonary TB

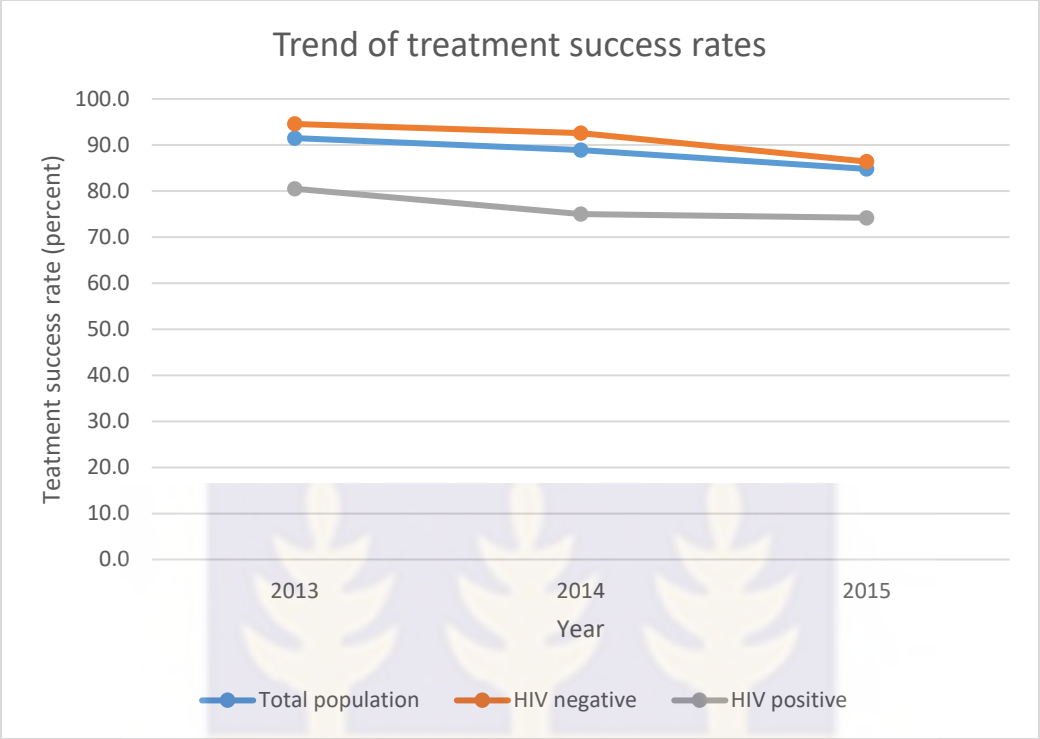


Figure 2: Trend of treatment success rates from 2013 to 2015

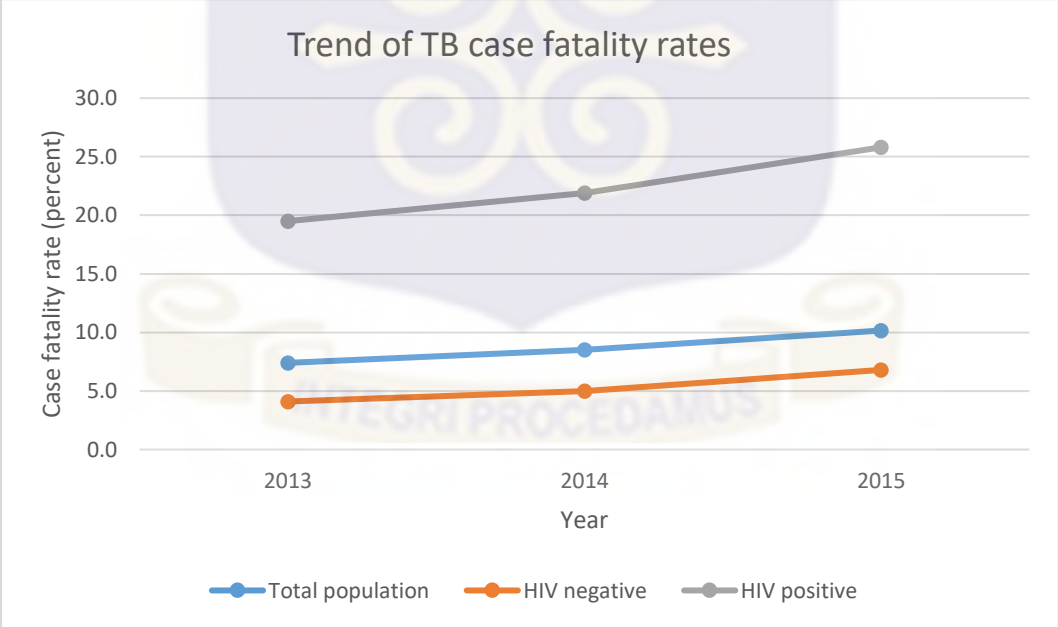


Figure 3: Trend of case fatality rates from 2013 to 2015

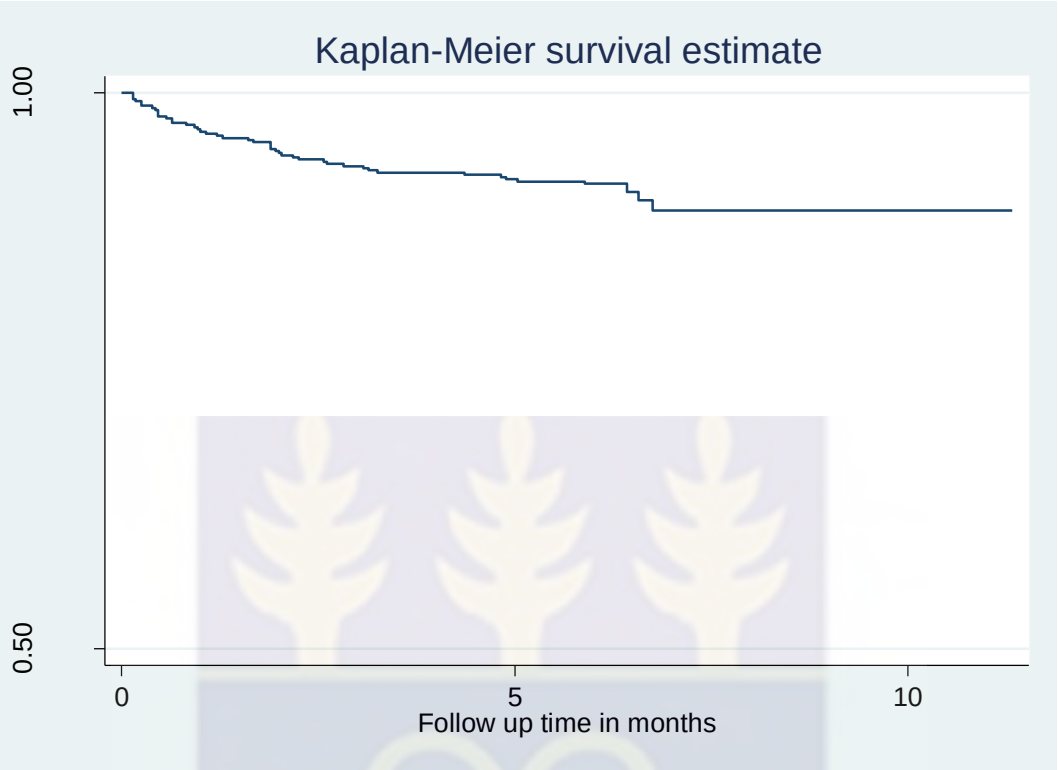


Figure 4: Survival curve of all TB patients

4.3 Survival of HIV positive and HIV negative on TB treatment

The total analysis time contributed by the 518 patients was 86,212 person days. Those with HIV co-infection contributed 16,171 person days (577.54 person months) and HIV negative patients also contributed 70,041 person days (2,501.46 person months). The probability of survival at the end of the analysis time among all TB patients was 89.4 percent. The overall probability of survival for HIV infected and uninfected TB patients were 0.73 and 0.93 respectively (log rank test =29.49, p-value<0.001). After adjusting for baseline weight the cumulative survival declined to 0.10 for HIV positive individuals and 0.61 for HIV negative individuals. Similarly, adjusting for age reduced the cumulative

survival to 0.62 and 0.99 for HIV positive and negative individuals respectively. Adjusting for other variables such as sex, TB type and TB history had no significant effects on the unadjusted curves of the two groups.

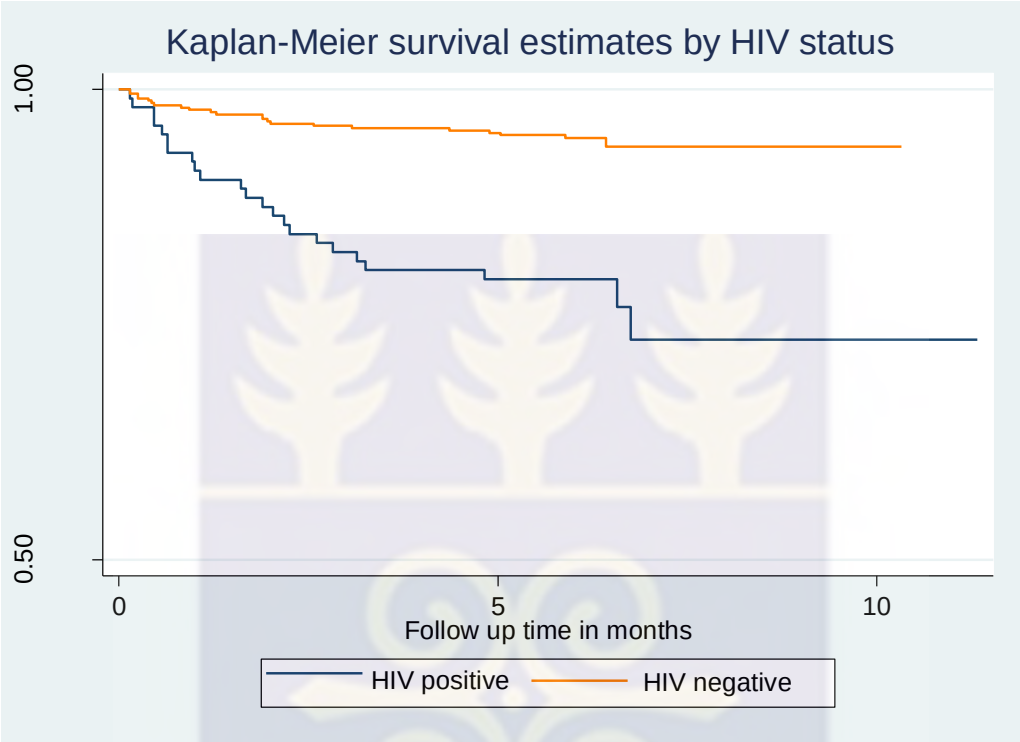


Figure 5: Survival curves of HIV positive and HIV negative patients

The incidence rate (IR) of mortality in the study population was 15 deaths per 1000 person month observations; 40 per 1000 person month observations and 9 per 1000 person month observations in the exposed (HIV positive) and unexposed (HIV negative) respectively. The risk of death was almost 5 times greater among HIV positive patients than in HIV negative patients (risk ratio 4.53 95% CI 2.41-8.52). About three quarters of deaths in HIV positive patients were attributable to HIV infection (AR%= 77.9% 95% CI 58.5 -88.3) and the attributable risk in the reference population was 39.8 percent.

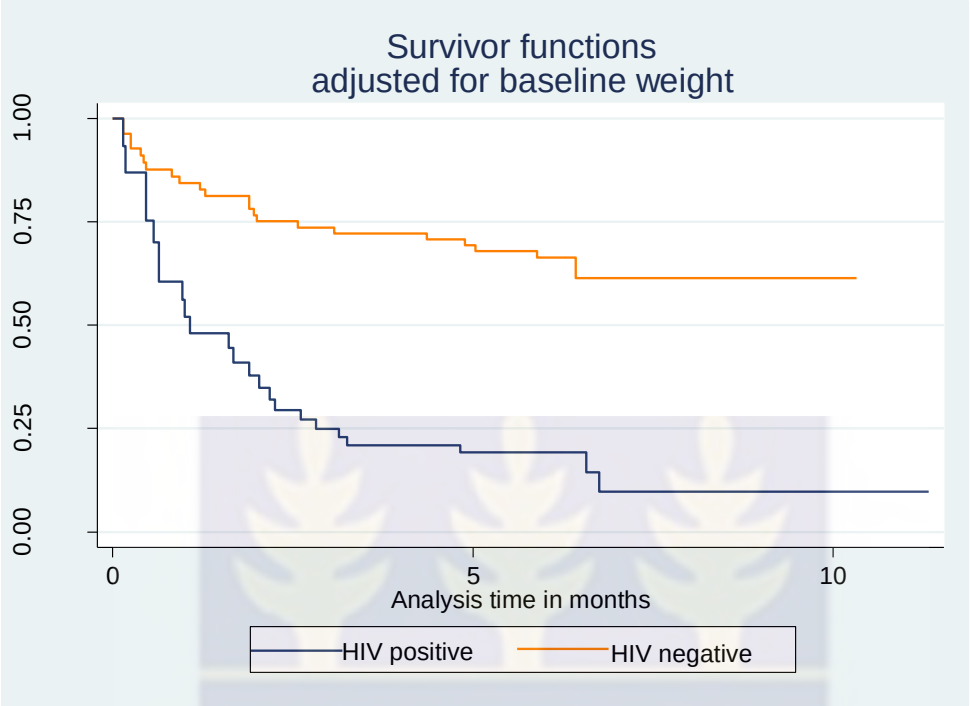


Figure 6: Survival curve of HIV positive and HIV negative patients adjusted for weight at baseline.

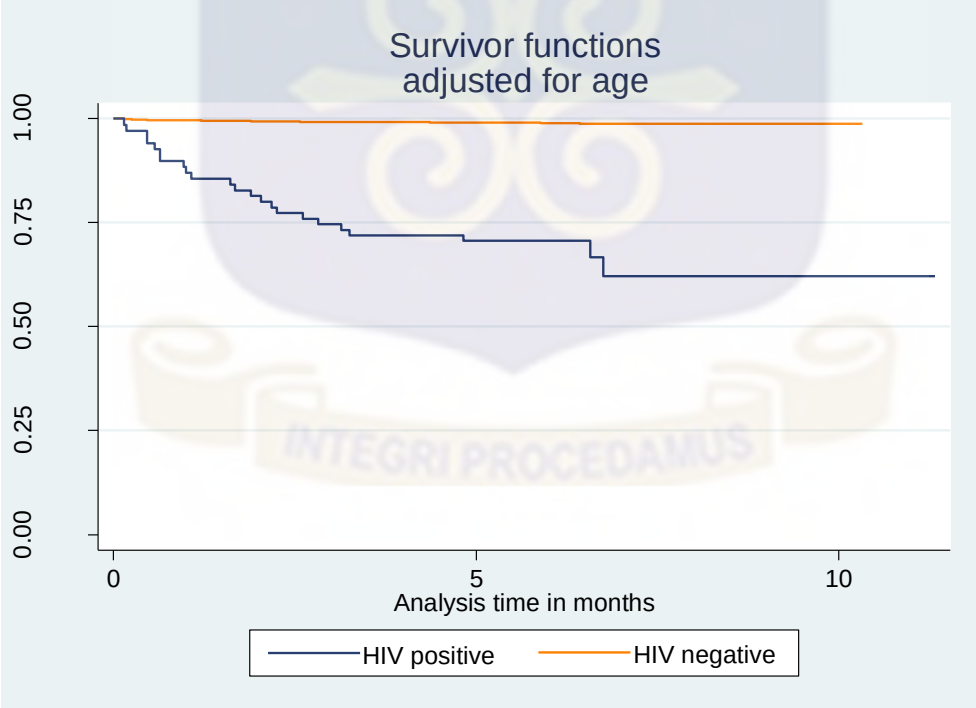


Figure 7: Survival curve of HIV positive and HIV negative patients adjusted for age

***Table 8*: Cox-proportional hazard regression predicting mortality among all TB patients.**

Mortality among TB patients				
Variable	**Crude HR (95% CI)**	**p-value**	**Adjusted HR (95% CI)**	**p-value**
Age (years)	1.02 (1.01-1.04)	0.04*	1.02 (1.00-1.04)	0.05
Baseline weight (kg)	0.95 (0.92-0.98)	<0.01*	0.96 (0.92-0.99)	0.01*
Sex		0.80		0.32
Male	1		1	
Female	1.08 (0.59-1.99)		0.73 (0.38-1.43)	
HIV status		<0.001*		<0.001*
Negative	1		1	
Positive	4.40 (2.45-7.89)		4.52 (2.40-8.51)	
Hospital		0.03*		0.03*
La General	1		1	
Achimota	2.09 (1.08-4.05)		2.30 (1.18-4.50)	
TB type		0.61		0.44
PTB+	1		1	
PTB –	1.21 (0.62-2.37)		0.69 (0.33-1.40)	
EPTB	0.68 (0.24-1.95)		0.60 (0.22-1.74)	
Year		0.63		0.42
2013	1		1	
2014	1.18 (0.55-2.51)		1.16 (0.54-2.50)	
2015	1.41 (0.70-2.83)		1.59 (0.78-3.24)	

HR= Hazard ratio Ref= Reference variable *= Statistical significance

PTB+ =smear positive pulmonary TB PTB – =smear negative pulmonary TB EPTB= extra pulmonary TB

CI= confidence interval

4.4 Predictors of mortality among all patients on TB treatment.

Hospital, baseline weight and HIV status were statistically significant predictors of mortality and no real evidence of confounding was observed on the associations by these variables and the other variables. The risk of death was decreased by 5 percent for every unit increase in baseline weight and being HIV positive was associated with 4.52 increased risk of mortality given other variables in the model are held constant. Patients from the Achimota Hospital also had an increased risk of mortality (2.30, 95% CI 1.18-4.50) compared to those in the La General Hospital in the adjusted estimates.

4.5 Factors associated with mortality among TB/HIV co-infected patients.

All other variables but CPT failed to show significant associations with the risk of dying among patients with TB/HIV co-infection. Uptake of CPT remained the only variable with significant associations in both crude and adjusted estimates.

4.6 Summary of key findings

1) A small proportion (3.9%) of TB/HIV co-infected patients were given ART during the course of anti-TB treatment.
2) TB patients who were HIV negative had a higher rate of treatment success and a lower rate of case fatality compared to TB patients who were HIV positive.
3) HIV infection increased the risk of death relative to successful treatment by a factor of 4.92.
4) Baseline weight decreased the relative risk of dying relative to treatment success by 5 percent for every unit (kg) increase in baseline weight.

5) Being treated at the Achimota Hospital had a significant increase in the relative risk of death compared to treatment success and a decreased relative risk of treatment failure or lost-to-follow up compared to treatment success.
6) The probability of survival among HIV positive patients was significantly lower compared to HIV negative patients.
7) The hazard ratio of mortality among TB/HIV co-infected patients who did not receive CPT during treatment was 3.65.
8) Hospital, baseline weight and HIV status were significant predictors of mortality.

Table 9: Cox-proportional hazard model predicting mortality among TB/HIV co-infected patients.

Mortality among TB/HIV co-infected patients				
Variable	**Crude HR (95% CI)**	**p-value**	**Adjusted HR (95%CI)**	**p-value**
Baseline weight (kg)	0.96 (0.91-1.0)	0.09	0.95 (0.89-1.01)	0.10
Sex				
Male	1	0.50	1	0.42
Female	0.75(0.33-1.72)		0.67 (0.26-1.77)	
CPT		0.02*		0.01*
Yes	1		1	
No	4.18 (1.7-10.21)		3.65 (1.35-9.85)	
TB type		0.90		0.71
PTB+	1		1	
PTB –	1.13(0.47-2.73)		1.07 (0.43-2.64)	
EPTB	0.85(0.23-3.10)		0.61 (0.16-2.33)	
Year		0.81		0.75
2013	1		1	
2014	1.13 (0.41-3.11)		0.85 (0.30-2.44)	
2015	1.38 (0.52-3.68)		1.26 (0.46-3.46)	
Hospital		0.51		0.80
La General	1		1	
Achimota	1.34 (0.57-3.16)		1.13 (0.45-2.82)	

HR= Hazard ratio *= Statistical significance CI= confidence interval

PTB+ =smear positive pulmonary TB PTB – =smear negative pulmonary TB EPTB= extra pulmonary TB

CHAPTER FIVE
DISCUSSION

The purpose of the study was to investigate the outcomes of TB treatment among HIV positive and negative patients in two hospitals in the Accra Metropolis. The number of records used in the analysis was 521 of which 65 percent were males. This is not surprising as it has been documented that more men than women are infected with TB. More than half of about 40,000 TB incident cases recorded in Ghana in the year 2015 were males. Some studies have attributed this phenomenon to smoking which is more common in men than in women (Elmadhoun et al., 2016), others suggest that men are biologically more vulnerable to active TB disease (Neyrolles & Quintana-Murci, 2009) and still other reports say it is difficult to diagnose TB in women (Begum, Colombani, Gupta, Salim, Hussain, Pietroni, Rahman, Pahan & Borgdorff, 2001). Infection rates are however, higher in women in a few countries including Afghanistan, Pakistan and Iran (WHO, 2014b).

The commonest form of TB recorded in the study was pulmonary TB (88%) which is similar to 92 percent for the country in 2015 (WHO, 2016b). Almost all (96%) patients were classified as new cases and the remaining 4 percent consisted of retreatment cases (relapse, treatment after failure and treatment after lost-to-follow up). This observation may be explained by the fact that treatment failure and LTFU as outcomes of treatment are generally very low, hence the low percentage of retreatment cases in the study.

About 99 percent of the patients knew their HIV status. Two out of the remaining 3 patients who did not know their status had not tested and one had indeterminate results after testing. The prevalence of HIV among the study population was 20 percent, conforming to the

national prevalence of TB/HIV co-infection of 22 percent and 24 percent in 2015 and 2014 respectively. Out of the 104 TB/HIV co-infected patients in this study, 87.5 percent were given CPT which exceeds the 67 percent coverage at the national level in 2014 and 74 percent in 2013. On the other hand, only 3.9 percent were given ART. Although the trend of ART coverage has decreased, (42% in 2013, 39% in 2014 and less than 25% in 2015) the estimates still far exceed what is observed in this study. The difference observed in ART coverage may be attributed to institutional differences and the fact that patients were made to complete anti-TB treatment before starting ART in the years under review in the two hospitals. This was because of the fear of possible Immune reconstitution inflammatory syndrome (IRIS) which is defined in the Guidelines for clinical management of TB and HIV co-infection in Ghana as:

> *A temporary exacerbation of symptoms, signs and/or radiographic manifestations of TB after beginning anti-HIV treatment. This paradoxical reaction in HIV-infected patients with TB is thought to be a result of immune reconstitution. This occurs as a result of reactivation of the dormant immune system after commencement of HAART especially within the 1st six weeks of treatment when TB is disseminated and CD4 cell counts are low*. (GHS, 2007)

Also the concern about the occurrence of side effects on both treatments discouraged health personnel from giving both at the same time. Patients with HIV infection who were already on ART were encouraged to take anti-TB treatment alongside their ART regimen.

The occurrence of smear positive and smear negative pulmonary TB among those in the HIV positive cohort was almost equally distributed, contrary to what was reported by (Gebremariam et al., 2016; Gebrezgabiher et al., 2016; Shaweno & Worku, 2012) where the prevalence of smear negative pulmonary TB was highest compared to the other types of TB presentation.

The trend of successful outcome and mortality among the study population in 2013, 2014 and 2015 were quite similar to that recorded at the national level. The study population failed to meet the WHO target of not less than 90 percent treatment success rate in 2014 and 2015. On the other hand, case fatality estimates in the study population were slightly lower in 2013 and 2014 (7.4 and 8.5 respectively) and higher in 2015 (10.2) compared to the national estimate of 10 percent. Treatment success rates among TB/HIV co-infected patients were also similar to national rates except in the year 2013 where 80.5 percent was recorded among the study population and that for the country was 73 percent.

Successful treatment outcome among HIV positive patients in this study was not very different from what was reported by Pimchan et al., (2012) which was 70.4 percent. Overall treatment success in HIV positive cohort was 77 percent and was significantly lower than that in the HIV negative cohort (91.3%). Consequently, mortality was 22.1 percent among the TB/HIV patients, significantly higher than 5.3 percent in HIV negative patients. These observations underscore the disproportionate burden people with TB/HIV co-infection bear with respect to prognosis of TB treatment.

In the multinomial logistic regression, adjusting for age, baseline weight, year, hospital, sex, TB type and treatment category, the impacts of HIV positive status on the outcome of treatment were similar to the estimates in the unadjusted analysis. A significant increase in the relative risk of death to treatment success was observed among HIV positive patients compared to those without HIV infection.

On the other hand, the relative risk of treatment failure/LTFU to treatment success was rather decreased among TB/HIV co-infected patients compared to HIV negative individuals and the association was not statistically significant. This further implicates the influence of HIV infection on the outcome of TB treatment especially death relative to successful treatment.

In India, cure rates in TB/HIV co-infected patients were significantly reduced (Ambadekar et al., 2015) and a 7 fold increase in the odds of death was reported among HIV infected TB patients in Ethiopia (Gebremariam et al., 2016). A similar odds ratio was also reported in another study where significant differences were not observed in the outcome of treatment among HIV positive and negative patients. The authors explained that HIV testing was done anonymously and results were not revealed to patients, thereby avoiding depression and indifference that could have affected compliance to TB treatment among those with HIV infection (El-Sony et al., 2002).

The incidence rate of mortality in this study population was 15 deaths per 1000 person months, and that of the exposed (HIV positive) and unexposed (HIV negative) were about 40 per 1000 person months and 9 per 1000 person months respectively. The incidence rate ratio was 4.53 and more than 70 percent of deaths among those with TB/HIV co-infection could have been prevented had it not been for HIV infection. These findings are internally consistent with earlier reports in this study about significantly greater proportion of deaths occurring in those with HIV infection. An earlier study in Ethiopia agreed with these findings: among HIV positive patients, the incidence rate of mortality was 20.6 per 1000 person months, risk ratio was 2, attributable risk was about 50 percent whereas an incidence

rate of mortality of 10.8 per 1000 person months was observed among HIV negative patients (Shaweno & Worku, 2012).

The mean duration of treatment was 155.5 days for the HIV positive cohort as compared to 169.2 in the HIV negative cohort. Most studies agree that majority of deaths occur in the first few weeks of treatment. Probability of survival among patients with HIV comorbidity at the second and sixth months were 87.5 percent and 79.8 percent respectively; similar to 90.7 percent and 82.8 percent reported by Ismail & Bulgiba (2013). Among the HIV positive cohort, Jacobson, Moll, Friedland, & Shenoi (2015) reported 27.5 percent of deaths occurring within 2 weeks of starting TB treament, Ismail & Bulgiba (2013) reported 40 percent in the first 2 months and this study reports 68.9 percent by the end of the first two months of treatment. It may be that those who die in the first few weeks of treatment report to the hospitals late and when the disease is far advanced. The causes of delay may be due to fear of stigmatisation and self-medication. The probability of survival at the end of the analysis time among the total sample of patients in this study was 89.4 percent. Plotting the curves separately according to HIV status showed that those with concomitant HIV infection had a lower probability of survival, confirming documented evidence that being HIV positive increases one's risk of mortality during TB treatment.

After adjusting for baseline weight for the cohorts under study the survival probability declined to 0.36 for HIV positive individuals and 0.78 for HIV negative individuals. Baseline weight as a predictor of mortality in the cox proportional hazards model was associated with a 5 percent decrease in the risk of mortality for every kilogram increase in weight. Similar findings were reported by Ismail & Bulgiba (2013) where a 3 percent

reduction in risk of death was observed for every kilogram increase in weight in Malaysia, although the association was not significant. Shaweno & Worku (2012) also reported an adjusted hazard ratio of 0.94 (95% CI 0.92-0.97) for a kilogram increase in weight. Study participants weighing 30-39 kg in an Ethiopian University Hospital were found to have an odds of unsuccessful outcome of 1.5 (95% CI 1.1-2.1) (Biruk et al., 2016). The association between baseline weight and survival in this study may be explained by the difference in mean baseline weight between the two groups where that of HIV positive cohort was significantly lower than the mean baseline weight of TB patients without HIV infection. Even though body mass indices were not calculated in this study due to a lot of missing data on height, it may be reasonable to assume that a considerable number of HIV positive patients were underweight or undernourished since 14.4 percent of them had baseline weight less than 40 kg as compared to 5.3 percent in the HIV negative group.

Older age has been reported to be associated with deaths or adverse outcomes during TB treatment (Elmadhoun et al., 2016; Kanungo et al., 2015). The risk of mortality among all TB patients increased by 1.02 for every unit increase in age in this study. Sileshi, Deyessa, Girma, Melese, & Suarez (2013) reported a stronger association; crude hazard ratio of 2.58, (95% CI 1.34-4.92) for those aged 45 years or more compared to 15 to 24 years. A study in Brazil reported an increase in odds of deaths due to TB and deaths due to other causes in people 40 years or older (do Prado et al., 2017). A decline in immune function and occurrence of comorbidities in older age may explain the increase risk of mortality (Rodriguez-Penney et al., 2013).

The adjusted hazard ratio for females compared to males in the total study population was 0.71 although not statistically significant. Likewise, two other studies found reduced hazard and odds ratios for TB/HIV co-infected women and women on TB treatment regardless of their HIV status, although not significant (Ali et al., 2016; Sileshi et al., 2013). Gadoev, Asadov, Tillashaykhov, & Tayler-smith (2015) and Jacobson et al. (2015) also found significant associations where males had higher odds of mortality among TB/HIV co-infected patients, similar to reports by (Gebremariam et al., 2016).

Subjects of this study presenting with extra pulmonary TB had a reduced risk of mortality (insignificant association) compared to those with pulmonary TB. Significant associations were reported by Gadoev et al. (2015), where extra pulmonary TB patients had a 30 percent reduced odds of dying compared to smear positive pulmonary TB (adjusted OR= 0.7 95% CI 0.6 – 0.8). Findings by Ambadekar et al., (2015), Elmadhoun et al., (2016) and Shaweno & Worku (2012) all agree with this association. Meanwhile, other studies in Ethiopia report that extra pulmonary TB patients had higher probabilities of dying or adverse outcomes in their studies compared to patients with pulmonary TB (Biruk et al., 2016; Gebremariam et al., 2016; Gebrezgabiher et al., 2016). The low prevalence of extra pulmonary TB might have contributed to the findings in this study.

Sileshi et al., (2013) in their study on predictors of mortality among TB/HIV co-infected patients reported a significant increase in the risk of mortality (adjusted HR=3.15 95% CI 1.95-5.11) among patients who were not given CPT during treatment. They also found that patients on ART had a hazard ratio of 0.35 (95% CI 0.19-0.64). Likewise, HIV patients in this study who were not given CPT during treatment had a hazard ratio of 4.18 (95% CI

1.71-10.21). This report is also consistent with that of a study conducted in Cameroun by Agbor et al., (2014). Additionally, according to Ali et al, (2016) and Pimchan et al., (2012) patients who do not take CPT have an increased risk of death or adverse outcome.

The risk of mortality associated with the intake of ART could not be estimated in this study because the number that was recorded to have been given ART was very low (3.9%) and hence could not be included in the analysis. The low uptake of ART during TB treatment likely contributed to the higher mortality among the HIV co-infected patients since several studies show that integrated therapy has significant survival benefit (Abdool Karim et al., 2011; Blanc et al., 2011; Havlir et al., 2011).

Limitations of study

The retrospective design of the study posed some challenges with respect to the information gathered. Missing data on some variables made it impossible to test their associations with the outcomes. Also, information on CD4 cell counts, drug adherence, co-morbidities and some socio-demographic variables that could have been confounders or independent predictors could not be taken.

The research team had to fill in data on the date treatment ended for some observations by counting the number of days from the start of treatment using the check boxes for DOTS. This may have introduced some error in calculating the duration of treatment for some of the patients.

CHAPTER SIX
CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusion

Positive HIV status had a significant increase in the risk of death relative to successful treatment compared to HIV negative status. Survival of HIV positive individuals was significantly lower than that among HIV negative patients during TB treatment. More than 60 percent of deaths among all TB patients occurred in the first two months of TB treatment. HIV status, intake of co-trimoxazole preventive therapy and weight at baseline were independent predictors of mortality. These results suggest that interventions focussed on improving the outcomes of TB patients with low body weight and HIV infection could reduce TB mortality in our settings.

6.2 Recommendations

The following recommendations can be considered in improving TB treatment outcomes and reduce case fatality rates:

Health workers and institutional coordinators

- Should link patients with TB/HIV co-infection to ART programs to start treatment within 2 to 8 weeks as indicated in the guidelines for clinical management of TB.
- Should ensure that all TB/HIV patients receive CPT in the early stages of TB treatment.
- Should link patients with low body weight to nutrition counselling and/or support to improve their nutritional status as early as possible.

Future Research

- Prospective studies can be conducted in future to assess the impact of other factors that may have associations on TB treatment outcome but could not be explored in this study as a result of the retrospective nature of the study design.

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APPENDICES

APPENDIX I: Data Extraction Form

Treatment outcome of tuberculosis in HIV positive and negative patients in selected hospitals in the Accra Metropolis.

Record code: _____ ID Number: _____

Year: _____ Hospital: _____

Section 1: Demographic characteristics

1) Sex: ❒ 0-Male ❒ 1-Female

2) Age (years): _____

3) Residence: _____

4) Occupation: _____

4) Treatment Supporter: ❒ 0 Yes ❒ 1 No

Section 2: Clinical characteristics			
5)	TB type	0-PTB (smear positive) 1-PTB (smear negative) 2-EPTB	
6)	Site of EPTB or type of EPTB	……..	
7)	History of TB treatment	0-New 1-Relapse 2- Treatment after failure 3-Treatment after lost-to-follow up 4- Transfer In. 5- Unknown 6- Other (specify)……...	
8)	HIV status	0-Positive 1-Negative	

		2-Unknown	
9)	Chest X-ray	0-Suggestive 1-Not done	
If negative or unknown go to (14)			
9)	Date of HIV clinic registration	…….	
10)	Co-trimoxazole preventive therapy (CPT)	0-Yes 1-No	
11)	CPT start date	……..	
12)	HAART	0-Yes 1-No	
13)	HAART start date	…….	
14)	Category of TB treatment	0-First line 1-Second line	
Weight at:			
16)	Baseline	…… kg	
17)	End of initial phase (month 2 or 3 if 2nd line treatment)	…… kg	
18)	End of continuation phase (month 6 or 8 if 2nd line treatment)	…….. kg	
19)	Height in meters	……m	
Sputum smear results (if applicable)			
20)	Month two	1-Positive 2-Negative	

		3- Unknown	
21)	Month three	1-Positive 2-Negative 3- Unknown	
22)	Month five	1-Positive 2-Negative 3- Unknown	
23)	Month six	1-Positive 2-Negative 3- Unknown	
24)	Month eight	1-Positive 2-Negative 3- Unknown	
	Days directly observed or days drug taken	**Days drug not taken**	
Month 1			
Month 2			
Month 3			
Month 4			
Month 5			
Month 6			
Month 7			
Month 8			

Month 9			
25)	**HRZE(S) Dose Schedule**	**HR(E) Dose Schedule**	
	(1) 2 Tablets Daily (2) 3 Tablets Daily (3) 4 Tablets Daily	(1) 2 Tablets Daily (2) 3 Tablets Daily (3) 4 Tablets Daily	
26)	Treatment outcome	1-Cured 2-Treatment completed 3-Died 4-Lost-to-follow up 5-Treatment failed 6-Not evaluated 7-Transfer out	
27)	Category of treatment outcome	0-Succesful outcome 1-Adverse outcome 2-Transfer/not evaluated	
28)	Date of initiation of Anti- TB (dd/mm/yy)	……	
29)	Date treatment ended (dd/mm/yy):	……	
30)	In case of interruption, date of last contact with patient or in case of death, date of death	……	

Name of reviewer: _____ Date _____

APPENDIX II: Ethical Approval

GHANA HEALTH SERVICE ETHICS REVIEW COMMITTEE

In case of reply the number and date of this Letter should be quoted.

My Ref. GHS/RDD/ERC/Admin/App/17/298
Your Ref. No.

Research & Development Division
Ghana Health Service
P. O. Box MB 190
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Tel: +233-302-681109
Fax + 233-302-685424
Email: ghserc@gmail.com

Lily Ogyiri
School of Public Health
University of Ghana
Legon, Accra.

The Ghana Health Service Ethics Review Committee has reviewed and given approval for the implementation of your Study Protocol.

GHS-ERC Number	**GHS-ERC: 35/12/2016**
Project Title	"Treatment Outcome of Tuberculosis in HIV Positive and Negative Patients in Selected Hospitals in the Accra Metropolis"
Approval Date	14th March, 2017
Expiry Date	13th March, 2018
GHS-ERC Decision	**Approved**

This approval requires the following from the Principal Investigator

- Submission of yearly progress report of the study to the Ethics Review Committee (ERC)
- Renewal of ethical approval if the study lasts for more than 12 months,
- Reporting of all serious adverse events related to this study to the ERC within three days verbally and seven days in writing.
- Submission of a final report **after completion** of the study
- Informing ERC if study cannot be implemented or is discontinued and reasons why
- Informing the ERC and your sponsor (where applicable) before any publication of the research findings.

Please note that any modification of the study without ERC approval of the amendment is invalid.

The ERC may observe or cause to be observed procedures and records of the study during and after implementation.

Kindly quote the protocol identification number in all future correspondence in relation to this approved protocol

SIGNED.....
DR. CYNTHIA BANNERMAN
(GHS-ERC CHAIRPERSON)

Cc: The Director, Research & Development Division, Ghana Health Service, Accra