FACTORS ASSOCIATED WITH TUBERCULOSIS TREATMENT OUTCOMES IN TB-HIV CO-INFECTED AND TB ONLY PATIENTS IN NYANDO SUB-COUNTY

BY

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DECLARATION

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This research thesis is completely my own work and it provides a true reflection of the proposed study which was to asses factors associated with tuberculosis treatment outcomes in TB-HIV co-infected and TB only patients in Nyando Sub-county.

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ABSTRACT

Tuberculosis is a serious health concern in Kenya which is ranked 15th among the countries with high TB burden globally and a TB/HIV co-infection rate of 39% among HIV positive patients in the country. This problem is further compounded by the high incidence of HIV in the country. This study described the demographic characteristics and the factors associated with TB treatment outcomes in TB patients by HIV status in Nyando Sub-County, which is located in one of the high HIV prevalent counties in Kenya. All TB patients with HIV information notified in the Nyando Sub-County TB program from January 2012 to December 2013 were categorized as either HIV negative or positive at the time of TB diagnosis. Co-infected patients were compared to TB only patients using a hierarchical logistic regression model Stata 13.0. The prevalence of TB-HIV co-infection was 69.80%. Data from 446 individuals was analyzed of which 443 had HIV status information. Of the 443, 312 were TB-HIV co-infected. The following factors increased risk of co-infection: female sex (OR=1.99, 95% CI 1.16-2.75), 20-39 years of age (OR=6.58, 95% CI 3.52-12.31), 40-59 years of age (OR=11.87, 95% CI 5.44-25.85), <18.5 BMI (OR=1.56, 95% CI0.27-9.07) and 18.5-25 BMI (OR=1.13, 95% CI 0.19-6.74). The study reported greater treatment success rates, cured (38.03%) and treatment complete rates (38.03%) with death, failure and default rates reported as 10.33%, 1.24% and 8.65% respectively. Factors associated with treatment success (cured and treatment complete) were: female sex (OR=1.19, 95% CI0.77-1.85), residing in rural area (OR=1.52, 95%CI=0.98-2.36), having pulmonary TB (OR=1.70, 95%CI=0.88-3.29), being HIV negative (OR=1.10, 95%CI=0.67-1.79) and being on ART (OR=1.14, 95%CI=0.12-11.11). The prevalence of TB-HIV co-infection is high among this population. Assessing factors contributing to this co-infection and affecting the treatment outcomes are important for ministry of health policy makers in developing and strengthening intervention programs targeted towards improving treatment outcomes and ultimately reducing TB-HIV co-infection. By identifying predictors of co-infection targeted interventions can be developed to prevent both TB and HIV, and to diagnose each disease earlier and ultimately decrease poor treatment outcomes and death.

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List of Abbreviations

AIDS – Acquired immunodeficiency syndrome

ARV – Antiretroviral therapy

DOT – Direct observed therapy

HIV – Human immunodeficiency virus

MDR TB – Multidrug resistant tuberculosis

MOH – Ministry of Health

TB - Tuberculosis

WHO – World health organization

XDR TB – Extensively drug resistant tuberculosis

CHAPTER ONE: INTRODUCTION

1.1 Introduction

Tuberculosis remains a serious global public health concern ranked second to Human Immunodeficiency virus (HIV) as the leading cause of mortality from infectious diseases(WHO, 2013). Indeed, in 2012, TB was associated with a global morbidity of8.6 million and a mortality 1.3 million annually with 320,000 of these deaths associated with HIV-TB co-infection(WHO, 2013). Of significance is that, developing countries like Kenya which is ranked fifteenth among the countries with the highest TB burden accounts for over 80% of global TB burden and also has the highest HIV prevalence(Who, 2009, , 2013). In addition, data suggest that TB is the leading cause of respiratory morbidity and mortality in HIV infected persons globally accounting for 44% of all acquired immunodeficiency syndrome (AIDS) related deaths(WHO, 2012). A recent study shows that although TB incidences is declining among HIV negative adults in Kenya, it still accounts for over 39% of all TB cases in HIV positive adults(Yuen *et al.*, 2014), suggesting that HIV is impacting on both the epidemiology and clinical outcomes of TB.

Sub-Saharan Africa is reported as the most affected region in terms of the impact of TB-HIV co-infection (Who, 2009). This high incidence rates are partly explained by the relatively high rates of HIV co-infection thus, TB and HIV co-infection pose a great public health challenge in this region (Who, 2009, , 2013). Moreover, data from Kenya which is ranked 5thin terms of TB burden in Africa indicate that out of the country notified, a total of 103,159 TB cases, 39% were TB-HIV co-infected (Ministry of Health, 2013). Additional data indicate that the mortality rate attributed to TB in patients co-infected with HIV is above 130 per 100,000 (Ministry of Public Health and Sanitation, 2009). The incidence of TB infection has remarkably increased by 10% in the past decade due to factors that influence tuberculosis trends, however the main reason for the increase is largely due to HIV epidemic and poverty (Borus *et al.*, 2013). The epidemiology

of tuberculosis has however evolved over time in Kenya, this being attributed to public health interventions by the National TB and leprosy Program, WHO Stop TB strategy and TB-HIV collaborative activities that have been adopted and implemented at different levels nationwide (Borus *et al.*, 2013).

Geographically, Nyanza region contributes up to 20% of TB cases reported in Kenya (Mohan *et al.*, 2001). The high incidence of TB cases in this region is partly attributed to high HIV prevalence since the region has a prevalence of 15.1%, which is almost three times the national average of 5.6% (Ministry of Health, 2013). Of note is that 75% of TB patients notified in Nyanza are HIV co-infected(Mohan, 2001), further indicating that HIV is impacting on the epidemiology of TB in this region. Moreover, Kisumu County has TB prevalence 317 per 100,000 and HIV prevalence of 18.7% (Ministry of Health, 2013) suggesting that co-infection with HIV impacts on the epidemiology of TB in this county. However, there is limited data on the prevalence of TB by HIV status in this region. Hence the current study assessed the prevalence of TB by HIV status in Nyando sub-County.

Studies have shown that TB-HIV co-infection in high burden TB countries is associated with different socio-demographic factors (Do Prado *et al.,* 2014; Prado *et al*., 2011). For example, in Ethiopia, TB-HIV co-infection is associated with lack of formal education, low body mass index, marital status (being widowed or divorced), having a history of diabetes mellitus and advanced WHO HIV/AIDS clinical staging (Hatoluf *et al.*, 2013).Other studies have shown that being male, poverty, ethnicity, low level of education and being aged between 20-59 years are some of the socio-demographic factors that predisposes individuals to HIV-TB co-infections(Muniz et al., 2006;Prado *et al.*, 2011; Do Prado *et al.*, 2014). Moreover, lack of awareness or engaging in risk lifestyles or sexual behaviors have also been demonstrated to increase vulnerability to HIV-TB

co-infections among young adults (Santos *et al.*, 2009). Although these data indicate that context specific socio-demographic characteristics strongly influence the proportion of TB-HIV co-infection in high burden TB countries (Hatoluf *et al.*, 2013), there is no such study that has been done in Kenya which ranked 15th amongst the 22 countries having the highest TB burden using the Kenya TB Epidemiological Surveillance System. More so in counties like Kisumu County where Nyando sub-county is, which not only has HIV prevalence but also high poverty levels standing at 64.6% (MINISTRY OF HEALTH, 2008, , 2012). The current study determined the socio-demographic risk factors for TB by HIV status in Nyando sub-County.

Apart from the socio-demographic factors, other factors like having diabetes (Coimbra *et al.,* 2014),non-adherences to TB and HIV treatment regimens due to extra burden of drug taking (Do Prado *et al.*, 2014), the emergence of multi drug resistance TB (MDR TB)(WHO, 2013), distance from home to health facility (Endris *et al.,* 2014)and delayed diagnosis of TB due to fear of getting HIV diagnosis in health facilities or due to the inability to identify multi drug resistant TB strains by the assays currently in use in poor resource countries like Kenya (Luby *et al.*, 2004; WHO, 2013) have been associated with poor outcomes in TB patients. Although the recent development of rapid sensitive and specific molecular diagnostics has revolutionized TB diagnostics both at local level hospitals and reference laboratories and have allowed TB patients to get the right TB treatments regimens early thus enhancing treatment outcomes (Becker *et al.*, 1994; Luby SP, 2004), these assays are not currently widely used in poor resource countries with high TB burden, especially in sub-Saharan Africa. In addition, other studies have associated different treatment outcomes to time of TB treatment and ART initiation in co-infected individuals (Ciglenecki *et al*., 2007; Gandhi NR, 2009), with poor treatment outcomes being

attributed to late treatment initiation from initial time of disease diagnosis (Ciglenecki*et al.*, 2007).Antiretroviral therapy initiation within 6 months of TB diagnosis reduces mortality rate substantially and is associated with greater survival rates among HIV-TB co-infected patients(Gandhi NR, 2009). Predictors of death from TB in TB-HIV co-infected patients include demographic, lifestyle, and clinical factors (Ciglenecki *et al.*, 2007). Although data show that TB-HIV concomitant therapy coupled with direct observed therapy (DOT) support improve TB treatment outcomes, with 84% of patients on TB-HIV treatment being reported to have completed treatment (Davies *et al.,* 1999; Gandhi *et al.*, 2009) and Kenyan government has rolled out intensive DOTS coverage within the Nyando sub-county, there is no data on the profile and treatment outcomes of TB patients by their HIV in this region. Moreover, the above data indicate that apart from HIV, other underlying factors may be associated with TB patient treatment outcomes. Hence this study used the sub-County TB register to evaluate treatment outcomes of TB patients by HIV status and the factors associated with treatment outcomes using hierarchical multivariate analysis.

1.2 Problem Statement

Tuberculosis has a global prevalence with devastating morbidity and massive mortality(WHO, 2013). More so in high burden like Countries like Kenya where high prevalence of HIV has further compounded this problem leading to resurgence of TB (Cegielski *et al.*, 2014). The emergence of multi drug resistance TB strains coupled with inefficient diagnosis is a major challenge to TB control leading to TB being one of the major public health problem in poor resource countries like Kenya (WHO, 2013;Cegielski *et al.*, 2014).In addition, the wide spread of TB-HIV co-infection makes TB diagnosis and treatment difficult, despite strengthened TB-HIV collaborative programs(Ministry of Public Health and Sanitation, 2009). The synergic

interaction between TB and HIV has driven TB epidemic in Kenya. For example, of all the index TB cases reported in Kenya, 39% occurred in HIV-positive individuals (WHO, 2013).A recent study also found a high prevalence of TB among HIV-exposed infants in Kenya (Cranmer *et al.*, 2014). TB-HIV co-infection is associated with poor treatment outcomes in patients due to none adherence to treatment regimens (Muture *et al.*, 2011). This led to up-scaling of antiretroviral therapy and integration of HIV testing, treatment and care to TB index cases by the Kenya ministry of health in 2004 (Lönnroth *et al.*, 2010). To date there is no data on TB prevalence by HIV status especially in counties with HIV prevalence like Kisumu County (Ministry of Health, 2013)as a result, the differential impact of public health interventions on tuberculosis incidence in the two groups is unknown. There is a paucity of data on the factors that influence TB-HIV co-infections in Kenya despite studies showing that socio-demographic factors can influence HIV-TB co-infection (Do Prado *et al.*, 2014; Endris *et al*., 2014; Hatoluf *et al.*, 2013). In addition, there is a paucity of data on factors that determine treatment in TB patients by HIV status in Kenya despite data showing that several factors may be involved (Do Prado *et al.*, 2014; Endris *et al.*, 2014). Hence this study first compared TB prevalence by HIV status to unravel the distinct epidemiology of TB in the two populations, and then determined the social-demographic factors associated with TB-HIV co-infection and finally determined the factors associated with poor treatment outcomes of TB patients by HIV status. The results of this study have shed light on the impact of current intervention on TB by HIV status and are critical in informing Ministry of Health (MoH) policy on developing specific programmatic interventions and control programs by HIV status.

1.3 OBJECTIVES

1.3.1 General Objective

To determine factors associated with tuberculosis treatment outcomes in TB-HIV co-infected and TB only patients in Nyando sub-County in western Kenya.

1.3.2 Specific Objectives

1. To determine TB prevalence by HIV status in Nyando sub-County.
2. To determine risk factors for TB by HIV status in Nyando sub-County.
3. To evaluate TB treatment outcome by HIV status in Nyando sub-County.
4. To determine factors associated with TB patients' treatment outcomes by HIV status in Nyando sub-County.

1.3.3 Research questions

1. What is the TB prevalence by HIV status in Nyando sub-County?
2. What are the risk factors for TB by HIV status in Nyando sub-County?
3. Does TB treatment outcome differ by HIV status in Nyando sub-County?
4. What are the factors associated with TB patients treatments outcomes by HIV status in Nyando sub-County.

1.4 Justification

The combined TB-HIV therapy is reported to improve survival in co-infected persons(Edqinto ME, 2002). Understanding the impact of combined TB and ARV treatment in TB treatment outcome is important if ARV and TB treatment are to be prioritized during health planning for resource allocation. In addition monitoring the treatment outcomes of TB and understanding the specific reasons for unsuccessful treatment outcome are important in evaluating the effectiveness of TB control program. The TB control program in Nyando sub-county offers concurrent TB and

HIV treatment however there is a paucity of data on the treatment outcomes in TB-HIV co-infected persons among this population.

1.5 Significance of the study

The findings and recommendations drawn from this study are useful to the TB control program, ministry of health and to other TB-HIV prevention and control stake holders in this region and nationally. Information on the TB treatment outcomes and factors associated with the outcomes will be useful in designing new strategies that will ultimately further reduce TB prevalence. The finding can also be used by future researchers intending to conduct similar studies by acting as reference as well as providing evidence on the need for future research on different variables associated with different TB treatment outcomes.

CHAPTER TWO: LITERATURE REVIEW

2.1Epidemiology of Tuberculosis

Tuberculosis (TB) is primarily a disease of the respiratory system caused by *Mycobacterium tuberculosis* (Frieden *et al.*, 2003). The main mode of transmission of the causative agent is through aerosols when droplet nuclei of *Mycobacterium tuberculosis* are expelled from a patient with active TB through coughing or sneezing, the droplets are then suspended in the air and inhaled by persons nearby (Frieden *et al.*, 2003).Following exposure the risk of infection depends on a multiplicity of factors including the infectious dose, proximity or length of contact with an infectious case or ventilation or sometimes blood transfusion (Frieden *et al.*, 2003). The bacteria then anchors itself in the lungs where it is engulfed within the alveolar macrophages, it then replicates and subsequently disseminate to the pulmonary lymph nodes or other extra pulmonary organs causing pulmonary TB or extra-pulmonary TB respectively (Bermudez *et al.*, 1996). Several studies have shown that pulmonary TB accounts for over 80% of notified TB cases and mainly affect the lungs (Frieden *et al.*, 2003). While extra-pulmonary TB affects other body tissues besides the lung tissues such as brain, spine, liver and bones (Ministry of Public Health and Sanitation, 2009). Although TB cases are asymptomatic and referred to as latent TB infection, the disease can progress to the active phase where it manifest myriad symptoms including chronic cough with blood stained sputum, fever, night sweats and weight loss (Frieden *et al.*, 2003). Moreover, if untreated active TB cases result in mortality rate of over 50% among TB patients (WHO, 2013).

Globally TB infects a third of the world's population with new infections occurring in 1% of the population each year. Indeed reports indicate that TB is associated with a morbidity of 8.6 million and mortality of 1.3 million with 80% of TB burden being borne by sub-Saharan countries and Asia (WHO, 2013).For example, Kenya is ranked 15th among the 22 countries with

high TB burden countries worldwide (WHO, 2013). Moreover, the resurgence of TB cases due to misuse of TB drugs or lack of adherence to proper dosages during chemotherapy has led to the emergence Multidrug resistant tuberculosis (MDR TB) and extensively drug resistant TB (XDR TB) that are resistant to rifampicin, isoniazid drugs, kanamycin, capreomycin or amokacindrugscommonly used in TB chemotherapy (Compoux*et et al.*, 2004). Thisproblem is further compounded with high HIV prevalence in sub-Saharan Africa that has led to high TB-HIV co-infection due to HIV induced immune-suppression (WHO, 2009). Hence there is a need to investigate the prevalence of TB by HIV status.

2.2 Tuberculosis (TB)-HIV Co-infection

Several studies have associated the resurgence of TB cases to HIV infection (Harries A.D, 2001; WHO, 2013; Yuen *et al.*, 2014).Of note is that high TB burden countries in sub-Saharan Africa are also high HIV burden countries and thus HIV is thought to be an important driver of TB epidemics (Yuen *et al.*, 2014). For example, 39% of all notified TB cases in Kenya were in HIV infected patients (WHO, 2013)while a study in Ethiopia reported that in some regions they can account for 52.1% of all the notified TB cases (Beza *et al.*, 2013).Yet studies in Uganda, Nigeria and Tanzania reported that HIV-TB co-infections occur in 54%, 40% and 29% respectively (Van den Broek *et al*., 1993;Richards *et al.*, 1995). These studies indicate that the high HIV prevalence in TB cases may in part be due to immune-suppression that reactivates latent TB disease resulting in more people progression to the acute phase of TB disease (Kirenga *et al*., 2015; Toossi, 2003).This argument is further supported by recent indication that the annual risk of TB among HIV positive individuals is 10% per year relative to 10% life time risk among HIV negative persons (Cole *et al.*, 1998). Similarly other studies have shown that HIV infection is a potential risk for recurrence of TB and the greatest risk factor for new TB infection (Toossi, 2003)and that development of active TB can either be due to recently acquired infection or from

reactivation of a past acquired infection and that these pattern of the disease occurs more frequent in persons infected with HIV(Lo, 2004). Together these data indicate there are geographical differences in HIV-TB co-infections and hence there are need for studies that address the TB prevalence by HIV status in high burden countries like Kenya to enable focusing of TB-HIV prevention and control programs. Hence this study will determine the prevalence of notified TB cases by HIV status in Nyando sub-County within Kisumu County with high HIV prevalence(Ministry of Health, 2013).Moreover, although TB disproportionately affects persons living with HIV, TB also occur in people who are HIV negative (Corbett *et al.*, 2006), suggesting that other factors may be driving the resurgence of TB cases by HIV status.

2.3 Risk factors associated with TB by HIV status

Several social, economic and demographic factors have been associated with TB-HIV co-infection in high burden TB countries(Prado *et al.*, 2011; Prado *et al.*, 2014).Social inequities like poverty has been associated with the increase in TB-HIV co-infection especially in sub-Saharan Africa, because poverty is associated with poor health and sanitation that drive TB infection(Pawlowski *et al.*, 2012). In addition to poverty, population clusters and unemployment are risks related to both TB and HIV infections(Do Prado et al., 2014; Prado *et al.*, 2014). Other studies have found that lack of formal education, low body mass index, marital status (being widowed or divorced) or having a history of diabetes mellitus. Advanced WHO HIV/AIDS clinical staging and exposure to risky lifestyles due to lack of awareness increased exposure to TB and HIV virus(Hatoluf *et al.*, 2013; Lönnroth *et al*., 2010). Yet other studies demonstrated that male-gender, ethnicity or race and ages between 20-59 years are some of the socio-demographic factors that predispose individuals to HIV-TB co-infections (Prado*et al.*, 2011; Do Prado *et al.*, 2014). Lack of awareness or engaging in risk lifestyles or sexual behaviors have also been demonstrated to increase vulnerability to HIV-TB co-infections among young

adults(Santos *et al.*, 2009). A study in South Africa indicated that the cultural believe that TB could be cured by traditional healers led to delayed presentation of TB cases to hospitals (Edqinto *et al.*, 2002). In addition to these, tobacco smoking, alcohol abuse, lack of vaccination against TB, family history of TB and being in close contact with TB index cases are also risk factors for TB (Kirenga *et al.*, 2015). Studies have shown that diagnosis of TB cases through passive detection of TB cases as opposed to active surveillance not only lead to delayed diagnosis but also lead to underestimation of the prevalence of TB in a population (Storla *et al.*, 2008; Sreeramareddy *et al.,* 2009;VantHoog *et al.*, 2012), potentially increasing the risk for TB infections. Although these data indicate that context specific socio-demographic characteristics strongly influence the proportion of TB HIV co-infection in high burden TB countries(Do Prado *et al*., 2014; Hatoluf *et al.*, 2013; Prado *et al.*, 2011), there is no such study that has been done in Kenya, which ranked 15th amongst the 22 countries having the highest TB burden. Therefore, the current study determined the socio-demographic risk factors for TB by HIV status in Nyando sub-County. Other studies have shown that these factors may also influence TB patient treatment outcome by HIV status (Ciglenecki *et al.*, 2007; Lawn *et al.*, 1999). Hence there is a need to investigate fcators associated with TB treatment outcomes by HIV status.

2.4 Factors associated with TB treatment outcomes by HIV status

Poor treatment outcomes in TB patient has been associated with socio-demographic factors, presence of other co-morbidities like having diabetes and HIV infection (Coimbra *et al*., 2014; Kirenga *et al*., 2015), non-adherences to TB and HIV treatment regimens due to extra burden of taking TB and HIV drugs (Do Prado *et al.*, 2014), the emergence of multi drug resistance TB (MDR TB)(WHO, 2013), distance from home to health facility (Endris *et al.*, 2014) and delayed diagnosis of TB due to fear of getting HIV diagnosis in health facilities or due to the inability to identify multi drug resistant TB strains by the assays currently in use in poor resource countries

like Kenya (Luby *et al.*, 2004; WHO, 2013). This is further coupled with delayed diagnosis of TB through passive detection of TB cases (Storla *et al.*, 2008; Sreeramareddy *et al.*, 2009.), have been associated with poor outcomes in TB patients. In addition, a study in Ghana associated poor treatment outcomes in TB patients increased age, treatment delay and defaulting in HIV-infected persons, residence in rural area, sputum smear negative disease, and prolonged symptom duration prior to initial diagnosis (Lawn SD, 1999). Yet another study found that age, low body mass index (BMI), low levels of hemoglobin and more advanced clinical stages of HIV at baseline are prognostic indicators of poor outcomes (Ciglenecki *et al.*, 2007). A study conducted in Agincourt, rural South Africa revealed that the rise in PTB mortality over time is due to PTB-HIV co-infection (Zwang *et al.*, 2007).

Although the recent development of rapid sensitive and specific molecular diagnostics has revolutionized TB diagnostics both at local level hospitals and reference laboratories and have allowed TB patients to get the right TB treatments regimens early thus enhancing treatment outcomes(Becker *et al.*, 1994; Luby *et al.*, 2004; WHO, 2013), these assays are not currently widely used in poor resource countries with high TB burden especially in sub-Saharan Africa. In addition, other studies have associated different treatment outcomes to time of initiation of TB treatment and ART initiation in co-infected individuals (Ciglenecki *et al.*, 2007; Gandhi *et al.*, 2009), with poor treatment outcomes being attributed to late treatment initiation from initialtime of disease diagnosis(Ciglenecki *et al.*, 2007).Antiretroviral therapy initiation within 6 months of TB diagnosis reduces mortality rate substantially and is associated with greater survival rates among HIV-TB co-infected patients (Gandhi *et al.*, 2009). Predictors of death from TB in TB-HIV co-infected patients include demographic, lifestyle, and clinical factors(Ciglenecki *et al.*, 2007). Although data show that TB-HIV concomitant therapy coupled with DOT support

improve TB treatment outcomes, with 84% of patients on TB-HIV treatment being reported to have completed treatment (Davies *et al.*, 1999; Gandhi *et al.*, 2009) and Kenyan government has rolled out intensive DOTS coverage within the county, but there is no data on the profile and treatment outcomes of TB patients by their HIV in this region.

2.5 Conceptual Framework

An understanding of the natural history and pathogenesis of TB as well as the impact of HIV on TB is needed in order to gain insight into the TB treatment outcomes among co-infected patients. In most cases tuberculosis infection comes first and HIV contracted subsequently. Once co infected, the progression to active TB occurs quite rapidly, which could be prevented through TB preventive therapy. Those who progress to active TB could be managed through DOTS and through provision of care and support including use of antiretroviral therapy.

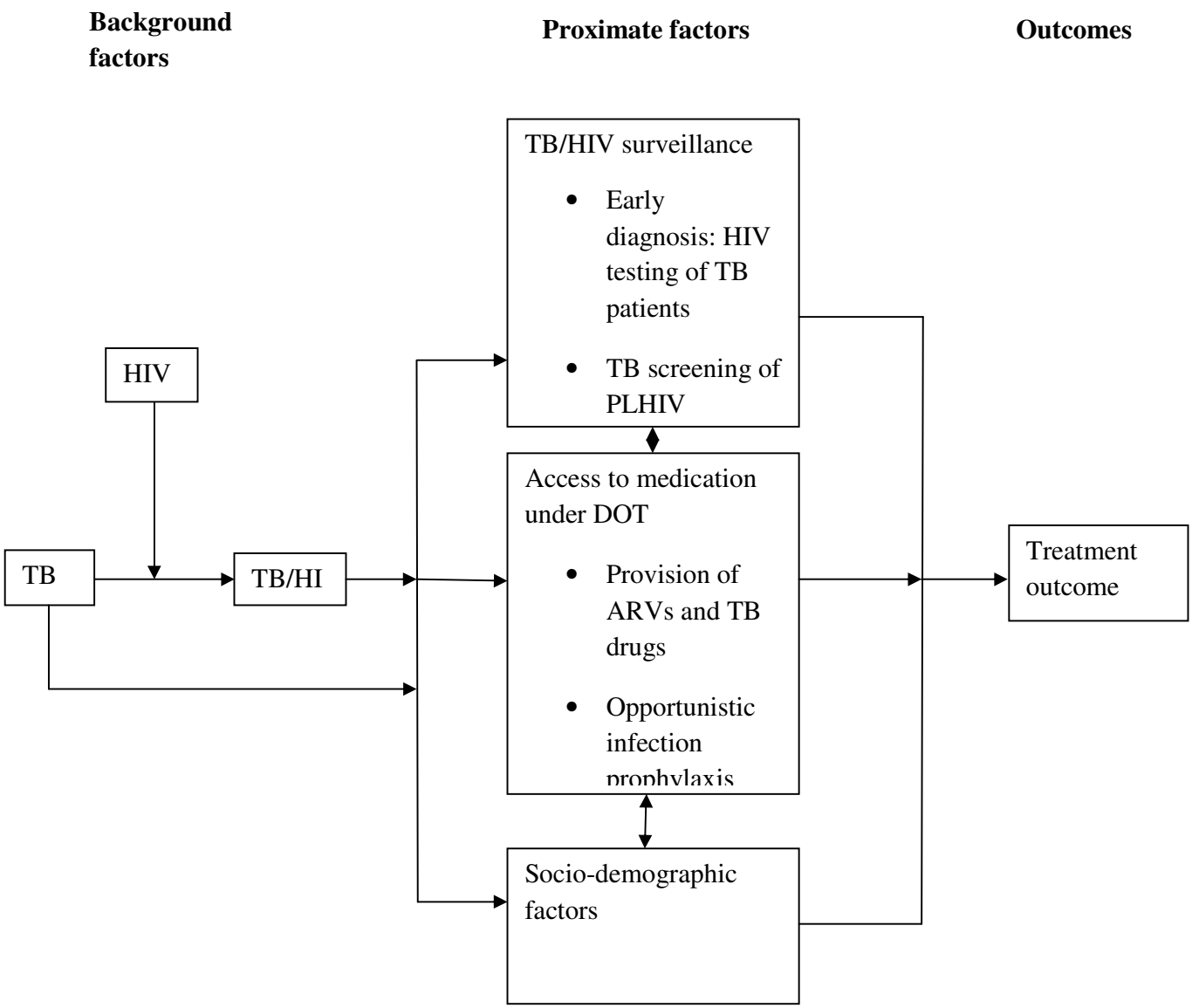

Figure 1 Conceptual frame work of TB treatment in TB-HIV co-infected patients adopted from social determinants of TB formulated by Starfield*et al.*, 2002. Showing TB treatment interventions points and treatment outcomes in TB-HIV co-infected patients

CHAPTER THREE: METHODOLOGY

3.1 Study site

The epidemiological data of TB patients was abstracted from TB registers from all 7 TB control program treatment sites in Nyando Sub County (Appendix I) namely; Ahero sub-County hospital, Awasi mission health center, Bunde dispensary, Holo dispensary, Nyabongo dispensary, Olasi dispensary and Kadinda dispensary. Nyando Sub County is located in Kisumu County, Kenya. It has a population of approximately 141,037 residents who are predominantly of Luo ethnicity and practice rice and sugarcane farming as the major economic activity. The latitude and longitude of Nyando sub-county is -0.159 and 34.981 respectively. The HIV prevalence in this area stands at 26.8% (NASCOP, 2014), in addition recent data indicate that TB prevalence in western Kenya where Nyando sub-County is located is 32.1% (Videlis *et al.,* 2015). This region also has high poverty levels standing at 64.6%(MINISTRY OF HEALTH, 2008, , 2012).The TB control program registers and gives medication to all TB patients in the sub county health facilities including those with HIV co-infection. The ministry of health as also integrated TB and HIV services since the year 2005 in the whole country (Sitienei *et al.,* 2013).

3.2 Study design

This was a retrospective cross sectional study utilizing the database of the Kenya national TB register. The register was developed with the objective of collecting and processing data on disease notification throughout the country. TB register is the primary information system from which data are extracted for epidemiological analyses since it has data on patient identification, tuberculosis type, HIV status, treatment provided, adherence to treatment and outcome of TB treatment. The TB registers have been modified to capture TB/HIV data. All TB patients are screened for HIV during enrolment as well as all patients found to be HIV positive at HIV testing site referred to TB clinics for TB screening. This study assessed the prevalence,

associated risk factors and treatment outcomes among TB patients by HIV status in Nyando Sub-county from January 2012 to December 2013. Treatment outcomes defined as cured, treatment complete, died, failure, and out of control for TB patients on TB treatment were compared with those of TB-HIV co-infected patients on TB treatment.

3.3 Study Population

The study included all TB cases aged ≥ 15 years notified in the Nyando sub county TB register from January 2012 to December 2013.

3.3.1 Inclusion criteria

The inclusion criteria for this study included all smear positive and negative pulmonary tuberculosis patients, TB-HIV co-infected patients enrolled in the Nyando district TB control program and TB and TB-HIV co-infected patients undergoing TB treatment or both TB and HIV treatment and all the patients diagnosed with extra-pulmonary or MDR TB.

3.3.2 Exclusion criteria

All TB patients who transferred out to other TB programs out of the district, HIV infected persons without tuberculosis, HIV infected TB patients not on TB treatment and HIV infected patients on TB preventive therapy will be excluded from the proposed study.

3.3.3 Sample size calculation

Since the primary aim of this study was to evaluate factors associated with TB treatment outcomes in an area with high HIV and TB prevalence (MOH, 2014; Videlis*et al.,* 2015). This study calculated the sample size using a formula developed by Daniel *et al.* (1999) for epidemiological studies as shown below;

$$n = \frac{Z^2 P\,(1-P)}{d^2}$$

Where, n = sample size

Z = Z statistic for a level of confidence

P = expected prevalence or proportion

d = precision

According to the Videlis*et al.,* 2015, the prevalence (P) of TB was 32.1% in western Kenya. Assuming a precision, d, of 0.05, which is half of P, and Z is 1.96 (95%CI)the sample size is calculated as shown below;

$$n = \frac{1.96^2 \times 0.321 \times (1 - 0.321)}{(0.05)^2}$$

$n = 335$

3.3.4Sampling technique

The study used simple random sampling technique. Nyando-district TB treatment register which contains information on all patients in all the 8 TB treatment sites was used. The register has information on treatment regimen, patient's HIV status, patients' demographics and TB treatment outcomes defined as cured, died, out of control, failure and transferred in.

3.5Data collection

Quantitative method was used to abstracted data from the TB register using a unique data abstraction form which has information about patient identification, tuberculosis type, HIV status, treatment provided, adherence to treatment and outcome of TB treatment. Data was abstracted using a specially designed excel data abstraction form. A unique identification number for each patient was used for data confidentiality. The following socio-demographic covariates were evaluated: age, gender (male, female) and area of residence (urban, rural or peri-urban). The covariates related to TB included the type of TB diagnosed during the study period,

classified as 1) New TB case (no prior TB diagnoses), relapse (completed a previous TB treatment) or, 3) return after default (individuals that defaulted from a previous TB treatment regimen and returned to continue treatment). This study also included site of TB at presentation (pulmonary, extra-pulmonary, pulmonary + extra pulmonary), existence of chest X-ray suspicious for TB, result of initial sputum smear test result of initial culture examination and receiving directly observed therapy (DOT). Final treatment outcome was classified as cured, default, death while on treatment, transferred or developed MDR TB.

3.6 Data processing and analysis

3.6.1 Data processing

All data abstracted from TB registry was checked and cleaned to ensure completeness, consistency, credibility and eligibility. This was done to exclude patients with missing or incomplete data.

3.6.2 Data Analysis

The individuals were stratified into those with TB-HIV and those with TB only, then according to socio-demographic and clinical characteristics. For associations this study used Pearson chi-square test. Covariates associated ($p \leq 0.05$) with the outcome of interest were further included in a hierarchical logistic regression model to capture the interrelationships between the factors that influence TB prevalence and treatment outcomes by HIV status. Associations resulting from the hierarchical regression model were adjusted for the variables in the same level and those in previous levels, taking into account both confounders and mediators. In multivariate analysis, all covariates associated with the outcome ($p \leq 0.05$) in each step were retained in the model. In case of missing information on HIV status, polynomial analysis based on the following TB treatment outcomes was done.

3.7 Ethics Approval

Ethical approval for use of TB registers to abstract data was sought from JaramogiOgingaOdinga Teaching and Referral Hospital Ethical Review Board (Appendix 3). The aim and purpose of all components of the study was discussed and agreed on before legal consent was obtained from the authorities. To ensure confidentiality and non-disclosure of individual identifiers the real name of the patients was not used.

CHAPTER FOUR: RESULTS

4.1 Social and demographic characteristics of TB patients

As shown in table 1 there was a total of 447 TB patients who were included in the study, whose ages were categorized as <20 years, 20-39 years, 40-59 years and >60 years. Among the 447 study participants, 203 (45.41%) were female and 244 (54.59%) were males. Of the 244 males, 89.34% had pulmonary TB while 10.66% had extra-pulmonary TB. Of 203 females, 90.15% had pulmonary TB while 9.85% had extra-pulmonary TB. Patients < 20 years of age accounted for 12.75% (57) of the total participants, those aged 20-39 years were the majority accounting for 57.49% (257) of the total participants, those aged 40-59 years accounted for 23.04% (103) and those aged ≥ 60 years accounted for 6.71% (30). Majority of the participants resided in urban area 51.45%(230).Most patients (99.1%) 443 were tested for HIV. A majority of TB patients 312 (69.80%) had HIV co-infection and nearly all the TB-HIV co-infected patients, 98.65% were on antiretroviral treatment. In addition,88.4% (275) of the TB-HIV co-infected patients had pulmonary tuberculosis. Overall, there was no statistical difference in all variables analyzed.

Table 1: social-demographic characteristics of TB patients by type of TB

Characteristics	Total n(%)	Type of TB n(%)		p value
		Pulmonary	Extra Pulmonary	
Sex				0.781
Male	244(54.59)	218(89.34)	26(10.66)	
Female	203(45.41)	183(90.15)	20(9.85)	
Residence				0.468
Urban	230(51.45)	204(88.70)	26(11.30)	
Residence	217(48.55)	197(90.78)	20(9.22)	
Age				0.067
<20 years	57(12.75)	47(82.46)	10(17.54)	
20-39 years	257(57.49)	233(90.66)	24(9.34)	
40-59 years	103(23.04)	91(88.35)	12(11.65)	
≥ 60 years	30(6.71)	30(100.00)	0(0.00)	
HIV test				0.399
Negative	131(29.31)	122(93.13)	9(6.87)	
Positive	312(69.80)	275(88.14)	37(11.86)	
Unknown	3(0.67)	3(100.00)	0(0.00)	
Declined	0(0.00)	1(100.00)	0(0.00)	
ART Status				0.092
Not on ART	132(30.99)	123(93.18)	9(30.99)	
On ART	294(69.01)	258(87.76)	36(12.24)	

All the data was analyzed using Pearson Chi-square

4.2 Socio-demographic characteristics of tuberculosis cases according to HIV status

As shown in Table 2, the TB patients were stratified by HIV status. The results of this study reveal that there were more males relative to females in both TB-HIV co-infected group (50.96% versus 49.04%) and TB only group (63.64% versus 36.36%), (p=0.014). Most TB-HIV co-infected patients lived in urban area relative to rural area (51.28% versus 48.72%) while for TB only it was (50% versus 50%), although there is no significant statistically difference (p=0.805). These data also reveal that patients within 20-39 years age group were more in both TB-HIV co-infected group (62.82%) and the TB only group (44.70%) relative to all the remaining age group (p <0.0001).

Table 2 Distribution of socio-demographic characteristics of tuberculosis cases according to HIV status in Nyando Sub-county from 2012-2013

Characteristics	TB-HIV n(%)	TB only n(%)	P value	
Sex				
Male	159(50.96)	84(63.64)		0.014
Female	153(49.04)	48(36.36)		
Residence				
Urban	160(51.28)	66(50.00)		0.805
Residence	152(48.72)	66(50.00)		
Age			<0.0001	
<20 years	20(6.41)	38(28.79)		
20-39 years	196(62.82)	59(44.70)		
40-59 years	86(27.56)	16(12.12)		
≥ 60 years	10(3.21)	19(14.39)		

Data was analyzed using Chi-square

4.3 Risk factors associated with HIV-TB co-infections

Table 3 Hierarchical multivariate analysis of the association of TB by HIV status

	Characteristics		OR	95%CI	p value
Level 1	**Gender**	Female	1.99	1.16-2.70	0.004
		Male	*ref.*		
	Age	<20 years	*ref.*		
		20-39 years	6.58	3.52 - 12.31	<0.0001
		40-59 years	11.87	5.44 - 25.85	<0.0001
		≥ 60 years	1.05	0.41 - 2.72	0.917
	Residence	Urban	*ref.*		
		Rural	0.99	0.63 - 1.56	0.963
Level 2	**DOT**	CV	-		
		H	1.16	0.59 - 2.26	0.674
		HCW	*ref.*		
		ND	-		
Level 3	**BMI**	< 18.5	1.56	0.27-9.07	0.621
		18.5 to 25	1.13	0.19 - 6.74	0.89
		> 25	*ref.*		
Level 4	**XRAY**	N	*ref.*		
		Y	1.2	0.61 - 2.36	0.594
	Culture	No	*ref.*		
		Yes	0.72	0.33 - 1.59	0.419
	Smear	Negative	1.76	0.90 - 3.46	0.099
		Positive	*ref.*		
	TB Type	Extra Pulmonary	4.95	1.00 - 24.31	0.049
		Pulmonary	*ref.*		
Level 5	**Outcome**	Cured	*ref.*		
		Died	3.5	1.08 - 11.35	0.037
		Failed	5.95	0.56 - 63.02	0.139
		MR	-		
		Out of Control	0.6	0.23 - 1.59	0.305
		Treatment Complete	1.58	0.54 - 4.66	0.405
		Transfer Out	1.74	0.40 - 7.54	0.461

*The multivariate analyses: step 1(Gender + age + residence); step 2 (variables retained from step 1 + DOT);step 3 (variables retained from step 2 + BMI); step 4 (variables retained from step 3 + TB type + smear + culture + X ray suspicious for TB); and step 5(variables retained from

step 4 + outcome.

The hierarchical multivariate analysis (Table 3) showed that individuals aged 20-39 years of age and 40-59 years of age are more likely to be TB-HIV co-infected, compared to individual <20 years of age (OR=6.58, 95% CI=3.52-12.31 and OR=11.87, 95% CI=5.44-25.85 respectively). In addition, individuals >60 years of age did not have a greater TB-HIV co-infection compared to those <20 years of age (OR=1.05, 95% CI=0.41-2.72). Those who resided in rural areas were less likely to be TB-HIV co-infected as compared to those in urban setting (OR=0.99, 95% CI= 0.63-1.56).

Direct observed therapy was done to all the patients. DOT provided by household member was 1.16 times greater than that offered by health care workers (HCW) (OR 1.16, 95CI 0.59-2.26). Patients who had smear negative results were 1.76 more likely to be TB-HIV co-infected as compared to their counterparts with smear positive results (OR=1.76, 95% CI=0.90-3.46). Similarly those with extra-pulmonary TB were 4.95 more likely to be reported as TB-HIV co-infected relative to those with pulmonary TB (OR=4.95, 95%CI= 1.01-24.30). With reference to cured patients additional data indicate that patient who died while on treatment were 3.5 times more likely to TB-HIV co-infected (OR=3.5 95% CI=1.08-11.35), those with treatment failures were 5.95 more likely to be TB-HIV co-infected (OR=5.95, 95% CI=0.56-63.02) while those who completed treatment were 1.58 times more likely to be TB-HIV co-infected (OR=1.58, 95CI 0.54-4.66). In addition patients who transferred out were 1.74 timely likely to be TB co-infected (OR=1.74, 95CI 0.40-7.54). There were no MDR cases and less chances of defaulters/out of control patients (OR=0.6, 95%CI=0.23-1.59) among the TB-HIV co-infected patients.

4.4 Distribution of presentation and treatment characteristics of TB by HIV status

Table 4 distribution of presentation and treatment characteristics of tuberculosis (TB) cases according to HIV status in Nyando Sub-county from 2012-2013

Characteristic	TB-HIV n(%)	TB only n(%)	P value
Regimen			**0.102**
First	291(93.27)	117(88.64)	
Second	21(6.73)	15(11.36)	
DOT			**0.165**
CV	1(0.33)	0(0.00)	
H	270(88.27)	109(83.85)	
HCW	31(10.13)	21(16.15)	
ND	4(1.31)	0(0.00)	
Patient			**0.337**
Failure	2(0.64)	1(0.76)	
New	275(88.14)	111(84.09)	
R+	13(4.17)	13(9.85)	
R-	5(1.60)	1(0.76)	
RAD	9(2.88)	3(2.27)	
REP	2(0.64)	0(0.00)	
TI	6(1.92)	3(2.27)	
X-RAY			
No	149(50.51)	64(54.70)	**0.443**
Yes	146(49.49)	53(45.30)	
Culture			**0.05**
No	288(92.31)	114(86.36)	
Yes	24(7.69)	18(13.64)	
Smear			**0.025**
Negative	123(45.72)	38(33.33)	
Positive	146(54.28)	76(66.67)	
Cotrimoxazol			**<0.0001**
No	2(0.64)	128(97.71)	
Yes	310(99.36)	3(2.29)	
ART			**<0.0001**
No	4(1.35)	127(98.45)	
Yes	292(98.65)	2(1.55)	
Outcome			**0.024**
Cured	108(34.73)	62(47.33)	
Died	34(10.93)	9(6.87)	
Failed	5(1.61)	1(0.76)	
MR	0(0.00)	1(0.76)	
Out of Control	19(6.11)	14(10.69)	
Treatment Complete	129(41.48)	40(30.53)	
Transfer Out	16(5.14)	4(3.05)	
BMI			**0.951**
<18.5	135(59.73)	58(59.79)	
18.5 to 25	85(37.61)	37(38.14)	

> 25	6(2.65)	2(2.06)	
Nutrition			**0.488**
No	44(14.10)	22(16.67)	
Yes	268(85.90)	110(83.33)	

Table 4 describes the patients according to TB presentation and treatment. The patients were put on either the first line or second line TB drug regimen. But a majority of the TB patients were on first line treatment. In addition, there were more patients in the TB-HIV group (93.27%) put on the first line regimen as compared to those on the same regimen in the TB only group (88.64%), although there is no statistical differences between the two groups (p=0.102).Similarly, among those on second line TB drug regimen there was no statistical significance between the TB-HIV co-infected group and TB only group. Information on direct observed therapy (DOT) was available for 436 cases. All cases in the TB only group had DOT performed in one way or another, while 1.31% (4 cases) of cases in the TB-HIV group did not have any DOT performed. DOT provide by house hold member was prevalent in both the TB only group and TB-HIV group. In the TB only group DOT provided by household member was 83.85% while in the TB-HIV group it was 88.27%.

There were more new TB patients in the TB-HIV group (88.14%) than the TB only group (84.09%) but there was no statistical difference (p=0.337). Most of the patients did not have culture test done them that is 92.31% in the TB-HIV group and 83.36% in the TB only group. For those who had culture test done, a greater proportion was from the TB only group 13.64% while TB-HIV group had 7.69% (p=0.05).Smear positive test was prevalent in the TB only group relative to the TB-HIV group (66.67% versus 54.28%; p=0.025). For smear negative test was more prevalent in the TB-HIV group relative to TB only group (45.72% versus 33.33%;p=0.025). Information on X-ray suggestive for TB was available for 412 patients,

however only 199 (48.30%) patients had X-ray done. Out of these there more patients from the TB-HIV group relative to the TB-only group (49.49% versus 45.30%) but there was no significant difference between the groups (p=0.443). On the other hand a greater proportion of patients in the TB only group 64 (54.70%) did not have any X-rays done to confirm suspicions of TB as compared to those in the TB-HIV group 149 (50.51%), but there was no statistical significance between the two groups (p=0.443).

Cotrimoxazol treatment was greater in TB-HIV group relative to the TB only group (99.36% vs. 2.29%, p<0.0001). In addition only 0.64% of patients in the TB-HIV group did not receive Cotrimoxazol treatment. Nearly all the patients 292(98.65%) of TB-HIV patients received Antiretroviral Therapy (ART) compared to those who were not on ART4(1.35%) did not (P<0.001). Cure was greater in the TB only group 62 (47.33%) as compared to the TB-HIV group 108 (34.73%) (P=0.024). Those who succumbed to death while on treatment were greater in the TB-HIV group, 34(10.93%) as compare to 9 (6.87%) in the TB only group (P=0.024). Additionally, there were more drug defaulters in the TB only group than in the TB-HIV group (10.69% versus 6.11%; p=0.024).

BMI of <18.5 was prevalent in both the TB-HIV group and TB only group (59.73% and 59.79% respectively). Those patients with BMI 18.5-25 were 85 (37.61%) in the TB-HIV group and 37 (38.14%) in the TB group only while those with >25 BMI were 6 (2.65%) in the TB-HIV group and 2 (2.06%) in the TB only group.

4.5 Tuberculosis treatment outcomes

As shown in Table 5, treatment outcome was successful for most patients, with both cured and treatment complete having 107 (38.03%) patients. Among females, cure rates and treatment complete rates were 40.69% and 37.25% respectively while death, failure and default rates were

9.8%, 1.47% and 6.37% respectively. Of note there was 1 (0.49%) case of MDR among the females. Among the male patients, cure and treatment complete rates were 35.95% and 38.84% respectively, while death, failure and default rates were 10.33%, 1.24% and 8.68% respectively. Successful treatment outcomes were reported among all age groups. For age group of <20 years there were 18 (31.58%) cured while for treatment complete they were26 (45.61%), for 20-39 years age group there 104 (40.47%) cured while treatment complete was 94 (36.58%). In addition there 36 (34.95%) cured and for treatment complete there 40 (38.83%) patients within 40-59% years age group and there were 12 (40%) of patients cured and treatment complete was 10 (33.33%) patients in >60 years age group. Death rates were greater in >60 years age, 6(20%) patients while in less than<20 years there 5(8.77%) deaths. In addition in 20-39 years there were 21(8.17%) deaths while in 40-59 years there were 13(12.62%). For treatment failure, in <20 years age group and >60 years there was 1(1.75%) patient, while for 20-39 years they were 4 (1.56%). No treatment failure was reported in 40-59 years age group. Moreover, there was only 1 (1.75) patient who presented with MDR. Default rates were greater in 20-39 years 21(8.17%) patients and 40-59 years 9 (8.74%) patients in the two age groups while in <20 years it was 3 (5.26%) patients and > 60 years age group there were 10 (33.33%) patients.

Stratifying treatment outcomes by TB type revealed that more patients who were cured among those with pulmonary TB 169 (42.14%) patients relative to those with extra-pulmonary TB with 1(2.22%) patient. Treatment complete rate was higher among the extra-pulmonary TB patients 29 (64.44%) as compared to those with pulmonary TB who were 140(34.91%) patients. Deaths were higher in the extra-pulmonary group 7 (15.56%) patients relative to those with pulmonary TB who were 38 (9.48%) patients. There was no treatment failure or cases of MDR in patients with extra-pulmonary TB while in those with pulmonary TB there were 6 (1.50%) treatment

failures and 1 (0.25%) case of MDR. In addition there are 33 (8.93%) patients who defaulted in the pulmonary group and 1(2.22%) patient in the extra-pulmonary group. HIV negative patients had slightly better treatment outcomes than HIV positive patients. Among HIV negative patients cure and treatment complete rates were 62 (46.97%) and 40(30.30%) patients respectively while among the TB-HIV co-infected patients it was 108(34.50%) patients cured and 129 (47.61) % patients that completed treatment. More HIV infected TB patients died 34 (10.86%) patients compared to HIV negative 9(6.82%) patients. Looking at treatment outcome in TB-HIV co-infected patients who were 291 with 13 transferred out revealed that there were 103 (35.40%) patients who were cured, treatment complete were 122(41.92%) patients, there were 32(11%) deaths and 5(1.72%) treatment failures and 16(5.50%) patients that defaulted. Further analysis revealed that those who were not on ART who were 4 patients had 2(50%) patients cure rate, 1(25%) treatment complete and 1(25%) defaulter but there was no death, treatment failure and MDR case reported in this group. However, it is noteworthy to note the number of patients not on ART was low and the treatment outcomes in this group cannot be compared to those on ART. Moreover, 21 patients transferred out hence there treatment outcomes are unknown.

Table 5 Treatment outcomes of TB patients with their characteristics

Characteristics		Treatment Outcomes n(%)						
		Cured	Died	Failed	MDR	OOC	TC	Transfer Out
Sex	Female	83(40.69)	20(9.80)	3(1.47)	1(0.49)	13(6.37)	76(37.25)	8(3.92)
	Male	87(35.95)	25(10.33)	3(1.24)	0(0.00)	21(8.68)	94(38.84)	12(4.96)
Age	<20 years	18(31.58)	5(8.77)	1(1.75)	1(1.75)	3(5.26)	26(45.61)	3(5.26)
	20-39 years	104(40.47)	21(8.17)	4(1.56)	0(0.00)	21(8.17)	94(36.58)	13(5.06)
	40-59 years	36(34.95)	13(12.62)	0(0.00)	0(0.00)	9(8.74)	40(38.83)	5(4.85)
	≥ 60 years	12(40.00)	6(20.00)	1(3.33)	0(0.00)	1(3.33)	10(33.33)	0(0.00)
TB type	Pulmonary	169(42.14)	38(9.48)	6(1.50)	1(0.25)	33(8.23)	140(34.91)	14(3.49)
	Extra Pulmonary	1(2.22)	7(15.56)	0(0.00)	0(0.00)	1(2.22)	29(64.44)	7(15.56)
HIV Status	Negative	62(46.97)	9(6.82)	1(0.76)	1(0.76)	14(10.61)	40(30.30)	4(3.03)
	Positive	108(34.50)	34(10.86)	5(1.60)	0(0.00)	0(0.00)	129(4.21)	17(5.43)
	Not Done	0(0.00)	1(50.00)	0(0.00)	0(0.00)	1(50.00)	0(0.00)	0(0.00)
	Unknown	0(0.00)	1(50.00)	0(0.00)	0(0.00)	1(50.00)	0(0.00)	0(0.00)
ART Status	On ART	103(35.40)	32(11.00)	5(1.72)	0(0.00)	16(5.50)	122(41.92)	13(4.47)
	Not on ART	2(50.00)	0(0.00)	0(0.00)	0(0.00)	1(25.00)	1(25.00)	0(0.00)

MDR: Multi drug resistance. OOC: out of control/defaulter. TC: treatment complete.

4.6 Factors associated with treatment success rates among TB patients

Multivariate analysis (Table 5) shows treatment success rates among TB patients revealed that female patients had betters treatment success rates (cure and treatment complete rates) as compared to their male counterparts (77.94% vs. 74.79%) with (OR=1.19, 95%CI 0.77-1.85). Patients in <20 years age group had 44 (77.19%) patient treatment success and 1.23 greater chance of treatment success as compared to those > 60 years of age who had 22 (73.33%) patients(OR=1.23, 95%CI 0.44-3.41)%. While those in 20-39 years age group and 40-59 years age group had 77.34% and 73.79% treatment success rates respectively with those in the 20-39 years age group having greater chance of treatment success in reference to those in >60 years old with (OR=1.24, 95%CI=0.53-2.93) and those in the 40-59 years age group having a greater chance of treatment success relative to those in the >60 years age group with (OR=1.02, 95% CI=0.41-2.57). In addition patients who resided in urban area had better treatment outcomes in reference to those in rural area (OR=1.52,95%CI=0.98-2.36), with an adjusted (OR=1.49, 95%CI=0.96-2.32). Further analysis revealed that patients with pulmonary tuberculosis had greater chances of treatment success in reference to those with extra-pulmonary TB (OR=1.70, 95%CI=0.88-3.29) and an adjusted (OR=0.6, 95%CI=0.31-1.17). This study also revealed that HIV negative patients had greater treatment success chances as compared to those co-infected (OR=1.10,95%CI=0.67-1.79). Additionally those on ART had a greater chance of treatment success compared to those not on ART (OR=1.14 and 95%CI=0.12-11.11).

Table 6 Treatment success rates among TB patients

Characteristic		Treatment success n(%)	Unadjusted OR 95%CI	p value	Adjusted OR 95%CI	p value
Sex				**0.4358**		
	Female	159(77.94)	1.19(0.77-1.85)			
	Male	181(74.79)	*ref.*			
Age				**0.8794**		
	<20 years	44(77.19)	1.23(0.44-3.41)	0.69		
	20-39 years	198(77.34)	1.24(0.53-2.93)	0.622		
	40-59 years	76(73.79)	1.02(0.41-2.57)	0.96		
	≥ 60 years	22(73.33)	*ref.*			
Residence				**0.0628**		
	Urban	167(72.61)	*ref.*			
	Rural	173(80.09)	1.52(0.98 - 2.36)		1.49(0.96-2.32)	**0.077**
TB type				**0.1267**		
	Pulmonary	309(77.25)	1.70(0.88-3.29)		0.6(0.31 - 1.17)	**0.136**
	Extra Pulmonary	30(66.67)	*ref.*			
HIV Status				**0.7058**		
	Negative	102(77.86)	1.10(0.67-1.79)	0.707		
	Positive	237(76.21)	*ref.*			
	Not Done	1(100.00)	_			
	Unknown	0(0.00)	_			
ART Status				**0.9134**		
	On ART	225(77.32)	1.14(0.12 - 11.11)			
	Not on ART	3(75.00)	*ref.*			

p-value for likelihood ratio test, adjusted for residence and TB type. Treatment success= cured + treatment complete.

CHAPTER FIVE: DISCUSSION

5.1 Socio-demographic characteristics of TB patients

This study aimed to investigate the factors associated with TB treatment outcomes by HIV status. The study found that there were more males with TB relative to females consistent with previous studies in Brazil (Muniz *et al.*, 2006; Do Prado *et al.*, 2014). However, studies in Ethiopia and Malawi found more females relative to males (Endris *et al.*, 2014; Sileshi *et al.*, 2013; Tweya *et al*., 2013). Although the reason for geographical differences in gender distribution is not currently known, a recent study in Taiwan indicated that being male is one of the independent factors associated with recurrence of TB (Chao *et al.,* 2015). Of significance this study also reported that more males relative to females presented with TB-HIV co-infection, further suggesting that identifications of social subgroups such as male gender should form a critical component of TB control programs. This study also revealed that the prevalence of TB-HIV co-infection was 69.80% among TB patients with known HIV status, which is relatively higher than the national prevalence of 39% (DTLC, 2013). This can be partly attributed to the high HIV prevalence in the study area, which is three times the national average (MoH, 2013; MoH, 2014). In deed similar studies in areas with high HIV burden have reported similar findings, for examples, studies in Ethiopia reported 52.1%, Uganda 54%, Nigeria 40% and Tanzania 29%, Malawi 68% (Van den Brooks *et al.*, 1993; Richards *et al.*, 1995; UNAIDS, 2011; Tweya *et al.*, 2013; Beza*et al.*, 2013). This has been linked to HIV-associated immune-suppression in HIV infected individuals, which is not only reactivates latent TB to active TB but is also a risk factor for development of new TB infection (Toossi, 2003;Kirenga*et al.*, 2015;Chao*et al.*, 2015). Together these data point to the fact that persons living with HIV have disproportionate burden of TB. Alternatively this disparity can be attributed to the small

population size and the fact that most of the TB patients in Nyando sub-county come from Ahero Township, which is a major urban area within study area. This finding is consistent with previous observations that associated TB-HIV co-infection with living in urban area (Prado *et al.*, 2011; Do Prado *et al.*, 2014). Moreover, TB-HIV co-infection was more prevalent in 20-39 years age group, an age group associated with risky life styles and lack of awareness to vulnerability to infections ultimately exposing them to both HIV and TB (Santos *et al.*, 2009).Of note, this study, similar to other studies has also associated TB-HIV co-infection with gender and age (Do Prado *et al*., 2014; Prado *et al.,* 2011). Overall, these data suggest that socio-demographic characteristics strongly influence TB-HIV co-infection.

5.2 Risk factors associated with TB-HIV co-infection

Previous studies have shown that TB-HIV co-infection is associated with ethnicity or race, gender, being male, living in urban area, being within 20-59 years age group, the level of education, lower socio-economic status and diabetes (Prado *et al.*, 2011; Do Prado *et al.*, 2014; Chao*et al.*, 2015). Consistent with these previous findings the results of this study also revealed that patients aged 20-39 years and 40-59 years were also found to have higher chances of co-infection as compared to those <20 years of age. This age group is associated with engagement in risky lifestyles or sexual behaviors that predisposes them to HIV-TB co-infections (Santos Mde et al., 2009). Of significance previous studies have reported that TB patients residing in urban areas are more likely to be TB-HIV co-infected relative to those in rural set-up(de Vries, *et al.*, 2010; Do Prado *et al*., 2014). This is attributed to overcrowding or high population density that can result in reactivation of TB infection acquired in other areas or increased transmission of TB (de Vries *et al.*, 2010). Consistent with these previous observations, this study also reports that TB patients who resided in rural areas were less likely to be TB-HIV co-infected as compared to those in urban setting. Of significance is that not only is HIV prevalence high in this

area but the prevalence are higher in urban settings (MOH, 2014) and this may explain the findings of the current study. Alternatively these results may also be attributed to health seeking behaviors in rural or poor TB diagnosis or inability to diagnose TB in rural health facilities in resource poor countries (WHO, 2012).

Similar to other studies (Tweya *et al.*, 2013; Do Prado *et al*., 2014), this study found that patients with smear negative results were more likely to be TB-HIV co-infected as compared to their counterparts with smear positive results. Several studies have shown that smear positivity to be more prevalent in TB only group (Tweya *et al.*, 2013; Do Prado *et al.*, 2014; Chao *et al.*, 2015). The acid fast bacillus (AFB) test negativity among TB-HIV co-infected patients is reported to be due to immunodeficiency caused by HIV virus (Do Prado *et al.*, 2014; Coimbra *et al.*, 2014; Huang *et al.*, 2015), which compromises diagnosis of TB by immunodiagnostic methods to confirm latent TB. This makes diagnosis of HIV associated TB difficult even with the development of advanced TB microbiological testing techniques due to frequent presentation of TB as sputum negative(Schutz *et al.*, 2010). Moreover, the cost associated with the new and more sensitive and specific techniques for diagnosis of TB compounds the problem of TB diagnosis among co-infected patients in resource-limited settings (Buijtels *et al.*, 2009).Significantly, this study further reveals that, TB patients with extra-pulmonary TB, which is also associated with immunosuppression were 4.95 times more likely to be reported as TB-HIV co-infected than those with pulmonary TB. Therefore, these data indicate the need to develop more sensitive diagnostic techniques to confirm TB in HIV infected individuals (Do Prado *et al.*, 2014). In deed WHO, recommends the use of more specific and sensitive assays like gene Xpert assay in detection of drug resistance TB and TB in HIV co-infected individuals in high TB burden countries in Asia and Africa (WHO, 2013). Moreover, other studies have

indicated that addition of proteins called resuscitation-promoting factors or mycolic acid significantly improve both viability and culturability of AFP thus improving TB diagnosis (Mukamolova *et al.*, 2010); Kaufmann *et al.*, 2013;Chao*et al.*, 2015). However, these assays are not currently widely applicable in countries with low laboratory capacities like Kenya.

Importantly in this study, children did not have any culture or smear test done to confirm suspicions of TB. A previous study indicated that there are challenges experienced in the diagnosis and treatment of tuberculosis in children who are TB-HIV co-infected (Coimbra *et al.*, 2014). This is partly due to HIV related illnesses such as lymphocytic interstitial pneumonitis that may present in a similar manner as PTB. These results are in line with those of other studies that have advocated for more sensitive and specific advanced diagnostic tools for TB among kids and young adults in TB-HIV co-infected populations (Coimbra *et al.*, 2014). Moreover, HIV testing, especially when the result is negative is quite helpful as it increases the chances of TB diagnosis, although a positive HIV test does not rule out possibility of TB infection (WHO, 2003).

Wasting is one of the features of both TB and HIV co-infection due to loss of appetite leading to reduction in energy intake. This subsequently impairs physical action and increases mortality rates among these patients (Paton *et al.*, 2003). Studies have shown that TB, HIV and malnutrition are related to emergence of drug resistant TB strains especially in TB-HIV co-infected patients (Buijtels *et al.*, 2009) this is attributed to poor absorption of drugs and conversion into active metabolites as a result of severe wasting. Optimization of nutritional intake as part of routine TB management is thus advocated for (Schwenk *et al.*, 2000) since nutritional support offered at time of drug initiation is reported to improve immune recovery (MOH, 2014).Significantly this study reports that a majority of TB only and TB-HIV co-infected

had <18.5 BMI and that BMI <18.5 increased the risk for TB-HIV co-infection. This is in line with a recent observation that a BMI of < 18.5 confers with risk factor for active TB and TB-HIV co-infection as compared to a BMI > 18.5 (Dharanaj*et al.*, 2015).

5.3 Treatment outcomes in TB patients by HIV status

In this study, cure rates were greater in the TB only group as compared to the TB-HIV co-infected group (47.33% and 34.73% respectively). This is relatively higher than the cure rates reported in Ethiopia where the curates for TB only patients was 19.2% while TB-HIV co-infected had 29.2% (Endris *et al.*, 2014) although the study did not indicate whether the TB co-infected group was on ART. Whereas in the current study all the TB-HIV co-infected were on ART. Moreover, a study in Malawi with ART coverage of 38% showed that successful treatment among those on ART relative to those not on ART due to ART enhancing immune response among HIV infected TB patients (Tweya *et al.*, 2013).Another study in Brazil where the TB-HIV co-infected patients were on ART reported a higher cure rate of 84.95% for TB only patients and 55.75% for TB-HIV co-infected which is higher than the cure rates reported in the current study and a previous study in Ethiopia (Endris *et al.*, 2014). This can be attributed to the fact that the Brazilian study used a scoring system used to diagnose smear negative pulmonary TB in children and adolescents or in HIV infected adults suspected to have pulmonary TB this enabled them to discriminate patients who did not have pulmonary TB and rapid initiation of TB patient in proper medication (Do Prado *et al.*, 2014). This method is still not widely applied in countries with limited laboratory capacities like Kenya.

Treatment of TB-HIV co-infected individuals is associated with poor treatment outcomes in TB patients (Tweya *et al.*, 2013; Do Prado *et al.*, 2014; Dharanaj *et al.*, 2015). Consistent with these studies this study reports a higher default rate among the TB only group. It is important to note

that there were no defaulters in the TB-HIV co-infected group suggesting integration of TB and HIV services can increase adherence to TB medication. This is contrary to previous suggestions that increased drug burden due to taking HIV and TB drugs can leads to lack of adherence (Fenner *et al.*, 2012; Do Prado *et al.*, 2014).Consistent with previous observation that TB-HIV co-infection is associated with poor outcomes relative to those with TB only (Sanchez *et al.*, 2012; Do Prado *et al.*, 2014; Dharanaj *et al.*, 2015). This study also found that those with TB-HIV co-infection were more likely to die relative to those with TB only and this partly attributed to enhanced immunosuppression due to co-infection with HIV (Dharanaj *et al.*, 2015).The treatment failures were also relatively lower in TB only group relative to TB-HIV group these results are also consistent with previous observations (Do Prado *et al.*, 2014; Dharanaj *et al.*, 2015).

5.4 Factors associated with TB treatment outcome by HIV status

Concomitant TB/HIV treatment has proven to be difficult due to the long term TB treatment coupled with drug interactions between ARV and TB drugs. The extra burden in taking these drugs results in high default rates as shown in some studies (Do Prado *et al.*, 2014). This has led to new strategies for monitoring treatment and development of a combine drug for both TB and HIV treatment. In this study, all the co-infected patients were on concomitant TB-HIV treatment and DOT was used as a treatment monitoring strategy for both TB-HIV co-infected and TB only groups. DOT was done either by a household member or a healthcare worker with a greater percentage being done by the household members. Data shows that TB/HIV concomitant therapy coupled with DOT support improve TB treatment outcomes, with 84% of patients on TB/HIV treatment being reported to have completed treatment (Davies *et al.*, 1999; Gandhi *et al.*, 2009). These findings are in agreement with the study's findings since most of the patients in this study were cured or completed treatment with a 83.85 % DOT coverage in the TB-HIV group and

88.27% coverage in the TB only group provided by a house hold member. The current WHO guidelines for TB treatment recommend DOT to monitor patient adherence to drugs (WHO, 2008). This ensures patients take the drugs in right doze and at the right intervals.

Antiretroviral therapy given to TB-HIV co-infected patients has been reported to improve survival among co-infected patients (Ciglenecki *et al*., 2007; Gandhi NR, 2009). This study is in agreement with these findings since patients on ART had 1.14 greater chances of successful treatment outcomes as compared to those not on ART. Initiation of ART within 6 months of TB diagnosis has been reported to improve survival among TB-HIV co-infected individuals (Gandhi *et al.*, 2009). In addition, patients in this study received Cotrimoxazol treatment, which is essential for boosting their immunity. The Kenyan government has set collaboration between TB and HIV national programs with an aim to reduce HIV burden among people with TB and reduce TB in PLWHIV. This strategy has further been strengthened by DOT (WHO, 2005). Data shows that TB/HIV concomitant therapy coupled with DOT, improve TB treatment outcome (Ciglenecki *et al.*, 2007).Antiretroviral therapy initiation within 6 months of TB diagnosis reduces mortality rate substantially and is associated with greater survival rates among HIV-TB co-infected patients(Gandhi NR, 2009). In this study favorable treatment, cured and treatment complete, is associated with the intensified ART treatment among TB-HIV co-infected patients coupled with DOT and provision of nutritional support to patients. Other studies have advocated for additional interventions such as prophylaxis, intensified surveillance and case findings to reduce and ultimately prevent TB-HIV co-infection (Nullis-Kapp *et al.*, 2005; WHO, 2005).

Studies have related unfavorable treatment outcomes (default and death) to TB-HIV co-infection (Coimbra *et al.*, 2014; Kirenga *et al.*, 2015). The explanation for this has been given as immune suppression due to HIV in these patients, mortality among these cohort is commonly related to

late diagnosis of TB due to stigma of being sent to HIV clinic for screening (Luby SP, 2004; WHO, 2013). Similar to these previous observations this study reported unfavorable treatment outcomes with more deaths, treatment failure and defaults in the TB-HIV group as compared to their TB only counterparts. In addition HIV negative patients had 1.10 greater chances of successful treatment outcomes as compared to their HIV positive counterparts. This clearly shows that HIV plays a very important role in TB treatment outcome. In this study only one patient did not have HIV results, this show that the Kenyan Ministry of Health through the collaborative TB/HIV control program strengthened the collaborative TB and HIV services to ensure all the patients are screed for both diseases on presentation to the health facilities. This will ultimately lead to early diagnosis and initiation of treatment leading to good health outcomes.

Other studies have also associated poor treatment outcomes to increase in age, defaulting of drugs and residence in rural areas (Lawn, 1999). This is in line with this study, which on the other hand associates successful treatment outcomes with age and living in urban areas. With those 20-39 and 40-59 years of age having successful treatment outcomes as compared to those >60 years of age and those residing in urban areas having a 1.52 better chance of successful treatment outcome as compared to those in rural areas. However, the reasons for successful treatment outcomes in these age groups are not clear. Poor treatment outcomes in rural areas are thought to be due to inadequate resources and late diagnosis of tuberculosis (Lawn, 1999).

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

This study provided a better understanding of social-demographic factors as well as factors associated with TB treatment outcomes by HIV status in Nyando Sub-County. TB-HIV co-infection in this population is higher than that of the national average with more male patients than female patients. In addition, most TB-HIV co-infected patients were from the urban areas and were between 20-39 years of age. Of importance is that almost all the patients had known HIV status, which indicates a good integration between the TB and HIV services.

In addition DOT, which is one of the WHO recommendations for monitoring treatment in patients with TB, was successfully covered in this population. This was coupled with a high intake of Cotrimoxazol and ART among TB-HIV co-infected patients. Treatment success rates were also high among this population and this can be attributed to the high DOT and ART coverage among this population. Despite much Nutritional supplements given to the patients, this did not reflect on their BMI. There was only one case of MDR reported in the study. The provision of both TB and HIV drugs to this population shows how adequate the Ministry of Health in partnership with other organizations is supplying drugs to the health facilities.

This study used routine program data and this provided limited information on other socio-demographic factors such as level of education, economic and marital status as well as clinical factors such as CD4 count and viral load for the co-infected patients. In addition the registers indicated whether culture test and X-ray were done for the patients or not but didn't indicate their results. Only few patients had information on whether the X-rays and culture test were done, indicating lack of or limited resources for these services.

6.2 Recommendations for action

The TB registers should be improved to capture other socio-demographic and clinical characteristics of the patients. This will provide detailed information for further analysis on factors associated with the patients that may affect their treatment outcomes. Time of ART and TB drug initiation from time of diagnosis should be well captured in the register. This will provide adequate information on how prompt the treatment is started once the disease is diagnosed.

The government of Kenya should improve on the testing services availability and acquire more advanced techniques for screening of TB especially in TB-HIV co-infected patients and children. This will confirm most of the smear negative TB cases and will also reduce the cases of wrong or late TB diagnosis as immunodeficiency in HIV patients has been reported to interfere with TB screening.

Lack of or limited resources such as diagnostic and testing services in resource limited areas such as Nyando sub-County should be evaluated and improved. This will ensure all the patients who go to the TB center or clinics are adequately screened rather than evaluated based on their symptoms before put on drugs.

6.3 Recommendation for future research

Further research can be done to evaluate knowledge and attitude of patients on TB treatment. This will shade more light on factors associated with the patients that might affect their attitude towards treatment and this will portray a clear picture on factors that lead to poor treatment outcomes such as defaults.

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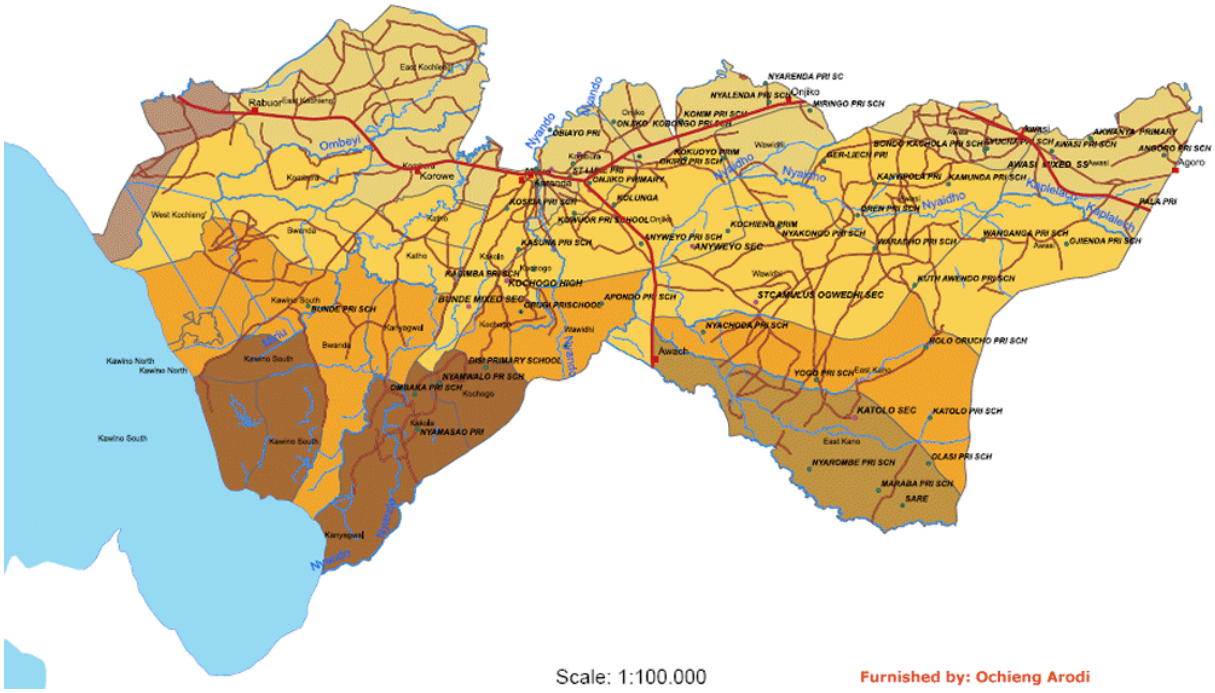
Appendix 1: Map of Nyando Sub-County


Scale: 1:100.000
Furnished by: Ochieng Arodi

Appendix 2: Data Abstraction form

REG	SEX	AGE	BMI	FACILITY	REGIMEN	DOT	TB TYPE	PATIENT	X-RAY	CULTURE	SMEAR	HIV STATUS	COTRIMOXAZOL	ART

Appendix 3 Ethical clearance

MINISTRY OF HEALTH

Telegrams: "MEDICAL", Kisumu
Telephone: 057-2020801/2020803/2020321
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JARAMOGI OGINGA ODINGA TEACHING & REFERRAL HOSPITAL
P.O. BOX 849
KISUMU

ERC.1B/VOL.I/180
Ref: .....

Date 21st May, 2015

Rebecca Loraine Achieng',
Reg. No. H152/4388/2013,
JOOUST.

Dear Rebecca,

RE: FORMAL APPROVAL TO CONDUCT RESEARCH TITLED: *"FACTORS ASSOCIATED WITH TUBERCULOSIS TREATMENT OUTCOMES IN TB-HIV CO-INFECTED AND TB ONLY PATIENTS IN NYANDO SUB-COUNTY"*

The JOOTRH ERC (ACCREDITATION NO. 01713) has reviewed your protocol and found it ethically satisfactory. You are therefore, permitted to commence your study immediately. Note that this approval is granted for a period of one year (21st May, 2015 to 22nd May, 2016). If it is necessary to proceed with this research beyond the approved period, you will be required to apply for further extension to the committee.

Also note that you will be required to notify the committee of any protocol amendment(s), serious or unexpected outcomes related to the conduct of the study or termination for any reason.

Finally, note that you will also be required to share the findings of the study in both hard and soft copies upon completion.

The JOOTRH ERC takes this opportunity to thank you for choosing the institution and wishes you the best in your endeavours.

Yours sincerely,

FRED OUMA AKWATTA,
SECRETARY - ERC,
JOOTRH – KISUMU.