PREDICTORS OF TUBERCULOSIS RECURRENCE IN ADULT PATIENTS TREATED IN SIAYA AND KISUMU COUNTY HOSPITALS

BY

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DECLARATION

1. THE STUDENT

I, Matemo Daniel declare that this thesis is my original work and no part of this work has been submitted for the award of a degree or diploma in any other University or college. No part of this thesis may be reproduced without the prior permission of the author, co-investigators and Maseno University.

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DEDICATION

I dedicate this thesis to Matemo's family for their moral support in carrying out this work.

ABSTRACT

Tuberculosis still remains one of the world's deadliest curable disease. Emergence of HIV, multi-drug resistance (MDR), high prevalence of post-treatment tuberculosis are some of the major setbacks which now poses a major challenge to attainment of tuberculosis control programme targets of 70% detection of infectious tuberculosis and 80% cure rate of detected cases. Despite the availability of effective anti-tuberculosis and ant-retroviral (ART) drugs, high incidence rate of approximately 9-11% of recurrence continues to be observed in Kisumu and Siaya county hospitals. The risk factors for recurrence in this area is poorly documented. To reverse this condition, new intervention mechanisms are needed but must be based upon sound epidemiological data derived from this community. Recurrence is often associated with weak health systems, poor treatment outcomes and MDR. Available data on predictors for recurrence yield conflicting information about whether socio-economic factors, lifestyle and immunosuppression increases the susceptibility of recurrence or not. Therefore, the aim of this study was to determine the predisposing factors associated with recurrence. This was a hospital based cross-sectional study where data were collected from both out and in-patients suffering from tuberculosis in Ahero, Kisumu, Bondo hospitals and Jaramogi Oginga Odinga Teaching and Referral Hospital. Between April 2014 and January 2015, 227 TB participants were enrolled. TB patients were approached from the chest clinic where they were briefed about the study. Upon consenting, a semi-structured questionnaire was completed from eligible participants. Predictors such as medical information, lifestyles and socio-economic characteristics were collected from eligible participants. Information captured was entered into an Access database and analyzed using STATA at CI of 95% and $p \leq 0.05$ level of significance. Chi–square test was used to analyze the proportion of recurrence and logistic regression was used to establish any existing associations between recurrence and predictors. Median age was 33 (IQR 26-40), 55% were male. HIV prevalence was higher among recurrent vs. incident TB cases (80% vs. 65%, p=0.02). Coverage of ART was higher among those with recurrent vs. incident TB (95% vs. 82% p=0.005).Recurrent TB was associated with older age (OR 1.05/per year increase, 95% CI: 1.01-1.09), male sex (OR 2.28, 95% CI: 1.06-4.87), HIV (OR 2.47, 95% CI: 1.18-5.19). There was less household crowding among those with recurrence (OR: 0.78/per household member, 95% CI: 0.64-0.96).Smoking, low weight, alcohol use, employment, were not associated with recurrence. The proportion of TB-HIV co-infection observed in this study was much higher compared to national rate. In conclusion, high prevalence of HIV infection among recurrent patients despite high coverage of ART observed in this study underscores the importance of developing new approaches on fighting against tuberculosis. There is need for further studies on ARV to determine whether ART adherence and resistance are associated with poor outcome in settings where uptake of HAART is high among tuberculosis patients.

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ACRONYMS

AIDS:	Acquired Immunodeficiency Syndrome
ART:	Anti-Retroviral Therapy
BCG:	Bacillus Calmette-Guérin
BMI:	Body Mass Index
cART:	Combined Antiretroviral Therapy
CRF:	Case Report Form
DLTLD	Division of Leprosy, Tuberculosis and Lung Disease
HAART:	Highly Active Anti-Retroviral Therapy
HIV:	Human Immunodeficiency Virus
IQR:	Interquartile Range
JOOTRH:	Jaramogi Oginga Odinga Teaching and Referral Hospital
KAIS:	Kenya AIDS Indicator Survey
MDG:	Millennium Development Goal
MDR:	multidrug-resistance
OIs:	Opportunistic Infections
TB:	Tuberculosis
TNF-α	Tumour Necrosis Factor-Alpha
WHO:	World Health Organization
DOTs:	Directly Observed Treatment, Short –course
XDR:	Extensively Drug-Resistant

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CHAPTER ONE: INTRODUCTION

1.1 Background Information

It is estimated that a third of the world's population is suffering from tuberculosis (World Health Organization, 2010). Recent data from WHO updates on TB demonstrate that in 2013, 9 million people were estimated to be newly infected with TB with Africa Region accounting for approximately one quarter of these cases .Of the 9.0 million newly infected cases in 2013, an estimated 1.1 million (13%) were HIV positive. Three quarter of these TB cases co-infected with HIV were estimates from Africa Region. In the same year, about 0.36 million deaths were estimated to be due to TB co-infection with HIV (World Health Orginization, 2014). Approximately, 0.3 million (5.2 %) of 5.7 TB notified in the year 2013 were due to secondary infection (World Health Orginization, 2014)

In Kenya, high rate of tuberculosis infection continues to be observed in settings with high tuberculosis incidence and HIV prevalence. According to Division of Leprosy, Tuberculosis and Lung Disease (DLTLD) report of 2010, Nyanza is one of the three high TB burden region in the country and it contributes approximately 18% of the national TB disease burden (DLTLD, 2010). While prevalence of 6.0 per 1000 has been reported in Nyanza region (van't Hoog *et al.*, 2011). In 2014, an estimated 12064 recurrence incidents were detected in the country and out this, approximately 5.8% (704) cases were reported from Siaya and Kisumu counties.(Dhis2, 2014)

One challenge of tuberculosis control is the emergence of post treatment tuberculosis, for which the world health organization DOTS and initiation of antiretroviral therapy among patients co-

infected with HIV/TB strategies are not enough. Understanding the predisposing risk factors for recurrence tuberculosis is therefore a key factor in reducing TB- related morbidity and mortality.

Second episode of TB which is known to occur after an initial successful treatment. Two mechanisms may explain the relatively increased TB recurrence risk, either that patients will have a recurrence through reinfection probably due HIV infection or due to relapse which is as a result of persistence of *Tuberculosis bacilli* (Crampin *et al.,* 2010; Lambert *et al.,* 2003).

In TB and HIV epidemic area, HIV infection has emerged as one of the major risk factors for post-treatment tuberculosis. HIV infection leads to loss of cell-mediated Immunity thus predisposing one to opportunistic infections (Angel *et al.,* 1998) such as secondary tuberculosis (Crampin *et al.,* 2010; Houben *et al.,* 2012).Initiation of anti-retroviral therapy therefore leads to rapid recovery of CD4 T-lymphocytes cells. This results in enhanced protection against both primary and post primary tuberculosis (Ahmad Khan *et al.,* 2012; Lawn *et al.,* 2011).

To date, little is known about the effect of HAART on secondary tuberculosis. Available data from previous studies conducted in Malawi (Houben *et al.,* 2012) and Brazil (Golub *et al.,* 2008) on highly active anti-retroviral therapy (HAART) demonstrated that ART use appeared to reduce tuberculosis recurrence in HIV infected patients rate by 50%.

The risk of post-treatment tuberculosis is not confirmed to HIV infection alone, poor adherence to treatment has been widely documented as risk a factor for post primary tuberculosis (Driver, Munsiff, Li, Kundamal, & Osahan, 2001). Noncompliance with self-administered anti-tuberculous drugs is the main cause of endogenous reactivation (Picon *et al.,* 2007) and the

prolonged absences from treatment and frequent interruption of treatment has been associated with four-fold increased risk of a poor outcome of therapy (Picon *et al*., 2007).

Available literature on risk factors for post primary tuberculosis yield conflicting data about whether socio-economic factors such as age, sex and employment increases the susceptibility of recurrence tuberculosis. Age has been inconsistently reported to increase recurrence tuberculosis (Charalambous *et al.,* 2008; Luzze *et al.,* 2013; Millet *et al.,* 2009; Moosazadeh, Bahrampour, Nasehi, & Khanjani, 2015; Picon *et al.*, 2007). It has been postulated that immune response against recurrence tuberculosis may decrease among elderly individuals. Although there are scant data regarding the influence of gender on post treatment tuberculosis, sex has nevertheless been documented as a risk factor for post primary tuberculosis (Millet *et al.,* 2009). However, this association of female with recurrent tuberculosis was not confirmed in two cohort studies exploring risk factors for recurrent tuberculosis (Moosazadeh *et al*., 2015; Picon *et al.,* 2007).

The contribution of alcohol uptake to the burden of post primary tuberculosis infection is not well defined. It is uncertain whether alcoholism increases susceptibility of recurrence tuberculosis among individuals who abuse alcohol compared to those who are not abusing alcohol, with studies reporting in favour (Anbesaw W. Selassie, Carol Pozsik, Dulaney Wilson, & Pamela L. Ferguson, 2005; Unis *et al.,* 2014) and others against (Millet *et al.,* 2009; Picon *et al.,* 2007). Smoking has been widely documented as an independent predictor of post treatment tuberculosis (Moosazadeh *et al.,* 2015; Thomas *et al.,* 2005a; Trinh *et al.,* 2014). Smoking results in major immunologic changes which play a key role in suppressing the intracellular growth of *Mycobacterium Tuberculosis.* This include low level of tumour necrosis factor – alpha (TNF-α) (Kotani *et al.,* 2000)

While risk factors such as weight and employment has been mentioned as predictors of recurrence (Consortium., 2002; Sonnenberg *et al.,* 2001) data on the impact of these two predictors on treatment outcomes among patients with tuberculosis are limited. Influence of underweight on rate of recurrence has been less consistently reported.

With this background in mind, this cross sectional study was aimed at determining predictors of tuberculosis recurrence in HIV infected and HIV non infected patients accessing tuberculosis care at Ahero County hospital, Bondo sub County hospital, Kisumu County hospitals and Jaramogi Oginga Odinga Teaching and Referral hospital, located in the Nyanza Rgion.

HIV prevalence in Nyanza region is estimated to be 15.1% (NASCOP, 2012). This cross sectional study was timely given that previous studies demonstrate that recurrence of tuberculosis after cure is common in region with high tuberculosis incidence (Eline Korenromp L, Scano, Williams, Dye, & Nunn, 2003) and high HIV prevalence (Fitzgerald *et al.,* 2000; Hawken *et al.,* 1993; Kelly, Cumming, & Kaldor, 1999; Mallory, Churchyard, Kleinschmidt, De Cock, & Corbett, 2000).

Ahero and Bondo hospitals are high volume government-run public health facilities which serve low- to middle-income rural populations while Kisumu county hospital is also a government hospital which serve both peri-urban and urban populations. JOORT is a referral hospital for both Nyanza and Western regions. This hospital serves both rural and urban populations. There are comprehensive care clinics and TB clinics in all of these four public hospitals.

1.2 Statement of the Problem

TB remains a major cause of death and morbidity worldwide and it is ranked second among the communicable diseases that represents a major public health threat to the global population. Despite availability of effective ant-TB drugs and HAART, tuberculosis recurrence still remains high in Kenya and in Nyanza region and the true burden of second episode of tuberculosis among individuals on highly active anti-retroviral therapy versus those who are HIV negative have not been well documented in Kenya.

In Kenya, the number of new and secondary tuberculosis has stabilized since 2007, following a marked increase between 1995 and 2006 (Appendix 4). However, in areas heavily burdened by HIV such as Nyanza region, recurrence rate seems to be even higher reaching 11% following standard treatment. While smoking, and alcohol use have been strongly associated with post primary tuberculosis in rich settings, other factors such as old age, sex, poor drug adherence, low weight and employment have been less consistently documented in poor settings. It remains unclear the main risk factor for recurrence in Nyanza region. Also, the cause of TB burden in this region has not been adequately explored and true burden of this event has been poorly documented. The purpose of this study was therefore to establish the predictors of post treatment tuberculosis in the background of high coverage of HAART and, tuberculosis and HIV infection.

1.3 Significance of the study

One challenge that receives little attention is recurrence of tuberculosis. To date, information on TB is very scarce and true magnitude of post primary tuberculosis is poorly documented in settings where prevalence of HIV/TB is high. Contribution of recurrence to epidemiology and

pathogenesis of tuberculosis has important implications for tuberculosis control, prevention, and vaccine development and evaluation drug regimen. Emergence and devastating effect of HIV and AIDs on susceptibility to TB, has disproportionately affected the sub-Sahara Africa and it is approximated to account for 80% cases of HIV-associated TB.

Although HIV infection has been cited as the key driver of subsequent episode after cure of new tuberculosis in HIV/TB endemic settings, other risk factors including age, sex, smoking, low weight have also been reported (Thomas *et al.,* 2005c). While there is plausibility association of sociodemographic risk and poor drug adherence, observation studies yield conflicting data about whether alcohol, low weight, age and sex increases susceptibility to post treatment tuberculosis. Although ART use is likely to reduce susceptibility of recurrence among HIV infected patients by 50% in other settings (Golub *et al.,* 2008),much of its preventive benefits for post primary tuberculosis control is yet to be realized in this setting.

Because post primary tuberculosis is strongly associated with low cure rate and acquisition of anti-tuberculous resistant (Murray, Sonnenberg, Shearer, & Godfrey-Faussett, 1999), it is therefore important to define the risk factors for recurrence and to build new strategies that can be incorporated into the recommended WHO preventive pathway for fighting against tuberculosis infection.

While WHO have primarily focused on the use of DOTs and scale up of ART as means of controlling tuberculosis, available data from district health information system (Dhis) on high rate of recurrent tuberculosis in Nyanza Region has clearly demonstrated that DOTs and ART strategies are insufficient as main control interventions. Understanding risk factors for post primary tuberculosis is therefore crucial and will be useful in the design of novel therapeutic agent and vaccine development.

Information generated will be shared through hospital continues medical education and international journal and conferences.

1.4 Main Objective

To determine predictors of TB recurrence in adult patients treated in Siaya and Kisumu County hospitals

1.4.1 Specific Objectives:

1. To establish association of social economic risk factors and TB recurrence among adults patients seeking TB care in Siaya and Kisumu County hospitals
2. To determine the association of HIV infection among adult patients with second episode of tuberculosis versus patients with primary tuberculosis in Kisumu and Siaya County hospitals.
3. To evaluate the potential association between lifestyle risk factors and post treatment tuberculosis among adult patients treated for TB in both Kisumu and Siaya County hospitals

1.5 Research Question

1. What are the socio-economic factors that are associated with secondary TB infection adult patients receiving TB care in Bondo sub-County hospital, Ahero and Kisumu County hospitals and Jaramogi Oginga Oginga Odinga Teaching and Referral hospital?
2. What proportional of HIV infections among adult patients with TB recurrence versus patients who are newly infected with TB attending Kisumu and Siaya County hospitals?
3. What are the lifestyle risk factors that are linked with recurrence tuberculosis among adult seeking TB care at both Siaya and Kisumu County hospital?

CHAPTER TWO: LITERATURE REVIEW

2.1 General Introduction of Recurrence Tuberculosis

Tuberculosis is a communicable disease caused by a bacterium known as *Mycobacterium tuberculosis.* This bacterium was first identified by the German scientist called Robert Koch who announced the discovery on March 24, 1882 (Lawn & Zumla, 2011). These bacteria usually attack the lung (Pulmonary TB) but can also affect other parts of the body such as central nervous system, lymphatic system, bone and genitourinary system (Kim et al., 2009).

There are two mechanisms that may explain the recurrent episode of TB after one being cured of the disease - either due to relapse that can occur when tuberculosis bacilli persist after treatment despite apparent cure, or exogenous reinfection probably due to high prevalence of TB in the population or due to immunosuppression caused by HIV infection . Inadequate treatment, either regimen or treatment duration or even pre-existing drug resistance may also explain an elevated risk of developing a relapse (Lambert *et al.,* 2003). It is plausible that some recurrences are due to reinfection by a different strains

Although TB disease burden continues to improve since the discovery of effective first line anti TB drugs and highly efficacious and less toxic ART, and the availability of BCG (Bacillus Calmette-Guérin) vaccine, the emergence of drug-resistant strains and recurrences of the disease across the world threaten to reverse gains made by worldwide tuberculosis control programmers (World Health Orginization, 2014) and therefore, tuberculosis remains one of the most common worldwide human infections. Its prevalence is being closely tied to the socio-economic conditions, overcrowded environment and malnutrition (Bates *et al.,* 2004; Cegielski & McMurray, 2004; Lonnroth, Williams, Cegielski, & Dye, 2010). In resource limited countries,

the prevalence of the infection is even higher and this is attributed to the prevailing socio-economic conditions and prolonged immunosuppression due to HIV in infection.

2.2 Global Burden of Tuberculosis

Despite the availability of isoniazid (INH) drugs since 1940s, and the discovery of Rifampicin which is a first line drug in 1960s, *M tuberculosis* complex organisms are increasingly becoming diseases of major public interest (World Health Organization, 2011; World Health Orginization, 2014). Each year, several people around the world becomes infected with tuberculosis with vast majority of these people being from Asia and sub-Sahara Africa (World Health Orginization, 2009) Estimates from recent WHO report on global tuberculosis control reveal that, 9.0 million incidents cases occurred in the year 2013, compared to 8.6 incident cases in 2012 (World Health Organization, 2013; World Health Orginization, 2014).While Americas and Western Pacific Region have already met the three 2015 MDG targets and South-East Asia is on tract of meeting these three targets, new cases, prevalence and mortality rate due tuberculosis epidemic in many less developed countries in Asia and Africa remains high. In 2013, the number of people infected with tuberculosis in sub-Sahara Africa was estimated to be 2.6 million (29%). Approximately,1.5 million people died of tuberculosis while an estimated 0.36 million death occurred among people co-infected with tuberculosis and HIV (World Health Orginization, 2014)

According to WHO global tuberculosis report of 2014, although tuberculosis disproportionately affected men than women approximately, 330,000 death were estimated to have occurred among HIV negative women and 180 000 death among HIV infected (World Health Orginization, 2014)

2.2.1 Global burden of TB co-infection with HIV

Despite tremendous progress in HIV and TB treatment, co-infection of HIV and TB still poses a major challenge to global health and HIV epidemic is one of key factors undermining the attainment of the 2015 Millennium Development Goals for TB control. The availability of potent and usually well tolerated ART, capable of reducing viremia to undetectable level has greatly enhanced CD4 T-lymphocytes recovery in treated individuals (Angel et al., 1998; Mocroft *et al*., 2007). Impaired immunological responses to antigens has been consistently associated with an increased risk of Acquired Immuno-Deficiency Syndrome (AIDS) - related opportunistic infections. Past studies on HAART have shown that recovery of CD4 T- Lymphocytes among HIV treated individuals is associated with an enhanced T- Lymphocyte responses to antigens and subsequently reducing the risk of developing Acquired Immuno-Deficiency Syndrome (AIDS) related opportunistic infections (Kaufmann *et al.*, 2003; Ledergerber *et al*., 1999). Supporting data on role of HAART in reduction risk of acquiring tuberculosis among HIV infected individual is derived from a cohort study. Investigators of this study observed a reduction of 44% of tuberculosis incidence among HIV infected patients started on a combined antiretroviral therapy (del Amo *et al.*, 2012).

Globally, the incidence (Korenromp, Scano, Williams, Dye, & Nunn, 2003) of HIV and TB co-infection cases is estimated to have peaked in 2005 and about 1.1 million (13%) of new TB cases that occurred worldwide in 2011 were HIV-associated (World Health Orginization, 2014)

The epicenter of the HIV-TB co-epidemic lies in Africa Region. HIV pandemic still poses a major challenge to tuberculosis control in African Region where in 2013 approximately, 34% of tuberculosis cases in this Region were estimated to be co-infected with HIV, which accounted

for 78% of tuberculosis cases among people living with HIV in Africa Region. This co-epidemic was particularly pronounced in southern Africa where more than half of tuberculosis cases were estimated to be co-infected with HIV (World Health Orginization, 2014).

2.2.2 TB Burden in Kenya

The scale of the recurrence is significant in Nyanza Region, given that in this region HIV infection and primary tuberculosis are concentrated.

Tuberculosis epidemic remains a major challenge to Kenya health sector, and co-infection of TB and HIV epidemic is one of the major stumbling blocks in controlling the spread of tuberculosis in the country (DLTLD, 2010).

Although Kenya is among 15 out of 22 High TB burden countries (HBC) that have achieved falling of tuberculosis incidence, data from WHO TB report of 2014 reveals that the country is not on tract of achieving the following two of three 2015 targets; halving tuberculosis mortality and halving the 1990 level of tuberculosis prevalence (World Health Orginization, 2014).

Available data from Global TB Report indicate that, in the year 2013, there were 89 796 new TB cases in Kenya that were notified to WHO. Among these 8 479 (9.4%) were due to relapse. Approximately 94% (84178), of all TB cases were aware of their HIV status where 31 380 (38%) were HIV infected and 84% of them were on combination of antiretroviral therapy (World Health Orginization, 2014).

2.2.3 TB burden in Nyanza

Geographically, the burden of tuberculosis is the highest in Nyanza, Nairobi and Eastern Regions where Nyanza and Nairobi together account for approximately 35% of the country tuberculosis cases (DLTLD, 2010).Nyanza Region has been severely affected by tuberculosis epidemic, fueled by HIV infection. Available data from a cross section survey on prevalence of bacteriologically confirmed pulmonary tuberculosis (PTB) and the fraction attributable to HIV, demonstrate a tuberculosis prevalence cases of 6.0/1000 (95% CI: 4.6-7.4) and slightly less than a half (48%) of prevalent of notified PTB cases were attributable to HIV (van't Hoog *et al.*, 2011). According to KAIS 2012 survey report, Nyanza Region has the highest HIV prevalence rate of 15.1% (NASCOP, 2012).

Data from previous studies reveals that tuberculosis recurrence rate is high in population with high tuberculosis incidence (Fitzgerald *et al.*, 2000; Korenromp *et al.*, 2003) and HIV prevalence population (Fitzgerald *et al.*, 2000; Mallory *et al.*, 2000). Recent data from Kenya health information system on retreatment tuberculosis in Luo Nyanza similarly demonstrate high rate (11%) of recurrence tuberculosis (Dhis2, 2014).

2.4 Risk factors for recurrence tuberculosis

Usually, recurrence due to reinfection may be expected to be a more or less constant risk over time while most of relapse cases are normally observed early and might be identified as treatment failures prior to treatment completion, if more sensitive clinical and laboratory investigations were available.

Perhaps, to understand the contribution of reinfection and reactivation towards secondary infection of tuberculosis, Vynnycky and Fine argues that these two mechanisms are likely to depend on the epidemiologic context. In a setting with an appreciable risk of primary episode of

tuberculosis, individuals may be at high risk of developing tuberculosis that could be due to reinfection. Similarly, in high tuberculosis incidence settings, the risk of tuberculosis reinfection is much higher than the incidence of primary tuberculosis in the general population (Glynn *et al.*, 2010; Verver *et al.,* 2005).High prevalence of HIV infection has been persistently associated with increased rate of recurrence and in population with HIV epidemics, secondary infection is strongly linked to reinfection rather than relapse (Crampin *et al*., 2010; Sonnenberg *et al.,* 2001). In contrast, population with a low risk of TB infection, in developed countries, for instance, the likelihood of re-exposure is small and thus most cases of secondary infection in adults probably results from reactivation (Vynnycky & Fine, 1997).

2.3.1HIV Infection

Tuberculosis once regarded as a disease of overcrowding, poverty and under-nutrition (Bates *et al.*, 2004) is now on the rise among immunosuppressed individuals.

The risk of developing tuberculosis among individuals infected with HIV is estimated to be more than 20 times greater than that of people not infected with HIV(Orginization., 2009). In poor-settings, high case-fatality rates are observed among patients co-infected with TB and HIV (World Health Organization, 2010).

Prior and recent literatures on HIV and tuberculosis reflect highly divergence results on post primary tuberculosis. While it has been proposed that relative risk of recurrence is high among HIV infected tuberculosis patients (Charalambous *et al.*, 2008; Connolly *et al.,* 1999; Fitzgerald *et al.,* 2000; Hawken *et al.,* 1993; Sonnenberg *et al.*, 2001), contrasting data argues that treatment failure rates are similar in HIV immunosuppressed and HIV negative tuberculosis patients (Kelly *et al.,* 1999; Murray *et al.*, 1999; Perriens *et al*., 1995), though high mortality rates are observed

among patients co-infected with HIV and tuberculosis. In a setting where HIV prevalence is high, overall tuberculosis recurrence is estimated to be as high as 20% (Panjabi, Comstock, & Golub, 2007).Individuals who are HIV immunosuppressed have low immunity to subsequent secondary infections. Use of HAART may therefore, influence HIV-1 RNA level, and data suggest that T cell response plays a key role in restoring T helper cells (CD4+) thus reducing episodes of tuberculosis recurrence. Available data from a retrospective cohort on recurrent tuberculosis in HIV infected patients in Rio de Janeiro Brazil argues that, use of triple therapy reduces tuberculosis recurrence by 50% (Golub *et al.*, 2008) While it has been noted that ART may reduce tuberculosis recurrences among HIV infected patient, to date, there is no study that has assessed the risk factors for recurrent disease in a population who are on HAART . In this study, we propose to identify the prevalence of recurrent tuberculosis among participants who were HIV positive versus negative during the first episode of tuberculosis, and also participants who are HIV un-infected during the second episode of tuberculosis.

2.3.2 HIV Gender

Available literature on gender and sex demonstrates uneven distribution of TB infection among male and female. In resource- limited settings, approximately twice as many cases of TB are reported among men than in women (Diwan & Thorson, 1999; van't Hoog *et al.*, 2011). Contradictory finding on association with the rate of recurrence has been reported. Some investigators support data from observational studies, which find that males have higher rates of recurrence (Dooley *et al.*, 2011; Santha *et al.*, 2002), however, several epidemiologic studies across the globe found no association between gender and recurrence (Moosazadeh *et al.*, 2015; Picon *et al.*, 2007; Singla *et al.*, 2009; Thomas et al., 2005b). Therefore. It is not clear whether gender influences rates of recurrence in settings where the TB and HIV prevalence is high.

2.3.3 Age

Age of patients has been inconsistently associated with increased risk of recurrence tuberculosis. Elderly people are more likely to suffer from recurrence tuberculosis possibly as a result of a diminished immunity. Strong association between age and recurrence tuberculosis has been reported. Patients older than 65 years were found to be approximately two-fold increased risk of recurrence infection (Anbesaw W. Selassie *et al.,* 2005). However, several others epidemiological studies have not confirmed association between age and recurrence (Charalambous *et al.*, 2008; Millet *et al.*, 2009; Moosazadeh *et al.*, 2015; Picon *et al.,* 2007).

2.3.4 Alcohol abuse

Alcohol abuse is one the major obstacles to increasing the treatment success of tuberculosis. Although, alcoholism has been inconsistently reported to increase the risk of post primary tuberculosis, nevertheless alcohol abuse has been strongly associated with risk for recurrence. Two possible casual pathways may explain the apparent elevated risk of recurrence among individual who are taking alcohol. First, social mixing pattern associated with alcohol use and secondly, the influence on the immune system either due to alcohol itself or due to alcohol related disorders such as malignancies, malnutrition and chronic illness (World Health Orginization, 2009). The relationship between alcoholism and treatment outcome among recurrent patients has explored in several epidemiological studies. In Indian, a cohort study exploring on risk factors associated with relapse among cured TB patients, found that individual who are consuming alcohol have two-fold increased risk of recurrent tuberculosis (Thomas *et al.*, 2005a) Among patients with recurrent tuberculosis in South Carolina, individual taking alcohol were found to have nearly four-fold greater risk of recurrent tuberculosis than those who have not been taking alcohol (A. W. Selassie, C. Pozsik, D. Wilson, & P. L. Ferguson, 2005). In addition, data from a Brazil study, showed an increased risk of recurrence tuberculosis

among individual who consumes alcohol (Unis *et al.,* 2014). While there is plausibility data on elevated risk of recurrence tuberculosis , relationship between alcoholism and secondary tuberculosis was not confirmed in a cohort of 610 patient with active pulmonary TB (Picon *et al.,* 2007).

The contribution of alcohol to the burden of post primary tuberculosis sub-Sahara settings is not completely defined and it is not uncertain whether alcoholism increases the risk of recurrence compared to individual who are not taking alcohol. Further research is necessary to define relationship between alcohol uptake and post treatment tuberculosis.

2.3.5 Smoking

Both tobacco smoking and tuberculosis are major global public health problems. The burden of smoking among patients with tuberculosis is poorly documented in our countries and understanding of the epidemiological relationship between smoking and post treatment tuberculosis is important because both smoking and tuberculosis cause extensive morbidity and mortality worldwide.

Increased risk of recurrence infection among smokers is unclear. However, one hypotheses supported by *in vitro* and *in vivo* data suggest that poor results of tuberculosis treatment outcomes among smokers is due to impairment of pulmonary host defense (den Boon *et al.,* 2005). Biological mechanisms related to smoking that impair host defense is determined by a complex set of factors, including increased iron levels in the bronchoalveolar macrophages during smoking period. This results in decreased synthesis of TNF-α and citric acid (Boelaert, Gomes, & Gordeuk, 2003.). These two effector molecules play a key role in containing the intracellular growth of *M. tuberculosis* (Weiss *et al.,* 1994*).*

Strong association between smoking and post primary tuberculosis has been reported. It has been noted, the odds of recurrent disease among smoker is more than 2 fold the odds seen in non-smoker patients (Moosazadeh *et al.*, 2015; Thomas *et al.*, 2005a) Individuals who are heavy smokers have been reported to be highly susceptible to tuberculosis infection and retreatment (Slama *et al.*, 2007; Tian *et al.*, 2014). In addition to supporting these evidence, a meta-analysis on tobacco smoke, indoor air pollution and tuberculosis revealed that compared to non-smokers, individuals who smokes have an increased risk of developing latent TB, active TB, and in fatal situation dying from TB (Lin, Ezzati, & Murray, 2007). While smoking has been strongly associated with post primary tuberculosis in settings where smoking rate is high, there are scant data regarding the impact of smoking on post primary tuberculosis in settings where smoking rate is not high.

2.3.6 Malnutrition

Although the relationship between weight and post treatment tuberculosis is inconclusive, available evidence from past studies suggest that low weight to height is closely linked to tuberculosis infection. Data from a past meta-analysis on malnutrition and tuberculosis support that low weight is a risk factor (Cegielski & McMurray, 2004). In addition to concern regarding the impact of low weight on primary tuberculosis, the contribution of underweight is also a risk factor for post primary tuberculosis. Supporting evidence comes from a large trial of tuberculosis treatment. Malnourished patients from this large trial were found to be at two-fold increased risk of recurrent infection (Khan, Sterling, Reves, Vernon, & Horsburgh, 2006). A Uganda study also reported similar evidence of a strong association between low weight and post- primary tuberculosis (Luzze *et al.*, 2013). Malnutrition may increase recurrence tuberculosis susceptibility through impairment of cell mediated immunity that plays a key role in host defense

against TB (Ministry of Public Health and Sanitation, 2010) however, this association was not confirmed in a cohort study that was exploring risk factors for relapse (Thomas *et al.,* 2005a).

2.3.7 Employment

At the time of this cross sectional study, few data had been published on the relationship between employment and recurrence tuberculosis and therefore it is less clear to what extent employment increases the risk of recurrence tuberculosis. Available literature have reported controversial results on this issue. In South Africa, a study on mineworkers found an increased likelihood of recurrence tuberculosis with increasing years of employment (Sonnenberg *et al.,* 2001). However, a later study on South Africa gold miner reported no correlation between employment and tuberculosis recurrence (Charalambous *et al.,* 2008).

2.5 Challenges facing tuberculosis control programs

Secondary tuberculosis poses a threat to control programs, as its treatment is associated with lower cure rates than treatment of new TB. This problem is further complicated by the association of tuberculosis recurrence with drug resistance. Despite the rollout of ART to all HIV/TB co-infected patients and WHO DOTs strategies in our clinic and defaulter tracing, Kenya continues to be among the 22 Countries with high burden of tuberculosis (World Health Orginization, 2015). It is therefore clear that poor outcome of tuberculosis treatment cannot be solved through these two strategies.

The influence of smoking and alcoholism to recurrence tuberculosis remains unclear. Past and recent studies have reported controversial findings on these two correlates. While some epidemiologic studies failed to reveal a significant association between cigarette smoking (Singla *et al.,* 2009) and alcohol (Picon *et al.,* 2007; Singla *et al.,* 2009) with recurrence tuberculosis

however, several studies have shown an increased likelihood of recurrence with alcoholism (Anbesaw W. Selassie *et al.,* 2005; Unis *et al.,* 2014), and cigarettes smoking (Moosazadeh et al., 2015; Santha *et al.*, 2002; Thomas *et al.*, 2005a)

It is uncertain whether socio-demographic variables such as gender and age increases the risk for recurrence where some of investigators reporting findings in favor of association (Santha *et al.,* 2002; Anbesaw W. Selassie *et al.,* 2005) and others against it (Moosazadeh *et al.*, 2015; Singla *et al.,* 2009). Understanding the mechanisms underlying increased risk to recurrence will enable the design of specific interventions to reduce the risk of both primary tuberculosis and MDR. This study sought to evaluate the risk factors associated with recurrence tuberculosis.

2.6 Conceptual Framework

Independent factors in this study were age, sex, employment, cigarette smoking, HIV infection, alcohol uptake and malnutrition. In the long run these influence the rate of tuberculosis which was primary outcome in this study. Some independent variables influence the outcome directly (Figure 2.1).

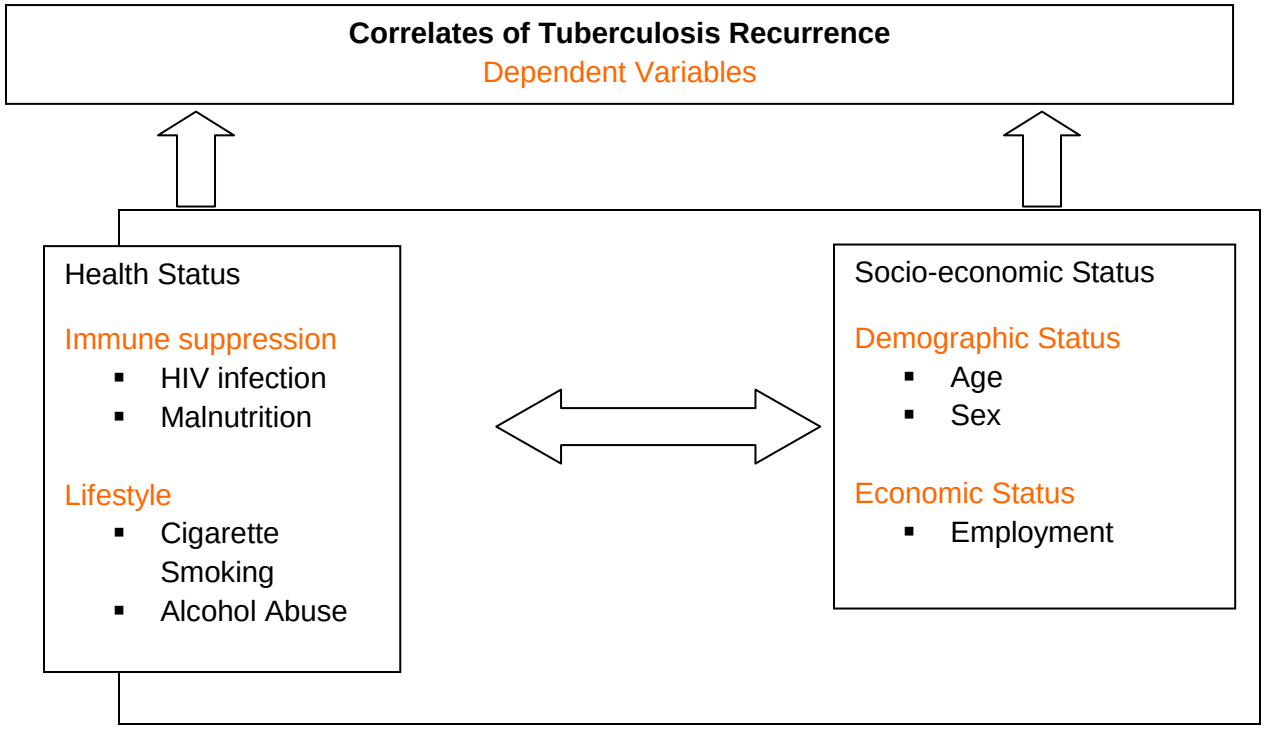

Figure 2.1: Conceptual Frame Work.
Determinants of tuberculosis recurrence adopted from Q.M. Trinh (Trinh *et al.*, **2014**)

CHAPTER THREE: METHODOLOGY

3.1 Study Site

Siaya and Kisumu counties are located in the southwest part of Kenya around Lake Victoria. This area is among three regions (Nairobi and Rift valley) in the country with high prevalence of tuberculosis 18% (DLTLD 2010) and HIV 15.1% (NASCOP, 2012). Furthermore, tuberculosis recurrence is estimated to be 11 % in this region (Dhis2, 2014) Study sites included Ahero County hospital which has a catchment population of approximately 34990. Bondo sub County hospital is in Siaya County and is located in a rural set-up. Bondo sub County has a catchment population of about 41215. Kisumu County hospital is located in Kisumu town which is a cosmopolitan city. The catchment population of Kisumu County hospital is approximated to be 86386. Jaramogi Oginga Odinga Teaching and Referral Hospital offers services to hospitals in both western Kenya region and Luo Nyanza region. The hospital serves patients form both rural and urban settings.

All these hospitals provide both tuberculosis care and patient support services among HIV infected patients in addition to primary health care services in Siaya and Kisumu Counties. These hospitals have an active tuberculosis clinics and on-site comprehensive care clinics for HIV infected patients. Again, tuberculosis and HIV data are readily available from hospital records.

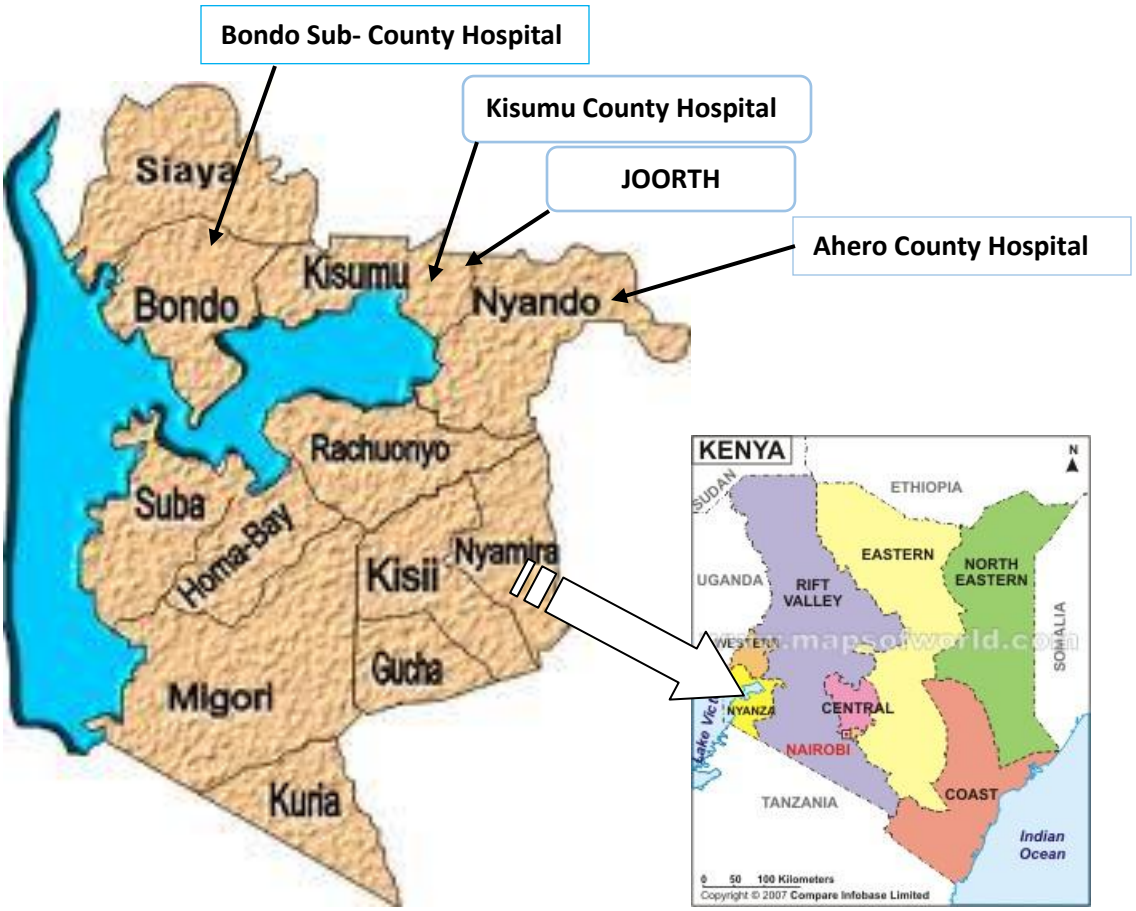

Figure 3.1: Kisumu **Figure 3.2: Map of Kenya**

3.2 Study Design

This was a cross-sectional study which enrolled tuberculosis patients seeking treatment in Ahero County hospital and Bondo sub-county hospital, Kisumu County hospital and JOOTRH.

3.3 Study population

Between April 2014 to January 2015, this cross-sectional study recruited 227 participants seeking tuberculosis services at Ahero County and Bondo sub-county hospitals, Kisumu County hospitals and JOORTH during the study period. The study enrolled inpatient and outpatient

tuberculosis participants. In 2013, an estimated 156 new and 18 relapse tuberculosis patients were reported from Bondo sub-County hospital. In the same year, 161 new and 25 tuberculosis recurrence patients were reported in Kisumu County Hospital. In 2012, there were 88 notification of new and 6 recurrent patients in Ahero County hospital while, an estimated 328 incidents and 49 tuberculosis recurrent patients were reported in Jaramogi Oginga Odinga Teaching and Referral Hospital. Population attending these clinics is reflective of people living in Nyanza region (Dhis 2, 2013)

Table 3.1 Estimated burden of disease caused by TB, 2013. (Patient who were 14 years and above)

	Ahero(N=88)	**Bondo(N=156)**	**KCH(N=161)**	**JOOTRH(N=328)**
TB Cases detected				
Male	39	80	93	139
Female	49	76	68	189
Re-treatment TB Patients	**N=6**	**N=18**	**N=25**	**N=49**
Male	3	6	17	19
Female	3	12	8	30

3.4 Inclusion criteria

- Tuberculosis infected patients attending Ahero, Bondo and Kisumu hospitals
- 18 years and above
- TB patients who are co-infected with HIV and

3.5 Exclusion criteria

TB patients who are suffering from MDR. All the participants who were on **Intensive Phase = (8 KM-Pto-Lfx-Cs-Z)** inj Kanamycin (Km) Tabs Prothionamide (Pto), Tabs

Levofloxacin (Lfx) , Tabs Cycloserine (Cs) Tabs Pyrazinamide (Z) and **Continuation Phase of 12 Pto-Lfx-Cs-Z)** treatment were defined as MDR patients. This information was readily available on the participant's appointment card.

3.6 Study Procedure

3.6.1 Recruitment

Eligible participants seeking tuberculosis treatment provided written consent before data was collected. TB patients seeking services in the study hospitals who met study inclusion criteria were enrolled from 8.00 am to 4.00pm.

In summary, at the chest clinic, the principal investigator approached patients suffering from tuberculosis after their normal TB clinic and briefly described the purpose of the study. All the interested TB patients were invited into a room designated for this study where they were assessed for eligibility and participation. If the patient was admitted, then the study introduction and subsequent procedures were done at the patient bed. The investigator emphasized that participation was completely voluntary.

In the interview room, eligibility criteria was assessed and if the patient was willing to participate, then they were offered a copy of ethic reviewed committee (ERC) - approved informed consent form (ICF) of their preferred language (English, or Luo) and they were asked if they felt comfortable reading through the ICF on their own (either Luo or English) Participants who were comfortable going through the ICF on their own were given time to read the consent form. All potential participants who were unable to read the consent form on their own, were

taken through the consenting process by a witness. After reading the ICF, the investigator asked the potential participants if they understood the study and the content of the consent form. After reading the consent, the study investigator explained details of the study, including benefit, risks and discomfort associated with asking personal questions. All the willing participants were requested to Sign and date the signature page using their first and last name or initials. For participants who were not literate, the study investigator wrote the date and name for the participant and then the participant was requested put a thumbprint on the appropriate line. A witness also signed and dated the signature page of the ICF in the designated spaces.

Following consenting a semi-structured questionnaire was administered to all eligible participants. To ensure consistency and professionalism, interviews with all the enrolled participants were conducted by the principal investigator and in case of a language barrier, a Luo nurse from the hospital was invited to assist in data collection. The interviews were done in either English or Swahili. It is worth noting that the median level of education in this study was form one (Table 4.1). After administering questionnaire, the investigator abstracted medical data such as TB regimen, initial height, from the participant's TB card and comprehensive care clinic (CCC) card incase if the patient was co-infected with HIV/TB. Other Medical data were abstracted from the patient's file. Following the completion of enrolment process, the investigator ticked the TB appointment card. This was done so as to ensure that the participant was not enrolled twice.

To ensure anonymity, each questionnaire was labeled with a code number and all questionnaires were separated from all consents. There was no link between questionnaire and consent. Study

questionnaire did not capture the following data Individual's names, patient identification numbers and any other unique identifying information. In total, 227 participants were recruited into this cross-sectional study.

3.6.2 Data collection tools

3.6.2.1 Questionnaires

A semi-structured case report form (CRF) was administered to all consenting study participants. At enrolment a questionnaire on socio-demographic factors and economic characteristics was administered. In addition, information on BMI characteristics of the subjects, CD4+ cell count, viral and HIV treatment data were obtained from study participants. Variables such as lifestyle, drug adherence and time after completion of tuberculosis treatment and history of TB contact were also captured from participating participants.

3.7 Data

3.7.1 Sample size

Data published in 2010 by Kenya, Division of Leprosy Tuberculosis and Lung Disease demonstrate that in 2010, 106, 083 people were estimated to be newly infected with TB with Nyanza region accounting for approximately 18% (19,152) (DLTLD, 2010).Sample size was therefore calculated based on this prevalence of TB in Nyanza Region. Lwanga and Lemenshow's formulae (1991) was used to calculate study sample size where:

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

3.7.2 Tuberculosis Infection

$$n = \frac{(1.96)^2(0.18)\,(1-0.18)}{0.05^2}$$

$$n = \frac{(0.5670)}{0.0025} = \mathbf{226.8}$$

Where:

n: was the required sample size

Z: was the critical value =1.96 for a standard normal distribution that correspond to 95%

Confidence level.

p: Proportional of tuberculosis recurrence in the Nyanza is approximated to be (18%)

d: was the range of error =5%

A minimum of 227 participants with primary and second episode of tuberculosis were enrolled

3.7.3 Data storage

All study questionnaires were stored in a lockable cabinets at the data office. On arrival to the office, all data were entered electronically to a password-protected computer and data was backed up weekly in a compact disk.

3.7.4 Data Analysis

All information was entered into an access database and analyzed at $p \leq 0.05$ level of significance using stata version 12.

Specific objective 1.The following characteristics were analyzed: socio-demographics, economic status, nutritional factors. Newly infected participants suffering from primary tuberculosis were compared with participants who were recurrent. Association of these variables and tuberculosis recurrence was analyzed using χ^2 test while logistic regression was used to determine the major independent valuables.

Specific objective 2. Association of HIV infection and second episode of tuberculosis was determined among HIV negative versus HIV positive participants. Participants who were on HIV treatment versus those were not on HAART were evaluated so as to explore association of immunosuppression and tuberculosis recurrence. The proportion of participants who were co-infected with tuberculosis and HIV was also calculated. Frequencies were used to determine proportion of HIV infected patients who were on HAART versus those who were not on HAART. Dichotomous variables were analyzed using chi-square test.

Specific objective 3. The following risk factor for recurrence: smoking and alcoholism among participants who were newly infected with TB verses recurrent cases were analyzed. Chi-square tests was used to compare associations for categorical variables.

3.8 Risk to Participants

All participating individuals were consented before completion of study questionnaire. The questionnaire had some sensitive and embarrassing questions and the participant had the option of not answering any of the questions that he or she felt to be uncomfortable with.

3.9 Protection against the risk

Information of the study participants was not linked to any identifier. No names were used in case report forms. In the health centers participant files were only accessible to researchers. All the study activities involving recruitment, consenting and data collection and analysis were coordinated by the principal investigator

3.10 Data validity and reliability

Prior to initiation of the study, 10 questionnaires were pretested at Mathare North Health Centre so as to make sure that questionnaire was well understood and to correct any ambiguous questions. The performance of pretest questionnaire was approximately 90%. The source population drawn from Mathare North Health Center is diverse in ethnicity, and of generally low socioeconomic status and peri-urban. Due to diversity in ethnicity, this population provided a unique opportunity to collect data from different tribes including Luo community who are majority patients in the clinic. The study questions were formulated in English language and not Dholuo.

3.11Ethical Approval

The study was reviewed and approved by Maseno University Ethic Review Committee and JOOTRH Research and Ethic Committee prior to initiation of data collection. No participant was recruited until the relevant human participant's approvals were obtained.

CHAPTER FOUR: RESULTS

4.1 Characteristics of the study population

From April 2014 to January 2015 a total of 227 tuberculosis patients were recruited into the study where 44 were from Ahero County hospital, 54 from Bondo sub-County hospital, 55 were enrolled from Kisumu County hospital and 74 were recruited from JOOTRH. All participants were enrolled cumulatively.

Characteristics of the enrolled participants are summarized in Table 1. Median participant age was 33 years (interquartile range (IQR) 26-54) and median duration of education was 9 years (IQR 7-12). The majority (62%) of participants were married where, 76% were in monogamous relationships. Lifestyles characteristics were assessed by cigarettes smoking and alcohol. Smoking and alcohol uptake in this population was less common where 46 (20%) and 87 (38%) of 227 participants reported to have ever smoked and taken alcohol respectively. In this setting tuberculosis was more common in male 124 (55%). Ultimately, 224 of all recruited participants that had information on type of tuberculosis available 195 (87%) were suffering from pulmonary TB and 29 (13%) reported to have extra-pulmonary tuberculosis. Of the participants with HIV results, 155 (68%) were HIV infected and 127 (85%) of 149 were on HAART.

Table 4.1:Demographic, life style behavior and medical characteristics of TB participants

	N	Median (IQR[1]) or n(%)
Demographic & relationship characteristics		
Age (years)	227	33(27-40)
Sex (male)	227	124(55)
Years of school completed	227	9(7-12)
Married (currently)	227	114(62)
Marriage type	140	
Monogamous		107(76)
Polygamous		33(24)
Employment	227	
Working		141(62)
Not working		86(38)
Number of the people in the room	227	4(3-5)
Life style behavior		
Smoking	227	46(20)
Alcohol	227	87(38)
Medical history		
BMI	191	19(17-21)
Exposed to some with TB	227	97(43)
Type of TB	224	
Pulmonary TB		195(87)
Extra pulmonary TB		29(13)
HIV infected	227	155(68)
HAART	149	127(85)
JOORTH	227	74(33)
Kisumu Conty Hospital		55(24)
Bondo sub Conty Hospital		54(24)
Ahero County Hospital		44(19)

Different demographic characteristics, lifestyle behavior and medical history were used to characterize the study population; data is shown in number, percentage, median and Interquartile range in each category

4.2 Predictors of tuberculosis recurrence

4.2.1 Socio-economic factors

Correlates of tuberculosis infection are shown in Table 4.3. Strong association of recurrent was observed with older age (OR 1.05/per years, 95% CI: 1.01-1.09; p=0.01) to patients suffering from first episode of TB, individuals with tuberculosis recurrence were more likely to be men (69 % vs, 51%), corresponding to OR of 2.28, 95% CI ranging from 1.06 to 4.87 and a *p*=0.03. There was less household crowding among those with recurrent TB (OR: 0.78/per household member, 95% CI: 0.64-0.96; p =0.02).

On the other hand, factors such as employment, marital status and level of education seemed not to increase recurrence.

4.2.2 HIV infection

HIV prevalence among tuberculosis individuals was assessed. Overall, 183 participants corresponding to 66% were confirmed to be HIV infected at the time of enrolment. High prevalence of HIV infection was observed among patients suffering from post-treatment tuberculosis as opposed to individuals suffering from primary tuberculosis (80% versus 65%). The overall coinfection of HIV was 72%). In this study, HIV infection appeared to be strongly associated with risk for recurrence where the HIV infection increased the risk by approximately three-fold compared to HIV negative. Again, among the HIV infected participants, the relationship between ART and recurrence was noted. Other medical factors including type of tuberculosis, BMI, and tuberculosis exposure failed to influence the recurrence rate.

4.2.3 Lifestyle behaviors

With the regards to the influence of lifestyle behaviours on recurrent TB, both smoking and alcohol uptake variables were found not to have an association with recurrence

(OR: 0.75, 95% CI: 0.30-1.91; p =0.55) and (OD: 1.05, 95% CI: 0.50 -2.19; p =0.89).

Table 4.2: Correlates of tuberculosis recurrence

Baseline Characteristics	Primary infection (N=176)		Secondary infection			
	N	Median (IQR[1]) or n(%)	N	Median (IQR[1]) or n(%)	OR 95% CI	*p*-value
Socio-economic						
Age (years)	176	32(26-39)	51	37(29-	**1.05 (1.01-1.09)**	**0.01**
Sex (male)	176	89(51)	51	35(69)	**2.28 (1.06-4.87)**	**0.03**
Years of school	176	9(7-12)	51	10(8-12)	1.00(0.90-1.11)	0.99
Married (currently)	176	109(62)	51	32(63)	1.01(0.75-1.36)	0.93
Marriage type	108		32		1.25(0.81-1.94)	0.31
Monogamous		85(79)		22(69)		
Polygamous		23(21)		10(31)		
Employment	176		51		0.77 (0.57-1.03)	0.08
Working		107(61)		34(67)		
Not		69(39)		17(33)		
Number of people	176	4(3-6)	51	3(2-5)	**0.78(0.64-0.96)**	**0.02**
Life style behavior						
Smoking	176	37(21)	51	9(18)	0.75(0.30-1.91)	0.55
Alcohol	176	66(38)	51	21(41)	1.05(0.50-2.19)	0.89
Medical						
BMI	149	19(17-21)	42	19(17-21)	0.96(0.86-1.07)	0.46
Exposed to some with	176	75(43)	51	22(43)	1.44(0.69-2.99)	0.32
Type of TB	174		50		1.26(0.43-3.67)	0.68
Pulmonary		152(87)		43(86)		
Extra –		22(13)		7(14)		
HIV infection	176	114(65)	51	41(80)	**2.47(1.18-5.19)**	**0.02**
HAART	109	89(82)	40	38(95)	**4.26(1.02-19.18)**	**0.05**

Methods: Chi square test for binary variables and and t-test for continuous variables.
Primary TB is defined as first episode of TB while Secondary TB is defined as post-treatment TB
OR=odds Ratio; IQR=interquartile ranges and CI= confidence interval.

CHAPTER FIVE: DISCUSSION

This cross section study was designed to explore the relationship of multiple socioeconomic, lifestyle and medical variables with the recurrence rate of tuberculosis in patients suffering from tuberculosis of two County hospitals in Kisumu, one sub-county in Siaya and in one Teaching and referral hospital in Kisumu. The prevention of secondary tuberculosis is still a challenge for the health care systems especially in less developed countries.

In the assessment of socioeconomic status, gender and age were strongly associated with recurrence tuberculosis. These findings were consistent with a recent literature on a retrospective review among recurrent tuberculosis patients from Uganda (Luzze *et al.,* 2013). Statistically significant, results of this study showed increase in post primary tuberculosis with increase in age after 37 years. In contrast to estimate observed in this setting , non- recurrent tuberculosis patients in Rio de Janeiro study, were more likely to be slightly older compared to recurrent cases (Golub *et al*., 2008).

High disparity of tuberculosis infection in gender has also been documented in previous literatures. According to WHO report of 2014, tuberculosis infection was more common in male than in female patients with a ratio of 1.6 (World Health Orginization, 2014). Although not statistically significant, data from three sub-Sahara Africa studies (Golub *et al.,* 2008; Houben *et al.,* 2012; Luzze *et al.,* 2013) showed high prevalence of tuberculosis among male participants. In line to results from a Barcelona study (Millet *et al.,* 2009), that assessed tuberculosis recurrence and its associated risk factors, data from this cross- sectional study demonstrated a two-fold increased risk of recurrence infection among male. These findings are not surprising since the overall tuberculosis recurrence in this study was more common in male than in female patients. In contrast, finding from a cohort study on recurrent tuberculosis from Malawi found

that post-treatment tuberculosis was more common in female than in male patients (Crampin *et al.*, 2010).

Initially, tuberculosis infection was once associated overcrowding (Bates *et al.*, 2004), However, in this study socio-economic factor was inversely associated with post treatment tuberculosis where post primary tuberculosis was not associated with increased household crowding. On the other hand, other social factors assessed in this study seemed not increase risk for recurrence. They include employment, marital status and education level.

Estimate of overall HIV infection among tuberculosis patients in this study is consistent with findings from other studies in Africa (Abdool Karim, Churchyard, Karim, & Lawn, 2009; Crampin *et al.*, 2010). In contrast, proportion of TB-HIV co-infection rate of 72 % in this cross-sectional study is much higher compared to national rate of 38% reported in the year 2014 (World Health Orginization, 2014). This could be due to high prevalence of HIV and tuberculosis in this setting.

The role of HIV infection in tuberculosis has been a topic of intense research during the last decades. Available data strongly associate HIV infection with tuberculosis recurrence (Charalambous *et al.*, 2008; Crampin *et al.*, 2010; Golub *et al.*, 2008; Panjabi et al., 2007). In this study, the high rate of HIV infection among individuals with post treatment tuberculosis are similar to those findings from other studies on secondary tuberculosis suggesting that HIV infection is strongly linked to post primary tuberculosis. In this study, the odds of recurrent disease in individuals with known HIV infection was approximately three- fold the odds seen in HIV negative individuals. These findings are in line with data found by past and recent studies (Charalambous *et al.*, 2008; Sonnenberg *et al.*, 2001; Unis *et al*., 2014),

While treatment of HIV using combination therapy is expected to restore individual immunity thus providing protection against opportunistic infections (Angel *et al.,* 1998; Golub *et al.,* 2007; Moreno *et al.,* 2008), high rate of HIV and secondary TB co-infection continues to be observed among patients who are on HAART. Despite high rate of HAART uptake (85%) in this study that corresponds with national rate of 84% (World Health Orginization, 2014), this study demonstrated high prevalence rate of TB –HIV co-infection among patients who were on combination of antiretroviral therapy (cART). In this study recurrent patients were more likely to be on HAART than non-recurrent patients. Nevertheless, our finding on high uptake of HAART among recurrent patients observed in this setting, does not correspond to estimate of ART uptake among recurrent verse non-recurrent patients found in a Reo de Janeiro study (Golub *et al.,* 2008).

Although co-infection of HIV–TB was high among patients with secondary tuberculosis compared to primary case, high uptake of HAART in this group was very encouraging since tuberculosis infection among HIV positive individuals defines WHO stage three and therefore all patients in this group should be initiated on HAART irrespective of their CD4 count.

Unlike recent meta-analysis by Cegielski & McMurray, (2014) that revealed association between underweight and recurrence, this study did not confirm that this condition is a risk factor for recurrence. Perhaps due to the factor that majority of the patients in this setting had a normal BMI at the time of re-treatment.

This study failed to reveal a significant association between cigarette smoking, alcoholism and the recurrence of tuberculosis. Epidemiological data have reported controversial results on this issue with Millet *et al* (2009) and Thomas *et al.,* (2005) demonstrating an increased likelihood of

recurrence with cigarette smoking and alcoholism. However, data from this study did not associate these determinants as risk factors for tuberculosis recurrence in this setup. Regarding these two predictors, it is possible that the lifestyle and environment in our setting is different from that one of Barcelona and South India. It is worth noting that in these two studies alcohol uptake and cigarette smoking persisted past primary tuberculosis while in our setup majority of the participants stopped smoking or taking alcohol after the first episode of tuberculosis

The following strengths were observed in this cross sectional study. This study was conducted in multiple sites which enabled the investigator to assess predictors of tuberculosis recurrence in rural per-urban and urban settings. However, this study was also subject to limitations. Missing data on key immunosuppression markers; HIV viral load and CD4 cell count thus, it was not possible to evaluate immunosuppression.

CHAPTER SIX: CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusion

In this setting, age, sex, were some of socio-economics factors that were associated with tuberculosis recurrence. While total number of house occupant was inversely associated with post primary tuberculosis. Other socio-economic variables including employment, education and marital status did not show any significant association with the recurrence

Strong association between HIV infection and tuberculosis was observed in this cross-sectional study. It is worth noting that people who were on HAART were more likely to report second episode of tuberculosis.

Results from this study reveal that smoking and alcohol uptake was not a risk factors for post treatment tuberculosis

6.2 Recommendations

High prevalence of HIV infection among recurrent patients despite high coverage of HAART observed in this study underscores the importance of developing new approach on fighting against tuberculosis.

Further studies on ARV are therefore, recommended to determine whether ART adherence and resistance are associated with poor outcome of tuberculosis treatment in settings where uptake of HAART is high among tuberculosis patients. Again more research is needed to better understand the contribution of each of these risk factors to the recurrence rates and more effort to prevent recurrence should also focus on sub-group at increased risk, such as elderly, and male .

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APPENDICES

Appendix 1: Written Consent Form

Investigator	Role on Project	Institution	Phone Number
Matemo Daniel N. MPH Student	Principal Investigator	Maseno University	0722-322 378
Professor Rosebella Onyango	Supervisor	Maseno University	0722-378 477
Dr. Bernard Guyah	Supervisor	Maseno University	0721-206 932

Collaborating Institutions:

1. Maseno University
2. Jaramogi Oginga Odinga Teaching and Referral Hospital

Investigator's statement

I am requesting you to participate in this research study. The primary reason of this consent form is to give you information you will need to assist you in making decision of whether to participate in the study or not. Please read the form carefully. You may ask any questions about the purpose of this study, the possible risks and benefits or anything else about this study which is not clear. This process is known as **informed consent.** Ifyou wish, you will be given a copy of this form for your record.

Purpose and Benefits:

The availability of TB drugs and HAART has drastically reduced TB mortality and HIV related death. However, these drugs can only be effective if adherence is observed, therefore I want to determine the predictors of recurrence tuberculosis among adult tuberculosis patients treated.

Patients with TB recurrence may be a higher risk of developing tuberculosis drug resistance. We are conducting a research study to learn how common post tuberculosis infection in Nyanza population. Findings from this study will benefit the society by providing information that can be used to prevent both tuberculosis recurrences and multi-drugs resistance.

Procedure:

If you choose to participate in this study, research assistant will fully explain to you about the study and answer any question you may have so that you can give an informed consent. After signing this form, a study questionnaire will be administered to you by a research assistant.

Interviews and questionnaires. During enrolment, we will ask you a series of questions about you, your health and the health of people in your household. These questions will help us understand why some people are at risk of developing tuberculosis recurrence. If you choose not to answer a question, you will still be able to stay in the study. We will keep the answers to these questions private.

Medical record review. We would like to access your clinical records so that we can record information on you. If you agree to allow us access to your medical records, we would like to obtain information including: your HIV history, medications, CD4 count, sputum microscopy and chest X-ray results. We may ask you about this information if it is not in your clinical records.

Risk stress, or discomfort

You may find it difficult to answer some personal questions.
We will do everything possible to safeguard the confidentiality of your data but no system for protecting your confidentiality is completely secure.

Alternatives to taking part in this study

There may be other studies going on here or in the hospital that you may be eligible to participate. There also may be other places where you can go for medical care. We will tell you about those places if you wish. **Whether or not you decide to participate in this research study, you can continue to receive your tuberculosis services at this clinic.**

Confidentiality

Your medical records and responses to questions will be kept private, and no identifying information of any kind will be released to any other person or agency that is not working on this study, without your permission in writing. We will not publish or discuss in public anything that could identify you. Your medical information will be identified by a code number. All of your information, including the link between your name and code number will be kept in a secure, locked location only. Once the study is completed, we will maintain the link for 3 years, after this time we will remove your name and all identifying information from the study files. Any publication of this study will not use your name or identify you personally.

Government or university staff may review studies such as this one to make sure they are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm.

Other Information:

Your participation will be anonymous, unlinked and only the investigators, Maseno University and University of Nairobi/Kenyatta National hospital Ethic and Research Committee (ERC) will have an access about your information. Your name, staff identification number or any other unique identifying information will not be collected or used in any publication reports.

If you have any question regarding this study, you can contact any of the Investigators listed above.

Completing of this questionnaire will take about 20-30 minutes.

You do not have to be in this study if you do not want to.

Signature of Investigator …… Date ……...

Name of Investigator ……. Date……

Participant's Statement

I have read this form. All my questions have been answered and I volunteer to take part in this research. If I have any question concerning my rights as a research subject, I can call Maseno University ethic review committee

Signature of subject …… Date ……...

Name of subject ……. Date……

Maseno University

P. O. Box Private Bag

Maseno.

Copies to: 1. Subject

2. Investigator

Appendix 2: AYIE MAKENDE

Investigator	Role on Project	Institution	Namba simu
Matemo Daniel N. MPH Student	Principal Investigator	Maseno University	0722-322 378
Professor Rosebella Onyango	Supervisor	Maseno University	0722-378 477
Dr. Bernard Guyah	Supervisor	Maseno University	0721-206 932

Collaborating Institutions:

3. Mbalariany mar Maseno
4. Hosiptal marJaramogi Oginga Odinga Teaching and Referral
5. Kisumu District Hospital
6. Bondo District Hospital
7. Ahero Sub- District Hospital

WECHE MAG JATIM NONRO

Akwayi ni mondo iyie ibed e nonro ni. Tiend oboke mar ayie en mar chiwo ler mabiro konyi yie chiwori kata dagi chiwori mondo ononi. Som oboke ni maber. Inyalo penjo penjo moro amora moluwore gi tiend nonroni, chandruok kata masira moro amora manyalo yudi, ber mare kod gimoro amora nono ma ok iwinjo maber. Mano iluongo ni timo ‘’Ayie makende ka ing’eyo chal mar gima idonje’ Wabiro miyi oboke machalo kama mondo ikan kaka rapar mar ayie mitimoni.

GINO MA OMIYO ITIMO NONRO NI TO GI BERNE

Yudruok mag yedhe/yiende TB to gi HAART oseduoko piny ahinya wito ngima koluore gi tuo mar TB to gi wito ngima mikelo gi kute mag HIV.Kata kamano yedhe gi tiyo maber mana ka ichimori tir gi tiyo kodgi.Mae ema omiyo adwaro timo nonro matut mar fwenyo kadipo ni jotuo madongo mane osethieth ne tuo mar TB nyalo yudo TB kendo,kata nuoruok mar tuo mar TB ne joma dongo mane ose thieth ne TB.

Jotuo mangi nuoruok mar TB nyalo bedo e rang'i ma malo mar tamruok tiyo yedhe mag TB kuomgi.Watimo nonro mar nono nuoruok mar TB e jodak ma Nyanza.Dwoko mar nonroni biro bedo gi ndhadho maduong e gwenge,ka nyiso ler mar yore mageng'o nuoruok mar TB to gi tamruok tiyo yiende mag TB.

CHENRO MAG NONRO

Ka iyie ni ibiro chiwori e nonroni ,jatim nonro biro nyisi maler tiend nonroni ,duok penjo duto e yo maler mondo ichiu dwoko maber ne ja tim nonro.Bang',keto seyi e obokeni jatim nonro biro chiwoni otese mag penj.

PENJ KOD OTESE MAG PENJ.

Seche duto ma itimo nonroni ibiro penji penjo mang'eny ma odok korka kori, ngimani duto to kod ngima jo odi. Penjo gi biro konyowa ng'eyo ang'o momiyo jok moko nitie e rangi' mamalo mar yudo TB ban'g ka negi setieko thieth . Inyalo neno ni penjo moko kuodo wich. Ponono ni ineno ni ok inyal dwoko penjo moro pod ibiro mana bedo e nonroni. Dwoko ma wayudo ok wabi nyiso ng'ato ang'ata (wabiro pandogi).

KITAPE MAG RAPAR MAR LIMBE MA BAN'G THIETH

Dwaher mondo wangi' ripodi mar klinik mar thieth mondo wandik,chalni. ka iyie,dwaher ng'eyo chalni mar kute mag ayaki,thiethni,CD4 count,sputum microscopy gi x-ray mar agogi.Wabiro hero mar penji penjo gi ka ok gi yudre e kitapi mar rapar mar limbe mabang' thieth.

PARO KATA ACHIEDH NADE

Wiyi nyalo kuot ,inyalo bedo kod luoro kata paruok kata iyi bende nyalo wang' seche ma ipenji penj ma odoko kor ka kori, Wabiro temo matek mondo kik wamoi elela kaluwore gi dwoko mari. Kata kamano, waonge kod yoo moro amora mawanyalo bedogo gi adiera mar pando chalni.

YORE MAMOKO MABENDE INYALO CHIWORIE E NONRO

Ka nyalo bet ni nitie nonro mamoko madhi nyime machalo kamae e hospitalni kata e hospital ma itime nonro ma inyalo chiworie, inyalo anyala chiwori . Nitie bende kuonde mang'eny ma inyalo dhi thieth. Wabiro nyisi kwondego tee kapo ni idwaro. Bende ka iyie kata idagi bedo e nonroni ok moni dhi nyime yudo thieth mari mar TB ehospitalni.

KANOWACH

Duoko mari manie kitabu mar rapar mar limbe mag thieth to gi meke penj ok bi nyis ng'ato ang'ata kata ne migawo moro amora kapod ok oyud thuolo kata rusa mari. Bende ok wabi lando nyingi kaluwore gi kit duoko moro amora ma imiyowa. Ok wabi ndiko kata wacho gimoro amora manyalo miyo ng'ato fwenyi . Wabiro kano gimoro amora mawakawo kuomi kaluwore gi thieth, kama opondo e Klinik kende. Bang' tieko nonroni wabiro kanogi kuom higni adek (3) kendo wabiro tudore kodi e kindego. Bang' higni adekgo (3) wabiro golo nyingi e rijista marwa to kod gimoro amora manyalo fwenyi. Ok eno luong nyingi e oboke kata gimoro amora ma enondiki kaluwore kod nonroni

Sirikal kata jononro mamoko matiyo e mbalariany nyalo tiyo kod nonro machalo kama mondo gibed kod adiera ni itimogi e yoo makare kaluwre kod chik. Sama gi ng'iyo nonroni, ginyalo neno wecheni kata kamano ok gibi wacho ne ng'ato. Oboke ni ok nyal ti godo mondo ohinyi kata keloni chandruok moro amora.

LER MAMOKO

Chwori e nonroni ok bi ng'ere ,joma nyalo ng'iyo nonro gin ;Mbalariany mar Maseno ,Hospital mar Jaramogi Oginga Odinga Teaching and Referral , Ethic and Research Committee (komiti ma ochung'ne chike mag timo nonro).Nyingi,nambani mar tich to gi gimoro amoro manyalo fuli ok bindiki e ripot moro amora.

PESA MI CHULO/CHUDE.

Onge chude/chudo moro amora ma ibiro chul kuom jogo ma ochiwore e nonro ni e Klinik magwa

HINYRUOK MANYALO BEDOE KUOM TIMO NONRONI. Ok yot mondo iyud hinyruok kuom bedoe nonroni . Onge chudo moro amora mar omenda kata e yoo moro amora ma ibiro miyi kaluwore gi hinyruogno. Bende bedo ni iketo lweti e obokeni ok omayi thuolo ma in godo mar luwo chik mar donjonwa.

PENJO KATA SHIDA

Po nono ka in gi penj moro amora ka luore gi nonroni ,penj Daniel Matemo kata jo nonro ma ondik malo kanyo.

Ka in gi penj moluore gi ratiro mari kaka ngama nitie e nonroni,ber mondo ine Daktari Jagoro mar Mbalariany ma Maseno komiti ma chung'ne chike mag timo nonruok.

Mondo itiek dwoko otese mag penj, ibiro kawo dakika pirariyo nyaka piero adek.Ok ochuni mar bedo e nonroni ka ok idwar.

Seyi mar Janono …… Tarik ……...

Nying' Janon ……. Tarik……

SING'O MAR NG'AT MA OCHIWORE MONDO ONON

Ayie mar chiwora e nonroni .Asesomo obokeni kata osesomna,ayie mar bedo e e nonroni.ka di po mi an gi penjo moro amora maluore gi ratiro mara kaka ngama inono anyalo goyo simu ne Mbalariany ma Maseno Komiti ma ochung'ne chike mag timo nonro.

Sei / nyie luedo mar ng'ama itomone nonro…. ……...Date ……...

Nying ng'ama itimone nonro …….…….Date……

Sei mar janeno……. Date……

Nying janeno……...……. Date……

Maseno University
P. O. Box Private Bag
Maseno.

Copies to: 1. Subject
2. Investigator

Appendix 3. Enrolment Case Report (CRF)

Date Day ☐☐ Month ☐☐☐ Year ☐☐☐☐

Name of clinic: ☐ Bondo ☐ Ahero ☐ KDH ☐ JOOTRH

Enrolment Eligibility

1. Client having TB ☐ Yes ☐ No
2. Client Having TB recurrence ☐ Yes ☐ No
3. Client over 18 years of age ☐ Yes ☐ No
4. Client willing to give consent ☐ Yes ☐ No
5. Client eligible to enroll (yes if answered YES to1, 2, 3, and 4) ☐ Yes ☐ No

Sociodemographic data

1. Date of birth ☐☐ ☐☐☐ ☐☐☐☐ Day Month Year
2. Age ☐☐ Years
3. Sex ☐ Male ☐ Female
4. Employment: Salaried ☐ Self-employ ☐ Housew… ☐ Unemployed ☐

If ticked, Skip to 5

4a Occupation _____

5. Years of education: ☐☐ Years
6. Number of rooms in house (excluding toilets): ☐☐ rooms
7. Number of people residing in the house (include client) ☐☐ people
8. Distance to clinic (tick one): ☐ ☐

	less than 5 km	20-29 km	> 50 km
	5-9 km	30-39 km	not sure
	10-19 km	40-49 km	

9. Marital status (tick one)

	Divorced/separated		currently married
	Come we stay		never married
	Widowed		If ticked, skip to 10

9a Relationship	monogamous	polygamous
9bHow many years together (less than 1 enter 0)		Years

Physical Examination

10. Height		cm
11. Weight	.	Kgs
12. MUAC (left):	.	m
13. BMI		

Health and Medical History

14. Have you been Smoking?	Yes	No
14a if yes, how many cigarettes per day		cigarettes
15. Have you been taking alcohol?	Yes	No
15a.If yes, drinks per week		drinks
16. Do you have any serious medical condition?	Yes	No
16 a If yes, specify ———		
17. Have been exposed to someone with TB	Yes	No
		if no skip to 18

17a. Does this person live in the same home?

17b. is the person a frequent contact?

Tuberculosis

18. First episode of TB ☐ Yes | No ☐
If ticked, skip to 20

19. Current regimen: (tick one only) ☐ 2RHZE/6EH ☐ 2RHZE/4RH

20. Post treatment TB infection Yes ☐ | ☐ No
If ticked, answer Q 20, 21, 22, 23, 24 25.

21. When was the first episode? ☐☐ ☐☐☐ ☐☐☐☐

22. When was the second episode ☐☐ ☐☐☐ ☐☐☐☐

23. How many months were you supposed to take your drugs? ☐☐ Months

24. Have you ever missed your dose Yes ☐ No ☐
if yes , answer 26 and 27

25. Why did you miss your dose?
- ☐ Forgot
- ☐ Learnt out of drug
- ☐ Travelling
- ☐ Drug
- ☐ Sick

26. How many times

Specify ……

27. Type of TB
a. Previous Extra pulmonary ☐ Pulmonary ☐
☐ ☐

b. Current Extra pulmonary Pulmonary

28. Previous regimen (tick one only) ☐ 2RHZE/6EH ☐ 2RHZE/4RH

HIV

29. Participant tested for HIV Yes ☐ No ☐

If yes complete 28 a

28. (a) Test results Negative ☐ Positive ☐ Indeterminate ☐

If ticked complete questions 28 b

28. (b) when were you tested? ☐ <1 mon 1-3 ☐ 4-6 mon
☐ 7-9 mon ☐ 10-12 mon ☐ 12 mon

30. Participant started on HAART Yes ☐ No ☐

If ticked complete 29.a and b if ticked skip to 30

29(a) If yes, when? 6 months ☐ 12 Months ☐
24 Months ☐ 36 Months ☐

29 (b) Drug regimens……

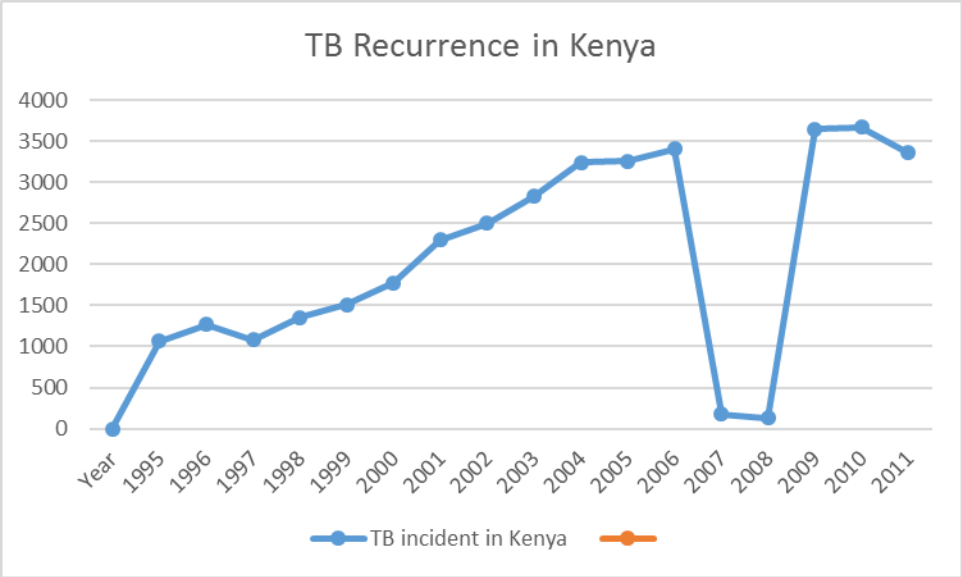
31. Baseline CD4 results

32. Baseline Viral load results

Appendix 4. World Health Organization Report 2012

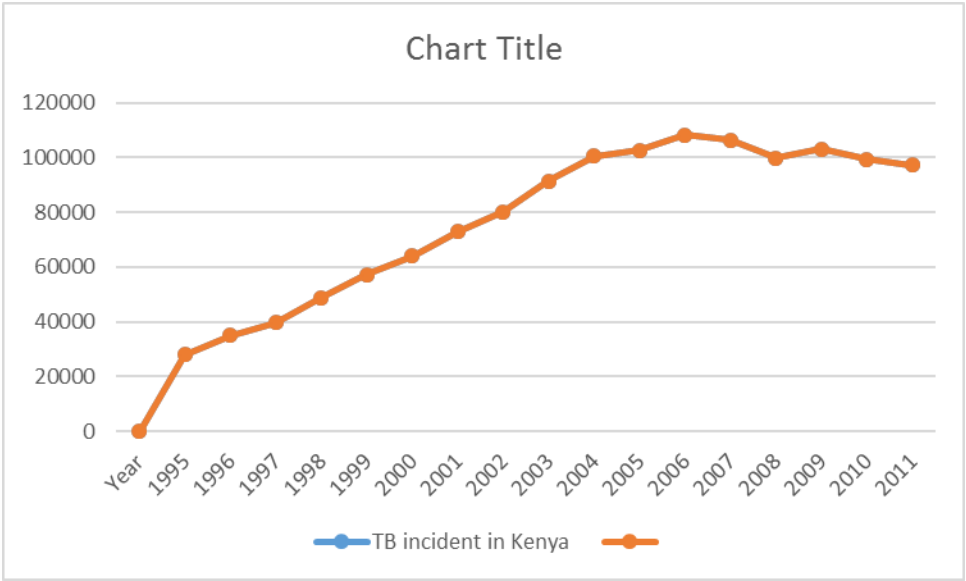
TB incident in Kenya from 1995 - 2011

Year	Relapse
1995	1064
1996	1266
1997	1079
1998	1355
1999	1513
2000	1773
2001	2294
2002	2503
2003	2826
2004	3237
2005	3254
2006	3407
2007	177
2008	134
2009	3643
2010	3668
2011	3356



TB incident in Kenya

Year	Total notified cases
1995	28142
1996	34980
1997	39738
1998	48936
1999	57266
2000	64159
2001	73017
2002	80183
2003	91522
2004	100573
2005	102680
2006	108342
2007	106438
2008	99941
2009	102997
2010	99272
2011	97320



Appendix 5. ERC Approval (MASENO)

Appendix 6. ERC Approval (JOORT)