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TUBERCULOSIS (TB) TREATMENT OUTCOMES IN ADULT TB PATIENTS ATTENDING A RURAL HIV CLINIC IN SOUTH AFRICA (Bushbuckridge).

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A RESEARCH REPORT SUBMITTED TO THE SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG, IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE (MEDICINE) IN THE FIELD OF EPIDEMIOLOGY AND BIOSTATISTICS.

`

September 2009

DECLARATION

I, Mashimbye Lawrence, declare that this research report is my own work. It is being submitted for the degree of Master of Science in Epidemiology and Biostatistics to the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in this or any other university.



L Mashimbye

03 September 2009

DEDICATION

This research report is dedicated to my parents Elias and Emelinah Mashimbye, and to my brothers and sisters Robert, Ronald, Tintswalo, Richardt, Constance, Tinyiko, and Lesley.

ABSTRACT

South Africa is ranked fourth on the list of 22 high-burden TB countries in the world. Intensifying the prevalence of TB in South Africa is the high TB/HIV co-infection rate, with 44% of new TB patients testing positive for HIV. This burden is intense for rural communities due to poverty and return of people with TB/HIV co-infection who previously migrated for employment. In rural South Africa, TB is the leading cause of mortality in HIV-infected persons, but limited information is available about predictors of death. This study measures TB treatment outcomes in Rixile clinic and assesses predictors of TB mortality.

Rixile HIV clinic is based in Tintswalo hospital, Acornhoek, Bushbuckridge, Mpumalanga province. This current study uses secondary data collected through a prospective cohort study conducted by PHRU and RADAR from March 2003 to March 2008 on 3 to 6 monthly intervals. Chi-square and logistic regression statistical tests were used to assess predictors of TB Mortality.

TB mortality among study participants was 62.5% during the pre-ARV rollout period (March 2003- October 2005), and treatment completion was 31.7%. Some 5.8% participants interrupted treatment during the pre-ARV rollout period as compared to 4.5% during the ARV rollout period (November 2005- March 2008). TB mortality among study participants was 7.5% during ARV rollout and treatment completion increased to 84.4%. Factors associated with TB mortality were age ($p=0.006$), sex ($p=0.017$), BMI ($p< 0.001$), marital status ($p=0.004$), education ($p=0.03$), alcoholic beverages consumption ($p=0.04$), and ARV treatment ($p<0.001$). However, only age, sex, and ARV treatment were found to predict TB mortality.

The proportion of TB treatment completion was higher and TB mortality was lower during ARV roll-out compared to pre-ARV roll-out. Being at the age of 40 to 75 years, not being on ARV treatment and male sex predicts TB mortality in this population. There is a need to expand ARV treatment and intensify TB care services for older people, particularly males living with HIV in this rural community.

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ABBREVIATIONS AND ACRONYMS

TB= Tuberculosis

MDR-TB=Multi-Drug Resistant-Tuberculosis

XDR-TB= Extensive Drug Resistant-Tuberculosis

HIV=Human Immunodeficiency Virus

AIDS=Acquired Immunodeficiency Syndrome

BMI= Body Mass Index

ARV=Antiretroviral

ART=Antiretroviral therapy

WHO=World Health Organization

DOTs= Directly Observed Therapy Support

PHRU= Perinatal HIV Research Unit

RADAR= Rural AIDS and Development Action Research

CRF= Case Report Form

CCF= Clinical Care Form

CI= Confidence Interval

RR=Relative Risk

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1 INTRODUCTION

1.1 BACKROUND

Tuberculosis (TB) is estimated to cause at least three million deaths per year worldwide **[1]**. In South Africa, TB is a major public health problem. According to the World Health Organization (WHO) the country is ranked fourth on the list of 22 high-burden TB countries in the world **[1]**. The incidence rate was estimated at 940 per 100,000 people in 2006 compared to 333 per 100,000 in 1996 **[1]**. Constraining the progress to combat TB in South Africa is the high TB/HIV co-infection rate, with 44% of new TB patients testing positive for HIV **[1]**. This burden of TB/HIV co-infection is worsened in rural communities by poverty **[2]**, and return of people with TB/HIV co-infection who previously migrated to urban areas for employment **[3]**. The impact of this high prevalence of TB/HIV co-infection in rural South Africa can be reduced by concomitant TB and HIV treatment **[4]**.

The advent of HIV and TB treatment is reported to improve survival among HIV/TB patients enrolled for both treatments **[4]**. To some extent this benefit of TB/HIV concomitant therapy can be explained by DOT support, **[5,6]** sensitivity of TB strain to the drugs used for treatment **[5]** and HIV stage of the person on treatment **[7]**. TB treatment outcomes are improved in people who take the therapy under the support of DOT **[5,6]**, with 84% of people taking TB/HIV treatment reported to have completed treatment **[6]**. Despite improved treatment completion and low mortality presented by a previous study conducted in Kwazulu-Natal province of South Africa **[6]**, death due to TB in HIV co-infected persons is still high in rural South Africa **[8]**.

Demographic factors, social factors, lifestyle factors, and clinical factors were reported to be the predictors of death due to TB among people co-infected with HIV and those infected with TB only **[7,9]**.

Depletion of CD4+ cells in HIV-infected persons increases the risk of both primary and reactivation tuberculosis **[10]**. HIV-positive people infected with TB are fifty times more likely to develop active TB in their lifetime than people who are HIV-negative **[2].** Interruption of TB treatment increases the risk for development of drug resistance strains of TB which are hard and expensive to treat **[5]**. Two strains of drug-resistant TB are Multidrug resistant tuberculosis (MDR TB) and Extensively drug resistant TB (XDR TB). MDR TB is diagnosed when there is in vitro resistance of *M. tuberculosis* against, at least, rifampicin or isoniazid **[11,12]**. XDR-TB is the MDR TB strain which is also resistant to one of the fluoroquinoles and one of the injectable drugs such as kanamycin, capreomycin or amikacin **[12]**. Drug resistant TB commonly arises from exogenous infection rather than activation of primary infection in HIV-infected persons **[13].** HIV is not associated with development of drug-resistant TB **[14]**, but high prevalence of drug-resistant TB in HIV-infected persons is primarily due to impaired immunity which confers them high susceptibility to infection **[10,15].** Infection with drug-resistant strains increases the risk of TB mortality, particularly in HIV-infected persons; **[15,16]** with XDR TB causing 98% mortality **[16]**.

1.2 STUDY SITE SETTINGS

HIV and TB treatments are free of charge for HIV-infected persons in Tintswalo hospital. Participants enrolled in the wellness study conducted by Rural AIDS and Development Action Research (RADAR) and Perinatal HIV Research Unit (PHRU) in Rixile clinic took HIV and TB treatments in Tintswalo hospital. The ARV programme in Rixile clinic (Tintswalo hospital) started in October 2005.

TB and HIV treatments in Tintswalo hospital are prescribed in line with South African standard treatment guidelines **[11]**. Regimen 1 treatment for active TB, is isoniazid, Rifampicin, pyrazinamide, and ethambutol for two months (intensive phase), then isoniazid and rifampicin alone for a further four months (continuation phase). If the organism is known to be sensitive, ethambutol need not be used. Regimen 2 is given to patients previously treated for TB and consists of isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin for the first two months to three months, and rifampicin, isoniazid and ethambutol for the further five months. Regimen 1 treatment for HIV consists of two nucleosides reverse transcriptase inhibitors, that is stavudine, lamivudine, and a non-nucleoside reverse transcriptase inhibitor, either efavirenz or nevirapine. Regimen 2 consists of two alternative nucleoside reverse transcriptase inhibitors, which are zidovudine and didanosine plus the protease inhibitor combination that is lopinavir/ritonavir.

DOTS (directly observed treatment short course) have been implemented in Tintswalo hospital. An important element of the strategy is the support and encouragement offered to TB patients

for the entire six- to eight-month treatment period, where patients are directly observed taking their medication at the clinic.

1.3 LITERATURE REVIEW

TB is primarily a disease of the respiratory system which spreads when the TB patients expel the droplets by sneezing, spitting and coughing and the people nearby inhale the droplets and become infected with mycobacteria, mainly *Mycobacterium tuberculosis* **[12]**. When mycobacteria reach the alveoli of the lung, they invade and replicate within the endosomes of alveolar macrophages. Infection can result in latent TB or active disease which clinically can be classified as extra-pulmonary or pulmonary TB **[12]**. Latent TB is asymptomatic and Symptoms for active TB are chronic cough, blood-tinged sputum, night sweats, and weight loss **[12]**. World Health Organization (WHO) estimates that a single TB patient with active disease if not treated can infect on average 10-15 people every year **[2]**. On laboratory test (Ziehl-Nielson Staining), TB can be smear-negative or smear-positive **[12]**. Smear-negative pulmonary TB is defined by South African TB Control Program by two positive cultures of *M. tuberculosis* with confirmed identical spoligotype; and smear-positive as a positive sputum smear confirmed with a second positive smear or culture of *M. tuberculosis.* **[17]**

HIV infection is characterized by progressive depletion of CD+ cells that eventually lead to AIDS, as defined by opportunistic infections **[18]**. Responsible for the massive depletion of memory CD4+ T-cells are on-going viral replication and virus-induced cell death **[18]**. Despite rapid depletion of CD4+ T cells early during HIV infection, most opportunistic infections typically cause complications only after extended periods of HIV disease progression **[10]**. HIV increases

the likelihood of people acquiring new TB infection **[18]**. It also promotes both the progression of latent TB infection to active disease and relapse of the disease in previously treated patients **[18]**. For TB/HIV co-infected persons ARV's and TB treatments are given concurrently to improve immunity and the outcomes of TB treatment in South Africa **[11]**. Drug-interactions and side-effects in TB/HIV co-infected people taking HIV and TB curative therapies have been reported **[19]**; however, the concomitant treatment of TB/HIV co-infection is reported to have improved adherence to treatment which is important for preventing the emergence of drug resistance TB. **[16]**

In 1991, the 44th World Health Assembly set two key targets for global tuberculosis (TB) control to be reached by the year 2000: 70% case detection of acid-fast bacilli smear-positive TB patients under the DOTS strategy recommended by WHO and 85% treatment success of those detected **[2]**. Studies reported that WHO's target of treatment success is achievable in people with smear-positive TB even in under-resourced developing countries **[20]**.

In Hlabisa (South Africa) a twice-weekly directly observed therapy (DOT) for TB in HIV-infected and non-infected persons have shown to be effective. At six months of follow-up; 71% of participants were cured, 3% completed treatment without being cured, 2% transferred out and only 2% treatment failure was reported. The study concluded that a twice-weekly rifampicin-containing drug regimen given under DOT cures most adherent patients irrespective of HIV status and previous TB treatment history **[5]**.

A study conducted in rural South Africa (Kwazulu-Natal) among 119 TB/HIV co-infected persons reported successful integration of TB and HIV treatment. After 12 months of concurrent HIV

and TB treatment by home-based, modified directly observed therapy (DOT); 84% of enrolled participants reported to have completed treatment and 11% died while on treatment. Concurrent home-based therapy resulted in excellent adherence to TB and HIV treatment **[6]**.

In a randomized control-trial conducted in Malawi (Karonga) and Zambia (Lusaka) HIV-negative and HIV-positive 996 and 198 participants respectively were followed-up from September 1996 to October 1998. During the follow-up 230 participants died, and 216 of these were HIV-positive, while at baseline only less than 70% of enrolled participants both in Karonga (56%) and Lusaka (67%) were HIV-positive. HIV-positive participants were receiving only anti-tuberculosis treatment and they were not receiving HIV treatment. One of the factors found to be the predictor for mortality was age. Other predictors of mortality were low Body Mass Index (BMI), low level of haemoglobin, and more advanced clinical stages of HIV at baseline **[7].**

In Uganda a study enrolled a cohort of 105 male and 109 female HIV-infected adults receiving treatment for initial episodes of culture confirmed TB between March 1993 and March 1995. In this study favorable outcomes were defined as cured or alive while unfavorable outcomes were not being cured or dead. At the end of one year of follow-up there was no difference in the likelihood of experiencing a favorable outcome (RR 1.02, 95 CI 0.89-1.17). While differences existed between males and females with HIV-associated TB at baseline, the outcomes at one year after initiation of TB treatment were similar **[21]**.

A study conducted in rural South Africa (Agincourt) from 1992 to 2000 reported higher PTB/HIV death rate for males than females for all ages combined (RRMH=2.48, 95% CI 1.53-4.04, $p<0.001$) **[22]**. This was not true for all ages as female mortality was not different from male

mortality before age 25 years. The excess male mortality was restricted to older age groups (25-34, 35-44, and 45-55 years). The median age at PTB/HIV deaths among males was 38 years. Death due to the co-infection PTB/HIV was 24.9% (95% CI, 20.0-29.8%), the proportion in men (32.1%) being higher than that in women (16.9%).

Associations between TB mortality and increased age, treatment delay, and defaulting treatment in HIV-infected persons were reported in a study conducted in Ghana **[9]**. In this study, mortality was associated with increased age ($p < 0.001$), residence in a rural area ($p < 0.05$), sputum smear-negative disease ($p < 0.01$), prolonged symptom duration prior to initial diagnosis ($p < 0.05$), and defaulting treatment ($p < 0.05$). The study concluded that HIV is strongly associated with TB mortality in persons with co-infection, however, increased age, residence in rural area, sputum smear-negative disease, more prolonged symptom duration prior to initial diagnosis and defaulting treatment causes increased TB mortality in HIV-infected persons.

The outcomes of TB treatment are improved in HIV-infected persons taking TB treatment under the support of DOT supporter **[5,6].** There is generally no disparity on the outcomes of TB treatment between males and females, **[21, 22]** except on people at 25 years of age and older **[22].** In HIV-infected and non-infected persons; age, Body Mass Index (BMI), low level of haemoglobin, sex and more advanced clinical stages of HIV at baseline were reported to be predictors of TB mortality **[7,26].** Age was further reported to be a predictor of TB mortality among with other factors such as residence in rural area, sputum smear-negative disease, defaulting TB treatment and prolonged symptom duration prior to initial diagnosis **[9].**

Although some people enrolled in these studies were co-infected with HIV/TB, they were receiving only TB therapy, and the predictors of TB mortality were explained in people receiving TB therapy only **[7,9]**.

1.4 DEFINITIONS

Case of Tuberculosis: A patient in whom tuberculosis has been confirmed by bacteriology or diagnosed by a clinician **[23]**.

WHO HIV staging: World Health Organization (WHO) HIV clinical stages **[24]**

1. Completed treatment

The participant completed initiation phase and continuation phase of TB treatment, and it is not known whether is cured or not.

2. Interrupted treatment

The participant reports failure to take TB treatment for two months or more consecutively or fails to appear to the clinic for two months or more consecutively without notifying the data collectors after the first follow up visit to the clinic.

3. TB Mortality

Death while on TB treatment with confirmed TB at the time of death.

4. Transfer out.

A participant was formally referred to another health facility from the clinic during the follow up period.

1.5 PROBLEM STATEMENT

Antiretroviral given with TB treatment improves survival in HIV-infected TB patients **[4]**. Concomitant TB and HIV treatments in TB/HIV co-infected persons under DOT observation were readily available from October 2005 in Tintswalo hospital. However, the researcher is unaware of another study measuring the outcomes of TB treatment among patients receiving TB treatment only and those also receiving TB/HIV treatments in Tintswalo Hospital. In particular, to measure TB treatment outcomes defined as completed treatment, interrupted treatment, death while on treatment with the reported cause of death to be TB (TB mortality), and transfer out in the period before and during ARV roll-outs in this rural community of South Africa. In rural South Africa, TB is the leading cause of mortality in HIV-infected TB patients **[8]**, but limited knowledge exists about risk factors for death **[6,8,22]**. One study examined pattern of PTB/HIV mortality in males and females **[22]**. Mortality rate disparity was apparent in male and female patients at and older than 25 years of age, with males having higher mortality rate; **[22]** however, it is uncertain whether demographic factors (sex, age, BMI), social factors (marital status, education, employment status), lifestyle factors (alcohol consumption habits, smoking habits) and clinical factors (ARV treatment) predicts TB mortality in TB/HIV co-infected persons.

1.6 JUSTIFICATION FOR THE STUDY

Studies call for expansion of ARV treatment to reach those in need, earlier ARV treatment initiation, and routine screening of TB in South Africa, **[8]** and the concomitant TB/HIV therapy is reported to improve survival in co-infected persons **[4]**. Understanding of the impact of concurrent TB and ARV treatment in TB treatment outcomes is important if ARV and TB treatment are to be prioritized during health planning for resource allocation. The specific reasons for TB mortality are important in order to improve treatment. In Malawi (Karonga) and Zambia (Lusaka) age, low BMI, low level of haemoglobin, and advanced stages of HIV at baseline were significant risk factors for mortality in the population of HIV-infected and HIV non-infected TB patients [**7].** In another study, age, residence in rural area, sputum smear-negative disease, defaulting TB treatment and prolonged symptom duration prior to initial diagnosis were found to be associated with TB mortality **[9]**. In South Africa, Identification of factors associated with TB mortality in HIV-infected persons will guide Public Health policy for screening of factors associated with TB mortality prior to TB treatment in order to improve TB treatment completion and prevent TB mortality**.**

1.7 RESEARCH QUESTION

What are the TB treatment outcomes and factors associated with TB mortality in adult HIV-infected persons receiving TB treatment in a rural HIV clinic in South Africa?

1.8 STUDY OBJECTIVES

1.8.1 Overall objective

To determine outcomes of adult (≥18 years) patients treated for TB attending a rural HIV clinic in South Africa.

1.8.2 Specific objectives

1.8.2.1 To measure TB treatment outcomes defined as completed treatment, interrupted treatment, TB mortality, and transfer out among adult patients receiving TB treatment.

1.8.2.2 To identify factors associated with TB mortality in adult TB patients receiving TB treatment in a rural HIV clinic.

2 METHODOLOGY

2.1 DESCRIPTION OF THE PRIMARY DATASET

Perinatal HIV Research Unit (PHRU) and Rural AIDS Research and Development Action Research (RADAR) conducted the wellness study in Rixile clinic, Tintswalo hospital, Bushbuckridge. The study was on HIV and TB. Hence, all enrolled participants were HIV positive, and some of the enrolled participants were co-infected with TB and they were receiving TB treatment. Data for the study was collected from March 2003 to March 2008 on 3 to 6 months intervals in all

enrolled participants. PHRU and RADAR data collectors used the case report form (CRF) to collect socioeconomic, demographic, TB treatment, and HIV information. ***[Appendix 1]***

This study analyzed secondary data on the basis of the information already collected in the PHRU and RADAR study. Exposure and outcome variables required by the current study were available on the dataset provided by PHRU and RADAR data managers. TB mortality was reported for people on stage four of HIV infection only. Therefore, HIV-staging could not be regressed as a predictor of TB mortality. Almost 75% of data on CD4 cell count was not available in the dataset. Therefore the confounding effect of cd4 cell count was not assessed on factors associated with TB mortality, and CD4 could not be regressed as a predictor for TB mortality.

2.2 STUDY DESIGN

The study applied a prospective cohort design. Data of HIV-infected persons on TB treatment who have at least one follow up clinic visit at Rixile clinic in the period March 2003 to March 2008 was analyzed. ARV treatment started in 2005 in Rixile clinic; therefore this study divided the follow up period into first (March 2003 to October 2005) and the second (November 2005 to March 2008) term with the purpose of describing TB treatment outcomes in the period before and during ARV roll-out. Proportions of outcomes were stratified into two terms: the first term, before antiretrovirals (ARV's) were dispensed in Rixile clinic, and the second term when ARV's were provided. The study design was also suitable for assessing the variation in TB treatment outcomes depending on the term. The cumulative proportions of TB treatment outcomes were also calculated with the numerator being the total number of each outcome

throughout the follow-up period (March 2003 to March 2008) and the denominator being the total number of enrolled participants throughout the follow-up period (March 2003 to March 2008).

2.3 STUDY AREA

Rixile clinic is an HIV clinic in Tintswalo hospital. Tintswalo hospital is based in the village of Acornhoek in Bushbuckridge. Bushbuckridge is located in Mpumalanga province of South Africa. Tintswalo hospital is right at the border of former Lebowa and Gazankulu homelands, but, the hospital fell under the Gazankulu homeland during the era of homelands in South Africa. From the year 1996 onwards, the hospital was under the then Northern province (now Limpopo province) and in the year 2006, the hospital was relocated to Mpumalanga province. Rixile clinic is amongst the clinic dispensing ARV's in Bushbuckridge. Participants were receiving an integrated TB/HIV treatment in Rixile clinic. The clinic also serves as the research center for national and international research.

2.4 STUDY POPULATION

The study participants were HIV infected tuberculosis patients attending Rixile HIV clinic from March 2003 to March 2008.

Inclusion criteria: -HIV-infected persons diagnosed with TB.

-Both sexes (males and females)

-18 years and older

Exclusion criteria: -HIV-infected persons without tuberculosis.

-HIV-infected TB patients not on TB treatment.

-HIV-infected patients on TB preventive therapy.

2.5 SAMPLE SIZE CALCULATION

Table 1: Estimate of the precision from data sample size

P-value (P)	Sample precision estimate (Δ)
0.01	0.006
0.02	0.010
0.03	0.012
0.04	0.014
0.05	0.015

Equation: $\Delta=Z_{\alpha/z}\sqrt{P(1-P)/n}$

The original data comprised of 2221 HIV-infected participants enrolled from March 2003 to March 2008. One thousands and ten (1010) of the enrolled participants were placed in TB curative treatment. The study sample size was the extracted 1010 participants with TB and receiving TB curative treatment therapy from the 2221 participants. However due to missing values, analysis was restricted to 785 participants.

At worst, the precision that can be achieved from the data of 785 participants at 95% confidence interval is within the range of three percent [(0.015*2)*100] ***[Table 1]***.

2.6 STUDY VARIABLES

2.6.1 The outcome variables

1. Completed treatment
2. Interrupted treatment
3. TB mortality
4. Transfer out

2.6.2 Exposure variables

2.6.2.1 Demographic factors

Age

Three categories generated following the normal distribution of the variable. The categories are: 18-30 years, 31-40 years, and 41 to 75 years.

sex

Males and Females

BMI

<18.5, ≥18.5-<25, ≥25-<30, and ≥30 **[25]**

2.6.2.2 Social factors

Marital status

Unmarried, divorced/widowed/separated and married

Occupational status

Unemployed, students, and employed

Education

No education, Primary, secondary, and tertiary

2.6.2.3 Lifestyle factors

Consumption of alcoholic beverages

Non-consumers and consumers

Smoking habits

Non-smokers and smokers

2.6.2.4 Clinical factor

ART treatment

Treated (Yes) and not treated (No)

2.7 DATA COLLECTION METHODS AND TOOLS

The case report form (CRF) designed by PHRU and RADAR was used for data collection. PHRU and RADAR data collectors received training to prior data collection. The unique identity number for each participant in CRF was used and this identity number was similar to the identity number in the clinical care form (CCF). Data was collected from two different sources; the clinical consultations and laboratory results. The information from these two different sources was recorded in the CRF ***[see Appendix 1]***. An interview was arranged for a date three months after the participant consented to the study. The CRF would be opened once the patient consented to participate in the study and the information from the CCF of that patient would be transferred to the CRF. Transferring of data from the CCF to the CRF was checked twice by different people to assess for error which might have occurred during the transferring process. The data collector conducting interviews during the follow up period differed from the person who enrolled the participant into the study. The participants were seen in the period between 3 and 6 months. The follow-up interviews were conducted when participants were coming for treatment in Rixile clinic.

2.8 DATA PROCESSING METHODS AND DATA ANALYSIS.

Data management was conducted by the use of Microsoft Office Access by PHRU and RADAR. For this secondary data analysis study, data was received in Microsoft Office Excel format. Stata version 9.0 was used for data cleaning and statistical analysis. Variables for the study were selected before importing data into Stata version 9.0. Data cleaning in Stata version 9.0 included assessing quality of data in terms of missing values, and internal consistencies of responses.

Proportions were used to describe categorical variables stratified across the first and second term follow up periods. The total numbers of TB patients on treatment were computed at the beginning of each term. Variables were categorized before assessment of their association with TB mortality.

The five year (2003-2008) data was analyzed prospectively, with the TB treatment outcomes of the first and second term carried out separately. Frequencies and proportions of TB treatment outcomes (completed treatment, interrupted treatment, TB mortality and transfer out) were computed. The denominator for calculation of proportions in each term was the total number of TB patients on treatment at the beginning of the term. The cumulative proportions for each outcome were carried out from the total number of participants in each outcome to the total number of participants enrolled throughout the follow up period. Histogram was used to explain and compare various outcomes over the two terms ***[Figure 1]***.

Chi-square test was carried out to assess the association between TB mortality and demographic factors (sex and age groups), social status (marital status, occupational status and educational level), lifestyle factors (alcohol consumption and smoking habits), and clinical factor (ARV treatment). The significance level was at chi-square value for one degree of freedom and 5% p-value. The results of the chi-square were presented on the table with the corresponding number and percentage of participants in each variable ***[table 3]***.

Logistic regression was carried out to construct the model of TB mortality against various suspected predictors of TB mortality. The following factors were included in the model: demographic factors (sex, age, BMI), social factors (marital status, education and occupational status), lifestyle factors (alcoholic beverages consumption and smoking habits), and clinical factor (ARV treatment). Univariate and multivariate models were constructed; the significance level of both models was at 5% with 95% confidence interval not crossing zero. The outcomes of the model were reported with relative risk [RR], and 95% confidence intervals. The outcomes of the univariate and multivariate models were presented in the table with corresponding number of participants in each category and the proportion of people died with the reported cause of death to be TB ***[table 4]***. Logistic regression models were constructed to assess for interaction by regressing the created interaction terms and the significance of interaction was reported at 5% significance level. Mantel Haenszel test was used to assess for confounding effects. The significance of Mantel Haenszel test was set at 5% significance level. Logistic model assumptions were assessed**.**

2.9 ETHICAL CONSIDERATIONS.

Approval for the primary study by PHRU and RADAR was given by the ethics committee of the University of the Witwatersrand.

Informed consent was given by all participants enrolled in the primary study conducted by PHRU and RADAR.

Approval for this study was obtained from the University of Witwatersrand Ethics Committee (Approval Number: R14/49). ***[APPENDIX B]***

Data was used for the purpose of the study only. Care and caution were exercised when data was handled. Careful considerations were given to anonymity, confidentiality and privacy issues surrounding the primary purpose which the data was collected for.

The individuals in the study sample were identified by the unique identifier. Any personal identifiers were removed prior the data being given to the researcher for analysis and as such, the researcher was not able to identify the individuals in the sample.

3 Results

3.1 Study participants description

One thousands and ten (1010) HIV-infected TB patients receiving TB treatment in Rixile clinic from March 2003 to March 2008 were eligible for inclusion in the study. A total of 225 participants had more than 50% missing observations in the variables of interest to the study and were excluded from the analysis. Therefore, only 785 participants were included in the

analysis. A total of 131 participants included in the analysis reported a history of TB: 118 were treated for TB once before, 10 two times and 3 three times. Data was collected from March 2003 onwards. The ARV treatment started in October 2005, and therefore, the periods of follow-up were divided into first term (March 2003 to October 2005) and second term (November 2005 to March 2008) representing the pre-ARV and ARV roll-out periods respectively. The demographic, social, lifestyle and clinical characteristics of HIV/TB co-infected participants are shown in *table 2*.

Demographic factors: At beginning of the first term, three hundred and sixty-three (68%) of participants were females; mean age at presentation was 35 years. Most participants (57%) were at the ages 31 to 40 years, while 17% were at the ages of 41 to 75 years. At the beginning of the second term, some 20% of participants were at the ages of 18 to 30 years and 38% at the ages of 41 to 75 years, and 40% of enrolled participants were males. During the first term 74 participants were underweight (BMI less than 18.5) compared to 99 participants during the second term ***[table 2]***. However, majority of participants presented with normal body weight (BMI ≥18.5-<25) during both terms ***[table 2]***. Throughout the follow-up time (March 2005 to March 2008) the race component was solely black/African.

Social factors: Over 50% of literate participants reported a secondary education and less than 4% tertiary education at the beginning of both the first and the second terms. Among categories of employment status, similar proportions were observed in each category (Employed/Unemployed/Students) during the first and the second terms ***[table 2]***. More than 80% of participants (86%) were unemployed compared to 13% reported to be employed during

both terms ***[table 2]***. Only one percent of participants were students at the beginning of both terms. Lower proportion reported to be unmarried (28%) during the first term compared to 36% during the second term ***[table 2]***. Some 43% of participants reported to be widowed or divorced or separated during the first term compared to 34% during the second term ***[table 2]***. There was a slightly difference in the proportion of those who reported to be married during the first (30%) and the second (29%) terms ***[table 2]***.

Lifestyle factors: Around 16% of participants reported to be consuming alcoholic beverages at the beginning of the first term compared to 20% at the beginning of the second term. Some 22% and 6% of participants reported to be consuming alcoholic beverages during the first and the second terms respectively ***[table 2]***. Amongst those who reported to be consuming alcoholic beverages 87% were males and 13% were females throughout the follow-up period. At the beginning of the first term some 24% of participants reported to be smoking at least one cigarette a day. Throughout the follow-up time, around 21% of participants reported to be smoking at least one cigarette a day and 65% of those who reported this were at 40 to 75 years of age. Proportion of women (6%) smoking at least one cigarette a day was less compared to men (44%) throughout the follow-up period.

Clinical factors: At presentation during the second term the percentage of participants in stage 3 of HIV infection dropped by 1% compared to the first term; in contrast the percentage of those who were in stage 1 of HIV infection was higher by 1% during the second term compared to the first term ***[table 2]***. Around 19% of participants were on ARV treatment during the first term compared to 58% percent during the second term ***[table 2]***.

Table 2: **Descriptive statistics of 785 participants receiving TB and HIV treatments in Rixile clinic during the 1st Term (March 2003 to October 2005) and the 2nd Term (November 2005 to March 2008).**

Factor	Variable	Category	First Term (March 2003- October 2005) N (%)	Second Term (November 2005- March 2008) N (%)
Demographic Factors	Age (years)	18-30	33 (15)	106 (19)
		31-40	92 (43)	200 (35)
		41-75	90 (42)	264 (46)
	Sex	Female	178 (67)	285 (57)
		Male	89 (33)	211 (43)
	BMI	<18.5	74 (28)	99 (19)
		≥18.5-<25	95 (36)	215 (41)
		≥25-<30	20 (8)	66 (13)
		≥30	72 (28)	144 (27)
Social Factors	Marital Status	Unmarried	44 (28)	177 (36)
		Divorced/widowed/separated	68 (43)	166 (34)
		Married	47 (29)	147 (30)
	Employment Status	Employed	22 (13)	65 (13)
		Unemployed	146 (86)	423 (86)

		Student	1 (1)	3 (1)
	Education	No Education	31 (18)	93 (19)
		Primary	50 (29)	84 (17)
		Secondary	90 (52)	297 (60)
		Tertiary	2 (1)	20 (4)
Lifestyle Factors	**Alcoholic beverages Consumption**	Non-drinkers	163 (78)	519 (94)
		Drinkers	45 (22)	31 (6)
	Smoking habits	Non-smokers	194 (98)	541 (99)
		Smokers	4 (2)	5 (1)
Clinical Factors	**ARV Treatment**	Yes	56 (19)	270 (58)
		No	240 (81)	200 (42)
	WHO HIV staging	Stage 1	30 (11)	53 (12)
		Stage 2	97 (35)	149 (33)
		Stage 3	108 (40)	179 (39)
		Stage 4	37 (14)	75 (16)

3.2 TB treatment outcomes

3.2.1 Completed treatment

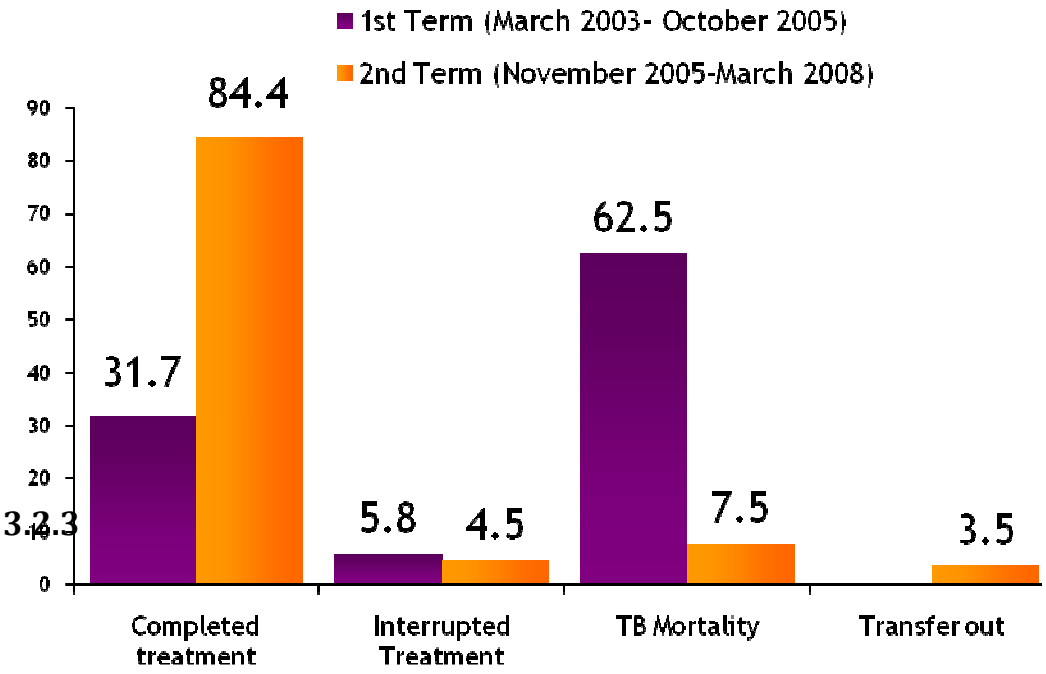
Treatment completion increased from 31.7% during the first term to 84.4% during the second term ***[Figure 1]***. Treatment completion was high among participants at the age of 31 to 40 years at 42% followed by participants at the ages of 41 years to 75 years (32%). Females (57%)

than males (43%) completed the treatment throughout the follow-up time. Around 38% of participants who never married completed treatment compared to 35% of married participants and 27% of widowed/divorced/separated participants. One hundred and eighty-one of 423 participants reported to be unemployed during the second term completed treatment. Participants who reported secondary education (62%) have completed treatment than participants with primary (18%) or tertiary education (6%). Only less than 25% of participants taking at least one cigarette a day (20%) and those consuming alcoholic beverages (23%) reported to have completed treatment.

3.2.2 Interrupted treatment

Treatment interruption was 4.5% during the second term compared to 5.8% during the first term ***[Figure 1]***. Treatment interruption was higher (59%) among participants at 41 to 75 years of age. Lower proportion of participants 18 to 30 years (10%) interrupted treatment compared to those at the ages of 31 to 40 years (60%) and at ages of 41 to 75 years (30%). The proportion of women (64%) who interrupted the treatment was higher than for men (36%). Higher proportion of Widowed/separated/divorced participants interrupted the treatment (50%). Around 30% and 9% of Alcoholic beverages consumers and those who are illiterate reported to have interrupted treatment respectively.

Figure 1: **TB treatment outcomes in HIV/TB co-infected participants receiving HIV and TB treatments during the first term (March 2003 to October 2005) and during the second term (November 2005 to March 2008) in Rixile clinic.**



The proportion of TB mortality was 62.5% during the first term and 7.5% during the second term ***[Figure 1]***. Fifty-four percent of TB mortality occurred to females. The highest rate of mortality (51%) occurred to participants between 31 to 40 years of age. TB mortality was high in participants reported to be divorced/widowed/separated (39%) compared to married (34%) and unmarried participants (27%). Sixty-five percent of TB mortality occurred in participants who reported to have obtained secondary education. Around 23% of the total participants died reported to be alcoholic beverages consumers. Calculated from the cumulative proportion value of TB mortality ***[table 3],*** TB mortality rate was at 2640 per 100 000 people in HIV-infected persons throughout the follow-up time (March 2003 to March 2008).

3.2.4 Transfer out

None reported to have transferred out of Rixile clinic during the first term ***[Figure 1]***. During the second term 83% of the participants transferred out were females and they were at the ages of 41 to 75 years. Those who transferred out were mainly unemployed, had primary education and reported to be not smoking cigarettes and not consuming alcoholic beverages.

Table 3: **Proportions of TB treatment outcomes in participants receiving TB and HIV treatments in Rixile clinic from March 2003 to March 2008.**

Outcomes	1st Term (March 2003-October 2005)		2nd Term (November 2005-March 2008)		Cumulative Proportion (CP)*
	Number	Proportion	Number	Proportion	
Completed treatment	33	31.7	168	84.4	66.3
Interrupted treatment	6	5.8	9	4.5	5.0
TB Mortality	65	62.5	15	7.5	26.4
Transfer out	00	0.0	7	3.5	2.3

*Total number of number of outcome throughout the follow-up time/total number of participants

Of the 785 participants remained for analysis, around 248 were reported to be still on treatment at the end of the study, the outcomes of 234 participants were reported to have died of other HIV related causes and not TB. Those who reported treatment ongoing on those who died of HIV related causes were excluded on the denominator when calculating the proportion of TB treatment outcomes. During the first term, the proportion of mortality was 62.5% and treatment completion was 31.7%, however during the second term proportion of mortality fell to 7.5% and the treatment completion rate rose to 84.4% ***[Figure 1]***. Mortality during the

second term (7.5%) was low compared with 62.5% during the first term ***[Figure 1]***. Treatment completion was higher during the second term (66.3%) as compared to the first term (31.7%).

3.3 Factors associated with TB mortality

The chi-square test of association was carried out to assess the association between TB mortality and demographic factors (age, sex, BMI), social factors (marital status, occupational status, education), lifestyle factors (alcoholic beverages consumption and smoking habits), and clinical factor (ARV treatment). All mortality cases were reported on participants on stage 4 of HIV staging, therefore clinical stages could not be included to assess if it's a predictor for TB mortality. *Table 4* represents the results of chi-square test of association. Demographic factors (age, sex, BMI), social factors (marital status, education), lifestyle factor (alcoholic beverages consumption) and clinical factor (ARV treatment) showed significant association with TB mortality.

Table 4: **Chi-square results on factors associated with TB mortality in participants receiving TB and HIV treatments in Rixile clinic from March 2003 to March 2008.**

Factor	Variable	Category	N (%)	Chi2 Value	P>Chi2
Demographic Factors	**Age (years)**	18-30	139 (18)	10.3	**0.006**
		31-40	292 (37)		
		41-75	354 (45)		
	Sex	Female	463 (61)	5.7	**0.017**

		Male	300 (39)		
	BMI	<18.5	173 (22)	86.4	**<0.001**
		≥18.5-<25	310 (39)		
		≥25-<30	86 (11)		
		≥30	216 (28)		
Social Factors	**Marital Status**	Unmarried	221 (34)	10.9	**0.004**
		Divorced/widowed/separated	234 (36)		
		Married	194 (30)		
	Employment Status	Employed	87 (13)	2.9	0.2
		Unemployed	569 (86)		
		Student	4 (1)		
	Education	No Education	124 (19)	9.3	**0.03**
		Primary	134 (19)		
		Secondary	387 (58)		
		Tertiary	22 (3)		
Lifestyle Factors	**Alcoholic beverages Consumption**	Non-drinkers	682 (96)	5.9	**0.04**
		Drinkers	28 (4)		
	Smoking habits	Non-smokers	735 (99)	0.8	0.4
		Smokers	9 (1)		
Clinical factor	**ARV treatment**	Yes	326	86.6	**<0.001**
		No	440		

3.4 Predictors of TB mortality

Univariate and multivariate logistic regression models were constructed to assess the predictors of TB mortality. All factors which showed significant association with TB mortality on chi-square test were modeled in the univariate model to assess if they are predictors of TB mortality.

3.4.1 Univariate analysis

Univariate analysis on the relationship between demographic factors and TB mortality showed an association with demographic factors (age, sex, BMI), social factor (education) and clinical factor (ARV treatment). In the analysis, those at the age of 31 to 40 years and those 41 to 75 years were at higher risk (relative risk [RR] 2.2, 95% CI (1.3-3.6)) and (relative risk [RR] 2.2, 95% CI (1.2-4.1)) of dying of TB respectively compared to lower age category (18-30 years). From the Social factors, education was significant; participants who reported primary education (relative risk [RR] 0.5, 95% CI (0.2-0.9)) and secondary (relative risk [RR] 0.5, 95% CI (0.3-0.9)) were at lower risk of TB mortality compared to participants with no formal education. Participants who were not on ARV treatment were at higher risk (relative risk [RR] 11.0, 95% CI (6.1-19.8)) of dying of TB compared to participants on treatment.

Table 5: **Univariate and multivariate logistic regression analysis of predictors of TB mortality in 785 participants receiving TB and HIV treatments in Rixile HIV clinic from March 2003 to March 2008.**

Factor	Variable	Category	Total (N)	TB mortality (%)	Univariate		Multivariate	
					Relative Risk (RR)	95% CI	Relative Risk (RR)	95% CI
Demographic factors	Age (years)	18-30	139	28.4	1	1	1	1
		31-40	292	45.7	2.2	**(1.3, 3.6)**	2.2	(0.8, 5.8)
		41-75	354	25.9	2.2	**(1.2, 4.1)**	3.2	**(2.4, 7.7)**
	Sex	Female	463	45.7	1	1	1	1
		Male	300	54.3	1.1	**(1.1, 2.6)**	8.7	**(3.3, 22.8)**
	BMI	<18.5	173	17.6	1	1	1	1
		≥18.5-<25	310	4.7	3.2	**(1.5, 6.9)**	2.0	(0.7, 5.5)
		≥25-<30	86	0.0	-	-	-	-
		≥30	216	32.9	0.3	**(0.2, 0.6)**	0.4	(0.2, 1.2)
Social factors	Marital Status	Divorced/widowed/separated	234	39.2	1	1	1	1
		Married	194	33.8	1.6	(0.9, 2.7)		
		Unmarried	221	27.0	2.4	(1.4, 4.2)		
	Education	No Education	124	13.8	1	1	1	1

		Primary	134	20.0	0.5	**(0.2, 0.9)**	0.2	(0.05, 1.0)
		Secondary	387	65.0	0.5	**(0.3, 0.9)**	0.4	(0.1, 1.3)
		Tertiary	22	1.3	2.8	(0.4, 23.2)	-	-
Lifestyle factor	**Alcoholic beverages Consumption**	Non-drinkers	682	75.4	1	1	1	1
		Drinkers	28	24.6	1.6	(0.8, 3.3)		
Clinical factor	**ARV Treatment**	Yes	326	30.8	1	1	1	1
		No	440	3.9	11.0	**(6.1, 19.8)**	23.2	**(8.7, 62.3)**

3.4.2 Multivariate analysis

The variables which were significant in univariate models were included in the final multivariate model: demographic (age, sex, BMI), social factor (education), and clinical factor (ARV treatment).

Being at 41 to 75 years of age was associated with the higher risk (relative risk [RR] 3.2, 95% CI (2.4 -7.7)) of dying of TB as compared to lower age category (18-30 years) when adjusted for age, sex, BMI, education, and ARV treatment. Males were nine times more likely to die of TB (relative risk [RR] 8.7, 95% CI (3.3-22.8)) compared to females in HIV-infected TB patients when adjusted for age, BMI, education, and ARV treatment. Participants who were not on ARV treatment were at higher risk of dying of TB (relative risk [RR] 23.2, 95% CI (8.7 -62.3)) compared to those who were on ARV treatment when adjusted for age, sex, BMI, education.

4 DISCUSSION

The study analyzed a five year cohort of 785 HIV-infected TB patients receiving TB treatment and/or HIV treatment in Rixile clinic from 2003 to March 2008. Although 19% of participants were on HIV treatment prior to October 2005, HIV treatment in Rixile clinic started in October 2005. Those who reported to be on HIV treatment before October 2005 received treatment from other clinics or hospitals. During the second term (during ARV rollout), the proportion of mortality was lower compared to the first term (before ARV rollout). In contrast, the proportion of treatment completion was low during the first term compared to the second term. Demographic factors (age, sex) and a clinical factor (ARV treatment) were associated with TB mortality in HIV-infected TB patients receiving TB treatment and HIV treatment or TB treatment only in Rixile clinic from March 2003 to March 2008.

The proportion of each TB treatment outcome was expressed as the percentage using the total number of a particular TB treatment outcome to the total number of enrolled participants during a particular term. Treatment completion during the first term was lower compared to treatment completion during the second term, and participants at 31 to 40 years of age completed treatment than those at younger (18-30) and older (41-75) age categories. The proportion of TB treatment completion during the second term was similar to the proportion of TB treatment completion reported in a study conducted in rural South Africa, Kwazulu-Natal. **[6]** In contrast, the proportion of people died while on treatment during the second term was slightly lower than the proportion reported in the previous study. **[6]** TB mortality case definition used in this study was different from the one used in the previous study, and this

explains disparity on proportions of TB mortality reported in this study and the study conducted in Kwazulu-Natal. **[6]** Slightly higher proportion of women died with the reported cause of death as TB while on TB treatment and this is in contrast with the higher male mortality on people at the age of 25 years and older reported by the previous study **[22].** Higher proportion of females interrupted treatment than males. Non-adherence to TB can cause TB strains to be resistant to the primary TB drugs such as isoniazid and rifampicin, **[5]** drug resistant strains is associated with high mortality in infected patients, particularly those co-infected with HIV **[15]**. Although drug-resistance is not analyzed in the study, higher proportion of TB mortality in females could be perhaps associated with higher TB treatment interruption. In the previous study conducted in Hlabisa, slightly higher proportion reported to have transferred out compared to the proportion reported to have transferred out from Tintswalo hospital in the period between November 2005 and March 2008. **[5]**

The chi-square test predicted association between TB mortality and demographic factors (age, sex, BMI), social factors (marital status, education), lifestyle factor (smoking habits) and a clinical factor (ARV treatment). These factors were further included in the logistic model to assess if they are the predictors of TB mortality. Considering the variables modeled by use of logistic regression, being at the age of 41 to 75 years of age was associated with death from TB in HIV-infected persons. Although the study conducted in other developing countries, Malawi and Zambia, was on HIV-infected and non-infected TB patients, the findings that age predicts TB mortality is in line with the results presented in this study. **[7]** Increased age was further reported as a predictor of TB mortality in HIV-infected TB patients **[9]**. Although BMI was

presented as predictor for TB mortality in the previous study, **[7]** in this study such association was not significant. Despite higher mortality reported in females when compared to males; males were at higher risk of TB mortality compared to females. This finding confirms the findings presented in the study conducted in South Africa where sex was the predictor of TB mortality **[26]**. ARV treatment predicts TB mortality in HIV-infected persons, with higher TB mortality in those not receiving ARV treatment compared to those receiving ART treatment. Although the study did not assess whether ARV treatment predicts TB mortality; after the six months of ARV Treatment initiation, the study reported reduced mortality due to TB in HIV-infected persons TB patients **[27]**.

LIMITATIONS OF THE STUDY

Data was not having information on drug-resistance TB. Drug-resistance TB cannot be cured with standard treatment (first-line drugs) and is often associated with high mortality **[15,16]**. Although several risk factors were examined, there is probably considerable residual confounding. CD4 counts, which would be a better measure of the degree of immune suppression was available with considerable missing data and was not included in the analysis. There was a considerable sufficient data for analysis on WHO HIV staging; however, TB mortality occurred to participants who were on stage four (4) only; as a result WHO HIV staging could not be assessed as a predictor of TB mortality. The incomplete dates of study enrollment and the exit limited the study to perform analyses such as survival analysis. Amongst the possible TB treatment outcomes, cure was not included, therefore, cure rate would be assumed from patients who completed the treatment, and perhaps not all patients completed

the treatment were cured. Like other cohort studies, loss to follow up has been the great limitation of the study. Loss to follow up during the study resulted in considerable missing information in various variables in the data. This study as a secondary data analysis study does not have control over data quality, collection methods and missing information. The problem of under-reporting of TB mortality may arise where a proportion of patients with "missing outcome" have in fact died with the reported cause of death as TB.

5 CONCLUSION AND RECOMMENDATIONS

Participants who started treatment during the ARV roll-out in Rixile clinic completed treatment than those started treatment before the ARV roll-out. Death due to TB in HIV-infected persons was lower during the ARV roll-out. Although there are considerable differences on definitions, the proportion of TB mortality during the ARV roll-out was lower compared to what the previous study reported. Concurrent TB/HIV treatment could be the notable approach to combat TB and HIV and to improve survival by preventing mortality in co-infected persons in this rural community of South Africa.

Participants at the ages of 41 to 75 years were at higher risk of death due to TB than those at other age groups. Males were at increased risk of death with the reported cause of death as TB when compared to females. This finding supports the call for age screening prior to TB treatment in HIV-infected persons with the purpose of intensifying the treatment to patients in this age category, particularly males. The expansion of ART could reduce death due to TB in HIV-infected TB patients. Death due to TB in HIV-infected persons is lower than the reported in

this rural community, and expansion of concurrent TB and HIV treatment could be the solution in prevention of death due to TB in HIV-infected persons in this rural community of South Africa.

PLAN FOR UTILIZATION AND DISSEMINATION OF RESULTS.

Copies of the final report will be submitted to Faculty of Health Sciences, Wits University. Results of the study will be presented to Wits University school of Public Health. Other copies of the final report will be available to Tintswalo hospital (Rixile clinic), and Department of Health (South Africa) on request. The results will be ready for publishing in a leading journal.

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APPENDIX A: Data collection form (CRF)

ANNEXURE A: Ethical clearance certificate