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CORRELATES OF DELAYED PULMONARY TUBERCULOSIS DIAGNOSIS AMONG HIV-INFECTED PULMONARY TUBERCULOSIS SUSPECTS IN A RURAL HIV CLINIC, SOUTH AFRICA

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A Research Report submitted to the Faculty of Health Sciences, University of Witwatersrand, in partial fulfilment of the requirements for the degree of Masters of Science in Epidemiology in the field of Biostatistics and Epidemiology

Johannesburg, August 2011

DECLARATION

I do hereby declare that this report is my own work. It has not been submitted either in part or in full for publication or award of a degree in any other university. It is being submitted for the degree of Masters of Science in Epidemiology, as applicable, in the University of Witwatersrand, Johannesburg.

Author:



Respicious L Boniface

Date: 20th July 2011

DEDICATION

To my family for their love and support.

ABSTRACT

Title: Correlates of delayed pulmonary tuberculosis diagnosis among HIV-infected pulmonary tuberculosis suspects in rural HIV clinic in South Africa

Background

South Africa is among the countries most heavily affected by Human Immunodeficiency Virus (HIV) and tuberculosis. Delay in pulmonary tuberculosis (PTB) diagnosis is more prevalent in HIV-positive patients and is one of the factors associated with the high prevalence of co-infection in this population. This study sought to determine factors associated with delayed PTB diagnosis among HIV-infected PTB suspects attending an HIV/AIDS clinic in rural South Africa.

Methods

This was a secondary analysis of the data collected in a retrospective cohort study conducted by Rural Aids and Development Action Research Programme (RADAR). Data were collected using record review of patients assessed as PTB suspects over 2 years from January 2006 to December 2007 at Rixile clinic. TB diagnosis delay was defined as PTB diagnosis after 8 weeks (56 days) from the date of first sputum for acid fast bacilli (AFB) collection, taking into account those diagnosed by culture as it takes up to 8 weeks to culture mycobacterium tuberculosis using Lowenstein Jensen method.

Results

PTB diagnosis delay was found in 78/162 (48.15%) of the participants with subsequent TB diagnosis. Median delay was 55 days (IQR = 20 – 302). The delay was between 1 to 30 days in 27/78 (34.62%) participants, between 31 to 180 days in 26/78 (33.33%) participants and 25/78 (32.05%) participants remained undiagnosed for more than 180 days. Factors predicting PTB diagnosis delay in multivariate analysis were older age > 40 years (adjusted OR 3.43 95%CI 1.38 – 8.55, p=0.008), high HIV viral-load (adjusted OR 3.13 95%CI 1.13 – 8.71, p=0.03) and being on Antiretroviraltherapy (ART) at the time of PTB diagnosis (adjusted OR 4.19 95%CI 1.66 – 10.58, p=0.002).

Conclusion

There is a considerable delay from PTB suspicion to diagnosis in these rural HIV-infected patients. Older patients, those with elevated viral load and those who are on ART at the time of PTB diagnosis are at higher risk of PTB diagnosis delay. Therefore active and collaborative efforts to reduce the PTB diagnosis delay are very essential.

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ABBREVIATIONS

BMI: Body Mass Index

ART: Antiretroviral therapy

HAART: Highly active antiretroviral therapy

WHO: World health organisation

SD: Standard deviation

IQR: Interquartile range

RADAR: Rural aids and development action research programme

PTB: Pulmonary tuberculosis

DOTS: Directly observed therapy, short course

MDR TB: Multi-drug resistant TB

XDR TB: Extensively drug resistant TB

CHAPTER ONE

1 INTRODUCTION

In this chapter the general overview of tuberculosis and HIV/AIDS is covered. The problem statement is stated and the research justification. The published literatures on TB/HIV co-infection and factors associated with tuberculosis diagnosis and treatment delay are reviewed and the chapter ends with the definition of terms and objectives of the study described in this research report.

1.1 Background

It is estimated that one third of the world's population are infected with tuberculosis. Tuberculosis (TB) is still one of the biggest killers among infectious diseases reported in World Health Organization. The global burden of tuberculosis remains high, mainly because of poor control in Southeast Asia, Sub-Saharan Africa and Eastern Europe, and because of high rates of mycobacterium tuberculosis and HIV co-infection in some African countries (1).

The HIV epidemic has aggravated tuberculosis situation in the world. It increases the risk of reactivation of latent tuberculosis, it also causes a more rapid progression of tuberculosis disease. HIV alters the clinical presentation of tuberculosis and compromises the response to anti-TB treatment. People with both HIV and tuberculosis are likely to die far earlier than those HIV patients

without tuberculosis. Likewise, TB patients with HIV infection are more likely to die earlier than TB patients who do not have an HIV infection (2).

Approximately 11% of sub-Saharan African adults are infected with HIV; this has caused TB cases to rise in sub-Saharan African countries. WHO (2007) estimates that the average incidence of TB in sub-Saharan African countries more than doubled between 1990 and 2005, from 149 to 343 per 100,000 population (3).

Recognizing the scale of the problem, in 2006, the World Health Organization launched the “Stop TB Strategy” (4) as the internationally recommended approach to reducing the burden of TB. The stop TB strategy was developed as the successor to the DOTS (Directly Observed Therapy, Short Course) strategy. The goal of the strategy is defined as: “To dramatically reduce the global burden of TB by 2015 in line with the Millennium Development Goals and the Stop TB Partnership targets”. The strategy has six major components:

1. Pursue high-quality DOTS expansion and enhancement;

2. Address TB/HIV, MDR-TB, and the needs of poor and vulnerable populations;

3. Contribute to health system strengthening based on primary health care;

4. Engage all care providers;

5. Empower people with TB, and communities through partnership;

6. Enable and promote research.

South Africa is among the countries most heavily affected by HIV and tuberculosis. An estimated 31% of all TB-HIV co-infection cases reported in Africa are in South Africa and tuberculosis rate in South Africa is ranked fifth highest among 22 countries with a high burden of tuberculosis. It is the second most serious infectious disease and has been made a priority program by the National Department of Health (5).

Along with HIV, another factor aggravating this public health problem is delay in pulmonary tuberculosis diagnosis and treatment. Delay in PTB diagnosis causes the disease to advance, results in more complications and leads to a higher mortality at the individual level and transmission within the community (6). One infectious TB case can infect up to 15 other people in the course of one year (7). For those patients co-infected with HIV mycobacterium tuberculosis causes increase in viral load making them more likely to transmit HIV and rapidly progressing immune suppression (8).

TB control programmes in Africa rely predominantly on passive case findings and diagnostics for TB are limited to sputum microscopy. Sputum testing is often ineffective among TB/HIV co-infected patients who are more likely to be sputum smear negative, atypical radiographic findings, higher prevalence of extra-pulmonary tuberculosis and resemblance to other opportunistic infections (9). This may contribute to the delay in pulmonary tuberculosis diagnosis in HIV infected patients, hence poor health outcomes and increases public risk of possible exposure to TB in the community without treatment.

Three essential activities that all HIV programmes should be doing to protect people with HIV from TB infection are; Aggressive TB screening which can lead to early diagnosis and prompt TB treatment initiation, Isoniazid preventive therapy to reduce the risk of developing active TB, and practicing TB infection control to reduce the spread of TB to vulnerable people with HIV, health care workers and the community (10). Therefore, a strong co-ordination between the national TB and the AIDS control programmes is required for effective management of HIV-TB patients.

1.2 Problem Statement.

The burden of tuberculosis is increasing globally. HIV epidemic has emerged as the most important predisposing factor for developing TB, and the burden of TB/HIV co-infection in South Africa is very high.

Delay in pulmonary tuberculosis diagnosis is more prevalent in HIV positive patients and is one of the factors associated with the high prevalence of co-infection in this population.

Undiagnosed TB accelerates the clinical course of HIV disease leading to poor patient's health outcome. Lack of TB diagnosis and treatment may also put more people with HIV and unrecognised TB at risk of serious immune reconstitution inflammatory reactions, when they are put on ART, and could be a factor in high mortality on ART. It also increases the cost both to patient and health care system due to additional clinic visits and the need for hospitalization.

Few studies have been conducted in developing countries, including South Africa to identify factors associated with the delay in pulmonary tuberculosis diagnosis among HIV infected patients.

Addressing factors that influence time to pulmonary tuberculosis diagnosis among HIV-infected patients is vital to achieving the goal of reducing the global burden of tuberculosis.

1.3 Justification

The goals of TB control are to reduce mortality, morbidity and transmission of the disease in the community.

It is therefore important to reduce the TB diagnosis delay in order to improve patient's health outcomes, reduce the infection duration in the community and thereby reduce the number of new infections. This requires exploration of factors influencing delay in PTB diagnosis. .

This study presented here aimed to examine factors associated with delay in PTB diagnosis among HIV/AIDS patients following entry into public sector HIV services in rural South Africa.

The results of this study will inform the evidence-base necessary to improve implementation and effectiveness of PTB investigations, with particular reference to a rural setting.

1.4 Literature review

Globally, the burden of tuberculosis is increasing. Apart from HIV/AIDS, undiagnosed cases in the community increases the burden of tuberculosis, this can be due to patients delaying seeking healthcare or failure of the healthcare systems to diagnose patients in a timely manner (11). Patient's health seeking behaviour and factors within the healthcare systems are the main determinants of the delay.

TB diagnosis delay time

There is no general agreement for how long acceptable delays could be. For effective TB control, it is generally considered that, the time from the onset of symptoms to the first contact with a qualified health provider should not be more than 2 or 3 weeks, and the time from first contact to the start of treatment should be only a few days (12). Various studies have reported about the delays in diagnosis of tuberculosis in high, middle and low income countries.

An overall management delay of up to 25 days among hospitalized patients with tuberculosis, was reported in Washington USA (13), whereas Golub et al (14) found the median heath care delay of 26 days among patients who were reported to the Maryland Department of Health and Mental Hygiene. Farah et al (15) reported the median health care system delay of 33 days in Norway. Chandrashekhar et al (16) in a systematic review reported that, among high income countries health care system delay ranged from a shortest of 7 days in

Japan to a longest of 36 days in Italy, whereas among low and middle income countries health care system delay ranged from shortest of 2 days in China to a longest of 87 days in Pakistan.

Median health care system delay of 22 days was reported in Sarawak, Malaysia (17), other studies have reported median health system delays of 24, 18 and 28 days from China, Nepal and India respectively (18-20).

Studies conducted in Africa have reported the median diagnostic delays of 15, 12 and 9 weeks from Tanzania, Uganda and Zambia respectively (21-23). Other studies have reported median diagnostic delays of 9, 8 and 5 weeks from Gambia, Ghana and Kenya respectively (24-26). Tatek et al (27) reported a median health system delay of 6 weeks in Ethiopia, patients from urban areas had shorter health system delay than patients from rural areas. Meintjes et al (28), reported a median total delay from the onset of symptoms to treatment of 8 weeks at G F Jooste Hospital, Cape Town, whereas Pronyk et al (29) reported a median total delay of 10 weeks in Bushbuckridge region, Mpumalanga province of South Africa.

Socio-demographic determinants

Most studies conducted in high, middle and low income countries have reported old age to be a risk factor for increased diagnostic delay (14-16, 23, 26). Elderly

patients often have co-existing medical conditions like heart diseases and chronic chest problems, which makes it more difficult to diagnose TB and can result in diagnosis and treatment delay.

Females have been reported to be at risk of diagnostic delay in most studies conducted in middle and low income countries (18-22). Several factors have been associated with increased diagnostic delay among females, some being cultural, social, low social economic status of women and women's tendency of placing family matters above their own health. In some communities, female TB patients and women who are suspected to have active TB are likely to be forced to get divorced and have fewer chances of getting married (30). Pronky et al (29) reported increased diagnostic delay among females in rural South Africa, whereas Meintjes et al (30) reported increased diagnostic delay among males in Cape Town, South Africa.

Socio-economic determinants

Low income and poverty have been reported to be associated with increased diagnostic delay in several studies conducted in middle and low income countries. Studies have found that financial difficulties account for delay in China (18). Transportation costs, which are associated with distance between residence and healthcare facility accounts for the delay in Zambia (23). Diagnostic delay is more likely when patients don't have health insurance or money to attend healthcare facility.

Being knowledgeable and perceived risk of TB within communities, influence the tendency to seek care. A number of studies have found association between knowledge and delayed diagnosis. As demonstrated in Tanzania, India and Vietnam (21, 20, 30), patients with low knowledge about the disease are more likely to postpone care seeking. It is also reported in study from Tanzania that, patients with low knowledge are more likely to visit traditional healers rather than a recognized health facility. Low education and knowledge about the disease, contributes to beliefs that TB is incurable, caused by evil spirits and stigma as it has been reported in a study conducted in Pwani region, Tanzania (31). Size of the households can also influence health care seeking behaviour. Pronky et al (29), reported that patients who came from larger households had significantly shorter delays in Bushbuckridge, South Africa. This is due to substantial influence of family members in motivating health seeking behaviour.

Health system determinants

Health care providers are expected to adequately and timely conduct patients examination and investigations. However inadequate TB knowledge among health workers and lack of diagnostic facilities may delay patient's diagnosis and treatment (32). Studies have reported that, TB diagnosis is often inadequate in primary health centres that have limited diagnostic facilities and poorly trained personnel especially in rural areas. Private practitioners with low awareness of

TB have also been reported to be risk factors for prolonged health system delay (33-34). This often results in patients repeated consultation of healthcare providers without a correct diagnosis.

A study to explore the ways in which provider and patient behaviour interact to exacerbate diagnostic delay in Cape Town, South Africa revealed diagnostic delay to be caused by, provider failure to diagnose TB at first contact, use of private sector which did not treat TB and multiple care seeking within and between sectors. Findings of this study suggest the need for strategies to encourage patients to visit their local public clinics, additional training or information about diagnosis and referral for private doctors and strategies to smooth the flow of patients within and between sectors will reduce diagnostic delay (35).

Missed chest X-ray at first visit has been reported to result in longer delays in diagnosis (36). Golub et al (14) in Maryland revealed, initially presenting to a private physician, not receiving a chest X-ray, not providing a sputum specimen at the initial health care visit and being diagnosed with another respiratory illness or receiving non-TB antibiotic therapy was associated with prolonged health system delay. The under – utilisation of smear microscopy, sputum culture or chest X-ray in the diagnosis of TB is associated with prolonged health system delay (37-38).

TB diagnosis delay in HIV infected patients

Delay in diagnosis and treatment of tuberculosis increases mortality in HIV infected patients. Tuberculosis accelerates the progression HIV infection, leads to high viral load, lower CD4 count (less than 200cells/mm^3) and increases the risk of mortality in HIV/AIDS patients (39-40). To improve the diagnosis, treatment and outcomes for patients with both diseases, the World Health Organization developed a framework of strategic collaborative activities to be performed as part of the health sector response to control HIV infection related TB. These activities include measures to decrease burden of TB among persons with HIV infection, and to decrease the burden of HIV infection among persons with TB (41).

Tuberculosis in HIV infected patients is often difficult to diagnose because of nonspecific symptoms, atypical or normal chest radiographic findings, negative results of sputum smear microscopy and lack of culture facilities in resource limited settings (42). This often results in delay in TB diagnosis in HIV infected patients. Undiagnosed tuberculosis in patients starting ART may result in morbidity during early ART because of immune reconstitution inflammatory syndrome (43), and increased mortality among patients on ART, as it has been reported in a previous study conducted in a source population of this study in which they noted a high TB related mortality among ART patients (44).

Delay in TB diagnosis in HIV infected patients may results in TB transmission among other patients in HIV clinics and in communities. Tuberculosis in HIV

infected patients is more likely to be sputum smear negative TB, which is less infectious than patients with sputum smear positive TB (45). However, patients with smear negative, culture positive pulmonary TB are capable of transmitting mycobacterium tuberculosis (46). Therefore, persons in contact with patients with smear negative TB are at risk of infection due to mycobacterium tuberculosis and subsequent development of active TB (47).

In high income countries, 10% to 20% of TB transmission at the population level is attributable to source cases with smear negative pulmonary TB (48). In Sub – Saharan Africa, the prevalence of undiagnosed TB, which is a key determinant of TB transmission, is very high, and the disease duration before diagnosis is prolonged (49). In a previous study conducted in Gugulethu Township, Cape Town, among all newly referred ART patients, found that more than twenty five percent of patients had culture confirmed pulmonary TB (48). Culture based diagnosis took more than 3 weeks, on average. This increases the chance of TB transmission and is the risk factor for the outbreak of Multi-drug resistant TB (MDR-TB) and Extensively drug resistant TB (EDR-TB), like what happened at an ART clinic in Tugera Ferry, South Africa (50). This brought to the world's attention that, urgent action is required to prevent, diagnose and treat TB in people living with HIV, their families and communities.

Highly active antiretroviral therapy (HAART) has been shown to decrease the occurrence of HIV/AIDS associated tuberculosis. A study to determine the effect of HAART on incidence of tuberculosis in South Africa found a decrease in the occurrence of HIV/AIDS associated tuberculosis by more than 80% among

patients who were receiving HAART compared to those who were not receiving HAART. The result of this study supports the WHO recommendation to increase antiretroviral therapy throughout sub-Saharan Africa and world-wide (51).

Conclusion

In conclusion, long delays in TB diagnosis result in patients presenting with advanced disease and hence high mortality. Diagnostic delay increases the burden of tuberculosis by increasing the period of infectivity in the community. Measures should be taken to reduce delays in TB diagnosis, with attention paid to patient-related factors, such as raising awareness of TB in general population, stigma, use of traditional healers and health system factors such as failure to investigate for TB, extensive and irrational use of antibiotics and improving accessibility of health services.

1.5 Definition of terms

Lag period- time from clinical suspicion of a pulmonary tuberculosis episode to diagnosis.

PTB Diagnosis – a clinical diagnosis of pulmonary tuberculosis by a clinician or initiation of PTB treatment

PTB suspects – Individuals suspected of having pulmonary tuberculosis infection from clinical presentation.

Socio-demographic correlates - Are social and population factors (eg age, sex, marital status, place of residence).

Clinical correlates – Are patient clinical presentation, clinicians and diagnostic factors.

HAART: Highly active antiretroviral therapies are different combinations of drugs which work by reducing multiplication of HIV in people infected with the virus.

PTB Diagnosis delay – As there is no scientifically agreed criteria for TB diagnosis delay definition which could be found in the literature, we defined TB diagnosis delay as PTB diagnosis after 8 weeks (56 days) from the date of first sputum for acid fast bacilli (AFB) collection, taking into account those diagnosed by culture as it takes up to 8 weeks to culture mycobacterium tuberculosis using Lowenstein Jensen method (52).

Recommended standard procedures applied to the diagnosis of TB in South Africa are summarized in figure 1 (53).

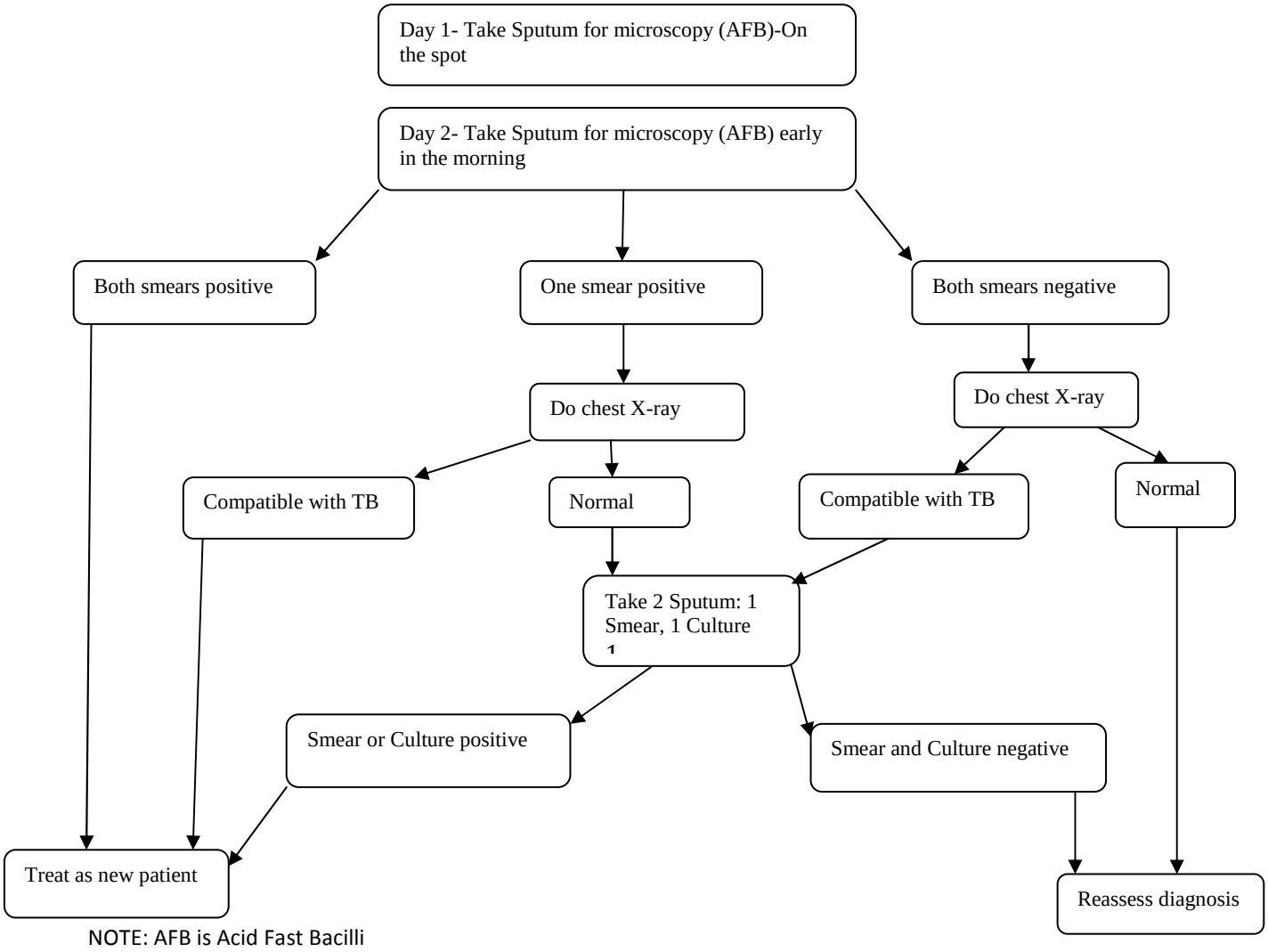


FIGURE 1: TB diagnostic algorithm in South Africa

1.6 Research question

What are the dynamics and factors associated with pulmonary tuberculosis diagnosis delay among HIV-infected pulmonary tuberculosis suspects?

1.7 Objectives of the study

Main objective

The main objective of this study is to investigate correlates of delayed PTB diagnosis among HIV-infected PTB suspects in a rural HIV clinic in South Africa.

Specific objectives

The specific objectives of this study are:

1. To determine the lag period to PTB diagnosis among PTB suspects attended at Rixile Clinic between January 2006 and December 2007.
2. To examine socio-demographic and clinical correlates of delayed PTB diagnosis among PTB suspects attended at Rixile Clinic between January 2006 and December 2007.
3. To assess the relationship between ART initiation and the lag period to PTB diagnosis among PTB suspects attended at Rixile Clinic between January 2006 and December 2007.

CHAPTER TWO

METHODS

This study was conducted in order to determine factors associated with pulmonary tuberculosis diagnosis delay among HIV infected pulmonary tuberculosis suspects. In order to answer this research goal, secondary analysis of the data obtained from the primary study conducted by RADAR was done. This chapter gives an overview of the methodology, and the details about data collection and analysis.

2.1 Study design

This was a secondary analysis of the data collected in a retrospective cohort study conducted by Rural Aids and Development Action Research Programme (RADAR). Data were collected using record review of patients assessed as PTB suspects over 2 years from January 2006 to December 2007 at Rixile clinic.

2.2 Study Setting

The study was conducted at Rixile clinic a dedicated rural HIV clinic situated at Tintswalo hospital in Mpumalanga Province of South Africa. The clinic is operated jointly by the Department of Health and Perinatal HIV Research Unit. The clinic has enrolled over 5000 people living with HIV/AIDS, and a further 2000 has been placed on HAART. The clinic is mainly nurse-driven and doctor-

supported. The clinic attends to an average of 20 TB suspects per month. Diagnostic ability for TB is limited, yet many patients are not placed on isoniazide prophylaxis for fear of resistance and poor adherence. The area has been designated one of the 13 most rural nodes of South Africa. The population is predominantly black, Shangaan and SePedi-speaking, and largely poor with most households headed by women due to high levels of job migration.

2.3 Study Population

The study population comprised of adult PTB suspects co-infected with HIV identified by clinical symptoms and seen at Rixile Clinic, between January 2006 and December 2007. The case definition was patients for whom Sputum Acid Fast Bacilli (AFB) test were requested by nurses and who appeared on the 'Specimen collection and treatment refill' forms between January 2006 and December 2007.

Inclusion criteria were:

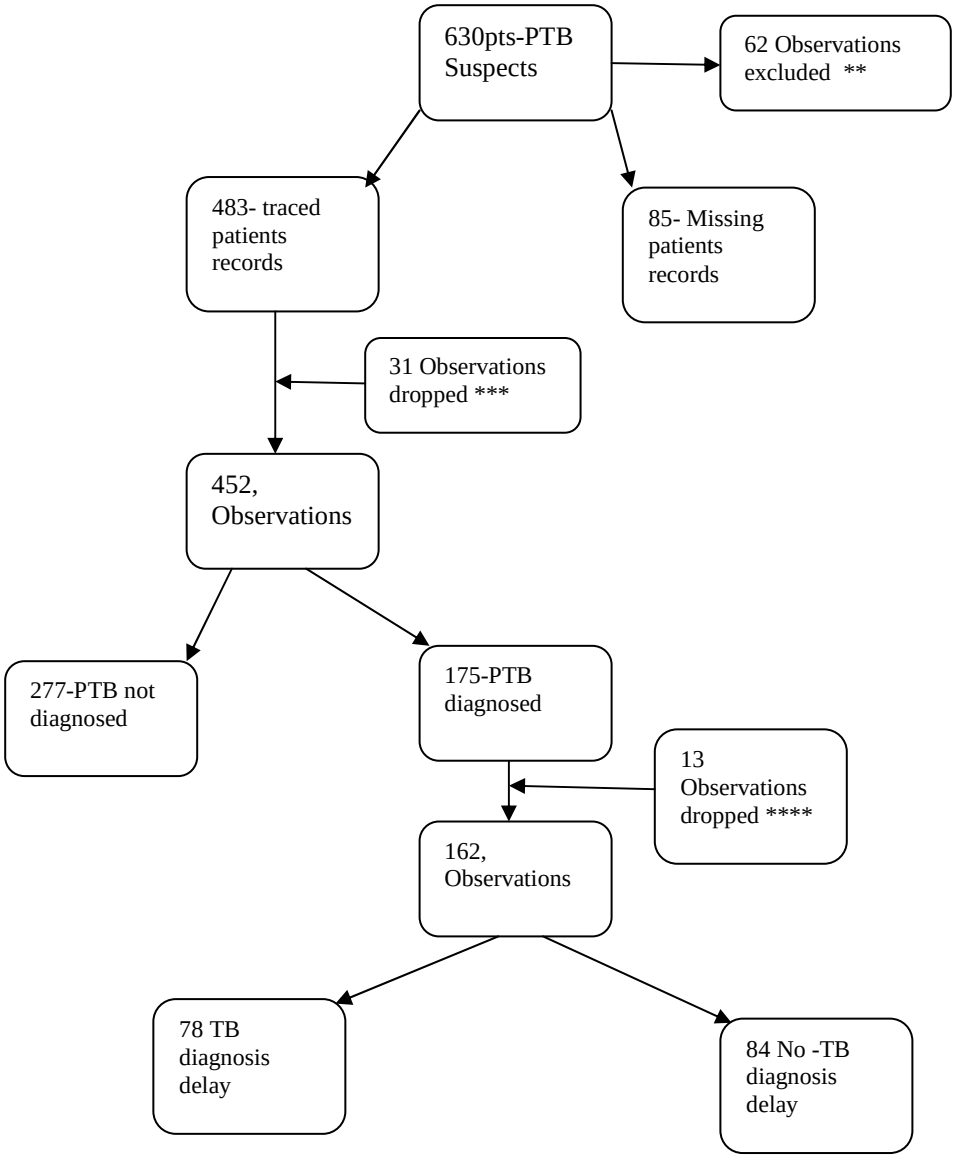
1. Chronic cough for at least two weeks
2. Drenching Night sweats
3. Loss of weight
4. Loss of appetite
5. 18 years of age and above.

Exclusion criteria were:

1. Suspected exclusive Extra-pulmonary TB (without PTB suspect)

2.4 Sampling and sample size:

Data on 452 participants enrolled by RADAR in a cohort study were used. The original primary study used TB suspect register to sample participants. In two years period 630 participants were identified from the TB suspect register. Sixty two participants were excluded from the study: 7 were under 18 years old, 39 had no AFB investigation requested, 1had extra pulmonary TB, 15 had noTB diagnosis information. Eighty five participants' medical records were missing and 31 were duplicates. Therefore, 452 participants were included in the study, and PTB diagnosis delay predictors analysis was among 162 participants. Figure 2 below summarizes the number of participants seen.



**7-Under 18years old, 1-Extrapulmonary TB, 39-No AFB investigation requested, 15-Absence TB diagnosis information.

*** 31-Observations were duplicates

****8-Negative time interval to TB diagnosis, 2-Too long time interval to TB diagnosis (>4years), 3-No information about TB diagnosis date.

FIGURE 2: Study participant's flow chart

2.5 Measurement and data sources

A questionnaire was used to capture data from patient's medical records. Outcome variable was diagnostic delay (Defined as PTB diagnosis after 8 weeks, from clinical suspicion of PTB).

Explanatory variables were:

- Socio-demographic factors; Age, Gender, Marital status, Cigarette smoking, Alcohol drinking, Education level, Occupation status, Main material walls of house, Number of people in household.
- Clinical factors; Presenting symptoms, How was the diagnosis made, WHO-HIV clinical stage, CD4 counts, BMI, Viral load, ART duration, TB prophylaxis, Previous TB diagnosis and TB treatment outcome

2.6 Data management

Data entry was done using Epi info version 3.5.1. The created dataset was transferred to STATA 11 to check for the data completeness, outliers and missing data. STATA 11 was also used for categorizing variables and statistical analysis.

2.7 Data analysis

Descriptive statistics

Frequency distributions were used for categorical variables, means and standard deviation for continuous variables.

Inferential statistics

Chi-square test was used for bivariate analysis as all variables were categorized. For those variables with observed frequency less than five fisher's exact test was applied. A factor was considered significant if it had a p-value of ≤ 0.1. Variables that demonstrated significant bivariate association (defined as $p \leq 0.1$) with PTB diagnosis delay were entered into the unconditional logistic regression model to assess independent effects. Variables were retained in the final model if they demonstrated significant independent association (defined as $p \leq 0.1$) with PTB diagnosis delay. Parameter of measurement to assess association was Odds ratio.

2.8 Ethical considerations

Ethical approval for the study was obtained from **the University of Witwatersrand**Research and Ethics Committee, Johannesburg (ethics clearance number M10946; appendix 1). Permission to use the data was granted by the Director of Rural AIDS and Development Action Research Programme (RADAR). Confidentiality was maintained by not displaying patient names and their medical

Confidentiality was maintained by not displaying patient names and their medical test results.

CHAPTER THREE

RESULTS

This chapter provides the results of findings of a study to determine factors associated with delayed pulmonary tuberculosis diagnosis among HIV-infected pulmonary tuberculosis suspects in a rural HIV clinic in South Africa. Knowing factors associated with time to pulmonary tuberculosis diagnosis is crucial in planning control of tuberculosis in the population.

3.1 Descriptive Analysis

There were 452 study participants.

3.1.1 Demographic characteristics of study participants

The age of the participants ranged from 23 to 96 years with a mean age of 42.8 years and a standard deviation of 10.4. Sixty nine percent of participants were between 31 to 50 years, 22% were older than 50 years and 9% were between 18 to 30 years old. Seventy percents of participants (318/452) were females and thirty percent (134/452) were males (Figure 3).

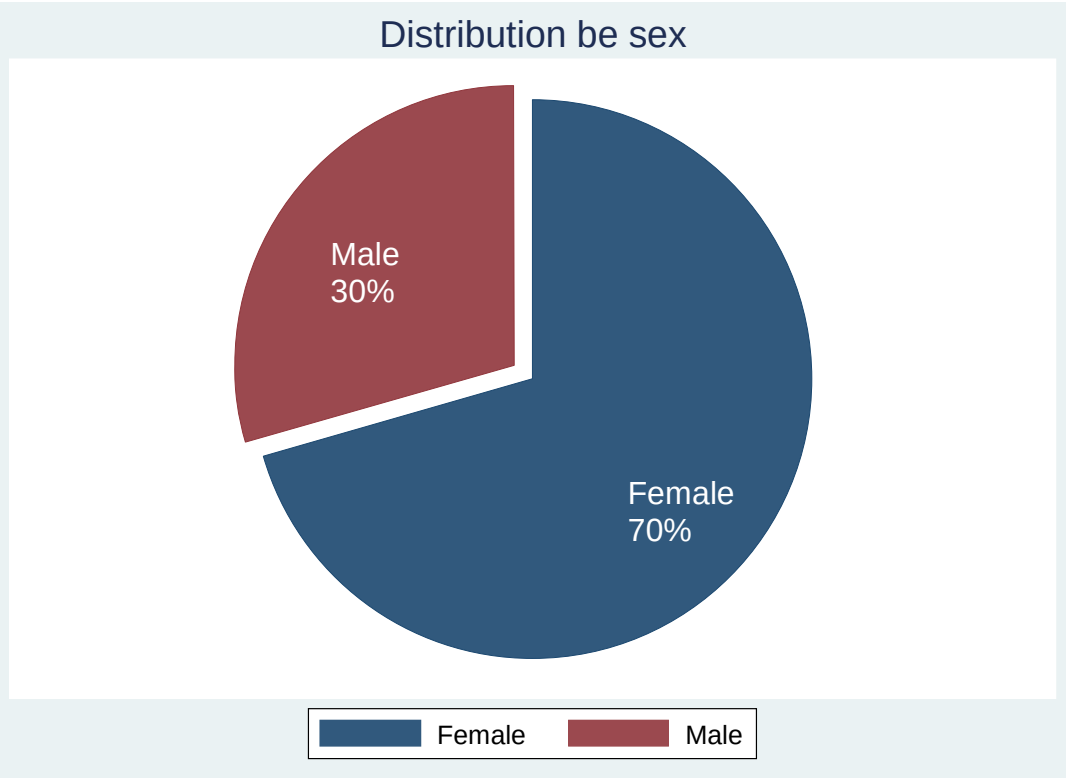


Figure 3: Distribution of study participants by gender

3.1.2 Socio-economic characteristics of study participants

Thirty nine percent of participants were single, 42.4% had been to primary school. More than half of participants (58.1%) were unemployed and not willing to work, 80% of participants were not cigarette smokers and 80% were not alcohol drinkers. Half of study participants had their houses made of block cement and there were one to five people in each household (Table 1).

Table 1: Frequency distribution of socio-economic characteristics of study participants

Variable	Number	Percent (%)
Marital Status		
Divorced	81	18.2
Married	131	29.4
Never Married	175	39.2
Widowed	59	13.2
Missing	6	1.3
Education level		
No education	90	20.1
Primary	191	42.7
Secondary	152	34.0
Tertiary	14	3.1
Missing	5	1.1
Occupation status		
Salaried worker	46	10.2
Unemployed and willing to work	142	31.6
Unemployed and not willing to work	261	58.1
Missing	3	0.7
Smoke Cigarette		
No	359	80.7
Yes	86	19.3
Missing	7	1.5
Alcohol drinking		
No	355	79.9
Yes	89	20.1
Missing	8	1.8
Main material walls of house		
Block cement	229	51
Brick	115	25.6
Mud	104	23.2
Wood	1	0.2
Missing	3	0.7
People in households		
1 to 5	239	53.1
6 to 10	187	41.6
>10	24	5.3
Missing	2	0.4

3.2 PTB diagnosis

Pulmonary tuberculosis was diagnosed in162/452 (35.8%) of the study participants. The diagnosis was made by clinical history and chest x-ray in 38/162 (23.5%) participants, sputum smear positive in 40/162 (24.7%) participants and 84/162 (51.9%) by smear negative but culture positive.

3.2.1 TB diagnosis delay

Pulmonary tuberculosis diagnosis delay was observed among 78/162 (48.15%) participants. Median delay was 55 days (IQR = 20 – 302). The delay was between 1 to 30 days in 27/78 (34.62%) participants, between 31 to 180 days in 26/78 (33.33%) participants and 25/78 (32.05%) participants remained undiagnosed for more than 180 days. Majority of participants with diagnosis delay, 47/78 (60.3%) had their diagnosis made by sputum culture (Table 2).

Table 2: Diagnosis delay duration by method of diagnosis

Method of TB diagnosis	1 to 30 days delay Number (%)	31 to 180 days delay Number (%)	> 180 days delay Number (%)	TOTAL Number (%)	P-value
Clinical history & chest X-ray	4 (15.3)	5 (19.2)	10 (40)	19 (24.7)	
Sputum smear positive	3 (11.5)	2 (7.7)	7 (28)	12 (15.6)	0.016
Sputum culture	20 (74.1)	19 (73.1)	8 (32)	47 (60.3)	
TOTAL	27 (100)	26 (100)	25 (100)	78 (100)	

3.3 Bivariate analysis

The difference in the distribution of factors associated with TB diagnosis delay in this study was determined using chi square test. For those variables with observed frequency less than five fisher's exact test was applied. A factor was considered significant if it had a p-value of ≤ 0.1. The following factors were significantly associated with TB diagnosis delay: Patient's age (p-value 0.006), method of TB diagnosis (p-value 0.025), viral load (p-value 0.018) and ART use at the time of PTB diagnosis (p-value 0.000).

There was no statistically significant difference when comparing factors association with TB diagnosis delay across gender, marital status, occupation, education level, main material walls of house, number of people in households, WHO HIV clinical stage, CD4 count, body mass index, cigarette smoking, alcohol drinking, previous TB diagnosis, presenting symptoms, TB prophylaxis and TB treatment outcome (p-value > 0.1). Table 3 and table 4, summarises the results of the bivariate analysis.

Table 3: Comparison of socio-demographic factors of participants with TB diagnosis delay

Variable	Diagnosis delay Number (%)	No delay Number (%)	P – value
Patient age			
18 to 40years	33(42.9)	54(64.3)	
>40years	44(57.1)	30(35.7)	0.006**
Sex			
Female	49(62.8)	58(69.0)	
Male	29(37.1)	26(30.9)	0.403
Marital Status			
Divorced	13(16.8)	13(15.4)	
Married	25(32.4)	21(25.0	0.592
Never Married	27(35.0)	38(45.2)	
Widowed	12(15.5)	12(14.2)	
Occupation status			
Salaried worker	9(11.6)	7(8.3)	
Unemployed and willing to work	21(27.2)	29(34.5)	0.538
Unemployed and not willing to work	47(61.0)	48(57.1)	
Smoke Cigarette			
No	57(74.0)	66(79.5)	
Yes	20(25.9)	17(21.4)	0.410
Alcohol drinking			
No	57(74.0)	65(79.2)	
Yes	20(25.9)	17(20.7)	0.434
Education level			
No education	16(20.8)	14(16.7)	
Primary	37(48.0)	33(39.2)	
Secondary	23(29.8)	33(39.3)	0.320
Tertiary	1(1.3)	4(4.8)	
Main material walls of house			
Block cement	38(48.7)	47(55.9)	
Brick	19(24.3)	22(26.2)	0.377
Mud	21(26.9)	15(17.9)	
Number of people in households			
1 to 5	44(57.1)	46(54.8)	
6 to 10	30(38.9)	33(39.3)	0.895
>10	3(3.9)	5(5.9)	

NOTE: ** p-value ≤ **0.1**

Table 4: Comparison of clinical factors of participants with TB diagnosis delay

Variable	Diagnosis delay Number (%)	No delay Number (%)	P – value
Method of TB diagnosis			
Clinical History & CXR	19(24.1)	19(22.9)	0.018**
Sputum smear positive	12(15.2)	28(33.7)	
Smear negative, Culture positive	48(60.8)	36(43.4)	
WHO-HIV Clinical stage			
1	2(3.6)	2(2.9)	1.000
2	9(16.4)	16(23.5)	
3	42(76.4)	44(64.7)	
4	2(3.6)	6(8.8)	
CD4 Count (cells/mm3)			
<50	4(6.9)	1(1.8)	0.193
50 - 200	15(25.9)	10(17.9)	
>200	39(67.2)	45(80.4)	
Viral load (copies/ml)			
<400	31(60.8)	39(81.2)	0.025**
>400	20(39.2)	9(18.7)	
BMI			
Underweight	16(25.4)	15(22.4)	
Normal weight	34(53.9)	38(56.7)	0.828
Overweight	12(19.0)	11(16.4)	
Obese	1(1.5)	3(4.5)	
ART use at PTB diagnosis			
No	38(50.0)	62(77.6)	0.000**
Yes	38(50.0)	18(22.5)	
TB treatment outcome			
Completed treatment	41(53.9)	45(54.9)	0.640
Died	7(9.2)	7(8.5)	
Lost to follow up	14(18.4)	20(24.4)	
Still on treatment	14(18.4)	10(12.2)	

NOTE: ** p-value ≤ **0.1**

3.4 Inferential statistics

3.4.1 Univariate Logistic regression

Variables with p-value ≤ 0.1 in bivariate analysis were considered significant hence were evaluated further in the univariate unconditional logistic regression model to assess independent association with TB diagnosis delay. The association between method of TB diagnosis and TB diagnosis delay was not statistically significant after univariate logistic regression analysis.

Therefore patient's age, viral load and ART use at PTB diagnosis were retained in the final multivariate logistic regression model. The results are summarised in table 5.

Table 5: Univariate logistic regression results

Variable	Univariate OR, 95%CI, P-value
Patient age	
18 to 40years	1
>40years	2.4 (1.27 - 4.53) 0.007
Method of TB diagnosis	
Clinical History & CXR	1
Sputum smear positive	0.43 (0.17 - 1.08) 0.074
Smear negative, Culture positive	1.33 (0.62 - 2.88) 0.463
Viral load (copies/ml)	
<400	1
>400	2.79 (1.12 - 6.99) 0.03
ART use at PTB diagnosis	
No	1
Yes	3.44 (1.73 - 6.87) 0.000

NOTE: OR is Odds Ratio, CI is Confidence Interval

3.4.2 Multivariate Logistic regression

Patient's age, viral load and ART use at PTB diagnosis remained statistically significant after multivariate logistic regression analysis. Patients older than 40 years have 3.43 times greater risk of TB diagnosis delay compared to those of age group 18 to 40 years. The risk of TB diagnosis delay was 3.13 times greater in those with viral load greater than 400 copies/ml compared to those with viral load less than 400 copies/ml. Those who were on ART at the time of PTB diagnosis were 4 times greater risk of TB diagnosis delay compared to those who were not on ART at the time of PTB diagnosis. The results are shown in table 6.

Table 6: Multivariate logistic regression results

Variable	Multivariate OR, 95%CI, P-value
Patient age	
18 to 40years	1
>40years	3.43 (1.38 - 8.55) 0.008
Viral load (copies/ml)	
<400	1
>400	3.13 (1.13 - 8.71) 0.03
ART use at PTB diagnosis	
No	1
Yes	4.19 (1.66 - 10.58) 0.002

NOTE: OR is Odds Ratio, CI is Confidence Interval

In summary, the results of this analysis revealed that patient age, viral load and ART use at the time of PTB diagnosis are significantly associated with TB diagnosis delay.

CHAPTER FOUR

4.1 DISCUSSION

The aim of this study was to investigate factors associated with PTB diagnosis delay among HIV-infected pulmonary tuberculosis suspects in a rural HIV clinic in South Africa.

The following factors were found to be significant correlates of PTB diagnosis delay in HIV infected patients in univariate and multivariate analysis: Patient's age, viral load and ART use at the time of PTB diagnosis.

The risk of TB diagnosis delay was greater in those older than 40 years, those with viral load greater than 400 copies/ml and those who were on ART at the time of PTB diagnosis.

4.1.1 TB diagnosis delay time

In our study the median TB diagnosis delay was 55 days which is almost similar to findings reported in most studies conducted in other African countries. Median diagnostic delays of 15, 12 and 9 weeks, have been reported in studies from Tanzania, Uganda and Zambia respectively (21-23). These are poor resource countries therefore; TB diagnostic facilities in these countries may be similar to those in rural South African settings. The study by Pronyk et al (2001), conducted in the same community as this study, found a median total delay to

hospitalization of 10 weeks (29), whereas Meintjes et al (28) in Cape Town found a median delay of 30 days, which is shorter than the delay found in this study. The Cape Town study was conducted at a secondary level hospital, where diagnostic facilities are expected to be much better than those in rural setting. Health facilities in rural settings are more likely to be having poorly trained personnel and limited diagnostic facilities contributing to delay in TB diagnosis, as it has been reported by Tatek et al (27) study in Ethiopia.

In this study 25/78 (32.1%) PTB patients remained undiagnosed and were not started on treatment for more than 6 months; this can lead to poorer health outcomes in TB/HIV infected patients because tuberculosis accelerates the progression of HIV disease (6). A national study done in Malawi found 40% of death occurred during the first month of anti-tuberculosis treatment, the reason suggested in that study was long delays in diagnosis and initiation of TB treatment (54).

4.1.2 Socio-demographic factors

Similar to the findings of most other studies, TB diagnosis delay was found to be significantly associated with patient's age. Older patients > 40years were at much higher risk of TB diagnosis delay compared to those younger than 40years. Elderly patients often have other co-existing medical conditions, which makes it difficult to diagnose TB in these patients resulting in diagnosis and treatment delay (14-16, 23, 26).

There was no association between sex and TB diagnosis delay in this study, which may be because the majority of the study participants (70%) were females. However several other studies have found longer delay to be associated with female gender, due to their heavy workload, lack of independence, lack of decision making, and fear of divorce or abandonment (18-22).

Level of education had no significant effect on TB diagnosis delay in this study similar to findings in Uganda (22). However several other studies have found association between level of education and delayed diagnosis, as it has been demonstrated in studies from Tanzania, India, Vietnam and China (31, 20, 30, 18), that patients with low education and knowledge about the disease are more likely to postpone care seeking and visit traditional healers rather than a recognized health facilities.

Number of people in households had no association with TB diagnosis delay in this study, however previous study done in the same community as this study, revealed people who came from larger households had significantly shorter delays, reason being substantial influence of family members in motivating health seeking behaviour (29).

4.1.3 Clinical factors

PTB diagnosis in this study was predominantly by sputum culture (51.9%), and the diagnosis could not be made by chest radiography or sputum smear in most of the patients. This is likely because the study was conducted among HIV infected patients, studies have reported reduced diagnostic sensitivity of sputum smears and chest radiography in HIV infected patients (9, 55). Patients with early HIV tend to have the classic clinical and radiographic manifestations of TB seen in HIV-negative population, tuberculosis in patients with advanced AIDS may present differently.

High viral load was associated with TB diagnosis delay in this study. Studies have shown that, mycobacterium tuberculosis can accelerate the clinical course of HIV disease (39-40), resulting in HIV/AIDS progression and hence high viral load and low CD4 counts. However, there was no association between patient's CD4 count and TB diagnosis delay in this study.

In this study 47/78 (60.3%) patients who had sputum smear negative but culture positive, had their TB diagnosis delayed. Studies have shown that patients with smear negative, culture positive pulmonary TB are capable of transmitting mycobacterium tuberculosis to other persons and subsequent development of active TB (56-57). Among sputum smear positive patients 12/78 (15.6%) had their TB diagnosis delayed. These are very infectious and it is estimated that, untreated sputum smear positive case infect up to 15 other individual each year, and are important factor in the occurrence of nosocomial outbreaks of TB (7,

58). This can also be a risk factor for the outbreak of Multi-drug resistant TB (MDR-TB) and Extensively drug resistant TB (EDR-TB) in this HIV clinic, like what happened in Tegera Ferry, South Africa (50). Initial outbreak in Tugera Ferry evolved locally and was spread to other patients at the hospital filled with people with HIV.

Timely diagnosis of TB is particularly crucial to minimize disease transmission, reduce morbidity and mortality in the community, as well as within health care facilities. There is a need for adoption of rapid tests for diagnosing TB like, new rapid molecular diagnostics, including the Gene Expert technologies which has very high sensitivity and provides a TB diagnosis within 2 hours in those with smear positive disease (59). This is an ideal solution to overcome the problem of high rates of undiagnosed prevalent TB-HIV in Sub-Saharan African countries.

4.1.4 ART use at the time of PTB diagnosis

Those who were on antiretroviral therapy at the time of TB diagnosis in this study were more likely to delay than those who were not on antiretroviral therapy.This provides evidence that there is a delay in TB diagnosis among ART patients in this HIV clinic. This can lead to high mortality among patients on ART, as it has been reported in a previous study conducted within the same study setting as this study, in which they noted a high TB related mortality among ART patients (44). High TB related mortality among ART patients was also reported in Haiti (60).

4.1.5 Study limitations

In considering the findings of this study it is important to bear in mind the following limitations:

- The study involved patients who were seen at one ARV clinic, thus limiting generalisability of these findings to patients treated in other health centers.
- This is hospital based study cannot provide information on individuals who were never treated in hospital and who may die untreated in the community.
- The study included patients who were18 years and above, so it is difficult to generalize the results of this study in those who are below 18 years.
- It only included patients with known HIV positive status and therefore it is not necessarily representative of delays experienced by patients with unknown HIV positive status.
- The use of secondary data, this relies on the accuracy of written records, it is difficult to control for information bias.
- Some important factors were not assessed; like diagnostic facilities, availability of trained staffs in the health care facility, the quality of services provided by the health care facility and effectiveness of staff's supervision. The delay in diagnosis may be due to these factors but were not assessed.

- The study had relatively small sample size when comparing delay to no delay in diagnosis. This might in part account for some of the non significant associations observed.

4.2 CONCLUSION

There is a considerable delay from PTB suspicion to diagnosis in rural HIV-infected patients. Older patients, those with elevated viral load and those on ART at the time of TB diagnosis are at much greater risk of PTB diagnosis delay. This delay may lead to the spread of TB within the community and poorer health outcomes for those living with HIV/AIDS.

Given challenges of identifying TB in HIV infected population it is important for clinicians caring for patients with HIV to be familiar with the presentation of PTB in HIV/AIDS patients and to evaluate suspected cases quickly and systematically. Therefore active and collaborative efforts to reduce the PTB diagnosis delay are very essential.

4.3 RECOMMENDATIONS

- Recognizing the difficulty of diagnosing TB in HIV patients and delays demonstrated in this study, more rapid tests for TB diagnosis, like rapid molecular diagnostics including Gene Expert technologies (59), would be recommended. They should be promoted and rolled out to reach areas such as this clinic.

- Emphasis on proper and quick PTB investigation should be done on both groups of PTB suspects including those on ART and those who are not on ART in HIV clinics.

- Regular health education to HIV/AIDS patients about PTB symptoms and the importance of early diagnosis and treatment, and regular training of health care staff caring for TB/HIV patients.

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APPENDICES

Appendix 1: Ethics clearance certificate

Appendix 2: Grant to use dataset from the primary study

Appendix 3: Data collection tool