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RETENTION AND ATTRITION OF ADULT PATIENTS ON ANTIRETROVIRAL THERAPY IN BOJANALA DISTRICT, NORTH WEST PROVINCE, SOUTH AFRICA, 2009 – 2014

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DECLARATION

I, Mapula Cathrine Pilusa Student no. 880480, hereby declare that this research report is my own work. I am submitting it in partial fulfilment of the requirements for the degree Master of Public Health in the Field of Health Systems and Policy Research at the University of the Witwatersrand, Johannesburg. This report has not been submitted in part or in full, for any degree or examination at this or any other University and all references I have used or quoted in this report have been acknowledged. Acknowledgements and required referencing conventions have been adhered to where I have used thoughts and ideas of others.

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DEDICATION

I dedicate this work to my supervisors, Ms Letta Seshoka and Dr Tshepo Molapo, who have inspired and supported me through various situations. Not forgetting my husband and friend; Mr Samuel Mafa for his support and encouragement throughout this process.

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ABSTRACT

Introduction: Globally, the HIV/AIDS pandemic continues to be a major public health problem. Despite efforts in Low and Middle Income Countries (LMICs) such as Kenya, Malawi, Eritrea, Botswana and South Africa to manage the public health burden of HIV/AIDS through Anti-Retroviral Treatment (ART) programmes; some challenges have been recorded. LMICs that have adopted ART programmes to treat HIV/AIDS have been lauded as successful in improving the health outcomes of people living with HIV/AIDS (PLWHIV). Consequently, while ART has been widely expanded in the public health facilities in LMICs and South Africa in particular, the majority of ART programmes are affected by low retention and attrition. The aim of this study was to explore the factors that influence retention and attrition of adults who started ART between 2009 to 2014 in Tlhabane Community Health Care (CHC), Bojanala District, North West Province in South Africa.

Methods: A retrospective review of 1000 electronic clinical records was conducted in Tlhabane CHC in 2017. The study included electronic records of patients who started ART between 2009 to 2014 and were followed up for 60 months. Stata (version 14) was used to analyse data. Descriptive statistics were used to summarise patient's demographics and baseline characteristics. Kaplan - Meier curves were used to graphically assess retention proportions. Univariate and multivariate Cox proportional hazard models were used to determine factors associated with attrition.

Results: The key factors associated with attrition in the study sample of adult patients aged 18 – 49 years, who started ART in Tlhabane CHC between 2009 -2014 were identified, 648 (64.8%) were female and 352 (35.2%) were male. Retention proportions declined over time from 92.9% (95% CI 91.1-94.3%), 88.5% (95% CI 86.3 -90.3%), 82.4% (95% CI 79.8 -84.6%), 77.1% (95% CI 74.3 -79.7%), 72.1% (95% CI 69.0 -74.9%) and 63.0% (95% CI 59.5 -66.3%) at 6, 12, 24, 36, 48 and 60 months respectively. Females were more retained as compared to their male counterparts. In the univariates analysis, age group of 36-49, patients with baseline CD4 count of 101-200cells/uL and those on D4T/3TC/EFV treatment regimen were significantly retained in care. Factors associated with attrition in Tlhabane CHC were WHO clinical stage II and IV, being a male patient and having an unsuppressed viral load (VL>1000copies/uL) in the cohort. The multivariate analysis showed that the number of missed appointment visits were associated with increased risk of attrition.

Conclusion: The findings of this study highlighted the key factors associated with attrition in the sample of adult patients aged 18 – 49, who started ART in Tlhabane CHC between 2009 - 2014. More sustainable interventions to reverse the ongoing trend of attrition in Tlhabane CHC might be beyond this study, although it suggested a number of recommendations. Among these are to offer ongoing intensive adherence counselling to asymptomatic patients, those with WHO clinical stage II and the virally unsuppressed to ensure commitment to lifelong treatment in Tlhabane CHC. Early ART initiation should be prioritized to patients in order to prevent advanced disease and poor prognosis while on treatment. Pharmacovigilance monitoring, education on the side effects of ARVs and encouraging patients to have treatment supporters is critical in order to prevent poor adherence and LTFU related to adverse drug events. Offering male-friendly services to motivate them to utilize the facility without fear of stigma and prejudice is highly recommended. Clinicians can minimize missing of clinic appointments by involving patients when scheduling their appointments. Stigma mitigation through community dialogues, campaigns and awareness will make patients to utilize services within their geographical area, thereby ensuring more patients' retention and reducing attrition.

Keywords: Retention, attrition, lost to follow up, mortality, transfer out

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ACRONYMS

ABC	Abacavir
ACs	Adherence Clubs
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
AZT	Zidovudine
CCMDD	Central Chronic Medicine Dispensing and Distribution
CD4	Cluster of Differentiation 4
CHC	Community Health Care
D4T	Stavudine
DHIS	District Health Information System
EFV	Efavirenz
FLR	First Line Regimen
FDC	Fixed dose combination
FTC	Emtricitabine
HAST	HIV/AIDS; STI and TB
HIV	Human Immuno Deficiency Virus
LMICs	Low and Middle Income Countries
LTFU	Lost to follow up
LPV/r	Lopinavir/ritonavi
NSP	National Strategic Plan
PEP	Post Exposure Prophylaxis
PHC	Primary Health Care
PLWHIV	People living with HIV
PMTCT	Prevention of mother to child transmission
SLR	Second Line Regimen
SSA	Sub Saharan Africa
TDF	Tenofovir
3TC	Lamivudine
WHO	World Health Organization

CHAPTER ONE

1.2. INTRODUCTION

This chapter discusses the background of HIV/AIDS and the ART programme globally, in Low and Middle Income countries (LMICs) and in South Africa. It also highlights the problem statement, the justification for the study, its aims and objectives.

1.2. BACKGROUND

The HIV pandemic is a major public concern and the cause of death around the world, especially in Eastern and Southern African countries (1). Although there is a decline in the statistics of HIV prevalence and incidences as compared to the period between 2002 - 2012; about 36.9 million people were living with HIV globally in 2017 (2). Among these, about 1.8 million were newly infected people, and 940 000 died from HIV related causes in the same year (2). During the same year, South Africa, had 7.5 million PLWHIV, making almost 30% of the 25.7 million in Sub Saharan Africa (SSA) (2).

In response to the HIV pandemic, LMICs such as Kenya, Angola, Botswana and South Africa mobilized resources and developed strategies to vigorously fight the disease between 2002 to 2012 (3, 4).These strategies included program budget, developmental partner support and mentorship programmes (3, 4). As a result, there was a 43% reduction of HIV related deaths since 2003 as well as a reduction in HIV incidences from 2.4 million to 2.1 million in 2015 (3, 4). However lower retention and high attrition rates reversed the gains made by the HIV programs so far (2).

Antiretroviral drugs contribute to the reduction of new HIV infections and improving the lives of HIV infected people by reducing morbidity and mortality in SSA countries (5). By the end of 2017, 21.7 million PLWHIV were on antiretroviral therapy globally (2). Among these, South Africa had about 3.9 million people in the same year, making it the largest ART program in the world, followed by Mozambique and Zimbabwe with 990 000 and 980 000 people on ART respectively (6).

The expansion of health facilities offering ART brought many gains to LMICs such as Kenya, Malawi, South Africa, Rwanda, Eritrea and Botswana as they bear the highest burden of HIV (7). South Africa launched the National ART programme in April 2004

although the first project to offer ART services started in Khayelitsha, Western Cape Province in May 2001 and Gugulethu in September 2002 (8).

Since 2004, ART services were decentralised to Primary Health Care (PHC) clinics and Community Health Care centres (CHC) (8). The programme has been rapidly scaling up with policy changes that included the introduction of fixed dose combination in 2013 and Option B+ for pregnant women in 2015 (1).

Increasing eligibility criteria to initiate ART from CD4 count of less than 350 cells/µl in 2010 to less than 500 cells/µl in 2015 for HIV infected adults increased access to ARV therapy (9). Moreover in September 2016, South Africa implemented the WHO HIV policy on initiating ART to PLWHIV regardless of CD4 count (9).

Due to the fact that it has the largest ART programme in the world, South Africa faces enormous challenges in retaining millions of adult patients in care (9). In 2015, KwaZulu-Natal province had more than 1.0 million people on ART, Gauteng province had 774 000 followed by Eastern Cape and Mpumalanga with 359 000 and 316 000 ARV patients respectively (10).

Although there were 674 700 ARV patients in Limpopo, Free State, North West, Western Cape and Northern Cape in 2015 collectively, the retention challenges faced by these provinces are similar to the more heavily burdened provinces (10).
These challenges are self-transfers, non-adherence to treatment, missing clinic visits due to travelling long distances and shortage of human resources that lead to long waiting time in rural areas of KwaZulu-Natal, Eastern Cape, Limpopo, Mpumalanga, North West and Northern Cape (10). These compromise accessibility to ART services and contribute to high lost to follow up (LTFU) for PLWHIV (10).

Constant monitoring of clinical outcomes for ART adult patients is key to ensure their long-term retention and improved life expectancy (11). The effectiveness of the ART programs depends on adult patients being adherent to treatment (12). Proper adherence counselling of patients during ART initiation, taking HIV services to communities and involving them throughout the health care continuum can contribute to retention of patients (10).

Reports from Nigeria, Rwanda and Senegal indicate that viral load suppression and increased CD4 cell count could be achieved after 18 months to five years of being >95% adherent to ART (13). On the contrary, new HIV infections and high mortality and morbidity can be expected in poorly retained patients, thus reversing the gains made by ART program so far (14, 15). A consequence of poor retention of adult patients on ART is HIV drug resistance (14). According to the surveillance conducted in 66 LMICs in 2017 by WHO, 70.7% of HIV drug resistance was reported globally and 87.3% in Southern Africa (14).

Attrition tends to be higher in the first year of being on ART according to the study conducted by *Chi et al* in 41 countries in 2010 and *Peltzer et al* in KwaZulu-Natal in 2011 (5, 16). Factors associated with attrition were lower CD4 count at baseline, age, duration on treatment, WHO clinical stage, baseline CD4 count of 300 to 500 cells/mm^3 (17-20). Type of ART regimen and missing of clinic visits were also highlighted to be predictors of attrition (21-23).

In 2008, *Boulle et al* conducted a cohort study of 12 587 adults who were on treatment from 2001 to 2006 in Cape Town, South Africa (8). The study used the Kaplan-Meier estimator and found that retention in care of adults ranged from 84.9% at 12 months to 75.6% at 48 months, lost to follow-up was 4.2% at six months, and 7.2% at 18 months (8). It showed a decline in the retention of patients and high attrition rate (9).

Mortality increased from 6.7% at six months to 23.1% at 48 months (9). This was due to advanced disease in patients who started ART with low CD4 counts and non-adherence while on treatment (9). The study was significant because of its historical background on challenges of retention in care when the ART program started in South Africa.

Another prospective cohort study of 735 adult ARV patients that was conducted in KwaZulu-Natal by *Peltzer et al* in Uthukela Health District and it came to the same conclusions as in *Boulle et al* study in Cape Town (8, 16). The study used logistic regression models to assess factors associated with attrition (16).

Death was seen as the most common reason for lost to follow in both men and women (16). This was due to delays in accessing health facilities or inappropriate treatment

regimens given to HIV patients (16). Lost to follow up was 14.1% and mortality was 11.2% in the first six months of being on ARVs, with 77.0% of females in care at 12 months versus 72.8% of men in 2011 (16).

Strategies to reduce attrition were identified by *Cornell et al* in a cohort study of 44 177 adult patients who started ART in KwaZulu-Natal, Western Cape, Free State and Gauteng between 2002 to 2007 (24). These included regular facilities follow up visits by patients and adherence to ART therapy (24).

Cornell et al study used univariate and multivariate analysis as well as Kaplan Meier to estimate retention and attrition (24). Retention proportions decreased overtime from 80.0%, 75.0%, 71%, 64.4%, 59.6% and 55.9% (95% CI) at 12, 24, 36, and 60 months respectively (24).

Factors associated with attrition were CD4 count, WHO clinical staging, age and the year of enrolment (24). The study adopted similar methods to this Tlhabane CHC study. It was conducted in various provinces, therefore it provides in-depth evidence on retention and attrition challenges in other provinces (24).

1.3. PROBLEM STATEMENT

Challenges of retention and attrition of patients on ART have been observed since 2005 when *Boyles et al* conducted a prospective cohort study of 1803 adult patients who started ART from June 2005 to May 2009 at Madwaleni HIV clinic, Eastern Cape, South Africa (11). The study had a bigger sample and was conducted during the earliest period of ART programme with a shorter follow up period. It is, therefore, an appropriate starting point from which the challenge of retention and attrition can be examined.

The study revealed high attrition due to LTFU and low retention after initiating ART. Retention was estimated to 83% after 12 months, 72% after 24 months and 68% after 36 months; suggesting increased loss to follow up over time (11). Attrition by mortality in South Africa between 2007 and 2013 as identified in the studies of Fox & Rosen, Cornell et al and *Fox et al* showed that lost to follow up was high in the first 24 months of starting ARVs (13, 17, 24). These studies showed that CD4 count of <100 and being over 36 years were factors associated with attrition (13, 17, 24).

The study of Fox & Rosen found that about 40% of patients, both male and female who were lost to follow up (LTFU) were found to have died but not recorded in the facility, mostly in the first six months of being on ART (17). This was due to late ART initiation with lower CD4 count and advanced disease progression (17).

Another study by *Geng et al* revealed that attrition rate due to LTFU in South Africa was 28, 6% at 12 months in 2015 (25). This was attributed to the rapid expansion of the ART program with limited technological resources such as telephones, unique patient identifiers and standardised appointment systems that can be used to trace patients that were (LTFU) (25). Attrition was mostly found in poor districts such as Sekhukhune, Vhembe and Mopani in Limpopo Province, Zululand and Umzinyathi in KwaZulu-Natal, Amathole in Eastern Cape and Dr Ruth Segomotsi Mompati in North West Province (16, 24, 25).

Studies by *Geng et al*, Fox & Rosen, *Fox et al* and *Cornell et al* were mainly conducted in SSA countries' public health sector where the majority of patients are accessing ART services (13, 17, 24, 25). The challenges of poor retention were due to overcrowding and long waiting times in primary and CHC facilities, as well as public hospitals (19, 25).

A study of 925 adult patients conducted by *Wang et al* in 2011; at Tapologo clinic - Rustenburg, North West Province, found that 2/3 (213) of 322 patients who discontinued treatment within six months were dead (26). This shows that more information is needed in order to identify the root cause of high attrition in ART patients.

Despite the improvements made to scale up access to ART in South Africa, LTFU negates progress of good clinical outcomes of patients (12, 19). Patients who were LTFU and non-adherent to treatment could not attain viral suppression according to a WHO study conducted in Zimbabwe, Zambia, and Malawi (27).

Patients who adhered to treatment in Zimbabwe achieved 86% of viral suppression, Malawi 91% and Zambia 90% after 12 months of being on ART (27).This resulted in improved life expectancy and reduced HIV transmission according to the 2017 Global Action Plan of HIV drug resistance (27).

There are currently limited ARV treatment options in South Africa and the country may face challenges of making costly ARVs available to newly diagnosed patients who may be found to have HIV drug resistance (27, 28). The ARV drugs that are currently being used for adult HIV patients in South African PHCs and CHCs are Tenofovir, Stavudine, Lamivudine, Emtricitabine, Nevirapine, Efavirenz, Lopinavir, Atazanavir, Abacavir and Zidovudine (29).

These drugs are either used as first line or second line regimens in the form of three single doses, or alternatively, fixed dose combinations according to patients' drug tolerability (29). Attrition of adult patients in the form of LTFU and death should be addressed promptly in order to avert HIV drug resistance and HIV related mortality (14).

1.4. JUSTIFICATION FOR THE STUDY

The 90-90-90 UNAIDS targets on HIV/AIDS for 2020 are geared towards ensuring that 90% of the people who are diagnosed with HIV should receive sustainable ART, 90% should be retained in care and 90% of all people taking ART should be virally suppressed (14). Despite the successes attained by the ART program by putting many people on ART to achieve the 2020 targets, the rate of attrition remains high and the emergence of HIV Drug Resistance is rising in Cameroon, Namibia, Uganda and Zimbabwe (27, 30).This is caused by non-adherence of patients on ART and, unless this problem is addressed, the UNAIDS goals which aim to eliminate AIDS as a public threat by 2030 will not be realized (14).

Retaining patients in care is the key to ensuring that the great strides made in enhancing ART programs are translated into improved life expectancy, reduced morbidity and mortality, including the elimination of new HIV infections by 2030 (9, 27).

The challenges identified in the ART program make it clear that more information is needed to help policy makers and program managers develop improvement plans aimed at addressing the challenge of retention and attrition. Tlhabane CHC in Bojanala District, North West Province in South Africa is a high volume facility that also serves the mining community. It was chosen for this study as it represents challenges of retention and attrition that are occurring in similar health facilities in South Africa.

An overview map of South Africa and where Bojanala Platinum District is situated in the North West Province as highlighted by marker in Figure 1: (https: //www. https://images.app).

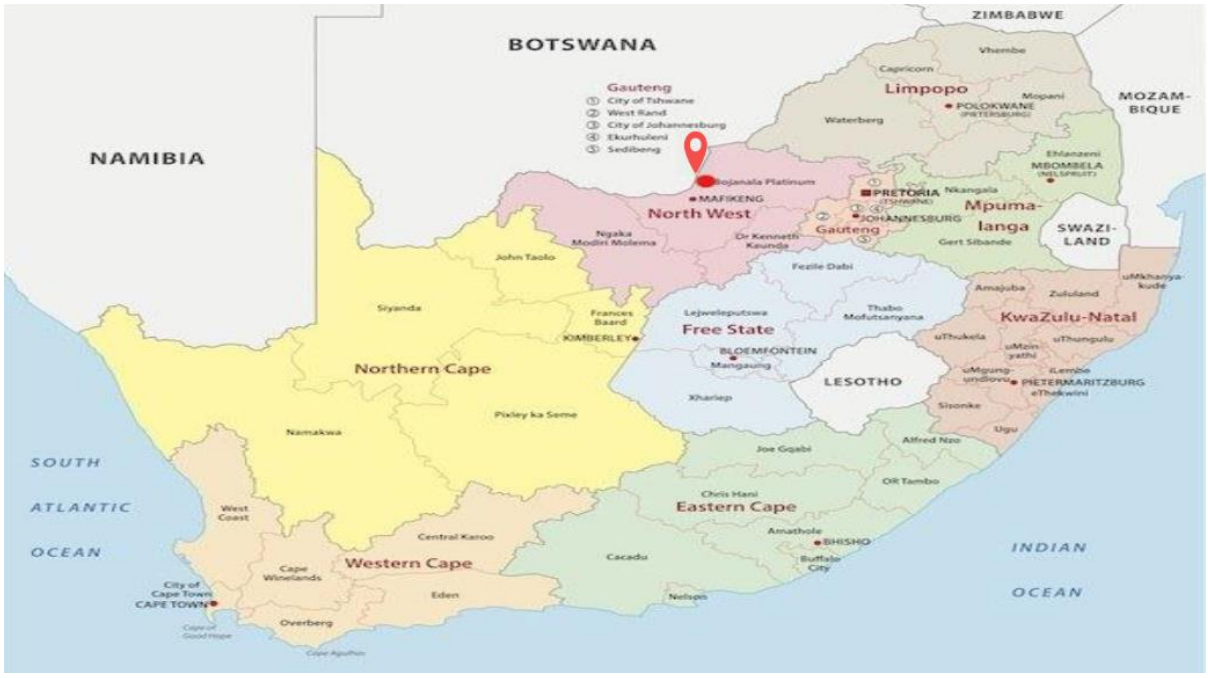

Figure 1: Map of South Africa, Provinces and Districts

1.5. AIM AND OBJECTIVES

The aim of the study was to explore the factors that influence attrition of adults who started ARV therapy between 2009 to 2014 in Tlhabane CHC, Bojanala District, North West Province, South Africa.

The study objectives were to:

1. Calculate the proportion of retention of adults aged 18 to 49 over a period of 60 months who started on ART in Tlhabane CHC, Bojanala Platinum district, North West province, 2009 to 2014.
2. Identify factors associated with attrition of adult patients aged 18 to 49 over a period of 60 months who started on ART in Tlhabane CHC, Bojanala Platinum District, North West province, 2009 to 2014.

CHAPTER TWO - LITERATURE REVIEW

2.1. INTRODUCTION

The aim of this chapter is to review literature on factors associated with retention and attrition globally, for LMICs and South Africa in particular. PubMed database was used for the literature search, which included quantitative studies of retention and attrition of HIV patients on ART. Prospective and retrospective cohort studies were reviewed based on their relevance to the topic.

2.2. DEFINITION OF TERMS

2.2.1. Retention

Retention in care "refers to patients that are alive and receiving ART at the end of a specific follow up period" (31, 32). It excludes those who died, transferred out or lost to follow up, but includes patients that are transferred into the facility (31, 32).

2.2.2. Attrition

It is defined as discontinuation of ARV treatment for any reason and including death (33). It refers to patients who did not come for clinic appointment for the past 90 days after the last scheduled visit (34). It is divided into three categories such as loss to follow up, mortality and treatment discontinuation (31). For the purpose of this study, Mortality and LTFU will be defined.

(a) Mortality

Mortality refers to patients that may die while still on ART care or after a patient has been lost to follow up for some time (34). This mainly occurs in patients who have interrupted clinic appointments as they stop treatment and are at risk for drug resistance, morbidity and mortality (34).

(b) Lost to follow up (LTFU)

LTFU refers to patients that missed clinic appointments follow up or visit, including medication pickups for more than three consecutive months (33, 35). The length of the elapsed time from the last visit determines whether the patient is lost to follow up or not, and the patients should have not returned to the health facility during the three months (31, 36).

2.3. GLOBAL OVERVIEW OF RETENTION AND ATTRITION OF PATIENTS ON ART

Since 2013, LMICs such as Botswana, Kenya, Angola, and South Africa initiated patients on ART with CD4 count of between 350 to 500 cells/mm^3 (37). This was in line with the 2013 WHO guidelines which recommended initiating of ART with CD4 of ≤500 cells/mm^3 (37).

Although the CD4 count threshold was increased to 500 cells/mm^3, about one in four people in countries such as Zimbabwe, Mozambique, Malawi, Uganda and Ethiopia were initiated at CD4 <100cells/mm^3 in 2013 (37). After initiating ART, retention rates were seen to be high and gradually declined over time in these countries (37).

Studies on cohorts done by WHO in 2012 in 18 SSA countries show that the average retention rates decreased from 86% to 82% and 72% at 12, 24 and 60 months respectively (37). These studies show that the quality and the success of the ART programme are compromised by low retention of patients and high rate of attrition in those 18 countries; which is a global concern according to the WHO reports (37).

Fox & Rosen conducted a systematic review study of 39 cohorts that included 226 307 patients who were on ART in SSA between 2007 to 2009 (17). Predictors of retention and attrition in their study were estimated by linear regression models over six, 12, 24 and 36 months (17). Outcome was measured as continuous, using the last observation carried forward from the last reported time through three years (17).

Factors associated with ART attrition included patient's demographics (age less than 36 and sex female); service utilization, duration on treatment, less than 100 CD4 cell count at the start of ARVs, WHO clinical stage and the ART regimen and number of counselling sessions prior to ART initiation (17). This study had larger sample size; however, it was included in this study as it represents various contexts of retention and attrition since the inception of the HIV programme. In these studies, common challenges have been identified by reviewing country-based literature.

A cohort study of 2023 adult patients in two public health facilities in Haiti between 2005 to 2011 initiated on a multi – drug regimen ART were followed up for a period of five years (38). The Haiti study used data from electronic medical records (38). Kaplan Meier and

Cox regression models were used to determine association between factors of attrition and some covariates (38).

Although the study sample in Haiti is bigger than the study of Tlhabane CHC, they shared similar contexts, follow up period and methods. Significantly, the year of ART start was found to be associated with attrition in Haiti (38). This was attributed to the patients having to travel long distances to access ART services (38). This lack of easy access to ART services in the patients' communities consequently increased the risk of attrition (38).

Another cohort study that included 7814 HIV patients attending a hospital called Rural Development Trust in Anantapur district; India was conducted between January 2007 to November 2011 by *Alvarez-Uria et al* (39). The study included patients from Pre ART stage and the ART initiated who were followed up for five years (39). Patients who were on antiretroviral therapy comprised 78.1% (3169) of the total population in the study (39).

The India study used Kaplan Meier survival methods and the results of adult patients who were retained and in attrition were not disaggregated according to sex (39). About 69.2% (1790) of 3169 adult patients that started ART between 2007 to 2011 in India hospital were retained and 30.8% (977) were not retained (39). Among the 30.8% (977) of those who were not retained,15 % (474) were found to have died, 15.1% (480) were LTFU and 0.7% (23) stopped ART (39).

Patients with viral load were 1946 and 1223 did not have a viral load (39). There were about 81.8% (1591) of men and women who were virally suppressed with <400 copies/ml in six months after ART initiation while 18.2% (355) were not virally suppressed (39). Patients who were virally suppressed had lower mortality than those that were not virally suppressed (P=0.0004) (39).

Similarly, *Giordano et al* conducted a retrospective cohort study that reviewed electronic medical records of 2619 men who started ARVs in an outpatient clinic at Veterans Affairs hospital in United States after 1997 (40). The study was conducted in a different context with a larger sample size of men. It did show however, that the challenge of retention and attrition among men is widely spread within various contexts (40).

These men were followed up for more than four years and the study found that death occurred within one year of starting ART in 425 (16%) patients (40). This was due to non-adherence to ARVs and that most patients started ART with advanced stage of HIV (40). Despite being on ARVs, their advanced disease negatively affected their prognosis (40).

Lower baseline CD4 count, older age and co-morbidities such as diabetes or heart diseases as well as Hepatitis C virus co-infection were associated with high risk of death for patients that were receiving ART in the same cohort study (40). Missing clinic visits was observed as an indication of being non adherent to treatment and was 59%, 68%, 74% and 79% during the four quarters of clinic visit in a year (40). This was contrary to >95% of being adherent to ART that is required by WHO (13, 40).

A Medical record data review of 22 984 adult patients receiving ART in 12 clinics in the United States of America HIV Research Network in 2001 to 2009 was done by *Fleishman et al* (41). Despite the large sample size and the study being done in many clinics, it used multivariate logistic regression analysis highlighting that women were more retained than men (41). On the other hand adults of 18 to 29 years were associated with high attrition rates as compared to ages of 40 years or older (41). This was because of poor health seeking behaviour among the 18 to 29 age group (41).

Other reasons were that 18 to 29 age group are not vulnerable to diseases as compared to older age group, even though males were likely to have poor health seeking behaviour as compared to females (41). Other findings from the study were that those with higher baseline CD4 count were less likely to be retained in care (41). Factors affecting LTFU included relocation by patients, dissatisfaction with health care workers, challenges with transport to the facility and convenience of scheduled clinic appointments (41).

2.4. RETENTION AND ATTRITION IN LMICs

A systematic review of SSA countries by Fox & Rosen in 2007 revealed that in Malawi, 24% of adult patients that were recorded as LTFU were re- enrolled at the same clinic two years later (42). About 50% of patients were found to have died and 27% could not be found (42). In Zambia 21% of the 16 000 adult patients who were in the study were reported LTFU after 24 months (42). The reason for LTFU was mainly death among patients who did not seek health care in other facilities (42).

In the 2010 systematic review study by Fox & Rosen in the 39 cohorts from LMICs, self-transferring was due to the fact that patients were shopping for better services, feared to be stigmatised in their local facility, or due to long distance from their home to the facility (17).

These predictors of attrition were assessed using linear regression models, being carried forward from the last time point and reported over three years (17). About 50% of LTFU patients were found to have been dead while 20% were re- started on ART in the same facility some years later (17).

A follow up systematic review of articles and abstracts on a cohort of adult patients who were on first line regimen was conducted by Fox & Rosen in 42 LMICs between 2008 to 2013 (13).The study revealed that 78% of adult patients were still in care after 12 months, 71% after 24 months and 69% after 36 months (13). LTFU and death were found to be the major causes of attrition, mostly among patients who were unemployed (13).

An average of 18.6% (95% CI 15.8-22.0%) adult patients who were LTFU in 12 countries were not recorded due to failures of administration such as self-transferring to another site or left HIV care facility (43). This was revealed in the systematic review that was done by *Wilkinson et al* in 2015, which searched published studies that reported on LTFU on adult ART patients in LMICs (43). Unrecorded deaths, self-transferring and taking extended breaks from ARVs or treatment discontinuation contributed to high loss to follow up in these countries (43).

In Ethiopia, *Bucciardini et al* conducted a prospective cohort study in seven health facilities which included two Community Health Centres, one University hospital, three general hospitals and one primary ART hospital unit (44). A total of 1198 patients who started ART first line regimen between January 2013 and December 2014 were included in the analysis (44).

Bucciardini et al used Kaplan – Meier analysis that estimated retention rates of 89.3%, 83.9%, 82.1% and 79.8% at six, 12, 18 and 24 months respectively (44). Lost to follow up estimates were 3.2%, 4.8%, 5.8% and 6.8% at six, 12, 18 and 24 months respectively in both Community health centres and Primary Health clinics (44).

Cox proportional hazards models were used to reveal that LTFU and mortality occurred in the first 12 months of starting ARV therapy (44). Low retention was found to be due to patients who stopped treatment when they felt better after being on ARV treatment for a while (44). Males were associated with a higher rate of attrition as a result of gender differences in health seeking behaviour and non-adherence to ARV therapy (44).

Another systematic review that surveyed 32 publications by *Geng et al* in 13 countries with 33 cohorts of patients who started ART in 2007 was carried out in public health clinics and hospitals (45). The study documented poor retention of adult patients on ART in Africa and the main causes were lack of transport to the clinic, lack of food that affect intake of medicine, fear of stigma and feeling well to erroneously render ARVs unnecessary (45).

In this systematic review, it was found that the average retention at 24 months was 70% and 64.8% at 36 months (45). *Geng et al* also found that 61% to 80% of 111 adult patients who were LTFU in Uganda were found to be alive in another clinic (45). In Malawi 70% of 2253 patients who missed clinic appointments by three weeks were also on ART somewhere else (45). Reasons of using other clinics were related to stigma and disclosure as patients wanted to receive ARVs where they would not be recognised (45).

In a subsequent study of 11 cohorts in West Africa by *Geng et al* in 2016 using Cox proportional hazards models, it was found that low CD4 count of <50 cell/mm^3 in adult patients was associated with poor retention as compared to CD4 >200 cells/mm^3 in Kenya and Mozambique (25). The literature also revealed that adult males with CD4 count of <100 cells/ mm^3 during ART initiation were at risk for death or LTFU at 12 months (25).

A retrospective cohort study reviewing routine data from medical records in public health clinics on adult patients who started ART from 2007 to 2009 was conducted in Zimbabwe by *Mutasa - Apollo et al* (46). Although the follow up duration was two years and not five years, the literature provides a better context regarding the HIV programme issues in relation to retention and attrition of ART patients.

Mutasa - Apollo et al studied a population of 3 919 in 2014 and similar to the other studies, it found that retention declined overtime and with duration on treatment (46). It was 90.7%, 78.1%, 68.8% and 64.4% at six, 12, 24 and 36 months respectively (46). This was

because more males as compared to females, left care due to death and LTFU among those who started ART with lower CD4 count (46).

LTFU increased from six, 12, 24 and 36 months from 4.9%, 16.1%, 23.5% and 25.2% over time and the same pattern was observed for death (46). Univariate and multivariate Cox proportional analyses showed that retention was higher in females as compared to males at 24 months; 71.1% versus 64.6% and at 36 months it was 66.9% and 59.7% respectively (46).

Males were found to start ART with advanced disease due to late health seeking behaviour (46). They became loss to follow up or died as they could not tolerate ARVs due to severe side effects such as vomiting, diarrhoea, and feeling worse during treatment (46).

A descriptive cross- sectional study over seven years conducted by *Babatunde et al* in 2015 in a Medical Centre in Nigeria included 621 adult patients, of whom 195 (31.4%) were males and 426 (68.6%) females (18). Although the literature has a follow up period of more than five years and despite having used a smaller sample size as compared to the Tlhabane CHC study, it provides a comparative idea of whether there is a difference in retention and attrition between smaller and larger sample sizes.

Data from *Babatunde et al* study was obtained from medical records of patients that started ART between 2005 to 2012 (18). It was found that the year of ART initiation was associated with retention of 72.8% from 2005 to 2007, 57.5% from 2008 to 2009 and 61.5% from 2010 to 2011 (18).

Patients who were enrolled in ART between the years 2007 to 2009 were found to be at higher risk of death at six months of starting ART (18). This was due to late HIV diagnosis and long waiting period of counselling sessions and treatment readiness programs which were done according to the 2004 Nigeria National HIV guidelines (18). Death and LTFU were also attributed to the types of drugs such as Stavudine (D4T) that were causing side effects of peripheral neuropathy (18).

Babatunde et al showed that age was statistically associated with retention where it was 65.3% for the ≤50 years (18). Patients with baseline CD4 count of less than 400 were found to be more retained than those with CD4 count of above 400 (18). This was because people with lower CD4 count have poor prognosis as they die while on treatment (18). Among the 621 adult patients that were on their cohort, 63% were retained and 37% were lost in care between March 2005 and December 2012 (18).

Babatunde et al found no association between gender and baseline WHO clinical staging with retention (18). However they found that duration on ART was associated with decreased retention as people die while on treatment (18). Some of these patients relocate to other areas while others felt that they were healthy, especially after a suppressed viral load (18).

Molfino et al conducted a retrospective cohort study in Maputo, Mozambique, using routine program data of adult 1657 patients, whereby 847 (51%) were males, 808 (49%) females (47). These patients started ART in an intermediary level health facility from January 2009 to December 2011 and were followed up until March 2013 (47).

They used Kaplan Meier survival curves to estimate attrition rates and found that they were higher among males due to late presentation to health care facilities, poor treatment adherence and poor health seeking behaviour (47). In their multivariate Cox proportional regression analysis, *Molfino et al* showed that patients with WHO clinical stage three or four were at higher risk of attrition (47). About 77% of attrition was found to have happened in the first year of being on treatment, whereby 50% of LTFU patients with advanced clinical stages were found to be dead (47).

In addition to the factors discussed above, *Molfino et al* study showed that there was a correlation between year of ART initiation and attrition among patients who started ARVs in 2010 and 2011 (47).

Mutasa- Apollo et al study in Zimbabwe showed that retention was higher in females as compared to males (71.1% versus 64.6%) at 24 months and (66.9% versus 59.7%) at 36 months (46). In addition to the difference in the health seeking behaviour between males

and females, relocation due to employment contributed to lower retention rates in males (46).

It was also highlighted that patients who initiated ART at urban sites were slightly associated with attrition as compared to rural health facilities (46). The reason was because urban sites are convenient to those who are employed, even though some patients would end up being LTFU resulting from a transfer to a new facility (46).

A retrospective cohort analysis and review of data from the electronic database of 5057 adult patients from the clinic in Mbarara, Uganda was conducted by *Asiimwe et al* (22). The study used multivariable adjusted proportional hazards regression models to assess risk factors of attrition among adult patients who initiated ART between January 2008 and December 2011 (22).

The major finding of the study was that some ARV drugs were associated with attrition (22). Patients who received Tenofovir (TDF) based regimen had a 1.4 times higher risk of dropping out as compared to patients on AZT based regimen (22). Furthermore, those on Stavudine (D4T) based regimen had a 1.2 fold higher risk of dropping out of care (22).

This was due to side effects that were related to TDF and D4T based regimens in the form of peripheral neuropathy, diarrhoea, vomiting and lactic acidosis (22). The overall attrition was 26.9%, cumulative death was 2.3%, and LTFU was 24.6% (22). Patients who were transferred out were 5.6% and 67% were retained in care (22).

Hassan et al conducted a retrospective cohort study of 928 adult patients that were initiated on ART between January 2008 and December 2010 in the HIV public clinic of Coastal Kenya (21). Patients were followed up for two years after ART initiation (21). Kaplan Meier survival curves were used to describe probability of attrition (21).

The study found that patients who were retained in care were 523 (56.4%), 97 (10.5%) transferred out, 55 (5.9%) died and 253 (27.3%) were LTFU (21). Attrition at six and 12 months were 171 (18.4%) and 209 (23.2%) respectively (21). Men were more likely to be lost from care as compared to women, mainly during the first year of treatment (21). Patients with CD4 cells of 100 - 350 cells/mm^3 had a 50% rate of attrition in the first year

of ART initiation as compared to patients with CD4 cell count of less than 100 cells/mm³ (21).

Patients younger than 24 years were two times more likely to be lost in care as compared to those older than 45 years in the second year of treatment due to stigma, discrimination and lack of disclosure (21). Those with missing CD4 count were equally at risk of attrition as most of them started with advanced HIV disease, according to WHO clinical staging (21).

The growth of the ART programs in CHCs had been hampered by challenges in the retention rate of adult patients (17). In 2013, LMICs reported retention of about 86% at 12 months, 81% at 24 months and 73% at 60 months (17). According to *Lifson et al*, the effect of attrition for adults was observed in countries such as Ivory Coast where it was discovered that LTFU contributed to 9 years reduction in life expectancy (23). In Malawi, about 54% who were LTFU up were found to be dead (23).

2.5. RETENTION AND ATTRITION IN SOUTH AFRICA

A cohort study at Themba Lethu clinic (Johannesburg) found that retention of patients on ART prevents HIV Drug Resistance when one becomes virally suppressed, increases life expectancy and contributes to productivity at the workplace as people become healthier (28, 48). The study by *Fox et al* in the 2010 to 2012 cohort study used univariate and multivariate regression models (48).

South Africa faces high rates of non-adherence to treatment due to LTFU. This narrows the available treatment options if people fail on the first line ART Regimen, which is the initial ARV regimen to treat naive patients (49). Currently the Non-Nucleoside reverse transcriptase inhibitors (NNRTIs) are the backbone of the first line regimen (FLR) drugs, also affordable and accessible countrywide (28, 49).

Adult patients who do not adhere to FLR may experience treatment failure as evidenced by several unsuppressed viral load of >1000 copies/ml according to the South African HIV guidelines (49). These patients should be switched to second line regimen (SLR) and if they are resistant to it, they are switched to third line regimen (TLR), which is difficult to

get as complicated processes should be followed before the drugs can be approved for the patient (49).

The processes include genotype tests, waiting for the results, filling of application forms to motivate third line drugs and long waiting period for approval by a committee that oversees these drugs (49). The waiting period ranges from one to four months depending on individuals and the availability of selected third line drugs (50, 51). Treatment can either be deferred or modified with active drugs in the regimen that the patient has been taking while the patient is awaiting approval (50, 51).

Taking ARVs is a long term commitment which includes regular clinic follow up visits and adherence to treatment (52). The success and quality of the ART programme is measured by good clinical outcomes such as retention in care and viral load suppression according to 2016 UNAIDS report (52).

The retention in-care targets stipulated by South African National Strategic Plan (NSP) of 2012 to 2016 targets were 94% at 12 months, 88% at 24 months, 82% at 36 months, 76% at 48 months and 70% at 60 months (53). These targets served as a guide to provinces and likewise, North West province was informed by the same targets (54).

The goal of the South African NSP of 2012- 2016 was to improve life expectancy by 5 years for men and women (54). The success and effectiveness of the ART Program is measured by factors such as the number of patients that are retained in the program and their viral suppression rate (26). Evaluation on the outcomes of the patients depends on ART patients being in care, and better outcomes are mostly identified with long term retention (26).

Since 2004, South Africa was providing doctor driven ART services in public hospitals of all provinces (8). The programme started to decentralise ARV services from public hospitals to CHCs and PHCs since 2010 in order to increase access to treatment for PLWHIV (8, 11, 30). In the same year, the expansion of ARV services was accompanied by Nurse Initiated and Management of Antiretroviral Treatment (NIMART) training to allow nurses to initiate patients on ART (30).

A study of eight cohorts of 44 177 adult patients on ART between 2002 and 2007 was conducted by *Cornell et al* in the four provinces in South Africa, Western Cape, Free State, Gauteng and KwaZulu-Natal (24). They used univariate and multivariate Cox regression analysis and revealed that younger patients between 18 to 30 years as compared to older patients; were at risk of being LTFU (24).

This age group faces more socioeconomic challenges like migration in search for employment and study opportunities (24). They also lack experience with the health system utilization and are not vulnerable to diseases associated with aging (24). Risk of death for older patients was high at 12 to 36 months, and that occurred at four months of being on ART (24). This was due to co-morbidities such as hypertension, diabetes and heart diseases experienced by patients above 45 years, which make them to utilise the facilities more regularly (24, 40).

According to *Cornell et al,* the year of enrolment was associated with death as they found 31% of mortality in patients who were enrolled in 2007 (24). LFTU at 12 months increased with the year of enrolment from 1% in 2002 and 2003 to 13% in 2006 ($p<0.001$) (24). Mortality was 5% and 10% at six and 36 months while LTFU was 9% and 30% at six and 36 months respectively (24).

They also found that retention decreased from 86% to 64% at six months to 36 months respectively (24). CD4 count was associated with early mortality within four months of being on ART, especially at CD4 count of less than 50 cells/µL as compared to CD4 count of 200 cells/µL and above (24).

A prospective cohort analysis was conducted by *Boyles et al* with 1803 adult patients who started ART from June 2005 to May 2009 in Madwaleni HIV clinic, Eastern Cape, South Africa (11). Madwaleni HIV clinic had seven referral PHCs for patients (11).

The study revealed high rates of attrition due to loss to follow up and low rate of patient's retention after initiating ART, estimated to 83% after 12 months, 72% after 24 months and 68% after 36 months; suggesting increased LTFU over time (7, 11).

The results of Kaplan Meier revealed that LTFU was 11.4%, 16.5% died and there were 26.1% patients who were unconfirmed lost to care after 48 months (11). The study found that mortality was higher in the first 12 months while LTFU was constant over 36 months (11). High rates of LTFU was attributed to accelerated ART initiation, reduced number of counselling sessions and lack of preparation for patients before starting ART (11).

Risk of attrition using Cox proportional hazard ratios indicated that death was associated with lower CD4 count at the start of ART for patients that were hospitalized (11). This was due to advanced stage of disease which made them unable to tolerate ARVs because of poor prognosis (11).

Grimsrud et al conducted a retrospective cohort study of 8150 adults who started ART from 2002 – 2012 in 25 Asian and African countries; including South Africa (12). The study was conducted in Gugulethu, Eastern Cape in South Africa where data was collected from the CHC clinical database, and patients were followed up until 2013 (12).

The results of Kaplan Meier methods and proportional hazards models revealed that an increased LTFU was associated with the year of ART initiation (12). Healthier patients who initiated ART with CD4 cell count of above 300 were also at risk for LTFU (12). It was suggested that these patients require different support and systems to effectively deliver ART (12).

According to *Rosen & Fox*, retention declines over a period of time, and also differs from one province to another (17). They observed that there was a retention decline from 84% to 79% in the five year period between 2004 and 2009 in KwaZulu -Natal, Western Cape and Gauteng provinces (17). Between 2008 and 2013, about 40% of attrition in South Africa was due to reported death, whereas 60% was due to LTFU up according to *Fox et al* (13).

Except for death related LTFU, *Peltzer et al* and Fox & Rosen indicated that a decline in retention was attributed to unreported death, self-transfers or shopping for better services in other clinics and lack of transport for those that stay far from the clinics (13, 16). This was revealed by *Peltzer et al* in a prospective cohort study of 735 adult patients who were

>18 years and on ART in Uthukela health District, KwaZulu-Natal, South Africa between 2007 to 2008 (16).

There were 518 (70.5%) females and 217 (29.5%) males in the cohort study and patients were followed up for 12 months (16). It was revealed that 558 (75.9%) of patients were still in care at 12 months while 177 (24.1%) were LTFU (16). Patients who were traced and found to be still alive were 73 (9.9%) and those who were found to be dead were 82 (11.2%), which was about 20% of the traced patients (16). Some of the patients were not traceable due to unknown reasons, meaning that those who were true LTFU were 104 (14.1%) in the studied cohort (16).

Tracing is a process of identifying and finding the whereabouts of a patient after missing clinic appointments with the aim of bringing the patient back to care (5). In South Africa, tracing is done by Community Health Workers (CHWs) who are linked to public health facilities (30).

A baseline CD4 of less than 50 cells/mm^3 was found to be a predictor of attrition compared to a baseline CD4 of 200 to 350 cells/mm^3 as observed in the study of *Clouse et al* (19). This was attributed to the pre ART waiting period in patients with low CD4 count (19).These patients could no longer tolerate treatment due to late ART initiation (8, 19).

A retrospective study of 3242 adult patients between 18 – 45 years who visited an HIV clinic in Tugela Ferry, KwaZulu-Natal, South Africa in January 2015 to June 2016 was conducted by Arnesen, Moll & Shenoi (20). The study reviewed electronic records from Tier.Net database, which is the facility's electronic patients' information system (20). There were 1868 (57.6%) females and 1374 (42.4%) males in the database (20).

Multivariate regression analysis was used to determine independent predictors of LTFU (20). The study found out that 1140 (35.1%) patients were still in care, 1262 (38.9%) were transferred out, 20 (0.6%) died and 820 (25.2%) were LTFU (20). Males were mostly LTFU (1.6 times) than females, 244 (51.4%) versus 231 (48.6%) for females (20).

A univariate analysis in the study showed that ages 18 - 45, CD4 above 500 and being on ART for less than 24 months were significantly associated with LTFU (20). Patients of

ages 18 to 35 were 2.0 times more likely to be LTFU as compared to patients over the age of 45 (20). The younger age who are LTFU might have moved to other areas for employment opportunities; especially males as stated by *Clouse et al* (19). Patients who were on ART for less than six months had 10.3 times higher likely to be LTFU according to Arnesen (20).

A multivariate analysis showed that age 18 - 35, CD4 count below 200 and being on ART for less than six months were the only factors that predicted LTFU (20). LTFU in patients with low CD4 count might have accounted to death within three to six months of starting ART (20). Poor adherence due to missing clinic visits and stigma were contributing to patients attrition within six months of starting ART (20).
Missing clinic appointments due to ARVs' side effects was revealed to be a predictor of LTFU as documented at Themba Lethu clinic (25). Patients who were LTFU (n= 90, 41%) were actually receiving ART care services in another clinic while others were really LTFU (25).

Patients who were LTFU were successfully traced and records were updated in the clinic (25). LTFU patients stated their reasons for stopping treatment as using alternative medicines like herbal products and lack of food due to poverty (25). Lack of finances for transportation to the facility due to distance, inadequate social support, stigma and disclosure as well as feeling sick were reasons for LTFU (25).

That retention in care was higher before the public sector started rolling out the ART program in 2004 in South Africa was a concern to Rosen & Fox (13, 55). This explained why districts and regional hospitals had a higher number of LTFU than PHC facilities (13, 55).

A study conducted in Lusikisiki, Eastern Cape, South Africa in 2007; revealed that retention of ART patients was worse in hospitals than in CHCs and PHCs facilities (42). This was because patients used transport to access hospitals as they stayed far from such facilities, which was a barrier due to poverty (42). The situation was worse for ART patients with complicated cases and had no alternative but to be managed in hospitals (42).

The rate of LTFU was 19.3% in the hospitals and 2.2% at PHCs, indicating the need to have more decentralised ART services to the community level (42). While patients with complications and co-morbidities were transferred to hospitals mainly to be managed by medical doctors, transportation costs became a challenge and patients were lost in between transfers (48).

Decentralization of ART services from hospitals to clinics was aimed at improving rates of retention among PLWHIV and the coverage of services (30). However, there were challenges as it was introduced against the background of weak health information systems, limited infrastructure and various service providers with different reporting requirements (30).

Although there is increased access to ARV therapy, little is known in South Africa about improving rates of long term retention in care and future improvements are necessary to reduce patients' attrition (11). Retention and tracking of patients is a problem in South Africa as patients move from facility to facility within provinces, resulting in the over estimation of LTFU (30). According to *Bekker et al* the introduction of a single patient identifier in health facilities will help in the understanding of factors that determine retention of patients in care (30).

With the multi-faceted data gathered from the reviewed literature, the Tlhabane study explored the factors that affect retention and attrition respectively, using data of adult patients who started antiretroviral therapy between 2009 – 2014 in Tlhabane CHC, Bojanala District, North West Province, South Africa.

2.6. SUMMARY

The literature review has highlighted some of the challenges that are faced by the ART programmes globally and in the LMICs context, including South Africa. Death and LTFU were the major causes of attrition according to studies that were conducted in these countries (13, 25, 44).

Key global findings in these studies outlined decreased retention over time from 86% to 72% between 12 to 60 months since 2013 (37). LMICs had an average retention of 80% at 12 months and 60% at 36 months (13). According to these studies, females were better

retained in care than males because of health seeking behaviour (41). In Nigeria, Kenya and South Africa, patients who were above 30 years were more retained as compared to age group of 18 - 30 (18, 21, 24). The reasons were that older people utilize health facilities for other co–morbidities such as diabetes, hypertension unlike younger ones who are not vulnerable to these diseases (18, 21).

Attrition in countries like Ethiopia, Zimbabwe and Kenya ranged from 23.5% to 30.8% between 2010 and 2014 (13, 21, 46). Factors associated with attrition in the global, LMICs and South African context were age, duration on treatment, WHO clinical stage, baseline CD4 count of above 200 cells/mm^3, baseline CD4 count of 300 to above 500 cells/mm^3 (17-20). Type of ART regimen and missing of clinic visits were also highlighted to be predictors of attrition (21-23).

Reasons for high LTFU rates were unrecorded death, self-transfers and taking extended breaks from ARVs (5). Lack of social support was recorded to be contributing to poor retention in patients on ART in Africa, Asia and Latin America (25).

Strategies highlighted in these studies to reduce attrition were to allocate adequate human resources to trace patients and to have advanced electronic databases dedicated to ART programs, especially in LMICs (17). Early ART initiation with CD4 count of above 350, recording of patients on ART and decentralisation of health facilities to allow easy access of ARV services were recommended (12).

CHAPTER THREE – RESEARCH METHODOLOGY

3.1. INTRODUCTION

This chapter describes the methodology used in this study. The study setting, design and population as well as data collection processes and data collection tools are outlined. Ethical issues and limitations of the study are discussed.

3.2. STUDY SETTING

The study was carried out in Tlhabane CHC in 2017. Tlhabane CHC is a peri – urban clinic situated in Rustenburg Local Municipality, Bojanala Platinum District in North West Province in South Africa. It is a 24 hour CHC that provides services to community members living in Lefaragatlhe, Ga - Kgale, Buampsa, Photsaneng and Thekwane residential areas (56). In 2016, Rustenburg's Local municipality adult population was 626 522. About 63% of this population was between the ages of 18 to 64; the majority of them being employed. The residents of Tlhabane suburb speak mostly Tswana (56). The CHC also serves as a referral facility for various clinics within the Rustenburg Municipality (56).

Figure 2: Tlhabane Community Health Centre

Professional Nurses and doctors provide a wide spectrum of health services, chronic and minor ailments during the day. Emergency services and obstetric care services are provided for 24 hours a day. Tlhabane CHC is a high volume facility that started offering ART services in December 2004. ART services were offered during the day, Monday to

Friday at the time of the study. Data from the facility database (Tier.Net) since December 1994 until 30th April 2017 showed that about 17 083 patients were registered in their database, with a breakdown of 11 591 (68%) female and 5492 (32%) male.

Tlhabane CHC initiates an average of ±40 patients on ART per week. According to the HIV electronic database, 3588 adult patients aged 18 to 49 were recorded to have started ART during the study period in the facility; 2217 (62%) were female and 1371 (38%) were males. Patients come from Tlhabane township and neighbouring villages which are located within the Rustenburg Municipality, which is ±15 km to access the facility (56).

The facility is in a walking distance for the majority of patients; even though some prefer to use public or private transport. Information on the electronic database showed that some patients who tested HIV positive in the facility were screened for TB, WHO clinical staging, monitored baseline CD4 cell count, viral load and enrolled in support groups. Some patients were allowed to identify people that can support and remind them to take their ARV medication on time.

Patients who were not eligible for ART were recorded in the Pre- ART register, given continuous counselling and their CD4 count was monitored every six months until they were eligible. Treatment literacy and adherence counselling which lasted three to six months for eligible patients to start ART were mandated by the 2010 South African HIV guidelines (28). This included assessment of treatment readiness before patients can be started on ART (28).

Data on the number of patients who tested HIV positive, who were on Pre ART register and received counselling sessions was not captured on the electronic database during data collection. Information on counselling, addresses, and marital status are kept in the manual file of the patient including detailed nurses or doctors notes that explain management of patients, e.g. reasons for switching to second line, side effects or if a patient is on other medicines.

Demographic information such as gender and age were captured in the electronic database, including telephone numbers of treatment supporters for some patients. Professional nurses and Doctors record information from patients using HIV clinical

stationery or ART register during consultation. Some of the information was transferred into Tier.Net which is the electronic database used in South Africa to store electronic records of HIV patients. It was developed in 2011 by the Centre for Infectious Disease, Epidemiology and Research (CIDER) from the University of Cape Town (57).

Monthly clinic appointments were scheduled for patients that were started on ART. Pill counting was done with every monthly visit and recorded by the Professional nurses that initiate ARVs. All the reviewed patients' electronic records had the next date of appointment and patients who missed their clinic appointment were identified.

Data capturers extracted reports of patients who missed appointments from the database on weekly basis and shared with Community Health Care Workers (CHCWs) and support group leaders who physically trace patients who are LTFU. However, tracing of LTFU patients was a challenge as patients who came back to care were not always updated on the electronic information system. This failure to update the database made patients that were in care to be counted as LTFU even if they were not.

Since 2015, the facility implemented three differentiated service delivery models, a patient centred approach to reduce facility overcrowding for PLWHIV who were stable (58).They consist of the following:

(a) Adherence clubs (AC) - stable ART patients meet every two months in a group of 30 at the facility or in the community (58). Patients were managed by lay counsellors, enrolled nursing assistant or home based carer (58).

(b) Spaced fast lane appointment (SFLA) - clinically stable patients are granted quick access to the pharmacy or clinic to collect two months treatment (58). They are on a six months prescription and only see a clinician when having clinical problems (58).

(c) Central Chronic Medicine Dispensing and Distribution (CCMDD) - This is for stable ART patients who pick up pre packed medicine from collection points or in a designated place within or outside the facility (58). They are given a three to five month's prescription and only attend clinic appointments for blood monitoring and prescription reviews (58).

According to the standard operating procedures of Adherence guidelines, information of these patients should stipulate multiple months of appointments when captured in the

clinic database by data capturers (58). If information about these patients is not updated within 90 days, it automatically counts them as LTFU (57, 58).

The population, which utilized Tlhabane CHC, were predominantly migrant labourers from other provinces and outside South Africa, who lived in the villages and worked around Rustenburg and in the mining Industry. This contributed to high LTFU that could not be traced due to incomplete, false or frequently changing addresses and contacts.

3.3. STUDY DESIGN

This was a retrospective cohort study that reviewed 1000 randomly selected electronic records of adult patients aged 18 to 49 who started ARV therapy in Tlhabane CHC between 2009 and 2014. The number was representative of the total patients who started ARVs in this facility during the study period.

Computers installed with Tier.Net software are managed by data capturers who capture patients' information from the manual folder. These data capturers were sourced from the Aurum Institute to assist the facility as it previously had two data capturers.
Data capturing starts after the patient has been diagnosed as HIV positive and advised to start ARV therapy. This is done during every clinic follow up as long as the patient is still receiving care in the facility. Patient records were filtered according to the date of birth, sex, ART start date and whether patients were transferred or moved into the facility in order to extract eligible patients' records.

All the data collected was from the electronic database except data on marital status and distance from the facility. Data was analysed over 12, 24, 36, 48 and 60 months to better understand factors that affect attrition in the study population. Because these patients have been in facility for a while, the data was used to identify the proportions of those that are still in care and to determine their clinical outcomes during treatment. This information is mainly available in the electronic records. It is, however, dependent on proper recording from the clinical file, as capturing is done from these clinical files as the initial source of data.

The researcher collected data from electronic records on multiple outcomes such as retention in care, LTFU, transfer out, died, and viral suppression. Baseline characteristics

such as CD4 count, WHO clinical staging, drugs and drug regimen, date of ART start and TB co-infection were collected, including demographic data such as age and gender.
A spreadsheet data extraction tool was used, (see Appendix 2). The facility Manager delegated two data capturers who assisted the researcher on an alternate basis and when access to Tier.Net was needed. All the data extracted was then transferred to an Excel spreadsheet.

3.4. STUDY POPULATION

A sample of 1000 electronic records of adult patients were reviewed, females 648 (64.8%) and males 352 (35.2%).

Inclusion criteria

Electronic records of adult males and females aged 18 to 49 at the start of ART, who were newly started on antiretroviral therapy in Tlhabane CHC, were reviewed. These patients were on standardised first line regimen and second line regimen according to the South African National Treatment Guidelines (49).

Exclusion criteria

Records of adults who were transferred into the facility, PMTCT and PEP patients prior to ART start in 2009 to 2014 were excluded.

3.5. STUDY PERMISSION AND ETHICS APPROVAL

Ethics clearance certificate no. M170248 was granted by the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg. Thereafter, application to conduct the study at Tlhabane CHC was done. Permission was granted by the North West Province and Bojanala Health District (see Appendix 1).

3.6. DATA MANAGEMENT AND ANALYSIS

Variables included in the study analysis were: - age, gender, WHO stage, baseline CD4 count, duration of switching to second line regimen, duration on ART, first viral load, TB co infection, the number of missed days, types of drug regimen and the year of ART initiation 2009 to 2014.

3.6.1. Definition of dependent (outcome) variables

For this study, *an outcome variable* is defined as the end results that patients achieved after they started ART between 2009 and 2014 until the end of the study in 2017. These

were classified as retention and attrition either in the form of LTFU or death. Outcome variables were measured at six, 12, 24, 36, 48 and 60 months and were influenced by predictor variables that will be discussed in the next section. In May 2017, patients who started ART in May 2013 and May 2014 were in care for 48 and 36 months respectively.

Retention for this study is defined as having started ART and being alive in Tlhabane CHC at the beginning of this study in 2009 and until the end of the study in May 2017. It was determined by the last clinic visit or ARV pick up dates of less than three consecutive months. Patients who were transferred out to continue treatment in other facilities were regarded as retained. The follow up period was six,12, 24, 36, 48 and 60 months.

At the end of the study, patients who started ART in May 2013 and May 2014 were in retained for 48 and 36 months respectively. Patients who were enrolled on the CCMDD program or Adherence Clubs (ACs) had their next date of appointments of between two to six months as captured on the electronic database for HIV patients (59).

Attrition is defined as the discontinuation of ARV treatment for any reason and including death (5). It refers to patients who missed clinic appointments for more than 90 days after the last clinic visit or medicine pick up date (19). Such patients were classified with an outcome date as LTFU or died on Tier.Net.

LTFU is defined as patients that missed clinic appointments or follow up visits, including medication pickups for more than three consecutive months or more than 90 days (5, 60). It was determined by the last date of clinic visit and patients should have missed appointment for more than three consecutive months. These included patients who were recorded as being unconfirmed lost to follow (uLTFU) as they were not active on treatment in the facility. The classification meant that patients had not returned to the health facility during the three months and the date of outcome was captured on Tier.Net.

Death was captured by the facility after verifying with the family, in some cases patients would have been LTFU for a while before death can be reported. This was captured as an outcome in Tier.Net.

3.6.2. Definition of predictor variables

ART start date is the first date the patient was recorded to have started on ART in Tlhabane CHC, excluding those with date of transfer in. ART start date was categorised as 2009, 2010, 2011, 2012, 2013 or 2014.

The last clinic appointment date attended or last ARV pick up date had to be less than 90 consecutive days for the patient to be regarded as being retained and more than 90

consecutive days for LTFU. They were categorised as 1-3 months, 4 - 6 months, 7-12 months and above 12 months

Date of next clinic visit was used to assess the frequency of patients' visit to the facility. The next date of appointment was measured post ART start and it varied according to the status of the patient. This started from one to two months for new patients and three to four months for stable patients. Patients who were on CCMDD and community ACs had up to six months.

Drug regimen was categorised as first line and second line regimens and *types of drugs* such as Tenofovir (TDF), Lamivudine (3TC) or Emitricitabine (FTC), Efavirenz (EFV) or Nevirapine (NVP), Abacavir (ABC), Zidovudine (AZT), Stavudine (D4T), Lopinavir/ Ritonavir (LPV/r) were analysed according to the South African treatment guidelines relevant to a particular year as there have been changes over time.

These were categorised as AZT/3TC/EFV, AZT/3TC/NVP, D4T/3TC/EFV, D4T/3TC/NVP, TDF/3TC/EFV, TDF/3TC/LPVr, TDF/3TC/NVP, TDF/FTC/EFV ABC/3TC/EFV, which included either all the three single or fixed dose combination drugs. These were assessed at the start of ART.

Switched to second line regimen (SLR), *duration of ART switching* and *reasons for switching* were used to assess the clinical management of patients while on ART. Patients were either switched to SLR or not, and the duration on ART switching was determined by the date that was captured on Tier.Net, comparing it with the ART start date. Reason for switching was determined by either high viral load or it would be unknown if the viral load was suppressed or unavailable.

Duration on ART is defined as being retained or in attrition for a specific follow up period. It was determined by the number of months from the ART start date in 2009 until the end of the study in 2017, irrespective of missed clinic appointments during treatment. The categories were six, 12, 24, 36, 48, 60 months as the researcher wanted to determine period of low retention and high attrition.

Missing clinic appointment is the total number of months that the patient missed clinic appointments and came weeks or months later after the set date during treatment. It was determined by the last date of appointment where the patient did not honour the appointment. The variable assessed how well patients adhered to treatment when they were active on treatment. A patient might have missed appointments intermittently or regularly during the 60 months period on ART.

Baseline CD4 count is defined as the initial value after testing HIV positive and before ART start (9). It was classified using the standard clinical cut-off of less than 100 cells/mm^3 for HIV to AIDS progression. Categories were 1-100, 101-350, 351-500 and above 500.

Viral load is defined as the first test after starting ART (9). Patient's duration on ART and the date of first viral load test was important to determine the implementation of the South African treatment guidelines and the clinical management of patients.

Viral load results were categorised as virally suppressed for less than 1000 copies/ml and virally unsuppressed for above 1000 copies/ml according to the South African Treatment guidelines (27). These were recorded from six months and 12 months after ART initiation considering changes of policy regarding viral load monitoring.

TB co-infection is defined as having TB and being on TB treatment before starting ARVs, categorised as "yes" for those with TB co-infection and "no" for those without TB. T*reatment supporter* is a person who was registered as supporting a patient during treatment and can be contacted to trace a patient if they missed clinic appointments. Patients who had a treatment supporter were classified as "yes" and those without were classified as "no".

WHO clinical staging was determined from the pre-ART initiation as being asymptomatic to being symptomatic according to the classification of symptoms. These were WHO clinical stage I, WHO clinical stage II, WHO clinical stage III and WHO clinical stage IV.

Age in this study was 18 to 49 years at the start of ART and *sex* was defined according to how the patient was recorded in the electronic records. Age group was categorised as 18 - 25, 26 -35 and 36 – 49.

3.6.3. Statistical analysis

The results of patients' characteristics are summarised by frequencies and percentages for categorical variables and mean, medians and interquartile ranges (IQRs) for continuous variables. The independent variables analysed were CD4 at baseline, gender, age, type of ART regimen, WHO staging and TB co infection. Primary outcome variables measured were retention and attrition and the secondary outcome variable analysed was viral load suppression.

Analysis of retention: Retention was measured as the number of patients that were receiving ART and alive at the time of the study, including patients who were transferred out to other facilities. It was reported at post ART initiation of 6, 12, 24, 36, 48 and 60 months follow up period to determine periods of high and low retention proportions among adult patients in Tlhabane CHC. Data was censored and time to survival was determined by ART start date (2009, 2010, 2011, 2012, 2013 and 2014) until the last clinic visit or pick up date at the time of the study in 2017.

At the time of the study, patients who started ART in 2009 were more than 60 months on treatment. The cut off follow up period for this study on retention was 60 months; however, those who started ART in 2013 and 2014 were 48 and 36 months on treatment respectively. Kaplan- Meier survival methods were used to calculate retention proportions at different time in points. A stratified log rank test to compare survival curves for male and female, as well as age groups at 5% level of significance was done. Retention proportions were tabulated and graphically plotted on Kaplan Meier Curves, disaggregated by gender and age categories of 18 - 25, 26 -35, and 36 - 49.

Analysis of attrition: Time to attrition was the end point of this study and it was calculated in months from ART start date and the last clinic or pick up date. It was determined by the date of LTFU or death as captured on Tier.Net. Univariate and multivariate Cox regression models were used to determine hazard ratios of attrition at 95% Confidence Interval and 5% level of significance. Data analysis was performed using Stata version 14.

3.6.4. Management of missing data

A sensitivity analysis of missing data was done and a complete case analysis was performed to estimate the risk factors of attrition. Cases with incomplete data or missing values were not entered in the final multivariate analyses to eliminate some bias in the results of factors affecting attrition.

3.7. SUMMARY

The study setting, methods, data extraction tool and the study population (electronic records) from the facility database have been described. Stata version 14 was used to analyse data and statistical methods of Kaplan- Meier were used to determine retention proportions. Univariate and multivariate Cox regression models were used to report hazard ratios of attrition. In the next chapter, the study findings will be reported.

CHAPTER FOUR – RESULTS

4.1. INTRODUCTION

This chapter presents the results of the study on retention and attrition of adult patients on antiretroviral therapy in Bojanala district, North West Province, South Africa, 2009 – 2014. The key results are:

4.2. BASELINE CHARACTERISTICS

Table 1 shows the baseline demographic, clinical characteristics and clinical management of adult patients (18 to 49 years) in Tlhabane CHC who started ARV therapy between 2009 to 2014. Demographic data on employment, education, marital status and distance from the facility were not captured in the electronic database and therefore they were not included in this research. The majority of patients who started ARVs between 2009 to 2014 in Tlhabane CHC were female 648 (64.8%) and 352 (35.2%) were male.

The 36 - 49 age group accounted for 49.5% of patients and was the largest in the sample of this study. The 26 - 35 age group had the second highest, accounting for 41.9% of the patients. Only 8.6% of the patients belonged to the age group of 18 - 25. The median age at time of ART initiation was 35.1, (Interquartile range (IQR)=30.0-40.5). Although the facility database does not have data on the number of patients that were counselled, that information was recorded in the manual HIV registers of the facility.

4.3. CLINICAL BASELINE CHARACTERISTICS

Among the sampled adult patients who were started on ARVs, those on WHO clinical stage one were 563 (56.3%), WHO clinical stage two were 179 (17.9%), WHO clinical stage three were 236 (23.6%) and WHO clinical stage four were 22 (2.2%). Patients with baseline CD4 count were 985 and data was missing for 15 (1.5%). There were 304 (30.4%), patients who started ART with baseline CD4 count of less than 100, and about 47 (4.7%) patients started ART with CD4 count of above 350. The median CD4 was 155, (IQR = 81-227).

The policy to initiate ART therapy at baseline CD4 count of ≤350 cells/mm³ for adult patients was updated in the 2013 South African HIV guideline, and in January 2015 the CD4 threshold was changed to ≤500 cells/mm³ (27).

Eight hundred and seventy one (87.1%) patients were not co-infected with TB at start of ART. About 997 (99.7%) patients were on the standardised FLR according to the South African treatment guidelines (27).

Table 1: Baseline demographic, clinical characteristics and management of the ARV patients in Tlhabane CHC 2009 – 2014

Characteristics	Categories	Frequency/Percent	Female	Male
Age group (n=1000	18-25	86(8.6)	72(83.8)	14(16.2)
	26-35	419(41.9)	285(68.0)	134(32.0)
	36-49	495(49.5)	291(58.8)	204(41.2)
WHO stage (n=1000)	I	563(56.3)	377(67.0)	186(33.0)
	II	179(17.9)	120(67.0)	59(33.0)
	III	236(23.6)	140(59.3)	96(40.7)
	IV	22(2.2)	11(50.0)	11(50.0)
ART regimen (n=1000)	First line	997(99.7)	646(64.7)	351(35.2)
	Second line	3(0.3)	2(66.7)	1(33.3)
TB co-infection (n=1000)	No	871(87.1)	578(66.3)	293(33.7)
	Yes	129(12.9)	70(54.2)	59(45.8)
Baseline CD4 count (n=985)	1-100	304(30.8)	193(63.4)	111(36.6)
	101-200	371(37.6)	240(64.7)	131(35.3)
	201-350	263(26.7)	174(66.1)	89(33.9)
	351-500	26(2.6)	15(57.7)	11(42.3)
	500+	21(2.1)	13(62.0)	8(38.0)
Types of Drugs (n=1000)	ABC/3TC/EFV	1(0.1)	1(100)	0
	AZT/3TC/EFV	38(3.8)	22(57.9)	16(42.1)
	AZT/3TC/NVP	18(1.8)	15(83.3)	3(16.7)
	D4T/3TC/NVP	173(17.3)	105(60.7)	68(39.3)
	D4T/3TC/EFV	42(4.2)	35(83.3)	7(16.7)
	TDF/3TC/EFV	383(38.3)	238(62.1)	145(37.9)
	TDF/3TC/LPVr	3(0.3)	2(66.7)	1(33.3)
	TDF/3TC/NVP	115(11.5)	93(80.9)	22(19.1)
	TDF/FTC/EFV	227(22.7)	137(60.3)	90 (39.7)
Switched to 2nd line regimen (n=1000)	No	974(97.4)	634(65.0)	340 35.0)
	Yes	26(2.6)	14(53.8)	12(46.2)
Reason for switching (n=26)	unsuppressed VL	13(50.0)	7(53.8)	6(46.2)
	Suppressed VL	13(50.0)	7(53.9)	6(46.1)
Missed clinic appointments (n=1000)	No	324(32.4)	209(64.6)	115(35.4)
	Yes	676(67.6)	439(64.9)	237(35.0)
Viral load done (n=1000)	No	286 28.6)	178(62.2)	108(37.8)
	Yes	714(71.4)	470(65.8)	244(34.2)
Viral load suppression (n=714)	Suppressed	648(90.76)	413 (63.7)	235(36.3)
	Not suppressed	66(9.24)	42(63.6)	24(36.4)
Retention status (n=1000)	Retained	545(54.5)	360(66.0)	185(34.0)
	LTFU	26(26.1)	157(60.2)	104(39.8)
	Died	49(4.9)	32(65.3)	17(34.7)
	Transfer out	145(14.5)	99(68.2)	46(31.8)

Patients on Tenofovir (TDF) based regimen were 728 (72.8%) and 215 (21.5%) were on Stavudine (D4T) based regimen. These regimens were either administered with Lamivudine (3TC), Emtricitabine (FTC), Efavirenz (EFV), Nevirapine (NVP) or Lopinavir (LPV) as single or three drugs combination (27).
According to the 2010 ART Guidelines, patients were started on D4T (27), TDF and AZT based regimens as the FLR, and in 2013, fixed dose combination of TDF/FTC/EFV was introduced while the D4T based regimen was gradually phased out (27).

Table 1 shows that 997 (99.7%) patients were started on first line regimen (FLR) and three (0.3%) patients were also started on second line regimen (SLR) as new, two of them (0.2%) in 2011 and one (0.1%) in 2012. There were no reasons stated in Tier.Net, it was unknown if they were ART experienced or not.
Among the 997 (99.7%) patients who were on FLR, 26 (2.6%) were switched to SLR. Seven (27.0%) patients were switched within the first 12 months of being on ART, five (19.2%) at 24 months, 6 (23.0%) at 36 months, three (11.6%) at 48 months and five (19.2%) were switched at 60 months of being on ART. These patients exclude the three patients who were on SLR at the start of ART.

The South African HIV guideline of 2015 requires counselling of patients that are not virally suppressed in order to encourage adherence; however, this information was not recorded in the electronic facility database. Since physical folders were not reviewed, information on counselling and the reasons for switching was not included in this report.

Patients with viral load results post ART start were 714 (71.4%); however, data was missing for 286 (28.6%) patients. The median follow up period for patients with the first viral load in Tlhabane CHC was 12 months, [IQR=6-41], meaning not every patient had their first viral load tested at six months. Six hundred and fifty five (91.7%) of patients had their first viral load test 24 months after starting ART and their viral load suppression was 596 (83.4%). Viral load suppression at six months was 18 (2.5%) and 34 (4.8%) at 12 months. Cumulatively, there were 648 (90.7%) patients with viral load suppression during the study period.

Table 2 shows the proportions and duration of patients who missed clinic appointments, and their outcomes. This was measured according to the next date of appointment where

patients came weeks or months later after the set date. About 676 (67.6%) patients who started ART between 2009 to 2014 were observed to have missed clinic appointments either intermittently or continuously during the study in 2017.

More females as compared to males missed their clinic appointments, 439 (64.9%) versus 237 (35.0%) (See Table 1).Three hundred and seventeen (46.9%) patients had missed between one and three months of clinic appointments, 136 (20.1%) had 6 months, 158 (23.4%) had 12 months and 65 (9.6%) had 24 months of missed appointments.

Among patients who missed appointments, 213 (31.4%) became LTFU and 15 (2.2%) died between 2009 to 2017. Patients in the less than three months missed appointments accounted to 80 (30.6%) of the LTFU in Tlhabane CHC. Information on the proportion of the working group who missed clinic appointments was missing in Tier.Net.

A total of 445 (65.8%) patients were virally suppressed even after missing appointments for some time. Of the 445 patients with suppressed Viral Load, 204 (64.4%) had missed clinic appointment for less than three months and 98 (72.0%) for six months; either intermittently or continuously. Among patients who missed clinic appointments, 398 (58.9%) returned and continued care at Tlhabane CHC, 50 (7.4%) were transferred out to other facilities, 213 (31.5%) remained LTFU and 15 (2.21%) were reported dead within 24 months of missing clinic appointments.

Table 2: Outcomes of adult patients who missed appointments in Tlhabane CHC between 2009-2017

	Patients who missed appointments on ART in Tlhabane CHC between 2009-2017				
Variables	≤3 months	6 months	12 months	24 months	Total
Proportion of missed appointments	317(46.9%)	136(20.1%)	158(23.4%)	65(9.6%)	676(67.6%)
Died	11(3.5%)	0	1(0.6%)	3(4.6%)	15(2.2%)
LTFU	80(25.2%)	35 (25.7%)	57(36.1%)	41(63.1%)	213(31.5%)
Transferred out	36(11.4%)	5(3.6%)	7(4.4%)	2(3.1%)	50(7.4%)
Returned to care	190(28.1%)	96(14.2%)	93(13.8%)	19(2.8%)	398(58.9%)
Suppressed VL	204(64.4%)	98(72.0%)	108(68.4%)	35(54.0%)	445(65.8%)
Unsuppressed VL	20(6.3%)	9(6.7%)	18(11.4%)	2(3.0%)	49(7.2%)
Missing Viral load	93 (29.3%)	29 (21.3%)	32 (20.2%)	28 (43.0%)	182(27.0%)

4.4. RETENTION PROPORTIONS

Retention proportions for 1000 adult patients between 18 to 49 years who started ART between 2009 to 2014 at Tlhabane CHC are summarised in Table 3 and plotted on Kaplan Meier survival estimates graphs in Figures 2,3, and 4. Duration on ART was measured in months at 6, 12, 24, 36, 48 and 60 months, disaggregated by gender and age group.

Retention proportions declined over time from 92.9% (95% CI: 91.1 - 94.3%), 88.5% (95% CI: 86.3 - 90.3%), 82.4% (95% CI: 79.8 - 84.6%), 77.1% (95% CI: 74.3 -79.7%), 72.1% (95% CI: 69.0 -74.9%) and 63.0% (95% CI: 59.5 - 66.3%) at 6, 12, 24, 36, 48 and 60 months respectively. The median follow-up duration of adult ART patients at Tlhabane CHC between 2009 to 2017 was 21.70 months, [IQR =16 - 47]. Therefore, this study shows that retention declines overtime at Tlhabane CHC due to LTFU and death, while some were transferred out to other facilities to continue treatment.

Females were more retained as compared to males, 89.1% (95% CI: 86,5 - 91.5%) versus 87.3% (95% CI: 83.3 - 90.4%), 84.0% (95% CI: 80.9 - 86.6%) versus 79.4% (95% CI: 74.7-83.3%), 78.5% (95% CI: 75.0 - 81.6% versus 74.6% (95% CI: 69.6 - 78.9%), 74.5% (95% CI: 70.7 -77.8%) versus 67.5% (95% CI: 61.9 -72.4%) and 65.2% (95% CI: 60.9 - 69.2%) versus 58.9% (95% CI: 52.7- 64.5%) at 12, 24, 36, 48 and 60 months respectively.

Higher retention proportions were observed among the age group of 36–49 as compared to 18 - 35 age group. Retention proportions in the 36-49 age group ranged from 91.0% (95% CI: 88.1 - 93.2%) to 70.5% (95% CI: 65.7 - 74.7%) while the 26–35 age group were 85.2% (95% CI: 81.4 - 88.3%) to 54.6% (95% CI: 49.0 - 59.9%) between 12 to 60 months respectively.

A decline in retention over time is attributed to death while on treatment or might be due to other health conditions. Figure 3 graphically represents survival curves for the full cohort of Tlhabane CHC in 2009 – 2014 over 60 months. Figure 4 and 5 represent survival estimates for the same period and follow up, disaggregated by gender and age.

Table 3: Overall Survival probability of ART patients who started ART at Tlhabane CHC between 2009 and 2014,

Time/months	Beg. Total	Fail	Net Lost	Survivor Function	Std. Error	[95% Conf. Int.]	
6	1000	71	33	0.9290	0.0081	0.9112	0.9433
12	896	42	30	0.8855	0.0101	0.8639	0.9038
24	824	57	43	0.8242	0.0123	0.7987	0.8468
36	724	46	101	0.7718	0.0137	0.7436	0.7974
48	577	38	93	0.7210	0.0151	0.6902	0.7493
60	446	56	390	0.6305	0.0174	0.5954	0.6634
Female							
6	648	42	23	0.9352	0.0097	0.9133	0.9517
12	583	27	19	0.8919	0.0123	0.8651	0.9136
24	537	31	30	0.8404	0.0147	0.8092	0.8669
36	476	31	57	0.7857	0.0167	0.7508	0.8163
48	388	20	63	0.7452	0.0181	0.7076	0.7787
60	305	38	267	0.6523	0.0212	0.6090	0.6921
Male							
6	352	29	10	0.9176	0.0147	0.8836	0.9420
12	313	15	11	0.8736	0.0178	0.8339	0.9044
24	287	26	13	0.7945	0.0219	0.7474	0.8338
36	248	15	44	0.7464	0.0239	0.6960	0.7898
48	189	18	30	0.6754	0.0268	0.6196	0.7248
60	141	18	123	0.5891	0.0301	0.5276	0.6455
18-25 years							
6	86	6	6	0.9302	0.0275	0.8513	0.9680
12	74	2	1	0.9051	0.0320	0.8190	0.9514
24	71	4	6	0.8541	0.0390	0.7571	0.9145
36	61	4	11	0.7981	0.0454	0.6909	0.8715
48	46	8	8	0.6593	0.0583	0.5318	0.7597
60	30	3	27	0.5934	0.0637	0.4579	0.7055
26-35 years							
6	419	38	13	0.9093	0.0140	0.8775	0.9332
12	368	23	15	0.8525	0.0175	0.8145	0.8833
24	330	29	16	0.7776	0.0207	0.7337	0.8151
36	285	23	36	0.7148	0.0228	0.6673	0.7568
48	226	17	41	0.6610	0.0245	0.6105	0.7067
60	168	29	139	0.5469	0.0280	0.4904	0.5999
36-49 years							
6	495	27	14	0.9455	0.0102	0.9215	0.9623
12	454	17	14	0.9101	0.0129	0.8810	0.9323
24	423	24	21	0.8584	0.0159	0.8239	0.8867
36	378	19	54	0.8153	0.0179	0.7770	0.8476
48	305	13	44	0.7805	0.0196	0.7392	0.8161
60	248	24	224	0.7050	0.0230	0.6573	0.7474

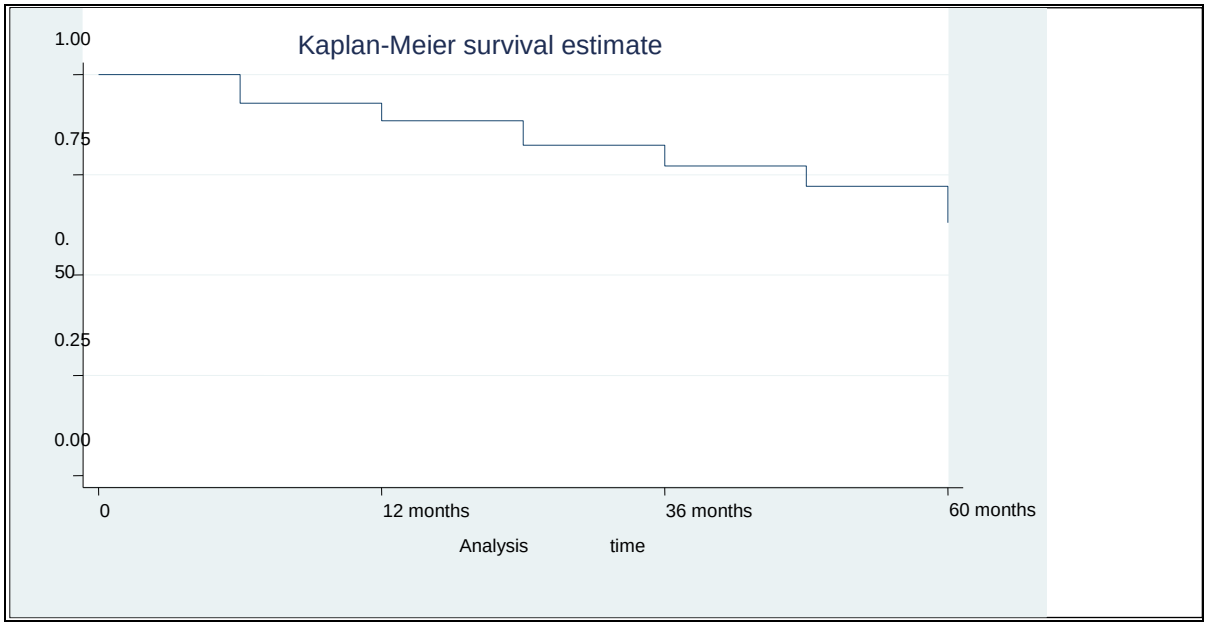

Figure 3: Unadjusted Kaplan- Meier survival estimates full cohort in Tlhabane CHC: 2009-2014

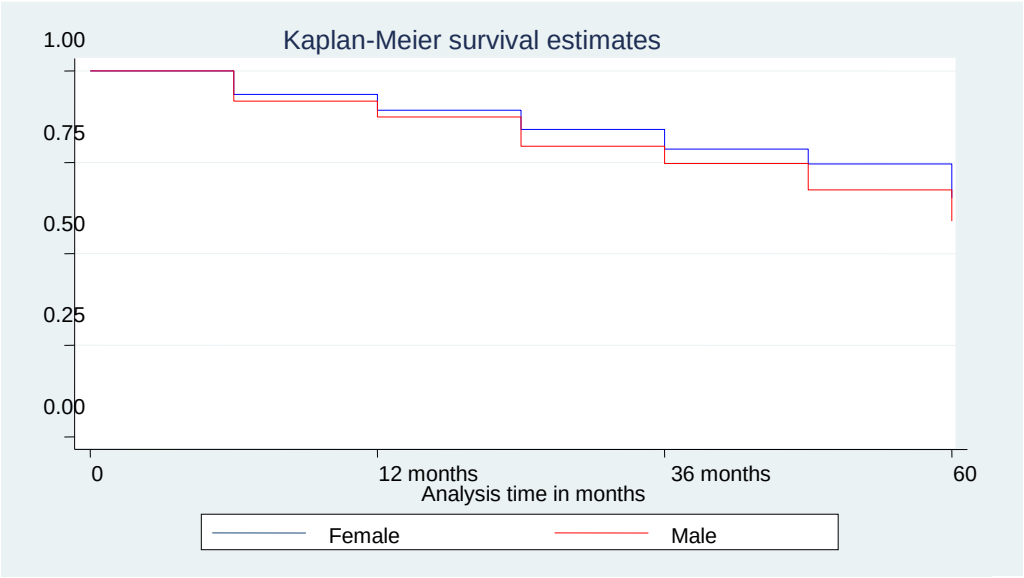

Figure 4: Kaplan Meier for ART patients in Tlhabane CHC by gender 2009-2014

(a) Log-rank test for equality of survivor functions in Tlhabane CHC by gender

Gender	Observed	Expected
female	648	669.15
Male	352	330.85
Total	1000	1000.00

chi2 (1) = 4.26

Pr>chi2 = 0.0391

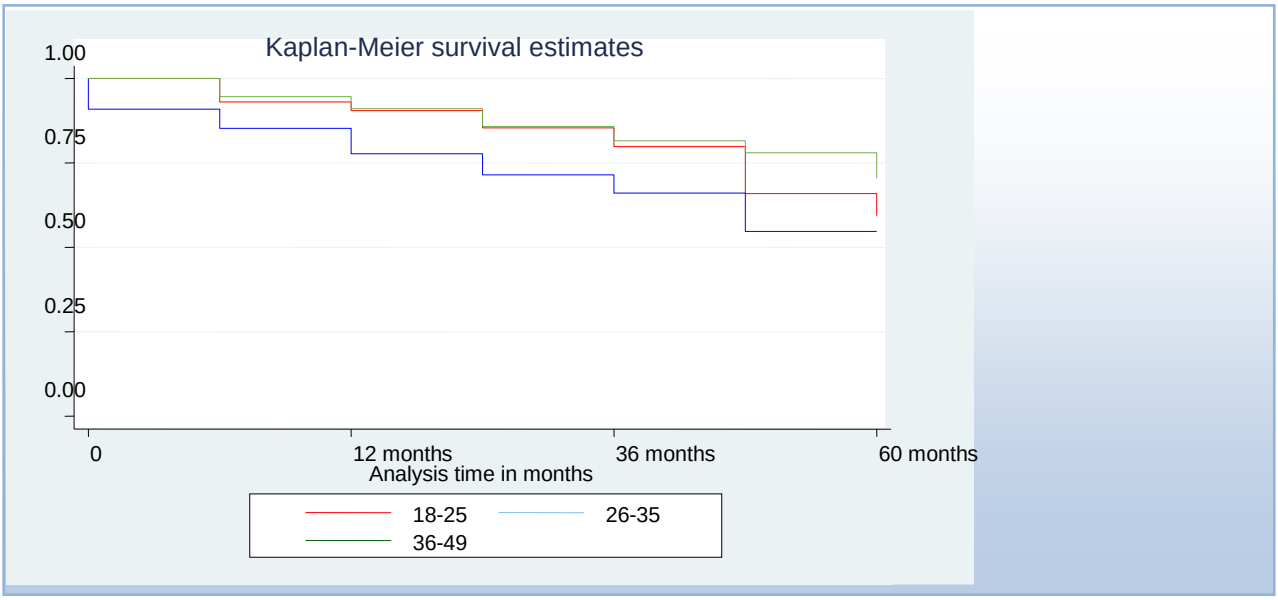

Figure 5: Kaplan Meier for 1000 adult ART patients in Tlhabane CHC by age: 2009-2014

(b) Log-rank test for equality of survivor functions in Tlhabane CHC by age

Age at ART start	Observed	Expected
18-25	86	76.34
26-35	419	390.37
36-49	495	533.29
Total	1000	1000.00

chi2(2) = 12.89

Pr>chi2 = 0.0016

4.5. FACTORS ASSOCIATED WITH ATTRITION

Table 5 presents the results of univariate and multivariable Cox proportional hazard analyses of factors associated with attrition for patients who started ART in Thlabane CHC between 2009 to 2014. The univariate and multivariate cox proportional analysis results show that factors associated with attrition were age, gender, WHO clinical stage two and four, a suppressed viral load, missing clinic appointments. Table 4 represents the Univariate and multivariate Cox proportional models used to analyse hazard ratios of attrition.

Table 4: Univariate and multivariate Cox proportional models used to assess the association between demographic and clinical characteristics with attrition.

Factor	Univariate Haz. Ratio [95% Conf. Interval]	P>|z|	Multivariate Haz. Ratio [95% Conf. Interval]	P>|z|
Gender				
Males	1.25(1.00-1.58)	0.048*	1.32(0.91-1.91)	0.140
Age groups				
26-35	1.10(0.73-1.65)	0.643	1.42(0.78-2.58)	0.240
36-49	0.65(0.43-0.99)	0.045*	0.95(0.51-1.78)	0.885
WHO Stage				
Stage II	1.47(1.10-1.97)	0.008*	1.05(0.67-1.66)	0.815
Stage III	1.16(0.88-1.52)	0.276	1.00(0.58-1.73)	0.990
Stage IV	2.04(1.13-3.67)	0.017*	1.18(0.27-5.15)	0.823
Baseline CD4				
101-200	0.73(0.55-0.96)	0.027*	0.75(0.47-1.22)	0.257
201-350	1.14(0.85-1.51)	0.359	1.29(0.81-2.06)	0.270
351-500	1.29(0.67-2.46)	0.441	1.23(0.36-4.16)	0.734
501+	0.41(0.13-1.29)	0.130	0.48(0.11-2.03)	0.321
First viral load Results				
>1000	1.91(1.25-2.92)	0.003*	1.11(0.64-1.93)	0.691
Number of missed days				
4-6 months	0.84(0.56-1.24)	0.383	1.34(0.82-2.20)	0.234
7-12 months	1.32(0.95-1.84)	0.095	1.67(1.08-2.59)	0.021*
13-24 months	2.53(1.76-3.62)	<0.001*	2.44(1.41-4.21)	0.001*
Type of drugs				
AZT/3TC/EFV	0.22(0.03-1.67)	0.146	-	-
AZT/3TC/NVP	0.49(0.64-3.72)	0.492	-	-
D4T/3TC/EFV	0.12(0.01-0.90)	0.039*	0.77(0.25-2.33)	0.649
D4T/3TC/NVP	0.22(0.29-1.63)	0.139	1.26(0.30-5.30)	0.745
TDF/3TC/EFV	0.37(0.52-2.2.65)	0.324	1.42(0.50-4.00)	0.504
TDF/3TC/LPV	0.51(0.04-5.68)	0.588	-	-
TDF/3TC/NVP	0.39(0.05-2.81)	0.350	1.55(0.51-4.69)	0.436
TDF/FTC/EFV	1.05(0.14 -7.52)	0.961	2.29(0.79-6.61)	0.125

*Significant at 5%

Univariate Cox proportional analysis results

The results of the univariate Cox proportional analysis of 18 to 49 years adults in Tlhabane CHC showed that males had a 25% increased risk of attrition compared to females (HR= 1.25; 95% CI: 1.00 -1.58;p-value= 0.048). Patients in the age group 36-49 were 35% protective of attrition to the age group of 35 and below (HR= 0.65; 95% CI: 0.43 - 0.99; p-value 0.045). With reference to those patients who were classified in WHO clinical stage I, the attrition risk increased by 47% among patients in WHO clinical stage II

(HR=1.47; 95% CI: 1.10-1.97; p-value=0.008) while those in WHO clinical stage IV were 2.04 times more at risk of attrition (HR= 2.04; 95% CI 1.13-3.67; p-value= 0.017). Patients with a baseline CD4 cell count of between 101-200 cells/mm³ showed a significant 27% lesser risk of attrition as compared to patients with CD4 count of less than 100 cells/mm³ (HR= 0.73; 95% CI 0.55 - 0.96; p-value=0.02). Patients with an unsuppressed viral (VL>1000copies/uL) load were 91% more likely to experience attrition compared to those with suppressed (VL ≤1000copies/uL) (HR= 1.91; 95% CI: 1.25- 2.92; p-value= 0.003).

Patients who missed appointments for 13 to 24 months were overwhelmingly associated with an increased risk of attrition as compared to patients who missed appointments for less than 4 months (HR =2.53; 95% CI: 1.76- 3.62; p-value <0.001). Patients on the D4T/3TC/EFV combination therapy were 88% less likely to experience attrition compared to those on a single dose therapy (HR=0.12, 95% CI: 0.01-0.90; p- value=0.03).

Multivariable Cox proportional analysis results

A multiple Cox model was fitted to adjust for the possible effects of confounding in this study. All the variables found significant in the univariate analysis were considered for the multiple regression model. No significant association were observed between gender, age, WHO clinical stage III, CD4 cell count, viral load and the type of regimen the patients was on and attrition. However, after adjusting for these cofactors, the number of missed appointments was associated with attrition in a dose-response pattern, that is, the more the number of missed appointments the higher the risk of attrition.

With reference to the patients who had less than 3 months missed appointments, the risk of attrition increased by 67% (HR=1.67; 95% CI: 1.08=2.59; p-value=0.021) if the patient had 7 to 12 months missed appointments while those who had 13 to 24 months missed appointments were 2.44 times more likely to experience attrition (HR=2.44; 95%CI: 1.41-4.21; p-value=0.001).

4.6. SUMMARY

This study found that adult patients aged between 18 to 49 years who started ART in Tlhabane CHC between 2009 to 2014 (N=1000) had a 54.5% likelihood of retention;

26.1% likelihood of LTFU, 4.9% likelihood of death and 14.5% likelihood of transfer out. Retention proportions decreased overtime and were significantly higher in females as compared to males. From the univariates analysis, patients in 36-49 age group, CD4 cell count of 101-200cells/uL, those on D4T/3TC/EFV treatment regimen were significantly retained in care, while males patients with WHO clinical stage II and IV, and unsuppressed viral load (VL>1000copies/uL) had an increased risk of attrition in this cohort. In the multiple variable analysis, only the number of missed visits were associated with increased risk of attrition.

CHAPTER FIVE- DISCUSSION

5.1. INTRODUCTION

The chapter discusses the findings from this study. As stated, the purpose of this study was to explore retention and attrition of adults aged 18 to 49 who started ARV therapy between 2009 to 2014 in Tlhabane CHC, Bojanala District, North West Province, South Africa, and were followed up to time of LTFU till 2017. The specific objective in studying the 1000 cases that were examined was not only to calculate the proportion of retention of adult patients in the 18 to 49 age group, but also to identify the various factors associated with attrition. The researcher reviewed global and regional as well as LMICs literature on retention and attrition, and were compared to the Tlhabane CHC study, taking into consideration the context and methods used in these studies.

The key findings were decreased retention proportions overtime at 12, 24, 36, 48 and 60 months and females being more retained as compared to males. The age group of 36- 49 was more retained than the age group of 18 -35. Patients with CD4 cell count of 101-200cells/uL and those on D4T/3TC/EFV treatment regimen were significantly retained in care. Attrition as LTFU and death was higher in the first 12 months of ARV treatment.

Factors that were associated with attrition were gender, WHO clinical stage II and IV and and unsuppressed VL of ≤1000copies/uL. In the multiple variable analysis, the number of missed visits were associated with increased risk of attrition. These key findings will be discussed in relation to other findings in the literature, compared, and contrasted where necessary.

Cumulative outcome results of adult patients N=1000 aged 18 to 49 who started ART in Tlhabane CHC between 2009 to 2014 were death at 49 (4.9%), of the 49 who died, 32 (65.3%) were female and 17 (34.7%) were male. Patients who were LTFU was 261 (26.1%). Of the 261 who were LTFU, 157 (60.2%) were female while 104 (39.8%) were male. Those who were transferred out were 145 (14.5%), of which 99 (68.2%) were female and 46 (31.8%) were male. Retained in care/in-active follow up patients were 545 (54.5%), 360 (66.0%) were female while 185 (34.0%) were male.

5.2. PROPORTION OF RETENTION

The key findings from the calculation of the proportion of retention from the sampled adult ART patients who started ART in Tlhabane CHC between 2009 to 2014 were as follows:

Cumulative results of this study show that 545 (54, 5%) of the 1000 patients that were started on ART were still receiving care in the facility; 360 (66.0%) were female and 185 (34.0%) were male. Retention proportions were 92.9%, 88.5%, 82.4%, 77.1%, 72.1% and 63.0% at six, 12, 24, 36, 48 and 60 months respectively, which indicated decline overtime.

The cumulative retention of Tlhabane CHC study of 54.5% was lower than that of Kenya clinic with 56.4% by *Hassan et al*. The study had a cohort of 928 adult patients that started ART in the Kenyan clinic between 2008 and 2010 and were followed up for two years (21). While the study sample is less than that of the Tlhabane study and with a shorter follow up period; there are similarities between the context and methods of the Kenya clinic's and Tlhabane CHC studies. This indicates that retention of patients on ART is a universal challenge, as many patients who are on ARVs are not accounted for within a short period of starting treatment (21).

Nonetheless, retention proportions at Tlhabane CHC is higher than the Zimbabwean (78.1% and 68.8%) and Ethiopian clinics (83.9% and 77.6%) at 12 and 24 months respectively (44, 46). The Zimbabwean study was conducted by *Mutasa – Apollo et al* with a larger sample size of 3 919 adult patients between 2007 and 2009 (46). The Ethiopian study *by Bucciardini et al* had almost a matched sample size of 1198 patients who started ART between 2013 and 2014 (44). Although the follow up period was shorter, both studies were conducted in similar context using similar methods as in the Tlhabane CHC study (44, 46).

The key reasons for declining retention proportions were that some patients stopped treatment when they felt healthy and stable overtime. Similar findings were observed in Nigeria as reported by *Babatunde et al* where some patients defaulted as they experienced treatment fatigue due to taking ARVS for a longer period (18). In addition to patients who stopped treatment, died or transferred out of the facility, poor data capturing of retained patients was observed to be a challenge in Tlhabane CHC. For instance, some

patients that were registered in Adherence Clubs (ACs) and CCMDDs were not captured as still active in the facility and this omission contributed to a decline in retention.

Females were better retained than males at Tlhabane CHC and this might have been attributed to the difference in health seeking behaviour among females as compared to males (45, 46). These results are similar to *Geng et al* and *Mutasa – Apollo et al* who found that females are more retained than males in Zimbabwe and South African clinics (45, 46). Although they were more retained, there was a decline over time that could be due to shopping around facilities due to fear of stigma, especially when they become pregnant or relocated to other areas without asking for referral letter.

The possible reasons for poor retention in males as compared to females may be due to poor health seeking behaviour and stopping treatment when feeling better or worse and fear of being stigmatised by members of the community. Lack of men friendly services in health facilities, where male health professionals are few, may cause men not to access health services.

The age group 36 - 49 were more retained than age groups 18 – 35. This age group is frequently using health facilities as they might have co–morbidities such as hypertension, diabetes and other chronic diseases as compared to the age group of less than 35. The possible reasons for poor retention in the age group 18 - 35 are that they shop around for alternative facilities due to stigma attached to their local clinics. Lack of disclosure and inadequate treatment supporters may have also affected the retention of age group 18-35. Some may have relocated in search of work opportunities or studies and leave facilities without referral letters. The findings are consistent with *Arnesen, Moll & Shenoi* that age group 18 – 35 were 2.0 times more likely to be LTFU as compared to those over the age of 45 (20).

Retention of age group 36 -49 in Tlhabane CHC is consistent with the study of *Asiimwe et al* who indicated that older patients are less likely to drop out of ARV therapy than patients who are less than 35 years (22). Similar findings in the United States of America in adult patients by *Fleishman et al* revealed that older patients of above 40 were likely to remain in care as compared to patients of 18 to 29 age group (41). Age group 18 to 29 seem to

be less vulnerable to diseases and have poor health seeking behaviour as compared to older age groups (41).

Patients with CD4 101 -200 cells/mm³ were found to be significantly retained to care in the Tlhabane study. According to *Fleishman et al*, patients with symptoms have increased motivation to see a care provider regularly, which occur more commonly at low CD4 count levels (17, 41), which explained why patients with CD4 count of less than 200 cells/mm³ were retained in Tlhabane CHC study.

5.3. FACTORS AFFECTING ATTRITION

The key factors affecting attrition in this study were male gender, WHO clinical stage II and IV and unsuppressed viral load and missed clinic appointment.

These findings are similar to *Bucciardini et al* that males were associated with a higher rate of attrition due to gender differences in health seeking behaviour and non- adherence to ARV therapy (44). *Mutasa – Apollo* highlighted that in Zimbabwe, males were found to start ART with advanced disease due to late health seeking behaviour (46). That might have caused them to be LTFU or died as they could not tolerate ARVs due to severe side effects such as vomiting, diarrhoea, and feeling unwell during treatment (46).

Although early ART initiation contributes to better clinical outcomes according to *Geng et al* (25), in the Tlhabane CHC study; patients with WHO clinical stage II were found to be at high risk for attrition as compared to those with WHO clinical stage I. These patients are asymptomatic or have fewer symptoms as compared to those with WHO clinical stage III and IV. *Boyles et al* study indicated that high rates of LTFU was attributed to accelerated ART initiation, reduced number of counselling sessions and lack of preparation for patients before starting ART (11). This indicates that early ART initiation to patients who are asymptomatic needs to be accompanied by intensive counselling to establish long term commitment to treatment (28).

Patients with WHO clinical stage IV were having a two-fold risk of attrition as compared to other WHO clinical stages in Tlhabane CHC. This results are consistent with *Molfino et al'* study that was conducted in Mozambique HIV health facility in 2014 who revealed that patients with WHO clinical stage III or IV were at higher risk of attrition because of

advanced disease when they started ART(47). As a result, prognosis became poor, resulting in stoppage of treatment as they could no longer tolerate ARVs or eventually die (47).

Missing clinic appointments was associated with attrition in Tlhabane CHC according to the adjusted model. This was attributed to unconfirmed death, shopping around for alternative facilities, taking breaks and coming back to care in a worse condition. According to WHO, missing clinic appointments by more than 48 hours and without treatment predisposes patients to HIV drug Resistance (14). It is therefore important for ART patients to achieve >95% of adherence in order to be virally suppressed (14). The Tlhabane study correlates with *Asiimwe et al* & *Geng et al* that missing clinic appointments indicates that patients are not adhering to treatment and is a predictor for attrition (22, 25).

This study is also consistent with the study conducted at Themba Lethu Clinic by *Geng et al*, in South Africa in 2016, that missing clinic appointments due to ARVs' side effects was revealed to be a predictor of attrition (25). Patients who were LTFU in Themba Lethu Clinic were actually receiving ART care services in another clinic while others were really LTFU (25).

Poor adherence due to missing clinic visits and stigma were contributing to patients attrition within six months of starting ART according to *Arnesen, Moll & Shenoi* (20). The Tlhabane CHC study also found that the first unsuppressed viral load was associated with attrition. Although patients received adherence counselling; side effects, lack of understanding about HIV disease, treatment fatigue and stopping treatment whenever they do not have the symptoms of the disease might have caused unsuppressed viral load.

The Tlhabane study found that patients on D4T/3TC/EFV regimen were likely to be retained in care as compared to TDF and AZT based regimens. On the contrary, *Peltzer et al* & *Mekuria et al* found that patients on D4T based regimen were likely to miss their clinic appointments due to side effects such as vomiting, diarrhoea, peripheral neuropathy, lactic acidosis and change of body shape, leading to unsuppressed viral load when they stop treatment (16, 59).

5.4. RECOMMENDATIONS

This study found that there is a decrease in retention proportions over time. Females were more retained than their male counterparts while the age group of 36 – 49 were more retained than the age group of 18 - 35.

Factors that influence attrition among these patients were age, male gender, WHO clinical stage two and four and first unsuppressed viral load after ART initiation. Missing clinic appointments and the types of ARV drugs also influenced attrition among adult patients who started ART therapy at Tlhabane between 2009 -2014. These factors could be addressed by adopting the following recommendations to reduce attrition and improve retention of patients on antiretroviral therapy:

Early ART initiation should be prioritized to patients in order to prevent advanced disease and poor prognosis while on treatment. Patients with WHO clinical stage II or asymptomatic should receive intensive adherence counselling to ensure commitment to lifelong treatment.

Viral load monitoring and education of patients who are virally unsuppressed should be prioritised for patients on ART at Tlhabane CHC. Pharmacovigilance monitoring of adult patients on ART is critical in order to prevent death related to adverse drug events and LTFU. Health education on the side effects of ARVs should form part of adherence counselling while encouraging ART patients to have treatment supporters to help them with adherence. Clinicians can minimize missing of clinic appointments by involving patients when scheduling their appointment and identify challenges related to missing appointments.

Offering men friendly HIV services in this facility to attract males is necessary. This can be done by recruiting more male health professionals, having consultation rooms that are private and designed for males, conducting outreach and health talk sessions that relate to men’s health in the waiting area. Design and distribute pamphlets targeted at men and placed in waiting area. Stigma mitigation through community dialogues, campaigns and awareness will make patients to utilize HIV services within their geographical area, thereby ensuring that more patients are retained and attrition is minimised in Tlhabane CHC.

5.5. LIMITATIONS OF THE STUDY

This study was limited by challenges such as data capturing, lack of data verification with other sources, time limitations and lack of funding. The results of this study should be interpreted in light of this. Furthermore, study findings represent one facility so the results cannot be generalized to other facilities. However, since Tlhabane CHC is a high volume facility which serves large communities including the mining community, facilities with similar characteristics may apply recommendations of this study. A study that includes various types of health facilities in other districts might have been more representative for the province.

Records of patients who were transferred into the facility were excluded from the sample as the interest was to monitor the outcomes of patients who were started on ART within the same facility. As such, the outcomes of patients may be under or overestimated, as this study only represents patients who were initiated in the same facility. Furthermore, factors associated with attrition might be more than what this study has identified. A qualitative method of study could be useful in identifying more factors that a quantitative study might have missed.

Analysis on patients who died depended on the data captured in the facility database, and due to high LTFU; death reported in this study might have been underestimated. The reason is that LTFU due to unreported death could not be ascertained with Department of Home Affairs. As the report will be shared with the Province, District and facility, tracing and death confirmation will be done by the facility.

5.6. CONCLUSION

The findings of this study are consistent with many other studies on the same topic both globally and in LMICs. Among the many consequences of low retention and attrition are HIV drug resistance and death among PLWHIV. More sustainable interventions to reverse the ongoing trend of attrition in Tlhabane CHC might be beyond this study, although it suggested a number of recommendations.

The study shows that as much as early ART initiation is beneficial for good clinical outcomes; especially in patients with WHO clinical stage II and asymptomatic, non adherence to treatment may be a risk as adult patients feel that they are still healthy.

Offering ongoing intensive adherence counselling to asymptomatic patients and those with unsuppressed viral load in Tlhabane CHC is recommended. Offering male-friendly services to motivate them to utilize the facility without fear of stigma and prejudice will increase retention in men. Stigma mitigation through community dialogues, campaigns and awareness will make patients to utilize services within their geographical area, thereby ensuring more patients' retention and minimizing attrition.

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APPENDICES

APPENDIX 1: ETHICS DOCUMENTS

Wits University ethics clearance Certificate, North West and Bojanala District approval letters

R14/49 Ms Mapula Cathrine Naledi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170248

NAME: (Principal Investigator)	Ms Mapula Cathrine Naledi
DEPARTMENT:	Centre for Health Policy Tlhabane Community Health Centre, Bojanala District
PROJECT TITLE:	Retention and Attrition of Adult Patients on Antiretroviral Therapy in Bojanala District, North West Province, South Africa, 2009 - 2014
DATE CONSIDERED:	24/02/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Pascalia Munyewende
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	31/03/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in February and will therefore be due in the month of February each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 2017-03-31

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

health
Department of
Health
North West Province
REPUBLIC OF SOUTH AFRICA

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2030 NDP

POLICY, PLANNING, RESEARCH, MONITORING AND EVALUATION

Name of researcher : **Ms. M.C. Naledi**
University of the Witwatersrand

Physical Address
(Work/ Institution) CNITAS BUILDING
222 Thabo Sehume Street
PRETORIA 0001

Subject : **Research Approval Letter – Retention and attrition of adult patients on antiretroviral therapy in Bojanala District, North West Province, South Africa, 2009-2014.**

This letter serves to inform the Researcher that permission to undertake the above mentioned study has been granted by the North West Department of Health. The Researcher is expected to arrange in advance with the chosen facilities, and issue this letter as proof that permission has been granted by the Provincial office.

This letter of permission should be signed and a copy returned to the department. By signing, the Researcher agrees, binds him/herself and undertakes to furnish the Department with an electronic copy of the final research report. Alternatively, the Researcher can also provide the Department with electronic summary highlighting recommendations that will assist the department in its planning to improve some of its services where possible. Through this the Researcher will not only contribute to the academic body of knowledge but also contributes towards the bettering of health care services and thus the overall health of citizens in the North West Province.

Kindest regards.

Mr. L.P. Moaisi
Acting Director: PPRM&E

LEPAPHA LA BOITEKANELO
DEPARTMENT OF HEALTH
Kgetsana Posa /Private Bag X2068
Mmabatho,2736
11 APR 2017
NORTH WEST PROVINCE
REPUBLIC OF SOUTH AFRICA

10 April 2017
Date

Researcher

2017-04-12
Date

health
Department of
Health
North West Province
REPUBLIC OF SOUTH AFRICA

Boom street
1st Floor, Absa Building
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Cell: 083 2606727
email:
emangole@nwpg.gov.za

2030 NDP

BOJANALA DISTRICT

To the Sub-District Manager
RUSTENBURG Sub-District

REF: PERMISSION FOR CONDUCT OF RESEARCH BY : Ms.Mapula Cathrine Naledi

This is to notify you that Ms.Mapula Cathrine Naledi has been granted permission to conduct Research entitled Retention and Attrition of Adults patients on ANTIRETROVIRAL THERAPY in Bojanala District,North West Province,South AFRICA 2009-2014 at Tlhabane CHC.

Please allow her access to the Facility and Records.

Regards,

PROFFESSOR J.M.TUMBO
DATE:05 MAY 2017

APPENDIX 2: EXAMPLE OF DATA EXTRACTION SPREADSHEET

Age	Sex	RX supporter & No	WHO staging	baseline CD4	Date of ART initiation	TB co-infection at start of ART	Drug Regimen	Type of Drugs (FLR)	Switched to SLR/TLR	Duration on ART during switching	Reason for switching	VL done
28	Male	Yes	1	311	04-Oct-13	no	FLR	TDF/FTC/EFV	No	NA	NA	36 months
36	Male	Yes	1	214	22-Apr-13	no	FLR	TDF/3TC/EFV	No	NA	NA	9 months
32	Male	Yes	1	152	05-May-13	no	FLR	TDF/3TC/EFV	No	NA	NA	none
36	Male	Yes	3	233	12-Sep-13	Yes	FLR	TDF/FTC/EFV	No	NA	NA	6 months
49	Male	Yes	1	160	25-Sep-13	no	FLR	TDF/3TC/EFV	No	NA	NA	none
37	Male	None	1	206	30-Jul-13	no	FLR	TDF/FTC/EFV	No	NA	NA	6 months
42	Male	Yes	1	108	05-Sep-13	no	FLR	TDF/FTC/EFV	No	NA	NA	14 months
36	Male	Yes	1	19	18-Jun-13	no	FLR	TDF/FTC/EFV	No	NA	NA	none
30	Male	Yes	1	240	29-Oct-13	no	FLR	TDF/FTC/EFV	No	NA	NA	9 months
28	Male	None	1	165	24-Sep-13	No	FLR	TDF/3TC/EFV	No	NA	NA	none
37	Male	Yes	3	112	23-Oct-13	no	FLR	TDF/FTC/EFV	No	NA	NA	12 months
46	Male	None	3	441	04-Nov-13	Yes	FLR	TDF/FTC/EFV	No	NA	NA	7 months
36	Male	Yes	1	143	30-Sep-13	no	FLR	TDF/FTC/EFV	No	NA	NA	none
28	Male	Yes	3	16	12-Jul-13	Yes	FLR	TDF/3TC/EFV	No	NA	NA	16 months
41	Male	Yes	3	245	31-Oct-13	Yes	FLR	TDF/3TC/EFV	No	NA	NA	9 months
29	Male	Yes	3	340	05-Jul-13	Yes	FLR	TDF/FTC/EFV	No	NA	NA	8 months
41	Male	Yes	4	135	17-Jul-13	Yes	FLR	TDF/FTC/EFV	No	NA	NA	none
27	Male	Yes	1	117	05-Sep-13	no	FLR	TDF/FTC/EFV	No	NA	NA	11 months
28	Male	Yes	3	4	06-Mar-13	no	FLR	TDF/3TC/EFV	Yes	25 months	Unsp VL	11 months
28	Male	Yes	1	70	13-Dec-13	no	FLR	TDF/FTC/EFV	No	NA	NA	8 months
30	Male	None	1	84	03-Sep-13	no	FLR	TDF/3TC/NVP	No	NA	NA	36 months
37	Male	Yes	3	95	21-May-13	Yes	FLR	TDF/FTC/EFV	No	NA	NA	none
37	Male	Yes	3	12	27-May-13	Yes	FLR	AZT/3TC/EFV	No	NA	NA	6 months
31	Male	Yes	1	258	19-Aug-13	no	FLR	TDF/FTC/EFV	No	NA	NA	17 months

26	Female	None	1	50	2009/08/09	No	FLR	D4T/3TC/EFV	No	NA
29	Female	None	3	100	2009/09/07	Yes	FLR	D4T/3TC/EFV	No	NA
32	Female	None	3	90	2009/04/21	Yes	FLR	D4T/3TC/EFV	No	NA
49	Female	Yes	1	17	2009/08/04	No	FLR	D4T/3TC/EFV	No	NA
45	Female	Yes	1	221	2009/10/05	No	FLR	D4T/3TC/EFV	No	NA
35	Female	None	1	316	2009/03/21	No	FLR	AZT/3TC/EFV	No	NA
27	Female	Yes	4	76	2009/10/27	Yes	FLR	D4T/3TC/EFV	No	NA
39	Female	Yes	1	159	2009/05/22	No	FLR	AZT/3TC/NVP	No	NA
27	Female	None	3	68	2009/12/16	No	FLR	D4T/3TC/EFV	No	NA
41	Female	None	1	196	2009/09/29	No	FLR	D4T/3TC/NVP	No	NA
35	Female	Yes	2	158	2009/11/12	No	FLR	AZT/3TC/EFV	No	NA
32	female	Yes	1	160	2009/08/23	No	FLR	D4T/3TC/EFV	No	NA
28	Female	Yes	1	203	2009/06/28	No	FLR	D4T/3TC/NVP	No	NA
38	Female	None	1	68	2009/09/22	No	FLR	D4T/3TC/EFV	No	NA
35	Female	None	1	156	2009/04/19	No	FLR	D4T/3TC/EFV	No	NA
29	Female	None	1	139	2009/05/02	No	FLR	TDF/3TC/NVP	No	NA
37	Female	Yes	1	71	2009/04/12	No	FLR	TDF/3TC/EFV	No	NA
39	Female	None	1	165	2009/01/25	No	FLR	D4T/3TC/EFV	No	NA
35	Female	Yes	1	29	2009/08/04	No	FLR	D4T/3TC/EFV	No	NA
32	Female	None	1	38	2009/06/13	No	FLR	TDF/3TC/EFV	No	NA
43	Female	Yes	1	91	2009/07/28	No	FLR	TDF/3TC/EFV	No	NA
37	Female	Yes	1	87	2009/08/10	No	FLR	D4T/3TC/EFV	No	NA
36	female	None	1	278	2009/08/03	No	FLR	D4T/3TC/NVP	No	NA
34	Female	Yes	1	180	2009/07/13	No	FLR	D4T/3TC/EFV	No	NA
33	Female	Yes	1	70	2009/03/28	No	FLR	AZT/3TC/EFV	No	NA
27	Female	Yes	1	171	2009/08/18	No	FLR	D4T/3TC/NVP	No	NA
33	Female	None	1	368	2009/08/02	No	FLR	D4T/3TC/EFV	No	NA
30	Female	None	1	94	2009/07/28	No	FLR	D4T/3TC/NVP	No	NA
41	Female	None	2	96	2009/07/11	No	FLR	AZT/3TC/NVP	No	NA
47	Female	Yes	1	503	2009/11/21	No	FLR	D4T/3TC/EFV	No	NA
36	Female	None	2	126	2009/01/01	No	FLR	D4T/3TC/EFV	No	NA
26	Female	Yes	1	36	2009/06/08	No	FLR	D4T/3TC/NVP	No	NA

APPENDIX 3: TLHABANE CHC CODED RESEARCH DATA COLLECTION TOOL

Province	District	Sub - District	Name of facility:				
North West	Bojanala	Rustenburg Local Municipality	Tlhabane CHC				
Variables	Coding						
Age	1=18-25	2=26-35	3= 36- 49				
Gender	1 = Male	2 = Female					
Treatment supporter	1=Yes	2= No					
WHO staging	1 = WHO Stage I	2= WHO stage II	3= WHO stage III	4=WHO Stage IV			
TB co infection at start of ART	1= Yes	2= No					
Baseline CD4	1= 1-100	2=101 -200	3=201-350	4=351-500	5= >500		
Date of ART initiation	1= 2009	2=2010	3=2011	4=2012	5=2013	6=2014	
Drug Regimen	1= FLR	2=SLR					
Type of drugs (FLR)	1= D4t/3TC/EFV/NVP	2= TDF/3TC/EFV/NVP	3= TDF /3TC (FTC)/ EFV	4= AZT/3TC/EFV/NVP	5= ABC/3TC/EFV	6= TDF/3TC/LPVr	7=AZT/3TC/ NVP
Switched to SLR/TLR	1= Yes	2= No					
Duration on ART during switching	1= 1-6 months	2= 7 -12 months	3= 13-24 months	4= 25-36 months	5=37-48 months	6= 49-60 months	
Reason for switching	1=high VL	2= unknown					
VL done	1= 4-6 months	2=7-12 months	3=13-24 months	4= 25-36 months	5=37-48 months	6=49-60 months	
VL Results(copies/ml)	1= 1-1000	1=>1000					
Duration on treatment	1=1-12 months	2=13 - 24 months	3=25-36 months	4=37-48 months	5=49-60 months		
Last ARV pick up date	1=1-3 months	2= 3 - 6 months	3= 6 -12 months	3=>12 months			
No. of missed for appointment	1=1-3 months	2= 4-6 months	3= 7 -12 months	4=13 -24 months			
Next date of appointment	1= 1 month	2= 2 months	3= 3 months	4=other (specify)			
Outcome of patient	1= Died	2= LTFU	3=Transferred				
Date of outcome	1=6-12 months	2= 13-24 months	3= 25-36 months	4=37-48 months	5=49-60 months		