RESEARCH MINI THESIS

PREDICTORS OF LOST-TO-FOLLOW-UP AMONGST ADOLESCENTS ON ANTIRETROVIRAL THERAPY IN AN URBAN SETTING IN BOTSWANA.

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Student name: John Tonderai Farirai

Student number: 3517789

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Supervisor: Professor Diane Cooper

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Declaration

I declare that "PREDICTORS OF LOST-TO-FOLLOW-UP AMONGST ADOLESCENTS ON ANTIRETROVIRAL THERAPY IN AN URBAN SETTING IN BOTSWANA" is my own work and that it has not been submitted for any degree or examination in any other university and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Dr John Tonderai Farirai

Date: 13 March 2018

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Thank you

List of Abbreviations

ART Anti-Retroviral Therapy

ARV Anti-Retroviral

AZT Zidovudine

CD4 Cluster of Differentiation 4

D4T Stavudine

EFV Efavirenz

HIV Human Immunodeficiency Virus

LTFU Lost- To- Follow-Up

NNRTI Non-Nucleoside Reverse Transcriptase Inhibitor

NVP Nevirapine

PI Protease Inhibitor

PLHIV People living with HIV

PEPFAR President's Emergency Plan for AIDS Relief

TB Tuberculosis

TDF Tenofovir-Disoproxil-Fumarate

3TC Lamivudine

UNAIDS United Nations Program on HIV/AIDS

VL Viral Load

WHO World Health Organization

Definitions of Key Terms

Human Immunodeficiency Virus (HIV): The virus that causes AIDS

Anti-Retroviral Therapy (ART): Treatment given to HIV positive persons to prevent progression to AIDS

Lost-To-Follow-up on ART: a patient on ART who is not seen at the clinic "90 days after the last scheduled appointment"

Adolescent: World Health Organization (WHO) defines an adolescent as any person between ages 10 and 19.

Middle Adolescents: persons between the ages 15-16 years.

Late Adolescents: persons between the ages 17-19 years.

ABSTRACT

There has been a recent increase in the proportion of adolescents living with HIV being enrolled on anti-retroviral therapy (ART) in Botswana, with more than 90% accessing this life saving therapy. A significant proportion become lost-to-follow-up (LTFU) from the ART care, reversing the initial gains attained. The factors associated with lost-to-follow-up in this vulnerable HIV positive adolescent population in Botswana are generally unknown, as most studies on this subject are on the adult population.

This study investigated the rate and factors associated with lost-to-follow up amongst middle and late adolescents (15-19 years) on ART at Botswana-Baylor clinic in Gaborone, Botswana. The center provides comprehensive HIV prevention, treatment and psychological services to children and adolescents living with HIV. The research intended to assist HIV program managers to retain adolescents in care, which is vital in reducing morbidity, mortality and also new HIV infections amongst this population. The research design was an observational comparison between those LTFU on ART and those retained on ART. Simple random sampling was used and the study had 133 of those LTFU and 133 of those not LTFU. Data on the risk factors were retrospectively extracted from patient records stored in a data-base at the clinic. The data were analyzed using Epi-info 7 statistical software to determine if there were any statistically significant factors associated with lost-to-follow-up amongst adolescents on ART. The study involved a vulnerable population who are HIV positive and a proportion who were less than 18 years. However minimal harm was expected as this was a record review and data was anonymized prior to analysis. Ethical clearance was given by the Botswana Baylor Clinic Ethics Committee and the University of Western Cape Biomedical Ethics Research Committee.

The LTFU rate in the clinic amongst adolescents (15-19 years) was 4.6%. Using bivariate analysis there were significant associations between LTFU and the following variables: CD4 count (prior to LTFU), detectable viral load, past history of Tuberculosis, PI-based ART regimen and suboptimal adherence. However after multivariate analysis, only detectable viral load and suboptimal adherence were independent predictors of lost-to-follow-up. Middle and older adolescent patients lost-to-follow-up were 5 times more likely to have a detectable viral load and 4 times more likely to have suboptimal adherence than those not lost-to-follow-up. The findings in our study will assist clinicians at the Baylor-Botswana clinic identify adolescent patients

needing extra support to be retained in care and improve clinical outcomes. More studies of this type are needed in solely public sector clinics in Botswana and regionally, as there is a sizeable population of people living with HIV in middle and late adolescents in which lost-to-follow up appears to be greatest.

TABLE OF CONTENTS

CHAPTER 1: INTRODUCTION

1.1 Background

East and Southern Africa have the largest burden of the HIV epidemic compared to other regions in the world. According to UNAIDS, of the 36 million people living with HIV globally, 19 million reside in Eastern and Southern Africa (UNAIDS, 2016). Approximately 5% of people living with HIV (PLHIV) are adolescents (10-19 years)[1] and of the estimated 670 000 new infections amongst young adults (15-24 years) globally, approximately 37% were in the 15-19 years age category (UNICEF, 2016). Of the estimated 1,8 million adolescents (10-19 years) living with HIV globally, 1,1 million are located in East and Southern Africa, 52% of global new infections amongst adolescents (10-19 years) and 60% of adolescent HIV-related global deaths occur in this same region (AIDS Info, 2016). In this region adolescent females aged 15-19 years are reported to be four times at greater risk of becoming HIV infected compared to their male counterparts (Bekker & Hosele, 2015).

Overall antiretroviral therapy (ART) coverage[2] of PLHIV is estimated to be 53% in Eastern and Southern Africa (AIDS Info, 2016). Due to increased availability of ART, a significant proportion of children born with HIV are now reaching adolescence due to being on ART (Judd, Doerholt & Tookey, 2007). ART coverage rates amongst the adolescent population are frequently lacking, as data from most countries is not disaggregated by age category (Idele, Gillepsie & Porth, 2014). However ART coverage is thought to be generally lower compared to other age groups (Elizabeth Glazer Foundation, 2016). This may result in higher rates of HIV-related morbidity and mortality in this age group. According to UNAIDS between 2005 and 2012, HIV-related mortality amongst the adolescent population living with HIV had increased by about 50% although it had significantly fallen by about 30% amongst other age categories (Bekker & Hosele, 2015).

[1] Adolescents are defined as young people between the ages of 10-19 years (WHO, 2017))
[2] ART Coverage is defined as percentage of people living with HIV currently receiving ART among the estimated number of adults and children living with HIV (WHO, 2015).

Botswana has one of the highest burdens of the HIV epidemic. The HIV prevalence amongst adults 15-49 years in Botswana is estimated to be 25% and 16 000 children are living with HIV in a country with a population of about 2 million (UNAIDS, 2015). Despite low pediatric and adolescent coverage globally, Botswana has a relatively very high ART coverage rate of about 96% amongst adolescents (15-19 years) (UNICEF, 2014).

Adolescents' widespread access to ART in Botswana has improved their health status and clinical outcomes. Botswana, amongst sub-Saharan African countries such as Namibia, Zambia and Zimbabwe has seen a 50% decline of AIDS related deaths since 2005 (UNDP, 2013). Despite this significant decline in HIV/AIDS associated mortality, lifelong ART has created additional challenges, including retaining patients in HIV care. Whilst there is an estimated 12% attrition from ART in all age categories in Botswana, age-related data are lacking (Farahani, Vable & Lebelonyane, 2013). Medical measures of the success of an ART program can be measured by attributes such as virological suppression and survival of patients on ART, however the program cannot be deemed to be successful if there are significant rates of lost-to-follow-up (LTFU) in ART care. While there is high ART coverage through initiation on treatment (UNICEF, 2014) a great challenge is to retain adolescents on life-long ART treatment. Complex psychosocial and environmental conditions affecting adolescents may affect ART adherence and retention in care (Naidoo, Munsami & Archary, 2015). The majority of studies conducted in Botswana on LTFU, using data from the national ART program do not make a distinction between adults and adolescents. It is therefore important to conduct a study to elucidate both the rates and factors affecting lost-to-follow-up specifically amongst adolescents living with HIV in Botswana.

This study was conducted to provide information on rates of middle and late adolescent LTFU on ART and to examine the factors associated with adolescent LTFU at a children and adolescent HIV clinic in Gaborone, Botswana. This is intended to contribute to strategies to improve adolescent retention on antiretroviral (ARV) treatment and in care in this setting.

1.2 Research problem

Botswana is one of the few African countries' to have achieved universal access to antiretroviral treatment with over 90% of adolescents living with HIV requiring treatment being on treatment (UNICEF, 2014). Overall lost-to-follow-up (LTFU) in the Botswana national ART program is estimated to be approximately 17% at 2 years of follow up for all age groups (Farahani, Vable & Lebelonyane, 2013). These rates are expected to be higher in the adolescent age group given the social, behavioral and psychological challenges faced by teenagers in general and those living with HIV in particular. Information is lacking on the frequency of LTFU on ART amongst adolescent patients and its influencing factors in Botswana. This threatens to diminish the success of the antiretroviral program in Botswana. There is a need to address the gap in knowledge on the rates of adolescent LTFU on ART and to understand the factors associated with this.

1.3 Research Question

What proportions of adolescents are LFTU and which factors are associated with LTFU amongst adolescent patients on antiretroviral therapy in an urban setting in Botswana?

1.4 Purpose of study

The purpose of this study is to advance our knowledge and understanding of the extent of LTFU and factors associated with LTFU amongst adolescents on anti-retroviral therapy (ART). The study will benefit the HIV program in Gaborone, Botswana in contributing to developing effective strategies to retain adolescents on ART.

1.4 Thesis chapter outline

In Chapter 2 the literature on the subject of LTFU will be examined with emphasis on studies conducted in Eastern and Southern Africa. The review will focus of definitions of LTFU on ART, rates and factors associated with LTFU on ART in general and also specifically amongst the adolescent population.

Chapter 3 presents the methodology of the study. The aim of the study is to determine the rates and factors associated with LTFU amongst older adolescents. The study design, setting, study

population, sampling techniques, data collection and analysis are outlined. A research ethics statement is also included.

In Chapter 4 the results of the study are presented. The data is presented as univariate, bivariate and multivariate analysis. The results are presented in tabular form and also described.

Chapter 5 discusses the findings of the study, making comparisons with similar studies conducted in comparable settings

Chapter 6 concludes the study and also makes recommendations in line with the research findings.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

One of the greatest threats to the success of global ART programs is the persistent attrition of patients from such programs, also referred to as lost-to-follow-up (LTFU). This chapter will explore the different definitions of LTFU on ART and explain the choice of the definition used for this study. This chapter is also an overview of the rates and factors associated with LTFU in broader age categories and patient groups. Lastly factors associated with LTFU (on ART), particularly amongst adolescents is examined.

2.2 Definition of Lost-To-Follow Up

Due to the initial high morbidity and mortality associated with HIV-related illnesses, outcomes of success of HIV care programs have been traditionally measured by the prevalence of opportunistic infections and mortality rates. However as more people living with HIV readily access ART and remain alive, retention in care as estimated by LTFU rates has become more relevant in measuring program effectiveness (Brinkhof, Dabis & Myer, 2008). A standardized definition of LTFU is therefore required for comparative reviews of data on patient retention from different ARV programs. This will make it more feasible to compare attrition rates in ART programs within and between countries.

A review of HIV medical literature reveals a variety of definitions of LTFU. Shepherd, Blevins and Vaz (2013) found 17 different definitions used for LTFU of patients on ART in their reviews of studies. Using these different definitions of LTFU, the rates in this review varied from 22% to 84% (Shepherd, Blevins & Vaz, 2013). The definitions differed in the focus on the following indicators: duration on ART; time measured from last visit vs missed visit for ART and the visit for last encounter (clinic, laboratory or pharmacy). A study which analyzed data from ART programs in Sub-Saharan Africa also showed that by using different LTFU definitions, the rates vary considerably, making it difficult to compare programs (Brinkhof, Dabis & Myer, 2008). For example in the Brinkhof et al (2008) study LTFU rates of 9, 3% were estimated when one definition was used, compared to 1, 3% with an alternative definition. The former definition included amongst the LTFU, patients who were initiated on ART and never returned to the clinic after only one visit, whilst the alternative definition did not.

After an analysis of ARV programs in 19 countries in 2011, researchers recommended that the definition of LTFU should be that "180 days or more have elapsed since the patient's last clinic visit" (Chi, Yiannoutsos, Westfall, Newman & Zhou J, 2011: 10). Using this 180 day threshold, the rates of LTFU in countries ranged from 3% to 45%. The researchers reported that much of the variation in the definition of LTFU occurred when information was collected at facility level, with measures of LTFU used ranging between 58-383 days since the patients' last visits (Chi, Yiannoutsos, Westfall, Newman & Zhou J, 2011). The current WHO definition of LTFU is a patient on ART who is not seen at the clinic "90 days after the last scheduled appointment" (WHO, 2011:26). The appointment in this definition is considered to be either a clinic or pharmacy visit. This WHO definition allows for comparison of ART programs within and between different countries. In Botswana the WHO definition is used in defining lost-to-follow-up (Farahani, Vable & Lebelonyane, 2013).

2.3 Rates and reasons of Lost-To-Follow-Up on ART

2.3.1 Attrition rates in ART care

Studies on retention in care in ART programs have become increasingly relevant since most countries in sub-Saharan Africa have rapidly expanded and enrolled more patients on treatment than before. A systemic review of ART programs in sub-Saharan Africa showed that the retention of patients in programs after 2 years, ranged between 46% and 85% in different countries (Rosen, Fox & Gill, 2007). The study accepted the varying definitions of LTFU used by the different countries. The major causes of attrition from ART care in this analysis was reported to be LTFU (56%), followed by death (40%). The remaining 4% was due to patients having discontinued their antiretroviral treatment, but remaining in care in the facility. The highest retention rate at 3 years after ARV initiation was in South Africa (87%) and the lowest was recorded in a study in Botswana (64%) (Rosen, Fox & Gill, 2007). However this review of percentages of attrition in these studies does not include an analysis of the factors associated with LTFU in these countries and does not report the rates of LTFU up in the sub-populations of pediatrics and adolescents. In this review of studies in African countries, death was a sizeable contributor to the LTFU patients.

This is supported by study conducted in Malawi that showed that of the patients who were reported to be LTFU, 50% had died, 23% were alive but not on treatment whilst 27% could not be traced and so their outcomes were unknown (Yu, Chen, Wang, Chang & Makombe, 2007). Of those who were found to be alive and traced, the majority (64%) had stopped treatment due to high transport costs in attending an ART facility. This study does not report the rates and reasons for LTFU, specifically amongst adolescents. This is despite the fact that children make up approximately 12% of the people living with HIV in Malawi (UNAIDS, 2015). In a study conducted in South Africa which analyzed patients who were classified as LTFU while on ART found that, 31% had died, 25% were accessing treatment at other centers and 44% could not be located or had discontinued treatment (Dalal, MacPhail & Mqhayi, 2008). Those accessing treatment at other centers cannot be considered true LTFU, but rather indicates a need for better communication between centers on transfer of patients on ART out of one facility to another.

In contrast to studies conducted in African countries, in a study done in the UK, deaths contributed to only 3% of patients who were classified as LTFU (Gerver, Chadborn, Ibrahim & Vatsa, 2010). In this UK study, 48% patients who were initially classified as LTFU had actually transferred to other sites without informing the initial sites. In this study advanced immunosuppression as measured by low CD4 count was a key predictor of LTFU. Other predictors of LTFU in the same UK study was a detectable viral load (>400) at last clinic visit, earlier year of ART clinic registration and being a heterosexual African female. Similarly in a study conducted in New York of patients who were presumed to be LTFU, 2% had died (Udeagu, Webster, Bancour, Michel & Shepherd, 2013).

2.3.2 Factors associated with LTFU

This section provides an overview of the factors that influence patients on ART being LTFU, as reflected in peer reviewed literature. It will review the structural and psychosocial factors and also patient level factors, in particular immunological factors, virological status, adherence to ARV drugs, ARV drug regimens, WHO clinical status and tuberculosis history.

2.3.2 (a) Facility and psychosocial factors

Facility level and psychosocial factors may affect retention in ART clinics. A qualitative study amongst adults on retention in ART care in South Africa showed that transport costs and time patients spent seeking treatment were significant barriers and possible contributors to LTFU (Miller, Ketlhapile, Rybasack-Smith & Rosen, 2010). In this study, HIV related stigma was not found to be a significant factor resulting in patients defaulting from treatment. HIV-stigma was also not found to be a key factor affecting LTFU of adults on ART in a South African quantitative study (Evangeli, Newell, Ritcher & McGrath, 2014). However, in contrast, in a qualitative study in Kenya conducted amongst an adolescent population living with HIV, HIV-related stigma was found to be a compelling factor for LTFU (Wolf, Halpern-Felsher, Bukusi & Agot, 2014). In this study HIV- related stigma was mentioned as being experienced in the home, school and clinic settings. This may have resulted in poor clinical outcomes amongst adolescent compared to adults, as was shown by a retrospective analysis done in South Africa (Evans, Menezes & Mahomed, 2013).

2.3.2 (b) Immunological factors

There is conflicting evidence on whether there is an association between the immunological status (as measured by CD4 count) and LTFU amongst HIV positive persons on ART. A baseline CD4 is a measurement which is done on entry into care by a person living with HIV (CDC, 2016). According to the WHO, a CD4 count of less than 350cells/µL is an indicator of significant immunosuppression and if less than 200cells/µL it indicates severe immunosuppression (WHO, 2005). A retrospective review which was conducted in South Africa showed that the average CD4 count amongst LTFU patients on ART was low at 92cells/µL (Maskew, MacPhail, Menezes & Rubel, 2007). A low CD4 count amongst LTFU patients was also noted in a study which was conducted in Tanzania, in which the mean CD4 count was 122(67-180) cells/µL (Makunde, Francis & Kamugisha, 2012). A case-control study conducted in Uganda also showed that a CD4< 200cell/µl was associated with LTFU amongst patients on ART, with the association greatest when the CD4 count was <50cell/µL (Okoboi, Diring, Persuad & Wangisi, 2015).

In a retrospective observational study conducted in South Africa a baseline CD4 count above 200cells/µL was associated with becoming LTFU (Mberi, Dube, Kuonza & Nattey, 2015). In contrast, a baseline CD4 count of less than 200 was found to be a risk factor for LTFU amongst patients on ART in an Ethiopian study (Berheto, Haile & Mohammed, 2014). In contrast a different South African study showed no association between baseline CD4 count and LTFU (Shearer, Fox, Maskew, Sann & Long, 2013). Hence there is a need for further research to determine whether there is an association between baseline CD4 and LTFU whilst on ART.

2.3.2 (c) Virological failure

HIV Viral load is the measure of the amount of viral copies per ml of blood (AIDSMAP, 2017). According to WHO, virological failure is defined as two consecutive detectable viral load (VL) above 1000 copies/ml (WHO, 2016). Some studies have found an association between detectable VL and LTFU amongst patients on antiretroviral therapy. A cohort study conducted in South Africa found that a detectable VL was independently associated with LTFU, in multivariate analysis (Mberi, Dube, Kuonza & Nattey, 2015). This was also evident in a case control study conducted in France (Ndiaye, Ould-Kaci, Salleron & Bataille, 2006). In this study the association with LTFU on ART was greatest with VL of >10 000 copies/ml at the time of LTFU. A retrospective evaluation of data from a PEPFAR funded program conducted in Nigeria for the years 2004 to 2012 showed that 71% of the LFTU patients had detectable VL, 6 months prior to LTFU (Meloni, Chang, Chaplan & Rawizza, 2014). This analysis showed a statistically significant association between VL and LTFU.

2.3.2 (d) Adherence to ART medications

Adherence to ART medications is vital in achieving viral suppression and optimizing health outcomes amongst PLHIV. Adherence to ART drugs of less than 95% is associated with a significant (61%) risk of treatment failure (UNAIDS/WHO, 2011). Some of the factors affecting adherence to ART are ARV drug side effects, pill fatigue, stigma and lack of community support (UNAIDS, 2014). Hence it is important to investigate whether suboptimum adherence to ART is associated with LTFU in ART care. A case control study conducted in Ethiopia showed that adult patients with suboptimal adherence to ART of < 95% were 7 times more likely to be LFTU in ART care (Mergerso, Garoma, Etichia & Workineh, 2016). The link between poor ART

adherence and LTFU in ART care was also shown in a Nigerian study, in which patients with 100% adherence to ART had a 64% lower risk of LTFU in ART care compared to patients with an adherence of <50% (Meloni, Chaplain, Chang, & Rawizza, 2014). This association was also found in a study conducted in Kenya amongst HIV positive pregnant women, with patients having suboptimal adherence to ART being more likely to become LTFU in ART care (Clayden, 2012).

2.3.2 (e) Antiretroviral drug regimens

Different ART regimens have varying side effects, which could possibly influence adherence to medication and default in ART care follow up visits by patients. ART side effects have been shown to be a contributing factor in LTFU amongst PLHIV on ART (Dalal, MacPhail & Mqhayi, 2008). Some LTFU to ART care studies have shown statistically significant differences in LTFU rates depending on the ART regimen of a patient. An Ethiopian study showed that patients on AZT/3TC/NVP regimen were at more than 3-fold increased risk of LTFU compared to those on d4T/3TC/NVP (Tardese & Haile, 2014). The authors suggested that the difference may be explained by the fact that AZT-based regimens are associated with higher rates of side effects. Another Ethiopian study found that patients with a history of a regimen substitution had a 5- fold higher risk of LTFU compared to those with no regimen substitution (Berheto, Haile & Mohammed, 2014). However this evidence that certain regimens that have higher rates of adverse side effects are associated with a higher risk of LTFU is not consistent with the findings from some other studies. A Nigerian study showed that patients on TDF/FTC/EFV where more likely to be LTFU than those on AZT/3TC/EFV regimen (Meloni, Chaplain, Chang & Rawizza, 2015). Additionally another Nigerian study also found that patients on TDF-based regimens were at a higher risk of LTFU compared to those on AZT-based regimens (Eguzo, Lawal, Umezurike & Eseigbe, 2015). This is despite TDF-based regimen being associated with significantly less adverse side effects compared to AZT-based regimens (Bygrave, Ford, van Cutsem & Hilderbrand, 2011). Therefore, there is conflicting evidence on whether the difference of LTFU rates on between regimens could be explained by adverse effects associated with these particular regimens.

2.3.2 f) WHO clinical staging

Clinical staging of HIV/AIDS may impact on LTFU in care among those on ART. People living with HIV are clinically staged to determine the extent of progression of the illness as per WHO guidelines clinical stages I, II, III and IV. Stage IV indicates the most advanced disease stage (WHO, 2015). Several studies have shown that patients on ART with a more advanced WHO clinical stage are associated with LTFU in ART care. In a case-control study conducted in Ethiopia, patients classified as WHO stage IV were twice as likely to be LTFU in ART care compared to those classified with WHO clinical stage I illness (Mergerso, Garoma, Eticha & Workineh, 2016). This was also evident in a Togolese study, with those classified as WHO III/IV being associated with greater LTFU in ART care compared to those classified as WHO stage I/II (Saka, Landoh & Patassi, 2013). This association was also found in a South African cohort study, in which patients with a baseline WHO stage of III/IV were shown to have a higher risk of LTFU in ART care compared to those classified as stage I/II (Mberi, Dube, Kuonza & Nattey, 2015). However in contrast one Ethiopian study showed that patients with a baseline WHO stage III/IV were less likely to be LTFU (Berheto, Haile & Mohammed, 2014).

2.3.2 (g) Tuberculosis

Tuberculosis (TB) is a common HIV-related illness particularly in developing countries. According to WHO, people living with HIV are up to 31 times more likely to develop TB compared to those who are HIV negative (WHO, 2017). There is some evidence that TB is associated with LTFU amongst patients on ART. In a study conducted in Ethiopia, patients on ART with proven pulmonary TB were approximately twice as likely to be LTFU in ART care compared to those without TB (Tadesse & Haile, 2014). According to the study, the higher risk of LTFU was possibly due to adverse drug reactions associated with TB treatment drugs, which are more prevalent in patients also on ART medication. A study conducted in Kenya also showed that there were high rates of LTFU amongst TB-HIV patients on ART (Tayler-Smith, Zachariah, Manzi & Kizito, 2011). In this study there was 14% LTFU amongst TB patients who were commenced on ART. A cohort study in India found there was an attrition rate of 47% amongst patients who were diagnosed with TB whilst on ART compared with 35% among those without TB (Alvarez-Uria, Naik, Pakam & Midde, 2013). However the attrition rates amongst patients

who were diagnosed and treated for TB before ART commencement, the attrition rates were similar to patients without previous TB (36% vs 35%).

2.3.2 (h) Other factors

A study conducted in South Africa in ART community clinics run by Faith Based Organizations in which the rates of LFTU was 6% at 6 months after ART initiation, found that both pregnancy and lower CD4 count were associated with higher risk of LTFU in ART care (Wang, Losina & Stark, 2011). A similar case-control study conducted in Kenya also showed pregnancy to be associated with LTFU (Karche, Omondi, Odera, Kanz & Harms, 2007). However unlike in the South African study, CD4 count was not found to be a contributing factor to ART care LTFU. The Kenyan study also found lower educational status to be significantly associated with LTFU whilst on ART. This was supported by a Ugandan study which also showed an association between lack of formal education and LFTU in ART care (Burkley, Weiser & Fehmie, 2015). However in contrast, a multi-centred South African study amongst pregnant women on ART found no association between level of education and LTFU in ART care (Onoya, Sineke, Brennan & Fox, 2014).

2.4 Loss-to-follow up amongst adolescents on antiretroviral therapy

Adolescence is a period of physiological and social transition from childhood to adulthood and is associated with less dependence on caregivers. Adolescents on ART, particularly those who have been on treatment since childhood, begin to take extra responsibility especially in taking their medications and attending clinic consultations. Due to these factors, adolescents might be at greater risk of defaulting treatments and becoming LTFU, as supervision from caregivers becomes less. A study which analyzed data from 9 ART sites in Southern Africa showed that ART adherence rates where lower amongst adolescents (11-19 years) when compared to adults (Nachega, Hislop, Nguyen & Dowdy, 2010). Barriers to adherence to treatment amongst adolescents include fear of disclosure and anticipated HIV-related stigma (Denison, Banda, Dennis & Packer, 2015).

A study conducted in Ethiopia showed adolescents were associated with increased risk of LTFU. The study found that being an adolescent, having had a regimen substitution, being in good health and a low baseline CD4 were associated with higher rates of LTFU (Berheto, Haile &

Mohammed, 2014). Berheto et al. (2014) also showed that adolescents 11-19 years were at a higher risk of LTFU compared to children ≤10 years old. The adolescents were also twice as likely to be LTFU compared to adult patients in the same study. A study conducted in Nigeria showed no difference in lost-to-follow-up rates between adolescents and younger children (Ojikutu, Higgings-Biddle, Greeson & Phelps, 2014). Therefore contrasting findings exist in literature on whether adolescents are at higher risk to LTFU compared to children, but the findings are generally in the direction of increased LTFU for adolescents.

A retrospective study conducted in South Africa compared LTFU between adolescents and adults (Evans, Menezes & Mohamed, 2013). It found that middle and older adolescents (15-19 years) were about 2-fold most likely to be LTFU, whilst adolescents (10-14 yrs) were 2 times less likely to be LTFU when compared to adults. The middle and older adolescents also had other poorer treatment outcomes such as virological failure. A study in Ethiopia showed that middle and older adolescents and young adults (15-24 yrs) where about 6 times more likely to be LTFU compared to 25-34 years age category (Mergerso, Garoma, Eticha & Workineh, 2016).

Quality of medical care may influence LTFU amongst adolescents on ART. A Nigerian study showed that provision of high quality care to children and adolescents living with HIV, was associated with reduced risk of LTFU (Ojikutu, Higgings-Biddle, Greeson & Phelps, 2014). In this study, quality of care measures that reduced the likelihood of LTFU were adherence counseling and adherence measurements (pill counts) at clinic visits. These factors are important in reducing LTFU amongst HIV patients on antiretroviral therapy generally. A retrospective study also showed that patients who received higher levels of adherence support were associated with less risk of LTFU (Etienne, Burrows, Osotimehim, Macharia, Hossain, Redfield & Amoroso, 2010). The LTFU rates in this study were approximately 19%. Adolescents particularly those on treatment since childhood can have medication fatigue which can result in them defaulting from ART (Hogdson, Ross, Haamujompa & Gitau-Mburu, 2012).

2.5 Summary of Literature review

Lost-to-follow up in ART care is a threat to the control of the HIV epidemic. There are various definitions used for LTFU on ART, however most studies use the WHO (2011) definition of "Not seen in the clinic at least 90 days from last appointment date". There is significant research in this area, although studies particularly focusing only the adolescent population are few. Middle and late adolescents may be a particularly vulnerable group for LTFU. There is generally evidence that LTFU is associated with clinical variables associated with poor adherence to ART drugs.

CHAPTER 3: METHODOLOGY

3.1 Introduction

Chapter 3 presents an overview of the methodology used in this study. It includes a description of the aim and objectives, the study design, setting, population and sampling procedure, the study analysis, ethics considerations and the study limitations.

3.2 Aim

The aim of this study was to investigate the percentage and the causes of lost-to-follow-up amongst a sub-population of HIV positive middle and late adolescents on antiretroviral therapy in an urban health care facility in Botswana.

3.3 Objectives

Its objectives were, at the Baylor Clinic in Gaborone, for the period 2010-2015:

1. To identify HIV positive middle and late adolescents on ART who were lost-to-follow-up and those retained on ART.
2. To describe the rates of lost-to-follow-up amongst HIV positive middle and late adolescents on antiretroviral therapy (ART).
3. To compare HIV and ART related variables amongst LTFU and non-LFTU middle and late adolescents on ART.

3.4 Study type/design

The study was a retrospective observational study in which data from a sample of adolescent patients that were lost-to-follow-up and those who were not lost-to-follow-up (on ART and retained in care) were analyzed. Those LTFU and those not LTFU were selected from the same clinic for the same period.

3.5 Study site

The study site was Botswana-Baylor children's and adolescents HIV clinic, located in the city of Gaborone in Botswana. It provides comprehensive HIV preventive, curative and psychosocial services. The clinic is run by Baylor-Botswana, a partnership between Ministry of Health of

Botswana and Baylor College of Medicine from Houston, USA. The clinic has about 2200 children, adolescents and young adults currently on anti-retroviral therapy. Of these 1300 are between the ages 10- 19 years. The clinic staff is composed of two pediatricians, four medical officers, nine trained nurse prescribers, three pharmacy officers, a social worker, a psychologist, a monitoring and evaluation officer and a dietician. The clinic also hosts scholars and pediatric and adolescent specialists from Baylor College of Medicine for various durations.

3.6 Study population

The study population comprised all adolescents aged 15-19 years who attended the Botswana-Baylor clinic in Gaborone, Botswana from January 1st 2010 to 31st December 2015 with confirmed HIV infection and on antiretroviral therapy. The middle and late adolescent population group was chosen due to anecdotal evidence that defaulting from ART is more common as supervision from caregivers reduces.

3.7 Sampling

A probability sampling method was used in the study. In probability sampling, all the patients in the sampling frame have an equal probability of being selected. The specific type of sampling method used was simple random sampling. Simple random sampling was straightforward to apply as there was a readily available list of adolescent patients who were ever LTFU in ART care.

The sample size was calculated using Epi-Info 7 software. Epi-info stat calculator was used to calculate the sample size needed to illustrate a difference in follow up on ART. A 2-sided confidence level of 95% was used, with a power of 80%, ratio of those LTFU to those not LTFU of 1:1. A hypothetical proportion of those not LTFU with exposure 40% (CD4<350) and least extreme odds ratio to be detected =2. There were 133 LTFU and 133 not LTFU selected.

For the purposes of this study the WHO (2011) definition of not seen in the clinic for 90 days after the last scheduled appointment was used. The scheduled appointment was considered as either a clinic or pharmacy encounter. The LTFU register in the clinic was accessed and patients meeting the criteria as outlined in the inclusion criteria were selected i. e adolescent patients aged 15-19 years who were on ART, who were not seen in the clinic/pharmacy for at least 90 days

after the last scheduled appointment during the period 2010-2015. From this list the sample was selected by using random sampling software. Those not LTFU were selected at 1:1 with those LFTU, from adolescents (15-19 years) on ART who are retained in care at the same time of those LTFU. Those not LFTU were matched for sex, age and year of lost-to-follow (for those LTFU).

Patient records with no relevant data (demographic and clinical) were excluded and the next study subject in the list was selected as a replacement.

3.8 Inclusion and exclusion criteria

3.8.1 Inclusion criteria for LTFU

HIV positive

Middle and late adolescent 15-19 years on ART.

Not seen in the clinic at least 90 days from last appointment date.

3.8.2 Exclusion criteria for those LTFU

Insufficient data available in the IPMS (integrated Patient Management System) at the clinic

3.8.3 Inclusion criteria for those not LFTU

HIV positive

Middle and late adolescent 15-19 years, on ART

Non- defaulters from ART

Exclusion criteria were the same as for those LTFU.

3.9 Data collection procedures

Quantitative data were collected from the patient records in the Patient Management Information System (PIMS) at the clinic. PIMS is software in the clinic, which has all the relevant patient data i.e. demographic data, pharmacy encounters, laboratory data and patient consultation summaries.

The data collected was age, gender, date of enrollment in care, date of ART initiation, date of lost-to-follow-up (for those LTFU) and date of appointment kept (for those not LTFU), baseline CD4 count, CD4 count prior to lost-to-follow-up (those LTFU) and a similar date for keeping an appointment for those not LTFU, viral load prior to lost-to-follow-up and a similar date for those not LTFU, WHO stage (those LTFU) and a similar date for those not LTFU, ART regimen, viral load at last 2 visits, history of TB-HIV co-infection, adherence measurements by pill counts (in the year prior to LTFU or retention in care) and relationship with primary care giver.

3.10 Data collection tool

A standardized form was used to collect the data (See Appendix 1). For operational definitions of data to be extracted, see Appendix 1 a). I collected data as the investigator and patients were identified by a unique study number.

3.11 Validity of study

To improve the validity of the study there were clear definitions of the LTFU and not LTFU and risk factors for LFTU. The data collection tool was piloted using other patients' records, not included in the study. During this process it was noted that information baseline WHO staging (at ART initiation) of most patients was not available and hence was taken off the tool. However WHO staging at LFTU was consistently available. The data collection tool was also scrutinized by an HIV expert to ensure content validity. During data analysis, the researcher (myself), who analyzed the data was blinded as to which study patient numbers were LTFU and not LTFU.

3.12 Reliability of study

To improve reliability of the study, the data collector verified all the data collected. Data collected was also verified by a different medical practitioner trained to complete the data collection tool. There was consistency in data collected by the two data collectors i.e. observer variation was minimal hence reducing bias.

3.13 Generalizability of study

The study findings were extrapolated to Botswana-Baylor Clinic, amongst mid and older adolescents (15-19 years) and not to any other setting and population.

3.14 Data analysis

Data were analyzed with Epi-Info 7 software. Univariate analysis was conducted initially, to describe distributions. The software was used to conduct bivariate analysis so as to calculate the odds ratio for each variable collected and the confidence interval and P-value to determine statistical significance between the outcome and exposure variables. The outcome variable was LTFU in ART care. Bivariate analysis with EPI-info 7 was conducted to determine if there was any significant association between LTFU and the exposure variables. Multivariate logistic regression was used to identify independent associations between LTFU and a combination of risk factors associated with the odds of LTFU.

3.15 Ethics statement

The study involved a vulnerable population who are HIV positive and a large number of whom were less than 18 years. However minimal harm was expected as the study was a record review, rather than involving engagement with patients. The data were anonymized, through patients being assigned study numbers instead of names or folder numbers being recorded prior to extraction. Consent was not a requisite for this study as routine anonymized data was used.

The study was not aimed at directly benefitting those patients from whom data is collected as data was anonymized and individual patients were not being specifically followed up during the study. However the study aimed to benefit HIV positive adolescents on ART at the clinic in general. The findings of this study are being used to make recommendations to reduce rates of LTFU at the ART clinic. This can contribute to improving health outcomes amongst adolescents living with HIV by reducing morbidity and mortality rates.

The study ensured that there was fair selection of participants through random sampling techniques. No particular social group/class was targeted. Ethnicity and race was not used to select participants. During the process of data collection anonymity was ensured by not recording any individual identifying information and confidentiality was strictly maintained. Ethics approval for conducting the research was obtained from the Baylor Clinic Management and IRB (see attached letter, Appendix 2). Ethics clearance for the retrospective studies and data analysis in the clinic were covered by a medical audit permit from Health Research and Development Committee (HRDC) Board of the Ministry of Health, Botswana. The research proposal was

granted ethics approval by the University of the Western Cape Higher Degrees and Biomedical Research Ethics Committee (Ethics reference number: BM/16/5/30)

CHAPTER: 4 RESULTS

Baylor Clinic had 895 adolescents (15-19 years) who had ever been enrolled on ART as at end of September 2017. This excluded deaths and transfer-outs. Of these 41 were LTFU on ART, giving a current LTFU rate of 4.6%.

The eligible population for the study was 316 adolescents (15-19 years) who were ever lost-to-follow-up in the period 2010-2015. Using simple random sampling, 133 those LFTU were selected. The 133 not LTFU were selected from adolescents who were retained in care matching the year of LTFU, age and sex for those LTFU. During data collection 5 LTFU and 3 not LTFU had inadequate data and were replaced by the next subject in the study population. It was noted during data collection that almost all records had missing WHO staging data at the time of LTFU, hence this was excluded from the analysis. However the WHO staging at the time was ART initiation was available.

As can be seen in Table 1, in the total sample (n=133) there were slightly more females (53%) than males (47%). As those LTFU and those not LTFU were matched by sex, both groups had similar proportions of males and females. The majority of those in the whole sample (55%) were in the older age group (18 and 19 years) at the time of LTFU. The median age of the sample was 18 years. The age distribution of those LTFU and those not LTFU were similar, due to the two groups being age-matched in the selection of the samples. Pertaining to ART regimens, a slight majority was on PI-based ART[3] (51.9%), while the remaining patients were on a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-based HAART (Efavirenz and Nevirapine). The most common regimen was Combivir/Aluvia accounting for 26.3%. There were no patients on salvage regimens of ART.

In terms of CD4 count, a greater proportion of the respondents had lower CD4 counts (<350) at baseline compared to at the time of LTFU (43.6% vs 25.9%). This is expected as ART usually results in improved immunity which is measured by CD4 count. Most study patients had advanced HIV disease with 71.8% having either a WHO stage 3 or 4 clinical condition at the time of ART initiation. As mentioned, data on WHO staging at the time of LTFU was not

[3] A PI (Protease Inhibitor-based) regimen is an alternative ART regimen which is associated with more adverse gastrointestinal side effects and more pill burden compared to NNRT-based regimen (AIDS INFO, 2017). The PI used mostly at Baylor clinic is Aluvia.

available in the records. The majority of the respondents (59%) had a biological parent as the caregiver, whilst 43% were under the care of relatives and 3.4% were in an orphanage.

Adherence measured by pill counts was relatively good with 91% having an adherence of above 80%, with 68% achieving an optimal adherence above 95%. Previous history of Tuberculosis was found in 51 of the 266 respondents (19%). The majority (84%) of the TB cases had pulmonary disease, whilst the most common type of extra-pulmonary disease was Lymph node TB (7.8%). Virological failure defined as VL > 1000 copies/ml was found in 39.5% of the respondents with 5% having VL>100 000, which is usually associated with very poor adherence.

Table 1: Socio-demographic and clinical characteristics of respondents (n=266)

	Frequency (n)	**Percentage (%)**
Gender		
Male	126	47.4
Female	140	52.6
Age		
15	42	15.8
16	36	13.5
17	42	15.8
18	44	16.5
19	102	38.4
CD4 count Baseline		
0-199	49	18.4
200-349	67	25.2
350-499	69	25.9
>500	81	30.5
CD4 at LTFU		
0-199	21	7.9
200-349	48	18.0
350-499	51	19.2
>500	146	54.9

ART Regimen		
Combivir/Aluvia	70	26.3
Truvada/Aluvia	47	17.7
Abacavir/Lamivudine/Aluvia	21	7.9
Combivir/Efavirenz	44	16.5
Conbivir/Nevirapine	27	10.2
Abacavir/Lamivudine/Efavirenz	15	5.6
Abacavir/Lamivudine/Nevirapine	18	6.8
Atripla	17	6.4
Truvada/Nevirapine	7	2.6
WHO staging at ART initiation		
Stage 1	31	11.6
Stage 2	44	16.5
Stage 3	83	31.2
Stage 4	108	40.6
Caregiver		
Parent	157	59.0
Uncle/Aunt	73	27.5
Grandparent	24	9.0
Orphanage	9	3.4
Other	3	1.1
Adherence		
<60%	11	4.1
60-80%	13	4.9
80-95%	61	22.9
>95%	181	68.1

Viral load		
<1000 copies/ml	161	60.5
1000- 9999 copies/ml	42	15.8
10 000- 100 000 copies/ml	49	18.4
>100 000 copies/ml	14	5.3
Tuberculosis Cases		
Pulmonary TB	43	84.3
Lymph node TB	4	7.8
Pleural TB	2	3.9
TB meningitis	1	2.0
TB abdomen	1	2.0

Table 2 is a summary of the proportion of those LTFU and not LTFU, associated with a specific independent variable. Nearly half (48%) of those LTFU had a low baseline CD4 (<350) compared to those not LTFU (39%). There was also a higher proportion (38%) of those LTFU with a low CD4 at the time of LTFU compared to those not LTFU (14%). Virological failure VL>1000 was also common amongst those LTFU (61% vs 18%). The WHO staging at ART initiation was similar amongst those LTFU and those not LTFU (74% vs 69%), whilst more of those LTFU had a history of past TB (24% vs 14%). A greater proportion of those LTFU were on PI-based ART compared to those not LTFU (62% vs 41%), with also more of those LTFU having suboptimal ART adherence (47% vs 17%). A biological parent being the primary caregiver was comparable amongst the two groups (42%vs 40%).

Table 2: Clinical variables and their association with LTFU, Baylor Clinic (n=133)

VARIABLES	LTFU N (%)	Not LTFU N (%)
Baseline CD4		
<350cells/ml	64 (48)	52 (39)
≥350cells/ml	69 (52)	81 (61)
CD4 (LTFU)		
<350cell/ml	50 (38)	19 (14)
≥350cells/ml	83 (62)	114 (86)
VL		
≥1000 copies/ml	81(61)	24 (18)
<1000 copies/ml	52 (39)	109(82)
WHO Stage (Baseline)		
III/IV	99 (74)	92 (69)
I/II	34 (26)	41 (31)
TB history		
Present	32 (24)	19 (14)
Absent	101(76)	114 (86)
ART regimen		
PI- based	83 (62)	55 (41)
NNRTI- based	50 (38)	78 (59)
Caregiver		
Non-Parent	56 (42)	53 (40)
Parent	77 (58)	80 (60)
Adherence		
<95% (Suboptimal)	63 (47)	22 (17)
≥95% (Good)	70 (53)	111 (83)

Table 3 is a summary of associations between LTFU and different independent exposure variables that were tested using bivariate analysis. The table shows the crude odds ratio for each variable and also the p-value to show statistical significance.

In the bivariate analysis there were statistically significant associations between CD4 count (at LTFU) and LTFU from ART care, crude odds ratio of 3.61(95% CI: 1.98-6.57 P value<0.001). There was however no significant association between CD4 count at ART initiation and LTFU from ART care (OR=1.44 (95% CI: 0.89-2.35 p=0.139). Presence of virologic failure was statistically significantly associated with LTFU in ART care, with adolescents with VL >1000 copies/ml having about 7 times the odds of being LTFU compared to those adolescents with VL<1000 copies/ml (OR=7.07(95% CI: 4.03-12.41 p<0.001). Past history of Tuberculosis was also a predictor of LTFU (OR= 1.90 (95% CI: 1.01-3.56 p<0.005).

The adolescents who were on PI-based ART regimen had about 2 times the odds of being LTFU on ART compared to those on NNRTI-based regimens OR=2.35(95% CI 1.43-3.85 p<0.05). In this study having a suboptimal adherence (<95%) to ART drugs was also a strong predictor of LTFU, OR= 4.54(95% CI 2.57-8.03) p<0.001).

WHO stage at the time of ART initiation was not associated with LTFU in bivariate analysis (OR=1.29(95% CI 0.75-2.21 p=0.342) and so was not included in the model for multivariate analysis. The WHO staging at the time of LTFU was not available in the patients' records and therefore was not available for analysis. As there was also no significant difference in the prevalence of LTFU amongst adolescents with a biological parent as the primary caregiver compared to those with a non-parent as the caregiver (OR=1.09 (95%CI 0.67-1.79 p=0.709) this was therefore also excluded from multivariate analysis.

Table 3: Clinical variables and their association with LTFU (Bivariate analysis) (n=133)

VARIABLES	LTFU N (%)	Not LTFU N (%)	Crude odds ratio (95% CI)	p-value
Baseline CD4				
<350cells/ml	64 (48)	52 (39)	1.44(0.89-2.35)	0.139
≥350cells/ml	69 (52)	81 (61)	Ref category	
CD4 (LTFU)				
<350cell/ml	50 (38)	19 (14)	**3.61(1.98-6.57)**	<0.001*
≥350cells/ml	83 (62)	114 (86)	Ref category	
Viral Load				
≥1000	81(61)	24 (18)	**7.07(4.03-12.41)**	<0.001*
<1000	52 (39)	109(82)	**P<0.001**	
			Ref category	
WHO Stage (Baseline)				
III/IV	99 (74)	92 (69)	1.29(0.75-2.21)	0.342
I/II	34 (26)	41 (31)	Ref category	
TB history				
Present	32 (24)	19 (14)	**1.90(1.01-3.56)**	0.045
Absent	101(76)	114 (86)	Ref category	
ART regimen				
PI- based	83 (62)	55 (41)	**2.35(1.43-3.85**)	0.007*
NNRTI- based	50 (38)	78 (59)	Ref category	
Caregiver				
Non-Parent	56 (42)	53 (40)	1.09(0.67-1.79)	0.709
Parent	77 (58)	80 (60)	Ref category	
Adherence				
<95%	63 (47)	22 (17)	**4.54(2.57-8.03)**	
(Suboptimal)	70 (53)	111 (83)	Ref category	<0.001*
≥95% (Good)				

Table 4 is the summary of significant associations that were tested with multivariate analysis. The variables CD4 count (at LTFU), viral load, past TB, ART drug regimen and adherence which were found to be significantly associated with LTFU in the bivariate analysis were analyzed to determine if they remained independently associated with LTFU.

Virological failure was found to be an independent predictor of LTFU on ART amongst adolescents with an adjusted OR=4.97 (2.63-9.39) P<0.001. Suboptimal adherence was also found to be an independent predictor of LTFU in multivariate analysis, adjusted OR=3.74(2.00-7.01) P<0.001

Past TB history, CD4 count (at LTFU) and ART drug regimen were not found to be predictors of LTFU in the multivariate analysis.

Table 4: Clinical variables and their independent associations with ART LTFU (Multivariate analysis) (n=133)

VARIABLES	LTFU N (%)	Not LTFU N (%)	Crude odds ratio (95% CI) P-value	Adjusted odds ratio(95% CI) P-value
CD4 (LTFU)				
<350cell/ml	50 (38)	19 (14)	**3.61(1.98-6.57)**	1.56 (0.76-3.20)
≥350cells/ml	83 (62)	114 (86)	Ref category	P=0.2207
				Ref category
VL				
≥1000	81(61)	24 (18)	**7.07(4.03-12.41)**	**4.97 (2.63-9.39)**
copies/ml	52 (39)	109(82)	**P<0.001**	**P<0.001**
<1000			Ref category	Ref category
copies/ml				
TB history				
Present	32 (24)	19 (14)	**1.90(1.01-3.56)**	1.91 (0.93-3.96)
Absent	101(76)	114 (86)	**P=0.045**	P=0.079
			Ref category	Ref category
ART regimen				
PI- based	83 (62)	55 (41)	**2.35(1.43-3.85**)	1.49(0.82-2.68)
NNRTI- based	50 (38)	78 (59)	Ref category	P=0.1827
				Ref category
Adherence				
<95%	63 (47)	22 (17)	**4.54(2.57-8.03)**	**3.74(2.00-7.01)**
(Suboptimal)	70 (53)	111 (83)	**P<0.001**	**P<0.001**
≥95% (Good)			Ref category	Ref category

Results summary

The study results in the bivariate analysis showed that low CD4 (<350cell/mm^3) at LFTU, detectable VL (of >1000), past history of Tuberculosis, PI-based ART regimen and suboptimal adherence (<95%) were significantly associated with LTFU. However in multivariate analysis only detectable viral load and suboptimal adherence were found to be independent predictors of LTFU. Middle and older adolescent patients who were LTFU were about 5 times as likely to have a detectable VL and almost 4 times more likely to have suboptimal adherence than those not LTFU.

In the next chapter the findings in this study will be discussed and compared with existing literature on the subject on LTFU on ART amongst the adolescents living with HIV. The discussion will focus on similar studies done in sub-Saharan Africa where the HIV epidemic is comparable to Botswana.

CHAPTER 5: DISCUSSION

The study is one of the few LTFU studies aimed to investigate the proportion of and factors associated with LTFU amongst middle and late adolescents on ART at Botswana-Baylor clinic to be conducted amongst the adolescent population in the country. This is despite there being evidence that clinical outcomes in this age category are poor. The current LTFU rate amongst adolescents (15-19yrs) at the clinic is reported to be 4.6%. This is considerably lower when compared to the 12%, which was reported in public ART clinics in Botswana amongst all age categories (Farahani, Vable & Lebelonyane, 2013). The possible explanation for this difference is that a multi-disciplinary team, which has doctors, trained nurses, a psychologist and social workers providing intensive adherence assessments and support at this particular clinic. This is supported by evidence by Ojikutu, Higgins-Biddle, Greeson and Phelps (2014), which showed that clinics providing adherence counseling and adherence measurements had low LTFU rates. In addition the clinic has a Teen Club, whereby teenagers living with HIV meet once every month and discuss topics such as medication adherence, stigma, disclosure, sexual and reproductive health and human rights. These services are not readily accessible in public sector clinics in Botswana. The clinic is also a site where there are significant research activities; hence the patients are exposed to regular adherence information.

The majority of those LTFU (74%) and those not LTFU (69%) had advanced HIV disease (WHO III/IV) at ART initiation. This was also found in a study done in Ethiopia (76%), although it was amongst adult clients (Dessalegn, Tsadik & Lemma, 2015). This is in contrast to an analysis of program data from sub-Saharan countries which showed that at ART initiation 42% and 23% of patients had advanced HIV disease in 2006 and 2011 respectively (Lahuerta, Wu & Hoffman, 2014). It is however important to note that the majority of the sample population in this study commenced ART in childhood, when HIV is associated with rapid progression and advanced disease. An analysis done in 4 sub-Saharan countries had comparable findings to this study, whereby the proportion of children with WHO stage III/IV at ART initiation was 75% and 62% for 2005 and 2010 respectively (Davies, Phiri, Wood & Wellington, 2013).

In this study after bivariate analysis, CD4<350cell/mm^3, detectable VL, past TB history, PI-based regimen and suboptimal adherence where associated with higher risk of LTFU. However

in the multivariate model, only detectable viral load and suboptimal adherence where found to be independently associated with LTFU. Viral load was a strong predictor of LTFU with those with detectable viral load being 5 times likely to be LTFU. This is consistent with available studies looking at VL as a risk factor for LTFU on ART. Ndiaye, Ould-Kasi, Salleron and Bataile (2006) who conducted a case control study in France, found that a patient with a detectable viral load was almost 2 times more likely to be LTFU. The risk was higher with a VL>10 000 copies/ml. Our study did not analyze if different categories of viral loads had an effect on the risk to LTFU. A cohort study conducted in South Africa amongst patients above 14 years old, those with a detectable viral load had a 3 times higher risk of becoming LTFU (Mberi, Dube, Kuonza & Nattey, 2015). Our study shows that adolescents could be at a much higher risk of LTFU if they have a detectable VL, compared to the adult population. It is important to note that after a thorough search, there are few studies in this region which analyze the link between VL and LTFU. This could be due to the fact that most ART programs in sub-Saharan Africa do not use VL measurements for treatment monitoring amongst patients on ART, with only South Africa, Botswana, Namibia and Rwanda having VL available (IAS, 2014).

In this study patients with suboptimal adherence (<95%) were more than 3 times at risk of LTFU after multivariate analysis. This is consistent with a case control study conducted in Ethiopia by Mergeso, Garoma, Eticha and Workineh (2016), who found that adult patients with adherence <95% were 7 times more likely to be LTFU. The association between suboptimal adherence and LTFU was also found in a retrospective observational study conducted in Nigeria (Meloni, Chaplain, Chang & Rawizza, 2015) and another one conducted in Kenya amongst pregnant women (Clayden, 2012). It seems this study amongst an adolescent population is consistent with adult studies on the association between suboptimal adherence and LTFU. Adherence support is therefore critical in improving patient outcomes amongst all patients, including adolescents on ART.

Low CD4 count (at LTFU) has been identified as a predictor of LTFU in most studies. Maskew, MacPhail, Menezes and Rubel (2007) and Makunde, Francis and Kamugisha (2012) found that adult patients who were LTFU had a low median CD4 count, of 92 and 122 cells/μL respectively. This is in contrast with this study, which had the majority (62%) of those LTFU with an absolute CD4 count ≥350 cells/μL. This could be due the physiological difference of

CD4 count amongst children and adults. CD4 counts are generally higher amongst children when compared to adults (Denny, Yogev & Gelman, 1992). In this study the majority were commenced on ART in early childhood when CD4 counts are expected to be higher.

Bivariate findings in this study were inconsistent with a study done in Ethiopia in which Dessalegn, Tsadik and Lemma (2014) found no association between low CD4 count and LTFU in their study done amongst adult clients. However, similarly, there was no relationship after multivariate analysis, hence the results seem similar.

In this study there was no statistically significant independent associations between history of TB disease and LTFU after multivariate analysis (odds ratio=2.03 (0.93-4.41). This is despite an association in the bivariate analysis with 24% of those LTFU having a past history of TB compared to 14% in those not LTFU. In contrast a study done in Ethiopia by Tardesse and Haile (2014) showed statistically significant relationship between TB and LTFU in multivariate analysis. The difference with our study is that we looked at past history of both presumed and confirmed TB cases, whilst the Ethiopian study used proven cases of TB, confirmed by microscopy and so may be more accurate. Tayler-Smith, Zachariah, Manzi and Kizito (2011) and Alvarez-Uria, Naik, Pakam and Midde (2013) also showed increased risk of LTFU amongst HIV positive patients on ART who were diagnosed with TB. However, these studies examined the presence of TB at the time of LTFU, whilst our study used past history of TB disease. Increased risk of LTFU whilst on TB treatment could occur due to the increased pill burden and also side effects associated with concurrent ART and TB drugs. However this could not be investigated in my study.

This study did not find any independent association between LTFU and WHO clinical staging, with the odds ratio being 1.29(0.75-2.21) after multivariate analysis. This contradicts most studies on LTFU. Mergeso, Garoma, Eticha and Workineh (2016) in a study conducted in Ethiopia found that the risk of LTFU was 2-fold if a patient had a stage IV condition compared to Stage 1 in multivariate analysis. Also Saka, Landoh and Patassi (2013) in a Togolese study showed that patients with WHO stage III/IV were almost 2 times at risk of LTFU. A retrospective cohort study conducted in South Africa the risk of LTFU was also 2 times when WHO stage was III/IV compared to stage I/II (Mberi, Dube, Kuonza & Nattey, 2015). However,

Berherto, Haile and Mohammed (2014) found that higher WHO stages III/IV were associated with less risk of LTFU. All of these studies, which found associations between WHO stage and LTFU were adult studies. In our study the great majority of those LTFU and those not LTFU commenced ART in childhood. We found that the greatest proportion of those LTFU (74%) and those not LTFU (69%) both had advanced HIV disease (WHO stage III/IV), so differences in this association may be difficult to discern. This is with agreement with evidence that most children start ART in advanced stages of HIV. A study conducted in Malawi, Swaziland and Lesotho found that 70% of pediatric HIV positive patients had WHO stage III/IV at ART initiation (Kabue, Buck, Wanless & Cox, 2012).

In bivariate analysis there was an association between LTFU and the ART regimen. Adolescents on LPV/r-based regimen were twice as likely to be LTFU compared to those on an NNRTI-based regimen. Anecdotal evidence from the study site shows that adolescent patients complain of intolerance to LPV/r based regimens, in particular the size of the tablets, which could lead to defaulting medication, although this needs further study. However there was no independent significant association between LTFU and ART-regimen after multivariate analysis. No difference was found in LTFU with a parent or non-parent being the caregiver of the adolescent. This is in contrast to a study conducted in South Africa, which showed that the parent being the caregiver was associated with higher risk of LTFU (Sengayi, Dwane, Marinda, Sipambo, Farlie & Moultrie, 2012). However the South African study was amongst children less than 12 years old and may be related to a parent's own health condition and could be explored further.

The main limitation of this study is that the results cannot be extrapolated in other sites in Botswana, in particular public clinics that have a different set up and are solely public sector clinics. Hence this is most likely a 'best case scenario' situation. There may be some missed associations in public sector clinics. It is also important to conduct qualitative research such as focus group discussions and individual interviews at the site in order to determine psychosocial factors associated with LTFU so that counseling sessions can be focused on the particular factors which are identified as related to LTFU in bivariate analysis. In addition, it would be valuable to conduct quantitative studies in commoner public sector clinics.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

This study found that adolescent patients on ART at Baylor Clinic who had suboptimal adherence and detectable viral load were at higher risk of LTFU. Unlike most available studies conducted in sub-Saharan Africa there was no association between LTFU and the CD4 count. However increasingly, detectable viral load is the best marker for use in clinical adherence. The findings in our study will assist clinicians at the study site to identify patients who need extra support to be retained in care and hence improve clinical outcomes. The findings highlight the importance of paying closer attention to particularly middle and late adolescents with adherence challenges in this setting, so that factors leading to poor adherence can be addressed. Similarly among adolescents with a detectable VL, measures such as more regular follow up and intensified adherence counseling sessions should be implemented so as to prevent LTFU. Appropriate adherence information should be provided to all adolescents on ART who are at risk of LTFU at every clinic visit i. e both consultation and pill refill visits. This requires a multi-disciplinary team of doctors, nurses, pharmacists, counselors, peer educators and psychologists.

Adolescent patients who were LTFU had a greater proportion on PI-based regimen (Aluvia), although this was not statistically significant in multivariate analysis. This needs to be further explored with a qualitative study as anecdotal evidence at the site shows that most adolescents complain of intolerance due to the larger size of the tablets. If this is explored and shown to be the case, then other treatment options which are better are tolerated need to be identified so as to improve adherence and retention in care of adolescents on ART.

More studies of this type are needed in solely public sector clinics in Botswana and in this region of the world in where the epidemic is largest, as there is a sizeable population of patients living with HIV in middle and late adolescents in which LTFU appears to be greatest, identifying influencing factors and interventions are needed. My study findings can be used to guide these studies and help uncover further factors influencing LTFU in middle and late adolescents on ART.

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APPENDIX 1

Data collection tool (For operational definitions of variables, see appendix 1a)

Record No.	LFTU (1) or non-LTFU (0)	Age	Sex	Baseline CD4	CD4 prior to LTFU	Viral Load prior to LFTU	WHO Stage	ART Regimen	Prior TB/HIV	Primary Care Giver	Adherence >95%(Yes/No
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
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29											
30											
31											
etc											

Appendix 1a –Operational definitions of variables

Age- recorded as a continuous variable.

Gender- Male or Female

Baseline CD4- CD4 <350 or CD4≥ 350

CD4 at lost to follow- CD4<350 or CD4≥350

Viral load (at lost to follow) – Non-Detectable, VL <1000copies/ml in prior 6 months

- Detectable, at least one VL>1000 in the prior 6 months.

WHO staging - mild stage (stage 1 or 2)

-Advanced stage (stage 3 or 4)

ART regimen – NNRTI-based regimens or Protease Inhibitor (PI) based regimen.

TB/HIV co-infection- Yes or No

Adherence by pill counts- Poor (adherence <95% in the prior year)

- Good (adherence ≥95% in the prior year)

Relationship to primary caregiver- Biological Parents

- Other

Appendix 2

Botswana-Baylor Children's Clinical Centre of Excellence
An Affiliate of Baylor College of Medicine International Pediatric AIDS Initiative at Texas Children's Hospital
Plot: 1836, Hospital Way
(Off Notwane Road)
Private Bag BR129 Gaborone
Tel: (+267) 319-0083
Fax: (+267) 319-0079
Website: www.bipai.org

17 August 2016

University of Western Cape
Higher Degrees Committee
Private Bag X17
Bellville
South Africa

RE: APPROVAL TO CARRY OUT RESEARCH

This serves to inform that Dr John T. Farirai has been granted permission to carry out research at this centre on the topic: "Predictors of Lost to follow up amongst adolescents on anti-retroviral therapy in an urban setting in Botswana." The research proposal meets official rules and regulations governing research at our institution. I am informed that the aforementioned research is part of the Masters of Public Health degree course at your institution.

Should you have further questions, please do not hesitate to contact the undersigned.

Yours sincerely,

Gabriel M Anabwani, MBChB, MMed, MSCE, FRCPE (Edin)
Professor of Paediatrics and Executive Director

BOTSWANA BAYLOR CHILDREN'S CLINICAL CENTRE OF EXCELLENCE
PRINCESS MARINA HOSPITAL
TEL: 3190083
17 AUG 2016
TIME:
SIGNATURE:

UNIVERSITY of the WESTERN CAPE

OFFICE OF THE DIRECTOR: RESEARCH
RESEARCH AND INNOVATION DIVISION

Private Bag X17, Bellville 7535
South Africa
T: +27 21 959 2988/2948
F: +27 21 959 3170
E: research-ethics@uwc.ac.za
www.uwc.ac.za

22 December 2016

Dr J Farirai
School of Public Health
Faculty of Community and Health Science

Ethics Reference Number: BM/16/5/30

Project Title: Predictors of lost to follow up amongst adolescents on antiretroviral therapy in an urban setting in Botswana.

Approval Period: 21 December 2016 – 21 December 2017

I hereby certify that the Biomedical Science Research Ethics Committee of the University of the Western Cape approved the scientific methodology and ethics of the above mentioned research project.

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval. Please remember to submit a progress report in good time for annual renewal.

The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

PROVISIONAL REC NUMBER -130416-050