Assessment of Treatment Outcomes of HIV-Positive Adolescents on a Dolutegravir- based Regimen at a Specialized Paediatric HIV Clinic in Lesotho

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Keywords

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Acronyms and abbreviations

ALHIV	Adolescents living with HIV
ART	Antiretroviral Therapy
BCMCF	Baylor College of Medicine Children's Foundation
DTG	Dolutegravir
HAART	Highly active antiretroviral therapy
NNRTIs	Non-nucleoside reverse transcriptase inhibitors
PIs	Protease Inhibitors
PLHIV	People Living With HIV
VL	Viral Load
VLS	Viral Load suppression

Definition of terms

Adolescent refers to a person between the ages of 10 – 19 years old (WHO, 2013b).

Retention in care refers to patients on antiretroviral therapy (ART) who are alive and continue to attend ART services at a health center as scheduled or have been officially transferred out to another health center for ART services and are assumed to still be on ART (Massaquoi et al., 2009; WHO, 2013b).

Viral load suppression is defined as a viral load below 1000 copies of HIV-1 RNA per mL, measured after at least 6 months on ART (Ministry of Health, 2016).

ABSTRACT

Background: Globally, adolescents on antiretroviral therapy (ART) have comparatively worse treatment outcomes (i.e., low viral load suppression rates) compared to adults and children. Lesotho introduced Dolutegravir (DTG), to replace Efavirenz, as a more potent first line and second-line drug regimen for ART in 2018. However, no study has been conducted to date to assess the effectiveness of this change in regimen on treatment outcomes of adolescents on ART in Lesotho.

Aim: The current study described viral suppression of adolescents and its concomitant risk factors upon switching to DTG based ART regimen at a specialized pediatric HIV clinic in Lesotho.

Methodology: A retrospective quantitative cohort analysis of adolescents (15-19 years) initiated on a Dolutegravir-based ART regimen from November 2019 to November 2021 (N=559) at a specialized pediatric HIV clinic in Lesotho was done. The Statistical Package for Social Scientists (SPSS) Version 28 was used to determine the factors associated with viral suppression through bivariate and logistic regression analyses.

Results: The analysis included 559 adolescents who transitioned to a Dolutegravir-based regimen. Majority of adolescents were on ART for more than 9 years (59.1%; n = 327). More than half of the adolescents were females (54.2%; n=303). Viral load suppression (VLS) (<1000 copies/mL) was 87.8% before initiation on Dolutegravir and increased to 91% at 6 months after being initiated on DTG. The bivariate analysis showed that duration on DTG was significantly associated with VLS (p=0.01). In multivariate logistic regression, the odds of having full viral suppression were eight and four times higher among adolescents who were on DTG for a year or two years, respectively, compared to those who were on DTG for less than one year (adjusted odds ratio (AOR): 8.0, 95% confidence interval (CI): 1.64 - 39.06; AOR: 4.4, 95% CI: 0.85 - 23.41).

Conclusion: Our findings indicate that 91% of adolescents living with HIV in Lesotho achieved viral suppression within 6 months of being placed on a DTG based regimen; thus, supporting the switch to DTG for adolescents on ART, to ensure that UNAIDS target of 90% viral suppression is reached for this key population.

Declaration

I declare that *"The Assessment of Treatment Outcomes of HIV Positive Adolescents on Dolutegravir Based Regimen at a Specialized Pediatric HIV Clinic in Lesotho"* is my work, hasnot been submitted for any degree or examination at any other university, and that all the sources I have used have been indicated in the text and acknowledged in the References section.

Full Name: Motlatsi Letsika

Date: 03 August 2023

Signature: 

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CHAPTER 1: INTRODUCTION

1.1 Background

Globally, it is estimated that 37.6 million people were living with HIV (PLHIV) as of 2020, of which 2.8 million are children and adolescents (0-19 years) (UNAIDS, 2021). Nine in 10 children and adolescents (0-19 years) living with HIV reside in sub-Saharan Africa (UNICEF, 2020). Worldwide, there were 1.7 million adolescents aged 10-19 years living with HIV in 2019 (UNICEF, 2020). Although some countries are making significant strides towards achieving UNAIDS targets of 90-90-90 – that is, 90% of PLHIV know their HIV status, 90% of PLHIV on antiretroviral therapy (ART) and 90% of those on ART are virally suppressed) - the last target (90% viral load suppression (VLS) rate) remains elusive. In 2019 VLS among adults in Lesothowas 88% (Lesotho Population-Based HIV Impact Assessment (LePHIA), 2019), falling short of the UNAIDS target.

Globally, one-third of new HIV infections in 2015 occurred in adolescents and young adults aged between 15 and 24 years (Marcus et al., 2017), and 40% of these were adolescents aged 15 to 19 years. In sub-Saharan Africa, where about 82% of adolescents living with HIV (ALHIV) globally live, adherence levels are suboptimal, which in turn translates to poor treatment outcomes in this key population (Ammon, Mason and Corkery, 2018). VLS for ALHIV remains worse compared to adults living with HIV. In Namibia, for example, overall VLS was 87% at the end of 2016, with the highest percentage (90%) in people older than 20 years and lowest (68%) among adolescents 15 to 19 years old (Agolory et al., 2018).

Lesotho has the second-highest HIV prevalence globally, with 25.6% in the adult population in 2017, and an annual incidence of 1.1% corresponding to 10,000 new HIV cases per year (LePHIA, 2019). Adolescent girls and young women (15-24 years) and men (35-49 years) reported the highest incidences of 1.49% and 2.65% respectively. Lesotho has also adopted the UNAIDS 90-90-90 strategies to end the AIDS pandemic by the year 2020 - with targets of 90% of HIV-positive people knowing their HIV status, 90% of them on ART and 90% of those on ART virally suppressed (UNAIDS, 2014). In 2019 Lesotho reported that 81% of people living with HIV (PLWH) were aware of their positive HIV status; 91.8% of them were on HIV treatment and 87.7% of those on treatment achieved viral load suppression (VLS) (Lesotho Population Based HIV Impact Assessment, 2019). In the same year, Lesotho reported that the HIV prevalence in older adolescents (15-19 years) in Lesotho was 4.2%, with testing rates, treatment coverage and VLS of 72%, 54.8% and 50.1%, respectively (LePHIA, 2019). This

indicates a need for targeted interventions for ALHIV. This follows the global trend that adolescents on ART tend to have lower rates of VLS compared to adults (Chhim et al., 2018). The HIV impact assessment survey conducted in seven countries in Eastern and Southern Africa, including Lesotho, from 2015 to 2017 shows a 45% viral suppression rate among adolescent girls and young women (Rown et al., 2018). A study in South Africa on HIV care cascade for adolescents initiated on ART concluded that VLS remained low (47%) for ART-initiated adolescents (Haghighat et al., 2021).

The low levels of VLS amongst adolescents in Lesotho indicate possible sub-optimal adherence and retention challenges in this key population. Various interventions such as the teen club initiative, multi-month dispensing of ART and differentiated service delivery (DSD)have been implemented to improve VLS (Lejone et al., 2020). In other low and middle-income countries in sub-Saharan Africa, interventions that have shown promising results for adolescents include task shifting, community-based adherence support, use of mHealth (digital) platforms and group adherence counseling (Murray et al., 2017).

1.2 Introduction of Dolutegravir in Lesotho

Lesotho was the first country in sub-Saharan Africa to adopt World Health Organization (WHO) recommended 'Treat All' policy through the implementation of a test and treat strategythat removes CD4 count as a requirement to start ART in 2016 (Government of Lesotho, 2019).In 2018, Lesotho updated the National ART guidelines to include more potent first line and second-line drug, namely dolutegravir (DTG) to replace Efavirenz (EFV). The new guidelinesprioritize adolescents to be transitioned into DTG based regimens to improve treatment outcomes, mainly VLS. Criteria for switching to DTG included that all adolescents and adults withbody weight of 35kg and above who were newly diagnosed with HIV be initiated on DTG basedregimen, those already on ART for at least 6 months duration and above with undetectable VL weretransitioned to DTG. In case of detectable VL but lower than 1000 copies/mL, enhanced adherence counselling was initiated to address any adherence barriers. DTG was shown to be more effectivewith higher VLS rates and a lower risk of treatment discontinuation as compared to other drugs(Government of Lesotho, 2019). Dolutegravir is safe and effective for ALHIV (Briand et al., 2016). A study in Uganda assessing acceptability and VLS of patients on DTG-based regimensfound high acceptability in treatment-experienced and new patients, and higher VLS (94%) after 6 months of treatment (Nabitaka et al., 2020). In another study (DoLPHIN-2), it was found thatpatients on DTG suppressed viral load much faster than those who were on EFV-based (Kintu et al., 2020).

1.3 Problem Statement

Many countries - including Lesotho – routinely report HIV treatment outcomes for older adolescents (15-19 years) as part of adults, and young adolescents (10-14 years) as children due to delineated adult and pediatric HIV programs (Lesotho Population Based HIV Impact Assessment, 2019). Thus, monitoring of treatment outcomes for adolescents is not routinely done or reported. There is a paucity of studies assessing treatment outcomes such as retention in care and VLS in adolescents because most studies are done with adults only and adolescents 15 to 19 years are included in the adult population while those 10 to 14 years are classified with the pediatric population (Ferrand et al., 2016; Murray et al., 2017). It is conceived hat little has been done to assess the treatment outcomes of adolescents on ART in Lesotho. Furthermore, the use of DTG as a first and second-line drug regimen in adult HIV populations has been introduced in 2018,but its efficacy has not been assessed in Lesotho. It is, thus, essential to analyze routine healthdata to determine the rates of and the factors associated with VLS in adolescents on DTG-based ART regimens.

1.4 Study Aim and Objectives

The aim of the study was to assess the treatment outcomes of older adolescents since being initiated on a Dolutegravir-based ART regimen in a specialized pediatric HIV clinic in Lesotho.

The objectives of the study were:

- To describe the socio-demographic and clinical profile of adolescents (aged 15-19 years) on DTG-based ART regimen.
- To compare VLS between treatment naïve adolescents and treatment-experienced adolescents initiated on DTG based regimen.
- To describe retention in care for adolescents on DTG-based regimen and
- To determine factors associated with VLS in adolescents initiated on DTG-based regimen.

1.5 Outline of Thesis

Chapter 2 explores the literature on factors associated with viral suppression among adolescents globally, in the sub-Saharan and African region, and in Lesotho.

Chapter 3 describes the methodology of the study. The methodology outlines the study design,

the study's settings, the study population, sampling method used, the data collection method, and data analysis. This section explains the strategies that are implemented in the study to improve the validity and reliability of the results. The last section of this chapter is a summary of ethical considerations.

Chapter 4 presents the results from the descriptive and inferential analyses.

Chapter 5 presents a discussion of the study's results in relation to the existing literature.

Chapter 6 presents the conclusions based on the study results and provides recommendations drawn from research findings and study limitations.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

Viral suppression is a significant indicator of treatment success in ART programs, and has been associated with decreases in morbidity, mortality and HIV transmission (Maena et al., 2021). In this review, we define viral load suppression (VLS) and how it is measured and routinely monitored. We also review the literature on the determinants of VLS, retention and adherence among adolescents on ART.

2.2 Definitions

2.2.1 Viral Load

VL refers to the concentration of HIV-1 RNA in the plasma. It is measured as copies per milliliter (mL) of blood (Mellors et al., 1997). This measurement reliably predicts the rate of disease progression and decline in immunity status; the higher the concentration, the more immunity destruction and the faster the progression of the disease (Saag et al., 1996). VL below 50 copies/mL is referred to as undetectable and indicates no disease progression. Any VL above 50 copies of HIV-1 RNA /mL is referred to as unsuppressed and indicates active replication of HIV (Eisinger, Dieffenbach and Fauci, 2019; Lesko et al., 2020; Lesotho Ministry of Health, 2022).

2.2.2 Viral Load Suppression

VLS is defined by WHO as VL below 1000 copies of HIV-1 RNA /mL (World Health Organization (WHO), 2016). However, countries use different thresholds for VLS suppression. In a systematic review and meta-analysis by Kim et al. (2014), it was found that out of 53 countries, most countries used less than 400 copies/mL as a threshold for VLS. Nonetheless, there are other different definitions for VLS that use even lower thresholds such as less than 200, 50 or 20 copies/mL (Lesko et al., 2020).

In Lesotho VLS is defined as VL less than 1000 copies/mL. Any VL count that is 1000 copies/mL and above is defined as non-suppressed and requires interventions to address possible causes (Ministry of Health, 2016). VL above 1000 should trigger implementation of early interventions to reduce chances of developing resistance because of sustained low levels of viremia that increases risk of resistance.

2.2.3 Viral Load Monitoring

Viral load monitoring is recommended to determine the effectiveness of ART (WHO, 2016). Lesotho National ART guidelines recommend that viral load monitoring be performed 6 months after ART initiation for everyone on ART, and once every year thereafter (Ministry of Health, 2016). For children, regular monitoring every six months is recommended so that timely interventions may be initiated once VL is found to be unsuppressed. If VL is equal to or greater than 1000 copies/mL, enhanced adherence counselling is initiated, aimed at addressing possible causes of unsuppressed VL, and repeat VL testing will be done after three months. If VL is suppressed, the patient continues the same regimen but if unsuppressed, switching to the effective second line is recommended. Resistance testing before switching to the second line is recommended in patients who were on a protease inhibitor (PI), or integrase strand transfer inhibitor (INSTI) based regimen (Government of Lesotho, 2019). VL monitoring has led to the identification of different factors that are associated with VLS and these are discussed below.

2.3 Factors Associated with Viral Load Suppression

The factors that have been associated with VLS are categorized as socio-demographic, clinical, treatment and behavioral factors (Desta et al., 2020; Diress et al., 2020). I will discuss each of these categories in turn.

2.3.1 Socio-demographic Factors

The socio-demographic factors are variables that include gender, age, sexual orientation, race, marital status, educational level, employment status and household income that can affect individual response or behavior toward treatment or intervention (Haider et al., 2021). The most common socio-demographic factors that are associated with VLS among ALHIV are (current) age, age at ART initiation, gender and level of education.

2.3.1.1 Age

Several studies report higher VLS rates among younger adolescents (aged 10-14 years) on ART when compared to older adolescents (15-19 years) (Amzel et al., 2018; Chhim et al., 2018; Fokam et al., 2019; Van Wyk, Kriel and Mukumbang, 2020). Haghighat et al. (2021) argue that younger adolescents are more likely to receive social and parental support to take their medications which improves adherence to ART and thus leads to better treatment outcomes. In one study in the United States of America, it was concluded that VL non-suppression increased with age during adolescence (Kacanek et al., 2019). Several authors have observed in their studies that older adolescents struggle with several issues such as identity crises and transitioning into adulthood, physiological and psychological changes, self-management of their chronic condition, and decreasing parental or caregiver support in taking ART, which negatively impacts adherence to ART and VLS (Marcus et al., 2017; Van Wyk, Kriel and Mukumbang, 2020).

2.3.1.2 Age at ART Initiation

Perinatally infected adolescents who have been on ART for a longer duration are more vulnerable to developing drug resistance which results in unsuppressed VL (Kibalama Ssemambo et al., 2021). Adolescents who were initiated on ART when they were still very young may not have a strong motive to continue ART when they grow older as they are unlikely to experience illness associated with their HIV positive status (Marcus et al., 2017). Adolescents who delayed ART initiation or had late HIV diagnosis often have experienced HIV associated illness (Van Wyk et al., 2020). The latter may have a motive to adhere to ART after experiencing that their health improved on ART. In a study in South Africa, viral non suppression was associated with initiating ART at age of less than 15 years (Joseph Davey et al., 2018). More studies need to be done to determine how the age of ART initiation affects VLS across various settings.

2.3.1.3 Gender

Different studies show conflicting results on the relationship between gender and VLS. Studies in South Africa and the United States of America reported higher VLS for adolescent males compared to females (Mave et al., 2011; Van Wyk et al., 2020). In contrast, there is evidence from various settings that women have higher VLS compared to men. A study among PLHIV in South Carolina, USA, has shown that being male was associated with lower VLS as

compared to being female (Haider et al., 2021). Similar findings were reported in studies conducted in Cameroon, Ethiopia, Kenya and South Africa, where high VLS among females as compared to male counterparts were observed (Joseph Davey et al., 2018; Fokam et al., 2019; Desta et al., 2020; Diress et al., 2020; Njuguna et al., 2020).

There are also several studies in South Africa, Lesotho and Uganda that show no association between VLS and gender (Zanoni et al., 2017; Lesotho Population Based HIV Impact Assessment, 2019; Wakooko, Gavamukulya and Wandabwa, 2020; Brown et al., 2022). There are various hypotheses that have been put forward to explain gender differences including pharmacokinetics and behavioural differences (Njuguna et al., 2020). Thus, gender remains a factor that needs to be investigated in each specific context to determine its association with VL in ALHIV, and to differentiate risk levels based on gender.

2.3.1.4 Level of Education

Education has been reported as a predictor of VLS among PLHIV in South Africa, Ethiopia and Uganda (Dessie et al., 2020; Diress et al., 2020; Maena et al., 2021). However, there are limited studies examining the association between level of education and VLS in adolescents. The authors argue that no or lower education level is associated with low VLS because literate adolescents tend to have a better understanding of why they are taking medications and are thus more likely to adhere to treatment. It is also found that data on education level is poorly collected in routine health information.

2.3.2 Clinical Factors

Clinical factors refer to physiological attributes which, at a certain level, may positively or negatively affect an outcome of a disease (Scottish Public Health observatory, 2022). Several studies found that clinical factors such as WHO clinical stage at baseline, baseline and current CD4 count, pregnancy status and opportunistic infections (such as TB) were often associated with VLS in adolescents on ART.

2.3.2.1 WHO Clinical Stage

WHO clinical staging is a case definition system for HIV surveillance developed by WHO (Weinberg & Kovarik, 2010) to assist healthcare providers in making treatment decisions based on patient clinical presentation. WHO staging has four stages ranging from Stage 1 (mild

disease) to Stage 4 (severe disease). In the absence of ART initiation, an increase in VL correlates with the advance in disease severity from WHO Stage 1 to Stage 4 (Saag et al., 1996). PLHIV who started ART in Stages 3 and 4 are three times more likely to have virological failure than those who start in Stages 1 and 2 (Sithole et al., 2018). Similar results were documented in two other studies in Uganda where WHO Stages 2 and 4 were significantly associated with VL non-suppression (Maena et al., 2021; Nabukeera et al., 2021). However, VL improves over time after consistent use of ART. Van Wyk et al. (2020) found that after 24 months on ART, adolescents on WHO Stages 2, 3 and 4 were more likely to have VLS, and argued that illness motivated them to adhere to ART and achieve viral suppression.

2.3.2.2 CD4 Count

CD4 count is used to indicate the extent of immune suppression in HIV-positive individuals (Weinberg & Kovarik, 2010). There are different cut-offs for CD4 count to indicate the level of immunity in an HIV-infected individual. For example, a CD4 count below 200 cells/mm^3, 350 – 500 cells/mm^3, and above 500 cells/mm^3 indicate severe, moderate and mild immunosuppression, respectively (World Health Organization, 2013). Many studies have shown that the CD4 countin HIV-infected people plays an important role in predicting the treatment outcomes after ARTinitiation.

A study in Harare found that adolescents who start ART with baseline CD4 count below 350 cells/mm^3 are five times more likely to have an unsuppressed VL compared to those with CD4 count greater than 350 cells/mm^3 (Sithole et al., 2018). Studies in Rwanda (Ross et al., 2020), SouthAfrica (Okonji et al., 2021) and Switzerland (Phillips et al., 2001) have shown that baseline CD4 count of 200 cells/mm^3 or below is associated with low VLS.

Furthermore, studies in Kenya and Cambodia found that the likelihood of having low VLS remained significantly low among adolescents who had current CD4 count above 500 cells/mm^3 (Chhim et al., 2018; Mwangi & van Wyk, 2021). This suggests that adolescents who start ART early when CD4 count has not significantly dropped have a better chance of suppressing VL.

2.3.2.3 Pregnancy Status

Prevention of mother-to-child (PMTCT) programs aim to prevent HIV transmission by initiating ART early as soon as pregnancy starts to achieve full viral suppression throughout pregnancy and post-natally. Several factors associated with low VLS during pregnancy include

delay in starting ART, poor adherence, new HIV diagnosis during pregnancy and highVL prior pregnancy (Chagomerana et al., 2018; Denoeud-Ndam et al., 2013). Initiating ART early at the time of HIV diagnosis is important in reducing mother-to-child transmission of HIV. In South Africa it has been found that the prevalence of VLS was high (71%) among pregnant women who started ART before pregnancy as compared to those who started during pregnancy (67.6%) (Woldesenbet et al., 2020). Another study reports that women with unintended pregnancies are more likely to have detectable VL compared to those with planned pregnancies (Brittain et al., 2019). This may be due to poor health seeking behaviors that lead to delays in HIV testing and ART initiation.

2.3.2.4 Opportunistic Infections

Opportunistic infections are diseases that are associated with advanced immune suppression caused by a particular disease or age (Lesotho Ministry of Health, 2022). The initiation of effective ART is expected to improve one's immune system and sustain it at an optimal level to enable the body to fight any infections (Wilson & Sereti, 2013). Incidences of opportunistic infections among HIV-positive patients during ART are associated with an elevation in the viral load (Ekwaru et al., 2013). A high VL of more than 7000 copies/mL is associated with an increased risk of opportunistic infections (Gautam et al., 2009; Kaplan et al., 2001). Tuberculosis (TB) is one of the common opportunistic infections among people living with HIV (WHO, 2013a) and its occurrence indicates advanced immune destruction by HIV. Studies have shown that TB incidences are more common in patients with virologic failure (Bulage et al., 2017; Fenner et al., 2017). For example, one study in Ethiopia found high TB incidences among HIV-positive individuals and a sustained high VL in the post TB treatment (Wolday et al., 2003).

2.3.3 Treatment Factors

Treatment factors can be defined as factors that have a direct effect on the VL due to duration, combination of ART, previous exposure to the treatment, dosing and formulation of drugs used as treatment. The most frequent treatment factors that are associated with VLS to all PLHIV include ART regimen, duration on ART and ART exposure.

2.3.3.1 ART Regimen

The main objective of all antiretroviral (ARV) medication is to suppress VL to stop further HIV transmission and improve the quality of life of PLHIV (Eisinger, Dieffenbach and Fauci,2019). However, different ages and co-morbidities may influence the choice of ART regimen resulting in PLHV being initiated on different ART regimens (WHO, 2016). Many studies have documented that different ARVs have different efficacy in suppressing HIV. Consequently, some regimens are more efficient and superior to others. For example, Efavirenz (EFV) based regimen has shown superiority in suppressing VL when compared with the nevirapine (NVP) based regimen or Lopinavir/ritonavir (LPV/r) based regimen (Chouraya et al., 2019; Fokam et al., 2019; Njuguna et al., 2020). Dolutegravir, a new ARV drug, has been recommended for use because of its high potency, tolerability and superiority over older ARV drugs when used by both treatment-experienced and naïve PLHIV (Bruzzese, Lo Vecchio, et al., 2018; Osterholzer & Goldman, 2014a; Walmsley et al., 2013).

A study in Uganda has shown that a combination of ART regimen that involves taking more than one tablet is associated with 79% lower VLS compared to those taking only one tablet (Brown, Malagala and Bajunirwe, 2021). This indicates that simpler ART regimens are more effective in suppressing VL among PLHIV.

2.3.3.2 Duration on ART

Duration on ART is an important risk factor for VLS. VLS is expected after at least three months of ART initiation (Ali & Yirtaw, 2019; Government of Lesotho, 2019). Two studies in South Africa have reported that VLS was higher in adolescents who have been on ART for more than 2 years and 9 years respectively (Chhim et al., 2018; Haghighat et al., 2021). Consistent use of ART aims to maintain HIV suppressed to prevent new HIV transmission (Eisinger, Dieffenbach and Fauci, 2019). For example, a study in Malawi found that VLS was high among women who have been on ART for more than 12 weeks (Chagomerana et al., 2018).

However, some studies have found that a longer duration of ART of more than 24 months is associated with VL non-suppression in adolescents (Njuguna et al., 2020; Van Wyk, Kriel and Mukumbang, 2020). This may be due to treatment fatigue, which can lead to non-adherence and drug resistance over time (Maena et al., 2021b). A longer duration on ART may also result

in the build-up drug resistance overtime, which will result in an increase in VL. (Sithole et al., 2018).

2.3.4 Behavioural Factors

Behavioural factors that influence VLS include adherence to ART, retention in care and substance abuse, and they are discussed below.

2.3.4.1 Adherence

The effectiveness of ART in suppressing VL is highly dependent on good adherence to ART across all age groups (Mwangi & van Wyk, 2021; Nachega et al., 2009). Good adherence to ART is defined as taking 95% to 105% of ART medication as prescribed (Lesotho Ministry of Health, 2022). Nachega et al. (2009) argue that in Southern Africa, adolescents are less adherent to ART as compared to adults; as a result, they have lower rates of viral suppression. Adherence and VLS remain major challenges to adolescents on ART in low- and middle- income countries (LMICs). The existing interventions to address adherence challenges show inconsistent results in improving treatment outcomes (Reif et al., 2020).

Interestingly some studies have shown that VLS may be achieved at a lower adherence level, below 95%, due to the high potency of some medications (Bangsberg, 2006; Kristofich et al., 2021b). The authors of these studies have found that Non-Nuclease Reverse Transcriptase Inhibitors (NNRTIs) were more likely to suppress VL at <95% compared to Protease inhibitors (PIs). However, those with more than 95% adherence achieve higher VLS and are at lower risk of developing drug resistance (Bangsberg, 2006; Nachega et al., 2009).

2.3.4.2 Retention in Care

People living with HIV need to be *retained in care* to receive lifelong treatment and monitoring so that timely diagnosis of treatment failure and switch to alternative regimens can be made (Ramachandran et al., 2020). Retention in care is defined as people who are not registered as diseased or lost to follow-up but are known to be alive and continue to visit the clinic as appointed (WHO, 2013). Patients who are retained in care are more likely to achieve viral suppression compared to those with non-regular care (Crawford and Thornton, 2017).

In Lesotho, the highest retention in care at 12 months of follow-up was reported among adolescents aged 10 to 14 years and was lowest in the older age band above 15 years (Amzel et al., 2018) Similar results were reported in Namibia, where at 24 months retention in care for younger adolescents was 94% while in adolescents aged 15 to 19 years was 86% (Munyayi & van Wyk, 2020). Munyai and van Wyk (2020) further found that adolescents who were in their first-line ART and had disclosed their HIV status were more likely to be retained in care. In adolescents, being retained in care is associated with higher VLS rates. In a study conducted in South Africa, it was found that adolescents who were retained in care had higher VLS, 86%, 79.3% 68.8% at 4, 12 and 24 months respectively, when compared to 59.5%, 40% and 25% at 4, 12 and 24 months respectively of all adolescents (Van Wyk et al., 2020).

2.3.4.3 Substance Abuse

Substance abuse has a negative impact on VLS and other HIV care cascades (Palepu et al., 2004) In a study conducted in South Africa on mental health and substance abuse in adolescents receiving ART, it was found that adolescents who screened positive for substance abuse, or any other mental disorders, had an unsuppressed viral load (Haas et al., 2020). In a systematic review on the impact of alcohol and related disorders on the HIV cascade, 77% of the reviewed studies documented a negative association with more than one stage of the HIV cascade including VLS (Palepu et al., 2004; Vagenas et al., 2019).

2.4 Summary

There is limited research on factors that affect VLS in adolescents in Southern Africa. The most important behavioral factors that are associated with VLS are *adherence* and *retention in care*. However, adherence data is often not robustly collected, and clinical characteristics such as baseline CD4, baseline WHO staging, pregnancy status and TB are routinely collected in most countries and form an important part of the analysis of the effectiveness of ART. Socio-demographic characteristics such as current age, age at ART initiation, gender and level of education of ALHIV on ART are important as these indicate which adolescent groups have a greater risk profile in a particular setting. Health services factors can play a significant role in treatment outcomes in ART, but these are not robustly collected and are often omitted from analyses. New improved regimens are regularly introduced as HIV treatment options based on the evidence from clinical trials. However, the effectiveness of these regimens needs to be monitored, especially in ALHIV in pragmatic (real-world) health service conditions.

CHAPTER 3: METHODOLOGY

3.1 Study Design

A retrospective quantitative cohort study design was used to analyze treatment outcomes of adolescents aged 15-19 who were initiated on or transitioned to a DTG-based ART regimen from November 2019 to November 2021 in a specialized pediatric HIV clinic in Lesotho. This was a period at which adolescents who were transitioned or initiated on DTG from August 2018 will have at least had their VL drawn and subsequent routine VL available for analysis of their response overtime while on the DTG based regimen. A cohort design studies a group of people without the outcome of interest and establishes a temporal relationship between exposure and treatment outcome (Detels, 2004). A cohort studyallowed the researcher to measure more than one outcome. In this study, the dependent (primary outcome) variables, VLS and retention in care, were measured from a single exposureto DTG-based ART regimen (Acheson and Luesley, 2014). The further benefit of a cohort study design is that independent variables (socio-demographic, clinical, behavioral and treatment factors) that have been routinely collected and stored in the EMRx as patients are followed up can be analyzed.

3.2 Study Setting

The study took place at Baylor College of Medicine Children's Foundation (BCMCF). BCMCF is a specialized pediatric HIV clinic and runs other five specialized pediatric HIV clinics in five districts. BCMCF provides ART care to children, adolescents and their caregivers. As of June 2021, BCMCF had 4663 patients enrolled in all its sites of which 50% (2319) were adolescents 10-19 years old. BCMCF clinicians are local experts in pediatric ART care and often consult the most complicated patients receiving care in other health facilities. BCMCF supports other public primary health care facilities in Lesotho, in low and highlands districts, through mentorship and didactic training. All BCMCF clinics provide HIV care and ART services for the pediatric, adolescent, and adult populations. BCMCF clinics offer comprehensive adolescent care and are optimally staffed with pediatric doctors, medical doctors, nurses, social workers, professional counsellors, psychologists and pharmacists. BCMCF clinic in Maseru, the capital city of Lesotho, is the main clinic and has enrolled over half of all adolescents aged 15 to19 years.

3.3 Study Population and Sampling

The study population constituted HIV positive adolescents who fulfilled the following inclusion criteria:

Between 15 and 19 years at the time of the study;

- On DTG based ART regimen between November 2019 and November 2021;
- On DTG based regimen for at least three months;
- Received ART at a specialized pediatric HIV clinic in Lesotho;
- Had routine VL data captured and recorded between November 2019 and November 2021.

The adolescents were excluded if

- They were transferred out of specialized pediatric HIV clinics;
- They have been hospitalized for any condition during the period of study;
- The adolescents were discontinued from treatment due to severe illness or side effects during the study period.

The Baylor College of Medicine Children's Foundation is a specialized pediatric HIV clinic and had 1,369 adolescents aged 15-19 years enrolled on ART as of 2021. The minimum sample size for the study was calculated as **300,** using Epi Info version 7.2.2.6 (StatCalc), with the following parameters:

- Prevalence of VLS set as 50.1% (Lesotho Population Based HIV Impact Assessment, 2019),
- Margin of error of 0.05 and
- 95% level of the confidence.

However, the study made use of an inclusive sample, where all adolescents who met the inclusion criteria were included in the analysis (Acheson and Luesley, 2014). This was also possible because the data was already collected in the EMRx as part of the routine monitoring of HIV patients on ART in a specialized pediatric HIV clinic. The use of the largest possible sample ensures that the study had sufficient statistical power for conducting multivariate analysis and sensitivity to test VLS in numerous strata of interest.

3.4 Data Collection

The data for this study was extracted from EMRx using MySQL software. The EMRx is a health information system that the foundation uses as a reporting system for all health

programs. Healthcare workers at the specialized pediatric HIV clinics capture patients' socio-demographic and clinical information into the EMRx. EMRx allows data to be disaggregated by district to help identify specific sites that need support in improving certain indicators. The data was extracted into a Microsoft Excel spread sheet. Once the data extraction was completed, it was cleaned and then imported into SPSS v28 for analysis. The collected data included gender, age at ART start, age at DTG start, date of DTG start, last VL before DTG start, 6 monthly VL after DTG initiation, Last CD4 count before DTG start, last regimen before DTG start, current WHO stage, baseline DTG regimen, current DTG based regimen, adherence and retention on treatment. The CD4 count that was collected in this study was any available CD4 before DTG was initiated. The WHO stage was the current WHO stage at the time of data collection. The social and behavioral information was not routinely collected and updated in the EMRx and therefore it was not extracted.

VL and retention in care were the primary outcome variables. Each individual VL reading indicated treatment effectiveness and suppression of HIV. A VL of less than 50 copies/mL was categorized as fully suppressed (undetectable); VL between 50 and 999 copies/mL was categorized as suppressed (detectable), and any VL of 1000 copies/mL and above was categorized as unsuppressed (Ministry of Health, 2016).

Exposure variables that were extracted from the routine data were socio-demographic factors such as (current) age, age at ART initiation and gender; clinical factors such as WHO staging, and CD4 count; treatment factors such as ART regimen, duration of ART and previous ART regiment; and behavioural factors such as (self-reported) adherence and retention in care at 24 months. Adherence was calculated as percentage of pills taken over a 30-day period since date of last ART refill. Good adherence was categorized as 95-100%, fair adherence was between 86 and 94% and any adherence below 85% was considered poor.

3.5 Data Analysis

The EMR was used to identify all adolescents who were initiated or transitioned to DTG-based ART regimen between November 2019 and November 2021. Those who met the inclusion criteria were extracted using MySQL and exported into Micro soft excel. The data was then cleaned coded and exported into SPSS v28 for analysis. Descriptive frequency tables were created for categorical variables to show the number of adolescents in each category. Proportions, using percentages, were calculated. The mean with standard deviation, median with

interquartile range, and mode were calculated to summarize continuous variables. Primary outcomes (viral load suppression) and retention in care were described at 6, 12, 18 and 24 months on ART.

The bivariate analysis was done to determine the statistical significance of associations between viral load suppression (at 6, 12, 18 and 24 months) and demographic (age, gender and duration on ART), clinical (WHO stage and CD4), and treatment variables (ART regimen, duration on ART and past ART experience). Statistical significance was determined using the Chi-square test with significance set at $p<0.05$. The strength of association was calculated as odd ratios with a 95% confidence interval for those associations that were statistically significant. Multivariate analysis was used to identify factors that were independently associated with VLS. The analysis was only run on variables that were complete, incomplete data were not included in the analysis.

3.6 Validity and Reliability

Validity refers to the extent to which a measurement measures what it is intended to measure (Joubert and Ehrlich, 2007). To collect data from the HIV-positive adolescent on ART, EMRx is used across all the specialized pediatric HIV clinics to document all clinical information including laboratory findings for monitoring patients. Recording of ART data is done by trained clinical staff managing the ART program. All clinical staff is receiving training, orientation and on-going support on the use of EMRx. Each department that fills data into the EMRx fills specific sections relevant to the services they have provided. Every month and quarterly, the monitoring and evaluation (M&E) team runs a report and, together with program managers, ensure data accuracy. Facility audits are also done routinely to ensure the accuracy of ART data. A standardized data extraction tool was used to reduce measurement bias (Appendix 1).

To minimize selection bias, the inclusion and exclusion criteria of the study population were clearly defined. The calculated sample size was 300 participants; however, an inclusive sample was used to ensure that all eligible adolescents (15-19 years) were included in the study. Data was extracted from the EMRx, a database that collates all patients ever started on ART with all routinely captured data elements such as baseline and current clinical outcomes and socio-demographic factors.

Confounding was accounted for through multivariate analysis to eliminate positive or negative confounding effects of the independent variables on the outcome. Potential confounders in this study were the previous ART regimen and VL before enrolling in the study.

The reliability of data was ensured by how the primary variable of interest was measured. Laboratory tests were carried out on blood samples to obtain CD4 counts and viral loads. Viral load tests were used to measure the effectiveness of ART (Lima et al., 2012). The tests were carried out by the National Laboratory Services which is a reputable service provider with high-quality equipment and rigorous quality processes in place.

To check the reliability of the data extraction tools and process, the Monitoring and Evaluation officer completed the data extraction process on the sample data set and repeated this process for a second time on the same data set but on a separate occasion. The final products of the various data collection processes were compared. Consistency in the results was assessed and decisions were made on adjustments to the tools and extraction processes. This assessment was done through consultation and reconciliation processes where the results of data obtained were presented and differences in data obtained were discussed. If the data completion process on the tool was comparable, the reliability process was stopped. Where there were differences in data completion and findings, the process was continued by involving a third clinician to reach a consensus.

3.7 Ethics Considerations

The study received approval, for degree purpose, by the University of the Western Cape (UWC) Senate Higher Degrees Committee and ethics clearance from UWC Biomedical Research Ethics Committee (Appendix 2). In-country permission to use the study data was obtained from specialized pediatric HIV clinic (Appendix 3).

Informed consent was not required because there was no direct contact with adolescents for the duration of the study. The research involves no more than minimal risk to the participants. Personal information of participants was protected by creating unique identifiers during the analysis and reporting of study findings. The data extractor was requested to develop alphanumeric unique identifiers and link identifiers to patient names and folders before names were completely removed from the datasheet. Another data sheet was generated that only contains unique identifiers, which served as a final sheet to be used for data analysis. Access to

the database for this study was limited to authorized persons and the database remained on a password-protected computer. All data accessed was stored in a password- protected computer only accessible to the researcher for five years. All electronic data will be deleted once the retention period of 7 years had expired.

CHAPTER 4: RESULTS

4.1 Introduction

In this chapter we report the results of the study. It includes sections outlining the realization of the study sample and a description of the socio-demographic and clinical characteristics of the adolescents in the study. The chapter also looks at the bivariate analysis of VLS and the socio-demographic and clinical characteristics of adolescents. Multivariate analysis was also conducted to analyze whether socio-demographic and clinical variables were independently associated with VLS.

4.2 Realization of the Sample

Data from 1,369 adolescent patients aged 15-19 years enrolled at the specialized pediatric HIV clinic were obtained (Figure 4.1). Of these 1,369, adolescents who were not on DTG based regimen, or were less than three months on ART during the study period were excluded from the sample. Furthermore, those who had viral load and CD4 count missing for the duration of the study period were excluded from the sample. Therefore, the final sample size that was analyzed was 559.

4.3 Characteristics of the Study Sample

Table 4.1 below describes the characteristics of the adolescents who were included in the study. It provides description of socio-demographic and clinical characteristics of the study participants.

4.3.1 Socio-demographic Characteristics

The median ages were at 7.6 years (Inter Quartile Range (IQR) 4.9-11.3) at ART initiation and 17 years (IQR 15.9-18.4) at DTG initiation. More than half of the adolescent participants in this study were female (54.2%, n=303).

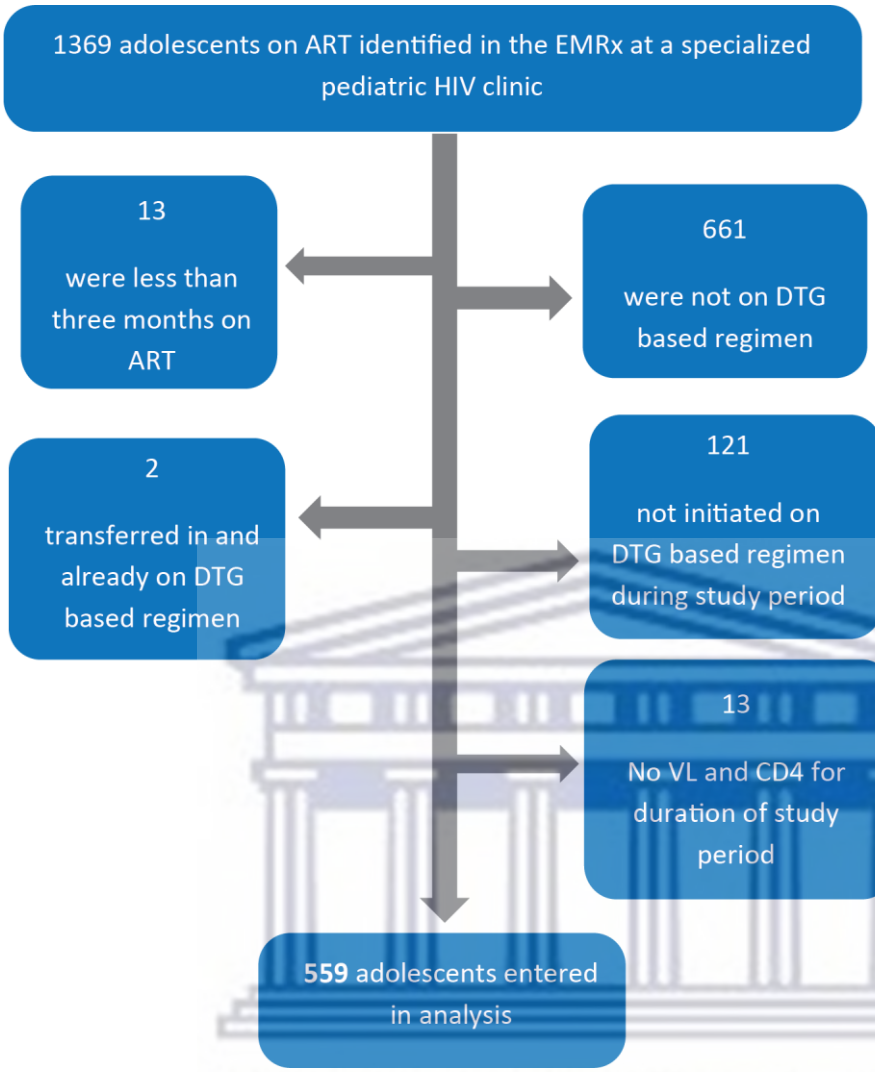

Figure 4.1 Realization of Study Sample

4.3.2 Clinical Characteristics

Before DTG initiation, 83.5% (n=467) of adolescents had CD4 count less than 200 cells/mm^3, which indicates severe immune suppression. Few adolescents (n=28) had CD4 counts recorded after initiation on DTG because CD4 count is not recommended as a measure of ART effectiveness according to Lesotho national guidelines on the use of antiretroviral therapy for HIV prevention and treatment. In patients already on ART in Lesotho, CD4 count is only drawn if there are compelling symptoms or illnesses that indicate severity of medical condition and to determine the need for prophylaxis or if a patient is unwell regardless of duration on ART. Of those adolescents who had CD4 counts done after DTG initiation, 50% (n=14) had no immune suppression (>500 cells/mm^3).

Almost all adolescents (98%; n=553) who had documented WHO staging were classified as WHO Stage 1. More than half (58.6%; n=327) of the study participants were on ART for more than 10 years while 34.8% were on ART for time between 5-9 years. More than half (56.5%; n = 316) of participants were on DTG based regimen for at least one year and 22.5%; n= 126, were on DTG for more than two years

Table 4.1 below shows the last regimen before transition to DTG based regimen, the baseline DTG based regimen and the current DTG based regimen. In adolescents with documented regimen before DTG initiation, 39% (n=544) were on AZT/3TC/EFV, 18% had unspecified ART regimen, 17% were on ABC/3TC/EFV and 15% were on AZT/3TC/NVP (Fig 4.1 a). After transition to DTG, 93.6% (n=551) of adolescents were on TDF/3TC/DTG regimen.

4.3.3 Behavioral Characteristics

Most participants (89.1%: n= 542) had good adherence (95-105%) on ART. All participants were retained in care (100%; n = 559).

Table 4.1 Socio-demographic Characteristics of Adolescents on DTG based ART Regimen between November 2019 and November 2021 (N = 559)

Variables	n	%
Age at ART Start (Median and IQR in years)	8 (5 - 11)	
Age at DTG Start (Median and IQR in years)	17 (16 - 18)	
Gender		
Female	303	54.2
Male	256	45.8
Duration on ART (in years)		
>9	327	59.1
5 - 9	194	34.7
1 - 4	29	5.2
<1	8	1.4
Missing	1	0.2
Duration on DTG (in years)		
>2	126	22.5
1-2	316	56.5
<1	117	20.9
Current WHO Stage		
I	542	97
II	7	1.3
III	1	0.2
IV	3	0.5
Missing	6	1.1
CD4 count before DTG initiation (in cells/mm^3)		
Severe Immune Suppression (<200)	467	83.5
Moderate Immune Suppression (201-349)	5	0.9
Mild Immune Suppression (350-499)	14	2.5
No Immune Suppression (>500)	73	13.1
Retention in Care (at 24 months)	559	100
Adherence		
Good Adherence (>95%)	483	86.4
Poor Adherence (<95%)	59	10.6
Missing	17	3.0

Table 4.2 Treatment Characteristics of Adolescents on DTG based ART Regimen between November 2019 and November 2021 (N = 559)

Variables	n	%
ART Regimen before DTG		
AZT-3TC-EFV	215	38.5
ABC-3TC-EFV	90	16.1
AZT-3TC-NVP	81	14.5
TDF-3TC-EFV	50	8.9
ABC-3TC-LPV/r	3	0.5
ABC-3TC-NVP	3	0.5
AZT-3TC-LPV/r	1	0.2
TDF-3TC-LPV/r	2	0.4
TDF-3TC-NVP	1	0.2
Other (specify)	98	17.5
Missing	15	2.7
Baseline DTG Regimen		
TDF-3TC-DTG	523	93.6
ABC-3TC-DTG	21	3.8
AZT-3TC-DTG	12	2.1
DTG-LPV/r	3	0.5
Current ART Regimen		
TDF-3TC-DTG	501	89.6
ABC-3TC-DTG	2	0.4
AZT-3TC-DTG	5	0.9
TDF-ETV-DTG	1	0.2
Other (specify)	50	8.9

ABC (Abacarvir), 3TC (Lamuvidine), EFV (Evaference), LPV/r (Lopinavir/ritonavir), NVP (Neverapine), TDF (Tinoforvir), DTG (Dolutergravir), AZT (Zidovudine) ETV (Etravirine)

4.4 Viral Load Suppression

Viral load was monitored for 531, 443, 379 and 273 adolescents at 6, 12, 18 and 24 months post-DTG initiation respectively. All 559 adolescents were treatment-experienced and had a documented VL before transitioning to DTG. It was noted that the National ART guidelines, which recommend six-monthly VL monitoring, were not strictly adhered to. VL monitoring intervals of greater than 6 months were seen; consequently, adolescents may not have had a VL drawn at the appropriate time intervals which in turn affects the expected results. Most adolescents (95%; n=531) had a 6-month VL monitoring after DTG initiation recorded (Fig 4.2). Of the 531 adolescents,91% showed VLS with an undetectable VL (<50 copies/mL), 5% were virally suppressed with VL of <1000 cps/mL, 4% were unsuppressed with a VL of >1000 copies/mL.

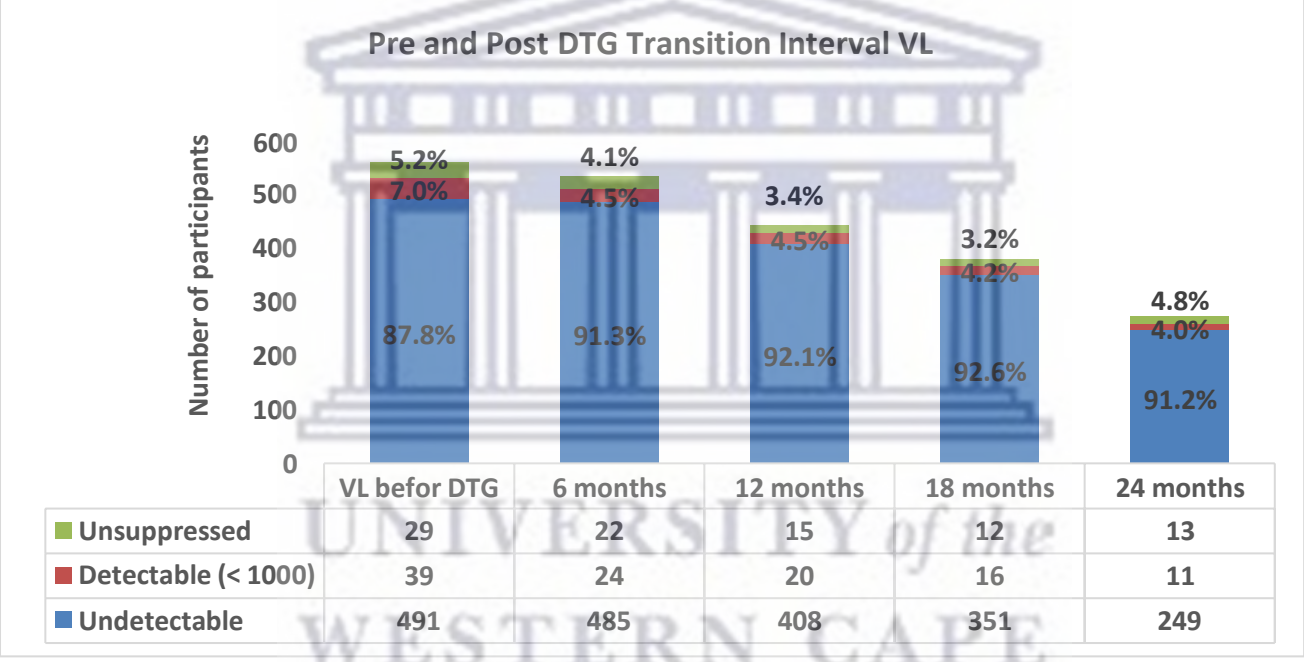

Figure 4.2 Viral Suppression of Adolescents before and after Initiation on Dolutegravir

4.5 Factors Associated with Viral Load Suppression

Table 4.2 represents the results of the bivariate analysis associated with VLS. In the bivariate analysis it was found that there were no statistically significant associations between full VLS and socio-demographic factors such as gender (p=0.543) and the number of years on ART (p=0.134).

Statistical significance was observed between VLS and duration on DTG (p=0.01), previous ART regimen before DTG (p=0.005) and current ART regimen (p=0.001). VLS was highest among those who were one year on DTG (n=298: 61.4%), followed by those who were two years (n= 114: 23.5%) and, lastly, those less than one year (n= 73:15.1%). Adolescents who were on EFV based regimen had the highest VLS (n= 330: 69.6%), followed by those on NVP-based (n= 80:16.9%), those on other unspecified regimens (12.7%) and, lastly, those on LPV/r-based regimen who achieved 0.8% VLS.

However, when accounting for other variables in multivariate analysis, only *duration on DTG* and *current ART regimen* remained statistically significant as indicated on Table 4.3. The odds of having full viral suppression were 4.4 times higher among adolescents who were on DTG for two years compared to those who were on DTG for less than 12 months (OR: 4.4, 95% CI: 0.85 - 23.41), holding all other variables constant. Compared to those on DTG for less than 12 months, those on DTG for a year were 8 times more likely to be virally unsuppressed at 6 months (OR: 8.0, 95% CI: 1.64 - 39.06), holding all other variables constant. Compared to those on the TDF-ETV-DTG regimen, those on AZT-3TC-DTG were 97% less likely to be virally suppressed at 6 months.

There was no statistically significant association between full VLS and clinical factors such as last CD4 count (p=0.066) and WHO stage (p=0263) before DTG initiation.

Table 4.3: Bivariate Analysis of Viral Load Suppression by Demographic, Clinical and Treatment Characteristics

		Fully Suppressed		
	Total	**Yes**	**No**	***p*-value**
		n (%)	**n (%)**	
Gender				
Male	242 (45.57)	223 (45.98)	19 (41.30)	0.543
Female	289 (54.43)	262 (54.02)	27 (58.70)	
Duration on ART (in years)				
≥10	313 (59.1)	287 (59.3)	26 (56.5)	0.134
5 - 9	184 (34.7)	167 (34.5)	17 (37)	
1 - 4	27 (5.1)	26 (5.4)	1 (2.2)	
<1	6 (1.1)	4 (0.8)	2 (4.4)	
Duration on DTG (in years)				
2	126 (23.7)	114 (23.5)	12 (26.1)	**0.01***
1	316 (59.5)	298 (61.4)	18 (39.1)	
<1	89 (16.8)	73 (15.1)	16 (34.8)	
CD4 Count before DTG Initiation (in cells/mm^3)				
<200	465 (87.6)	429 (88.5)	36 (78.3)	0.066
201 - 349	2 (0.4)	1 (0.2)	1 (2.2)	
350 - 499	8 (1.5)	7 (1.4)	1 (2.2)	
>500	56 (10.6)	48 (9.9)	8 (17.4)	
ART Regimen before DTG				
EFV based	355 (68.5)	330 (69.6)	25 (56.8)	**0.005***
NVP based	85 (16.4)	80 (16.9)	5 (11.4)	
LPV/r based	6 (1.2)	4 (0.8)	2 (4.6)	
Other	72 (13.9)	60 (12.7)	12 (27.3)	
Current ART Regimen				
TDF-3TC-DTG	489 (92.1)	451 (93)	38 (82.6)	**0.001***
AZT-3TC-DTG	5 (0.9)	2 (0.4)	3 (6.5)	
ABC-3TC-DTG	2 (0.4)	2 (0.4)	0 (0)	
TDF-ETV-DTG	1 (0.2)	1 (0.2)	0 (0)	

Other	34 (6.4)	29 (6)	5 (10.9)	
Current WHO Stage				
I	515 (97.9)	472 (98.1)	43 (95.6)	0.263
II	7 (1.3)	5 (1)	2 (4.4)	
III	1 (0.2)	1 (0.2)	0 (0)	
IV	3 (0.6)	3 (0.6)	0 (0)	

Notes: EFV based (ABC-3TC-EFV, AZT-3TC-EFV, TDF-3TC-EFV), NVP based (ABC-3TC-NVP, AZT-3TC-NVP, TDF-3TC-NVP) and LPV/r based (TDF-3TC-LPV/r, AZT-3TC-LPV/r, ABC-3TC-LPV/r)* Indicates statistical significance at p-value < 0.05

Table 4.4: Determinants of Viral Load Suppression among Adolescents who Transitioned to DTG based Regimen (N=559)

	Crude Odds Ratio (OR) (95% CI)	Adjusted Odds Ratio (AOR) (95% CI)	*P*-value
Age at DTG Start	0.94 (0.76 - 1.16)	0.92 (0.73 -1.16)	0.48
Sex *(Reference: Female)*			
Male	1.2 (0.65 - 2.23)	1.50 (0.76 - 2.94)	0.24
Duration on DTG *(Reference: Less than 12 months)*			
Two years	2.1 (0.93 - 4.65)*	4.4 (0.85 - 23.41)*	0.08
One year	3.62 (1.77 - 7.46)**	8.02 (1.64 - 39.06)**	**0.01**
Last CD4 before DTG *(Reference: Severe/ complete immune suppression)*			
201-349	0.84 (0.01 - 1.37)	0.40 (0.13 - 12.56)	0.61
350-499	0.59 (0.07 - 4.90)	3.17 (0.18 - 56.98)	0.44
>500	0.50 (0.22 - 1.150	2.51 (0.31 - 20.28)	0.39
Last ART Regimen before DTG *(Reference: Other)*			
EFV based regimen	1.13 (0.53 - 2.44)	1.24 (0.54 - 2.85)	0.62
NVP based regimen	1.40 (0.40 - 5.0)	1.66 (0.42 - 6.65)	0.47
LPV/r based regimen	0.43 (0.19 - 0.95)**	1.00 (0.10 - 9.77)	1.00
TDF-3TC-DTG	*omitted*		
Current ART Regimen *(Reference: TDF-ETV-DTG)*			
ABC-3TC-DTG	*omitted*	*omitted*	
AZT-3TC-DTG	0.11 (0.15 - 0.87)**	0.035 (0.003 - 0.377)**	**0.01**
TDF-3TC-DTG	2.05 (0.75 - 5.59)	0.82 (0.22 - 3.08)	0.77
TDF-ETV-DTG	*omitted*	*omitted*	

**** p<.01, ** p<.05, * p<.1*

OR- odd ratio

95% CI- 95% confidence interval

CHAPTER 5: DISCUSSION

5.1 Viral Suppression on DTG Based ART Regimens

Viral suppression amongst adolescents in a specialized pediatric HIV clinic after 6 months on DTG based ART regimen was 91%, which exceeded UNAIDS 90-90-90 global target. Compared to other studies that measured VLS in adolescents on EFV and NVP based regimen and found VLS <90% in Cambodia, South Africa and Eswatini (Chhim et al., 2018; Chouraya et al., 2019; van Wyk et al., 2020), our results found better VLS (>90%) among adolescents initiated on DTG based regimen.

Our results follow trends reported in other studies in Italy, USA and Uganda which found high VLS in adolescents and adult patients on DTG based ART regimen. In their study on effectiveness of DTG based ART regimen at the University of Naples Federico, Bruzzese et al. (2018) found that adolescents who were initiated on DTG due to poor adherence, multi drug resistance and side effects of their current ART regimen, achieved full VLS within four to eight weeks after starting DTG based ART regimen. In another study DTG showed effectiveness in suppressing VL in ART experienced adult patients in the United States. The VLS was 88% and 81% among ART experienced patients who received DTG and EFV based regimen respectively (Osterholzer & Goldman, 2014). In Uganda, in a study assessing acceptability and VLS of children, adolescents and adult patients on DTG-based regimens found high acceptability in treatment-experienced and new patients, and higher VLS (94%) after 6 months of treatment (Nabitaka et al., 2020).

5.2. Age and Viral Load Suppression

The results in our study indicated that age at ART initiation and current age at DTG start were not statistically significant in both bivariate and multivariate analysis. Our results yielded different finding from a study conducted in Kenya on factors associated with viral load on adolescents, which found that there was statistical significance between age at ART initiation and VLS (Mwangi & van Wyk, 2021b). In our study the median age of adolescents was 16 years and minimum age at ART initiation was 5 years. Furthermore, the study participants in our study were most likely perinatally infected with HIV as they were initiated when they were

five years, the age at which HIV transmission is from mother to child. It also means that they had longer exposure to ART.

5.3 Gender and Viral Load Suppression

In the current study gender was not associated with VLS. This finding is in line with several studies done in South Africa, Lesotho and Uganda that showed no association between VLS and gender (Zanoni et al., 2017b; Wakooko, Gavamukulya and Wandabwa, 2020; Brown et al., 2022; Mwangi and van Wyk 2021). In contrast, in some earlier studies, conflicting results were reported about relationship of VLS and gender, with some studies reporting that females were more likely to have higher VLS compared to males (Haider et al., 2021). In Uganda, a study on determinants of viral non suppression among adolescents found that male sex was associated with higher odds of non-viral suppression (Maena et al., 2021a). Other authors reported males having higher VLS compared to females (Mave et al., 2011; Van Wyk et al., 2020). Thus, gender specific interventions may not be necessary when addressing low VLS among adolescents; rather, significant factors such as treatment duration and ART regimen and adherence should be the focus.

5.4 Clinical Factors Associated with Viral Suppression

The clinical factors that were analyzed in this study were CD4 count and WHO stage. None of these factors were significantly associated with VLS. All our study participantshad at least CD4 count documented before they were initiated on DTG. CD4 count was only monitored for 28 participants and 50% of them were found not to be immune suppressed (CD4 >500 cells/mm^3). CD4 count is not recommended as a measure of ARTeffectiveness according to Lesotho national guidelines on the use of antiretroviral therapyfor HIV prevention and treatment. In patients already on ART in Lesotho, CD4 count is only drawn if there are compelling symptoms or illnesses that indicate severity of medicalcondition and to determine the need for prophylaxis or if a patient is unwell regardless of duration on ART. Our results showed no significant association between VLS and CD4 count before DTG initiation. Contrary to our findings in this study, many authors found that lower CD4 count (<200 cells/mm^3) is associated with lower rates of VLS (Okonji etal., 2021b; Phillips et al., n.d.; Ross et al., 2020b). However, unlike in our study where CD4 count used in the analysis was any available CD4 count before initiation DTG, thesestudies' results were based on the most recent CD4 count that was monitored while participants were on ART. In other studies, it was found that the CD4 count >500

cells/mm^3 was associated with high VLS (Chhim et al., 2018b; Mwangi & van Wyk, 2021b).

In our study there was no significant association between WHO stage and VLS. Nevertheless, in the literature, other authors contradict the results of this study. Sithole et al. (2018) in their study on virological failure among adolescents on ART in Harare found that adolescents with advanced HIV disease (WHO stage 3 and 4) were more likely to have virological failure compared to those on WHO Stages 1 and 2. In Uganda Maena et al (2021) found that adolescents who were on WHO Stage 2 had high odds of having viral non suppression. This literature suggests that adolescents who start ART in advanced HIV disease may poorly respond to ART.

5.5 Treatment Factors

In our study the statistical significance was observed between VLS and duration on DTG (p=0.01), previous ART regimen before DTG (p=0.005) and current ART regimen (p=0.001). However, on multivariate analysis, only duration on DTG and current ART regimen remained statistically significant.

In our study all our participants were treatment experienced; majority (59.1%; n=313) had been on ART for more than 10 years and 34.7% (184) were on ART for more than 5 years. After DTG initiation, multivariate regression showed that adolescents who were on DTG for one year had higher odds of VLS compared to those on DTG for two years. Our results corroborate the findings from a study conducted in Kenya on clinic level and individual factors that influence HIV viral suppression in adolescents and young adults, which reported that longer duration on ART was associated with VL non suppression (Njuguna et al., 2020b). According to Maena et al. (2021), this is due to treatment fatigue that results in low adherence to ART. In contrast, a study conducted in South Africa on HIV care cascade reported that longer duration on ART was associated with VLS (Haghighat et al., 2021b).

In the bivariate analysis the results of our study showed significant association between VLS, DTG and EFV based regimen. However, in multivariate analysis only current treatment had significant association with the VLS. Our results are similar to the results of the study conducted in Italy at the University of Naples. The study results show that all children who

were on DTG based regimen achieved VLS regardless of previous ART regimen and poor adherence (Bruzzese, lo Vecchio, et al., 2018). DTG has been proven to be clinically non inferior but superior to current first line TDF-3TC-EFV regimen in both treatment experienced and treatment naïve patients (Osterholzer & Goldman, 2014b).

5.6 Behavioural Factors

All participants in this study were retained in care. Our results indicated that adherence was not significantly associated with VLS. However, many studies found contradicting results. In Kenya, Mwangi and van Wyk (2021) found that good adherence was associated with VLS in their study on factors associated with VLS among adolescents on ART. Nachega et al. (2009) report that adolescents have low VLS due to poor adherence. Nevertheless, due to high potency of some medications, VLS may still be achieved at adherence level below 95% (Kristofich et al., 2021a) indicating that drugs with low potency will need high adherence to achieve the desired level of VLS, whereas drugs with high potency may still achieve same level of VLS at lower dose according to Bangsberg (2006).

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

Viral load suppression among adolescents who were initiated on DTG at a specialized pediatric HIV clinic surpassed 90% UNAIDS 2020 target. While adherence remains important in achieving VLS, high potent ART are far more effective in achieving VLS among adolescents. DTG has shown superiority over first line TDF-3TC-EFV regimen regardless of prior ART experience and adherence. Adolescents need to be prioritized to receive optimized ART regimen to achieve best clinical outcomes while on ART. Our study highlights the significance of DTG based regimen and its effectiveness in achieving VLS faster within a shorter duration. Our results showed that being on DTG for more than twelve months was significantly associated with higher VLS as compared to being on DTG for 24 months. It also showed that beingon AZT-3TC-DTG was significantly associated with VLS compared to those who were on TDF-ETV-DTG. Our results show that with DTG based ART regimen in adolescents can reach the 95-95-95 UNAIDS target by 2030.

6.2 Limitations of the Study

The main limitation of this study is that some of the records of adolescents who were included in the sample had some important variables such as viral load, CD4 count, WHO stage and adherence missing. As a result, records that were incomplete were excluded from the sample. This may have affected the analysis of variables associated with VLS. Our study did not analyze any behavioral and social variables because they were not routinely collected.

The study also involved retrospective extraction of data from a database, restricting us to routinely collected variables. This limited the extent to which other variables such as cultural, social and economic factors can be explored, which can potentially affect the results.

The sample size of this study was small (N=559) and mostly included adolescents attending ART services at the main clinic. Nevertheless, the sample size had sufficient power to detect differences. Our sample also was mostly composed of adolescents who were on first line treatment with generally good adherence >95% and VLS of 87.9% prior DTG initiation. This could have led to our results having less discriminatory results in detecting factors that influence VLS.

6.3 Recommendations

In addition to the strategies that are currently implemented such as those that improve retention in care, psychosocial support (teen clubs) and adherence, eligible adolescents should be prioritized to be put on high potent ART that will increase their VLS. Simplified and optimized ART regimens that only require single dosing should be prioritized among adolescents on ART as this simplifies dosing and improves adherence which is often a struggle among the adolescents.

Gender specific interventions do not necessarily have any significance in addressing VLS among adolescents and should, therefore, not be considered when addressing VLS in adolescents. To achieve the 95-95-95 UNAIDS targets for 2030, HIV program should ensure that all newly HIV diagnosed adolescents and those already on ART are initiated and transitioned to DTG based regimen.

Further studies in adolescents using different methodology such as prospective and qualitative studies or mixed methods should be conducted to analyze more variables that can potentially be determinants of viral load suppression, such as cultural, economic and social factors. These determinants should be routinely collected and analyzed to inform future HIV programming among adolescents. The use of health information systems such as Electronic Medical Record (EMR) should be maximized to capture wide range of variables that may play important role in adolescents' response to ART. Future studies should include adolescents enrolled in non-specialized facilities so that varying settings and experiences on ART may be analyzed.

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APPENDIX 1: Data Extraction Tool

Unique ID_____
SOCIODEMOPGRAPHIC INFORMATION
Gender: 1) Male 2) Female Age:_____
Education,
Primary
Secondary
No Education
Blank
Clinical Information
Age at ART start date:_____
Baseline CD4 Count Result:_____
Current WHO Clinical Stage
Stage I
Stage II
Stage III
Stage IV
ART Regimen at Initiation
Duration on ART
<12 Months
13-24 Months
>24 Months
Treatment Outcome
Viral Load Results post DTG Initiation/Transition.
1st VL_____ 2nd VL :_____ 3rd VL:_____ 4th VL:_____

Retention in Care	
6 Months 1) Yes 2) No 12 Months 1) Yes 2) No	24 Months 1) Yes 2) No
ART Regimen prior Current ART	
On TB Treatment at the Start of ART	
Yes	
No	
Blank	
Adherence	
Good (>95%)	
Fair (86-94%)	
Poor (<85%)	
HIV Disclosure	
Yes	
No	
Blank	
Pregnancy Status	
Yes	
No	
BEHAVIOURAL INFORMATION	
Alcohol Use	
Yes	
No	
Blank	
Substance Abuse	
Yes	
No	

Blank

UNIVERSITY of the WESTERN CAPE

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29 October 2021

Mr M Letsika
School of Public Health
Faculty of Community and Health Sciences

Ethics Reference Number: BM21/9/6

Project Title: Assessment of Treatment Outcomes of HIV Positive Adolescents on Dolutegravir-based Regimen at a Referral Health Facility in Lesotho.

Approval Period: **22 October 2021 – 22 October 2024**

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 and the requested amendment to the project.

Any further amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

Please remember to submit a progress report annually by 30 November for the duration of the project.

For permission to conduct research using student and/or staff data or to distribute research surveys/questionnaires please apply via:
https://sites.google.com/uwc.ac.za/permissionresearch/home

The permission letter must then be submitted to BMREC for record keeping purposes.

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

NHREC Registration Number: BMREC-130416-050

LESOTHO

Ministry of Health
P.O. Box 514
Maseru 100

Category of Review:
[ ] Initial Review
[ ] Continuing Annual Review
[x] Amendment/Modification
[ ] Reactivation
[ ] Serious Adverse Event
[ ] Other _____

REF: ID 170-2021 Modify 01
Date: February 14, 2022
To
Motlatsi Letsika
Student number: 4003908
University of the Western Cape School of Public Health

Dear **Mr. Letsika**

RE: Assessment Treatment outcomes of HIV Positive Adolescents on Dolutegravir-based Regimen at a specialized Pediatric HIV Clinic (Baylor College of Medicine Children's Foundation Lesotho) in Lesotho

This is to inform you that the Ministry of Health Research and Ethics Committee reviewed the above protocol and **APPROVED** the protocol modification and hereby authorizes you to continue the study according to the activities and population specified in the protocol. Departure from the approved protocol will constitute a breach of this permission.

This approval includes review of the following attachments:
[x] Protocol dated 02nd December 2021
[ ] Participant materials:
[x] Other materials: Letter of request dated 14th February 2022,

This approval is **VALID** until December 10th, 2022.

Please note that an annual report and request for renewal, if applicable, must be submitted at least 6 weeks before the expiry date. All serious adverse events associated with this study must be reported promptly to the MOH Research and Ethics Committee. Any modifications to the approved protocol or consent forms must be submitted to the committee prior to implementation of any changes.

We look forward to receiving your progress reports and a final report at the end of the study. If you have any questions, please contact the Research and Ethics Committee at rcumoh@gmail.com (or) 59037919/58800246.

Sincerely,

DR. 'NYANE LETSIE
Director General Health Services

DR. AMELIA RANOTSI
Chairperson National Health Institutional Review Board (NH-IRB)

Private Bag A191 | Botšabelo
Near Queen 'Mamohato Memorial Hospital
Maseru, Lesotho

Ph: +266-2222-2700
Email: info@baylorlesotho.org

February 28, 2022

To Mr Motlatsi Letsika

I have been asked to perform the Pre-study file audit on the **Assessment of Treatment Outcomes of HIV Positive Adolescents on Dolutegravir Based Regimen at a Specialized Paediatric HIV Clinic in Lesotho**and I have discovered that all the necessary documentation are present in the study file and to date, henceas the Audit team member I grant you the go ahead with the study.

Regards,

Dr Isaac Andreas Boy

aisaac@baylorlesotho.org