Determinants of viral suppression among adolescents on antiretroviral therapy in Thabo Mofutsanyane District Municipality, Free State province, South Africa

Balsam Ahmed Yousif Elashi

Student Number: 3311529

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Supervisor: Prof Brian van Wyk

Date: 22.11.2021

DECLARATION

I declare that *Determinants of viral suppression among adolescents on antiretroviral therapy in Thabo Mofutsanyane District Municipality, Free State province, South Africa*, has not been submitted for any degree or examination at any other university, and that all the sources I have used have been indicated in text and acknowledged in the references section.

Full Name: Balsam Elashi

Date: 22.11.2021

Signature:

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I would like to thank my parents; you have always instilled in me the passion to pursue my education.

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ABSTRACT

In 2018, it was estimated that 33,000 adolescent girls and 4,200 adolescent boys were HIV-positive in South Africa. The Free State province reports that 89% of people living with HIV are diagnosed; 72% of those diagnosed are receiving antiretroviral therapy (ART); of which 93% have achieved viral suppression (< 1000 RNA copies/mL). Thabo Mofutsanyane District has the highest HIV prevalence in the Free State province.

A retrospective, quantitative cross-sectional study was conducted to determine the predictors of viral suppression among adolescents on ART in Thabo Mofutsanyane District Municipality, Free State province, South Africa. Data for all adolescents, aged 10–19 years, receiving ART in 2019 (N = 6 300) was extracted from Tier.net electronic database into an Excel spread sheet and exported into Statistical Package for the Social Sciences – Version 26 (SPSS v 26) for analysis.

Seventy eight percent (n=4,520) of the adolescents on ART achieved viral suppression. The results of the multivariate logistic regression analysis have shown that age at ART initiation, CD4 count at baseline, baseline ART regimen, current ART regimen and retention in care were determinants of viral suppression. The odds of being virally suppressed reduced with increased age at ART initiation. Adolescents with CD4 count greater than 500 cells/mm^3 at baseline had higher odds of viral suppression (AOR =1.77; CI: 1.28–2.47). The odds of viral suppression were significantly lower amongst those who were not retained in care (AOR=0.45; CI: 0.35–0.58). Viral suppression for adolescents falls short of global target of 90%. Tailored interventions should be developed to improve long term adherence and retention in care for adolescents on ART.

Keywords: HIV, viral suppression, adolescents, retention in care, antiretroviral therapy.

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ABBREVIATIONS AND ACRONYMS

NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside reverse transcriptase inhibitors
NVP	Nevirapine
PCP	Pneumocystis pneumonia
PI	Protease inhibitors
PLHIV	People Living with HIV
PMTCT	Prevention of mother-to-child transmission
PrEP	Pre-exposure prophylaxis
UNAIDS	Joint United Nations Programme on HIV and AIDS
UNICEF	United Nations International Children's Emergency Fund
VL	Viral Load
VLS	Viral Load Suppression
WHO	World Health Organization
ZDV	Zidovudine
FDC	A Fixed-dose combination
InSTIs	Integrase Strand Transfer Inhibitors
CPT	Cotrimoxazole Prophylaxis Treatment
IPT	Isoniazid Preventive Therapy
ICF	Intensified case-finding
TST	Tuberculin Skin Test

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

Adolescents and young people represent a growing share of people living with HIV worldwide. UNICEF (2018) has reported that in 2018, about 1.6 million young adolescents between the ages of 10 and 19 years were living with HIV worldwide. Adolescents account for about 4% of all people living with HIV and about 11% of new adult HIV infections. In 2019, UNICEF (2020) indicated that 460 000 young people between the ages of 10 to 24 were newly infected with HIV, of whom 170 000 were adolescents between the ages of 10 and 19 years (UNICEF, 2020). To compound this, the most recent data indicate that only 27% of adolescent girls and 16% of adolescent boys aged 15–19 years in Eastern and Southern Africa the regions with a high HIV infectivity rate respectively have been tested for HIV in the past 12 months and received the result of the last test (UNICEF, 2020).

The sub-Saharan African region in Africa is home to only 14% of the global population (World Bank, 2021), yet it carries the highest burden of HIV among adolescents 10–19 years. In 2019, about 1.5 million [1.0 million–2.1 million] HIV-infected adolescents lived in sub-Saharan Africa, which is 88% of the total number of adolescent HIV infections globally (UNICEF, 2020). Within the sub-Saharan region, South Africa accounts for a third of all new HIV infections in southern Africa and has the highest profile of HIV epidemic in the world (Avert, 2019). It is estimated that there are 720 000 HIV-infected youth aged 15–24 years in South Africa (Zanoni *et al.,* 2016). Moreover, aggregate data on the HIV epidemic among South African adolescents, show significant sex differences, with 33 000 adolescent girls becoming HIV-positive in 2018, compared to 4 200 adolescent boys (UNAIDS, 2020a). HIV infections among young women (aged 15–24 years) in South Africa are eight times higher than among men of the same age (UNAIDS, 2020a).

Several health-related behaviours were suggested that put adolescents at an elevated risk of HIV infection. Unprotected sex is the most common route of HIV infection for young people (Idele *et al.,* 2014; UNAIDS, 2020b). Condom use among young people and adolescents remains relatively low; progress in the provision and use of condoms has largely stalled; and the gap in sub-Saharan Africa alone is more than 3 billion male condoms a year, over 50% of the estimated need (UNAIDS, 2016). Demographic and Health Surveys conducted in sub-Saharan Africa between 2010 and 2015 reported that less than 60% of young women (15 to 24

years) with multiple partners used a condom during their last sexual intercourse in 19 out of 23 countries (UNAIDS, 2016). In 15 out of 23 countries there were similar results for young men (UNAIDS, 2016). Moreover, young people under the influence of drugs are more prone to have sex without protection (such as using a condom or taking medicine to prevent HIV) (UNAIDS, 2020b). Sharing of infected needles during injection of drugs was reported to be the second cause of HIV infection among adolescents (Idele *et al.*, 2014; UNAIDS, 2020b).

Sexually risky practices that also increase the vulnerability of adolescents to HIV include early sexual debut where young people become sexually active at a young age; intergenerational sex where young people have sexual relationships with older people; and multiple or concurrent sexual partners (UNAIDS, 2019a). Older partners are more likely to be living with HIV; therefore, risking exposure to young people, and are more likely to expose a young person to unsafe sexual behaviours such as low condom use. Adolescents with many sexual partners and those that belong to key affected populations such as sex workers, men who have sex with men and transgender people are also more at risk to HIV (UNAIDS, 2016; UNAIDS, 2019b).

Other factors that increase the vulnerability of HIV among adolescents include, low rates of HIV testing among adolescents compared to other age groups, testing coverage remains below 20 per cent for adolescents (UNICEF, 2020). This means many adolescents and young people living with HIV may not know their status. Furthermore, boys are consistently less likely to have been tested for HIV than girls.

Moreover, lack of knowledge can impact young adults' informed prevention and treatment choices. (UNICEF, 2020). If young people could access comprehensive sexuality education (CSE) before becoming sexually active, they would be more likely to make informed decisions about their sexuality and approach relationships with more self-confidence and have the correct knowledge of HIV prevention in order to protect themselves from infection (UNAIDS, 2016; UNICEF, 2020). However, rates of comprehensive HIV and sexual knowledge remain below 50% in most countries globally with available data (UNICEF, 2020). In addition, girls and boys may have disparate levels of HIV knowledge depending on the country context (UNICEF, 2020).

It is also important to recognise the unfortunate structural, cultural and societal factors which has resulted in the disproportionate burden of HIV infection and health inequities, which affect the adolescents' ability to successfully navigate the HIV prevention process among the

marginalised African countries including South Africa (Institute of Medicine Committee, 2011).

Even more concerning, than the high number of HIV-infected adolescents (aged 10–19 years) globally, 1 740,000 (1 140 000–2 360 000) is the increase of AIDS-related death among this, age group. In 2019, the estimated number of adolescents dying of AIDS-related causes was 34 000 (23 000–50 000) (UNAIDS, 2020a). More than 90% of deaths worldwide from AIDS-related illness among adolescents occurred in sub-Saharan Africa (UNAIDS, 2019b).

ART is vital to decrease the morbidity and mortality rate among HIV-infected individuals (Antiretroviral Therapy Cohort Collaboration, 2017). South Africa has the largest ART programme in Africa and the world (UNAIDS, 2020a). ART aims to decrease the plasma level of the virus also known as viral load in the patients' system and achieve a sustained suppression of HIV replication (National Institute of Health, 2021). According to the national South African guidelines, viral suppression is defined as viral load below 1 000 copies/ml after at least six months of using ART (National Department of Health, 2019). ART and subsequent low levels of the HIV in the patient's body signals the re-formation of the immune system which results in the improvement in the patient's health and quality of life contributes to the decline in HIV-related morbidity and prevents transmission of HIV to their uninfected sexual partners (National Institute of Health, 2021). The achievement of viral load suppression in ART programmes is dependent on good retention in care (Cyrus *et al.*, 2017), exhibiting good adherence to prescribed medication (National Institute of Health, 2021) as well as consuming a balanced and healthy diet and adopting a lifestyle that decreases the risk of HIV transmission such as avoiding risky sexual behaviour and substance abuse (Kim *et al.*, 2014).

Although South Arica has the largest ART programme globally, AIDS-related mortality among South African adolescents remains high (UNAIDS, 2020a). The problem facing South Africa's HIV response is that the treatment scale-up has been delayed. Although the rate of new infections has decreased by 42% (UNAIDS, 2020a), this rate is still not fast enough to bend the curve of the epidemic. New infections in young men and women remain alarmingly high (nearly 87% of the total) and viral suppression rates, a key to preventing those living with the virus from passing it on, are under 50% for those 15–24 years old (Centre of Strategic International Studies, 2019). With approximately 45% of the population under the age of 25 years (United Nations, 2019), the total numbers of those becoming infected and overall

prevalence of HIV will stay alarmingly high without a massive decline in the new HIV infection rate (Central of Strategic International Studies, 2019).

Furthermore, adolescents aged 13–24 years receiving ART have the population highest AIDS mortality rates compared to other population groups (Casale *et al.*, 2019). These high mortality rates among adolescent population are explained by the high rates of attrition and LTFU for HIV treatment and care at all stages of the treatment cascade among this group (Adejumo, *et al.*, 2015; Grimsrud *et al.*, 2016; Reif *et al.*, 2016) and low ART adherence within the treatment programme (van Wyk *et al.*, 2020). A study conducted among adolescents who were newly initiated on antiretroviral therapy in the Cape Metropole in South Africa highlighted the low retention in care and adherence for adolescents over the first two years after initiation on ART (van Wyk *et al.*, 2020). Another study conducted among adolescents aged 12–20 years in Johannesburg, South Africa found that a total of 47 (38%) adolescents missed a scheduled visit within 24 months of enrolment. Older adolescents (18–20 years) were more likely to miss a visit compared to adolescents aged 12–14 years. Those who were identified as having difficulty in taking medication as a barrier to care were more likely to miss a visit compared to adolescents who did not (Maskew *et al.*, 2016).

The greater likelihood of detachment from health care among adolescents living with HIV may be partly explained by their unique psychological and medical needs (Ojwang *et al.*, 2016; Mutumba *et al.*, 2016); in particular, adolescents perinatally infected with HIV may face additional health and developmental challenges (Casale *et al.*, 2019). Young people, especially those who have been living with HIV since birth face challenges in the transition from paediatric treatment services – where the guardians are primarily responsible for their care – to adult treatment services, as they take greater responsibility and learn to self-manage their disease (UNICEF, 2016). Studies from Southern and East Africa reported on the barriers to successful transition from paediatric to adult care, highlighting several gaps. This included lack of adequate infrastructure, staff training and communication between paediatric and adult clinicians as well as the fear of stigma of adolescents and youth living with HIV, and the lack of specific national guidelines on when to disclose HIV status or when and how to transition to adult care (Dahourou *et al.*, 2017). Another issue that prevents adolescents from adhering to the ARV regimens during their transition from paediatric to adult care is the changing ARV regimens and doses (Centre for Disease Control and Prevention, 2020; 2021). Puberty is a time of somatic growth and sexual maturation with females developing more body fat and males

more muscle mass. These physiological changes may affect drug pharmacokinetics, which is especially important to consider when determining the dosing for antiretroviral (ARV) drugs (National Institute of Health, 2021). Optimising and simplifying treatment may be especially important when treating adolescents, as this can help improve adherence such as using a regimen with a fixed-dose combination tablet and therefore improving viral suppression (National Institutes of Health, 2021).

Furthermore, low adherence and retention among the adolescent population that result in low viral suppression rates among adolescents were also attributed to the lack of adolescent-specific services in health care facilities. Most ART programmes are focused on adult and child populations (Casale *et al.*, 2019). Adolescents generally access care either in paediatric or adult services. Furthermore, the inadequate experience and practice among healthcare workers in dealing with young HIV individuals has caused poor rates of retention among adolescents compared to other age groups (MacPherson *et al.*, 2015).

Other factors most frequently reported as barriers to adherence to ART are challenges to receive health care due to long travelling distance to the clinic, followed by the possibility that the adolescent's attendance at clinic visits would be noticed by friends or members of the school, having an elderly caregiver, high transport cost of the trip to the clinic and long waiting queues at the clinic (Maskew *et al.*, 2016).

The increasing HIV epidemic among adolescents highlights the pressing need for interventions and service models among the HIV adolescent population to improve retention in care and adherence to ensure viral suppression. Interventions focusing on improving adherence and retention are vital if we want to achieve global public health goals, namely, the 90-90-90 targets (UNAIDS, 2014).

1.2 PROBLEM STATEMENT

Irrespective of the suboptimal levels of viral load suppression (VLS) displayed by adolescents on ART, their situation is often overlooked because routine reporting in HIV programmes focuses mainly on outcomes for paediatric (0–14 years) and adult populations as mentioned previously. Furthermore, there are insufficient studies available examining the factors that results in lack of retention and adherence of ART among adolescents aged 10–19 years,

especially in the developing world. An analysis of the factors that affect viral suppression among adolescents (10–19 years) is critical to create interventions that target this key population and to realise UNAIDS 90-90-90 targets (UNAIDS, 2014).

Understanding the factors that affect the suboptimal viral suppression during the adolescent complex period (10–19 years) which is accompanied by rapid physical, psychological and physiological changes, which influence adolescent health-related behaviour (Ferrand *et al.*, 2016) will assist in creating intervention strategies that aim to narrow the gap between viral suppression among adolescents and adult. It was reported that young people (15–24 years) in Southern African countries were found to be two to three times less likely to be virally suppressed than middle-aged people (45–59 years), and viral non-suppression among men continue to be higher than women (Avert, 2020).

In South Africa, there is a relatively high proportion of adolescent patients with non-suppressed viral load. Zanoni *et al.* (2016) reported that among the estimated 867 283 HIV-infected youth aged 15–24 years in South Africa, only 10% of HIV-infected youth were virally suppressed in 2013. The low numbers of virally suppressed adolescents in South Africa reflect the lack of guidance on how adolescence can deal with their HIV situation and the low numbers of adolescents and young adults accessing ART (Centre for Disease Control and Prevention, 2021). These large numbers of non-suppressed adolescents are infectious agents that further increase the spread of the HIV epidemic.

To complicate matters further, there is a substantial national geographic variation in the distribution of HIV disease in South Arica (Shaikh *et al.*, 2006), and the response to the epidemic by provincial health authorities varies considerably. The Free State ranks eighth for the absolute number of 419 631 people living with HIV in the province and ranks third amongst the nine provinces in South Africa in terms of prevalence at 14.6% (MacDonell & Low, 2019). Moreover, the Free State province is still struggling to reach the UNAIDS's 90-90-90 targets adopted by South Africa, to contribute to the ending of HIV by 2030 (UNAIDS, 2014). Reports have shown that the Free State has 59.9% of people living with HIV in the province who are both accessing antiretroviral treatment and have a suppressed viral load (less than 1,000 copies/ml). It has been observed that the greatest barrier to achieve the 90-90-90 targets in all provinces including the Free State is ensuring that people with diagnosed HIV are receiving ART (MacDonell & Low, 2019).

In the Free State, Thabo Mofutsanyane District has the highest number of HIV cases (100 361 HIV cases) (IHME, 2017) and ranks second when it comes to the highest incidence rate of HIV (10.6 rate per 100 000 population) in the province (South African National AIDS Council, 2018). It was against this background that this study explored the predictors of viral suppression among adolescents on ART in Thabo Mofutsanyane District.

1.3 AIMS AND OBJECTIVES

The aim of the study was to determine predictors of viral suppression among adolescents on ART in Thabo Mofutsanyane District Municipality, Free State province, South Africa.

The objectives for this study were:

- To describe viral suppression amongst adolescents who have been on antiretroviral therapy for at least 6 months.
- To describe socio-demographic, baseline clinical profile, treatment, and retention in care of adolescents on ART in public primary health care facilities in the Thabo District, Free State.
- To determine socio-demographic characteristics associated with viral suppression among adolescents.
- To determine clinical factors associated with viral suppression among adolescents.
- To determine if retention in care is associated with viral suppression among adolescents.

1.4 OUTLINE OF MINI-THESIS

Chapter 2: Explores the literature on factors associated with viral suppression among adolescents globally, in the sub-Saharan and African region and in South Africa.

Chapter 3: Describes the methodology of the study. The methodology will outline the study design, the study's settings, the study population, and sampling method used, the data collection method and data analysis. This section will also explain the strategies that were implemented in the study to improve validity and reliability of the results. The last section in this chapter is a summary of ethical consideration.

Chapter 4: The study results are presented. Descriptive and analytical results are detailed to allow interpretations, inferences, and conclusions to be drawn.

Chapter 5: Presents a discussion of the study's results. Moreover, the study's results will be compared to the results of other related and similar studies in the literature.

Chapter 6: Presents the study's conclusions and recommendations drawn from the research findings and study limitations.

CHAPTER 2: LITERATURE REVIEW

2.1 INTRODUCTION

The sub-Saharan African region in Africa is only home to only 14% of the global population (Federal Reserve Bank, 2019), yet it carries the highest burden of HIV among adolescents of 10–19 years, 2019 reports indicated that about 1.5 million [1.0 million–2.1 million] (88%) HIV-infected adolescents live in sub-Saharan Africa, which is 88% of the total number of adolescent HIV infections (UNICEF, 2020). Within the sub-Saharan region, South Africa accounts for a third of all new HIV infections in southern Africa and has the highest profile of HIV epidemic in the world (Avert, 2019). In the sub-Saharan region, South Africa is considered as the largest ART programme in Africa and the world (UNAIDS, 2020a). The key goal of ART is to suppress the replication of the virus. Suppressed viral replication facilitates restoration of the immune function and significantly reduces the risk of onward HIV transmission (National Institute of Health, 2021). The South African National Department of Health (NDOH) guidelines use viral load monitoring as a gold standard to follow up the treatment effectiveness (NDOH, 2019), as recommended by WHO (2013a).

2.2 VIRAL LOAD MONITORING

The WHO (2013b) recommends viral load (VL) testing as the preferred method for monitoring the clinical response of patients with HIV to ART. The magnitude of VL decline after initiation of ART provides prognostic information about the probability of disease progression (NDOH, 2019; Murray, 1999). Moreover, VL monitoring is used to assess adherence to ART particularly in the case of VLS which serves as a reasonably reliable marker of good adherence (NDOH, 2019). According to the National South African guidelines, viral suppression is defined as VL below 1 000 copies/ml after at least six months of using ART (NDOH, 2019). The WHO (2013a) recommends routine VL monitoring after six months on ART and then at least every 12 months to detect treatment failure earlier and more accurately. In patients with unsuppressed VL, South African NDOH (2019) and the WHO (2013b) guidelines recommend adherence counselling and repeat testing.

Patients with repeated high VLs can eventually reach virological failure, which is defined as a plasma VL of more than 1000 copies/ml based on two consecutive VL measurements after three months with adherence support (NDOH, 2019; WHO, 2013a).

VL testing requires blood to be drawn from the patient, which is sent to a laboratory where the viral load is measured. The patient will then have to attend another appointment at the healthcare facility to receive his results. Point-of-care (POC) VL testing is another method of obtaining a VL result while the patient is present (Phillips *et al.*, 2016). It is currently being used in resource-limited settings, in research and technology development (Marcus *et al*., 2017). The advantage of the POC testing is that it provides an immediate result which gives the clinician a result which would immediately determine whether adherence support and interventions need to be initiated. This method provides immediate results and thus decreases the number of visits required to obtain and report the result to the patient which is more convenient to the patient.

2.3 VIRAL LOAD OUTCOMES IN ADOLESCENTS ON HIV TREATMENT

Previous studies have demonstrated that, even on treatment, adolescents exhibit the worst health outcomes compared to all other age groups (Adejumo *et al.*, 2015; UNAIDS, 2017). In South Africa, which houses the world's largest ART programme, adolescents have repeatedly demonstrated the lowest rates of retention in care and viral suppression compared to other age groups (Zanoni *et al.*, 2016). A meta-analysis of eight studies as part of a review of the adolescent HIV continuum of care in South Africa reported that the proportion of South African adolescents and young adults on ART who were virally suppressed was 81% (95% CI 74% - 87%) (Zanoni *et al.*, 2016). As part of a literature review, Ferrand *et al.* (2016) found that in six studies which assessed VLS at time points reported at one-year post-ART initiation, VLS rates of adolescents varied considerably, ranging from 27% to 89%. Data from clinical records in Eastern Cape, South Africa facilities revealed that 47.5% of adolescents were fully virally suppressed at the most recent test but only 23.2% were recorded as fully virally suppressed within the past 12 months. Younger adolescents (AOR 1.39 [95% CI 1.06–1.82]) and those on ART for ≥2 years (AOR 1.70 [95% CI 1.12–2.58]) were more likely to be fully viral suppressed (Haghighat *et al.*, 2021).

Previous studies in South Africa and in other African countries have demonstrated that predictors of unsuppressed viral loads and ART failure include individual-related factors (age, gender, mental health, forgetfulness, substance abuse, literacy level, perceived health status); medication-related factors (side effects, dosing frequency, treatment duration); health system factors (access to ART services, availability of medication, relationship with health care providers, quality of services delivery); socioeconomic factors (poverty, family support, transport, food, stigma, discrimination); and socio-cultural factors (religion, traditional health-seeking behaviour) (Mukumbang *et al.*, 2017).

2.4 DEMOGRAPHIC FACTORS

Several studies have shown associations between age and gender of the adolescent, and VLS (Avert, 2016; Nglazi *et al.*, 2012).

2.4.1 Age

Age was found to have a strong association with VLS in various studies with the risk and vulnerability of HIV-infected adolescents evident when comparing their VL outcomes to those of other age groups (Avert, 2016; Nglazi *et al.*, 2012). A descriptive study looking at VL detectability in paediatric, adolescent, and adult ART patients in Swaziland reported that patients had a significantly higher likelihood of having a detectable VL if they were younger than 20 years of age (Jobanputra *et al.*, 2015). Numerous studies found adolescents to have lower rates of virological suppression than adults (Avert, 2016; Nachega et al, 2009; Nglazi *et al.*, 2012; Ryscavage *et al.*, 2011). Nglazi *et al.* (2012) found that adolescents in the community-based ART programme in Cape Town, South Africa have a low rate of virological suppression and increased rate of virological failure, which he pointed out as concerning, considering the long-term antiretroviral need these adolescents have. Another study in the public health sector in the peri-urban settlement (Khayelitsha, Cape Town) by Van Cutsem *et al.* (2010) observed slightly different results, where virological outcomes were worse for young adults (20–24 years) when compared to those in the adolescents (10–19 years) and adults (≥ 25 years).

A study that followed adolescents initiated on ART in public health facilities in the Metropole District Health Services of the Western Cape province revealed that younger adolescents (10–

14 years) had better VLS rates at months 4, 12 and 24 compared to older adolescents (15–19 years); with significant differences at month 12 (63.4% vs 34.6%; p = 0.001) and month 24 (58.5% vs 17.3%; p < 0.001) (Van Wyk *et al.*, 2020). In addition, the study found that younger adolescents (10–14 years) demonstrated better retention in care compared to the older group, possibly resulting in better VLS rates (Van Wyk *et al.*, 2020). Lack of retention among older adolescents appeared to correspond to the transition of adolescents from paediatric to adult HIV programmes – a known high-risk period for disengagement with care (Cervia, 2013; Pinzón-Iregui *et al.*, 2017; Vijayan *et al.*, 2009). Moreover, this observation could also be attributed to the disproportionate attention offered to the younger group.

Although adolescents face unique challenges during ART, there is a shortage of comprehensive health services and interventions that attend specifically to this group to improve retention in care in sub-Saharan African regions (Adejumo *et al.*, 2015). Nonetheless, younger adolescents show better retention rates because they depend on their adult caregivers to manage their ART regimens. Conversely, a study conducted in Zimbabwe to investigate the retention in care rates between younger and older adolescents in Zimbabwe demonstrated no differences in attrition amongst younger versus older adolescents (Matyanga *et al.*, 2016).

2.4.2 Gender

The association between gender and VLS has been debated in the literature. Gender has been a factor with various results associated with VLS. In a study conducted in South Africa, males were found to be significantly more likely to be virologically suppressed at months 4, 12 and 24 than females (Kriel, 2017; Van Wyk *et al.*, 2020). Different results were observed in the PEPFAR statistics for the national sub-Saharan African countries' household survey (Avert, 2016). These statistics showed that in Zimbabwe suppression rates among the HIV-infected adolescents and young adult females (15–24 years) were 48.6% with lower suppression rates of 40.2% among the HIV-positive males. In Malawi, 51.9% of adolescent and young adult women had virological suppression compared to the 36.7% of men (Avert, 2016). Another retrospective cross-sectional study among adolescents and adults on ART in northern Ethiopia revealed that the likelihood of developing viral non-suppression for male patients was 1.27 times (AOR = 1.27, 95% CI: 1.18, 1.37) more likely than with female patients (Desta *et al.*, 2020). Several authors claim that the reason why males were prone to viral non-suppression might be due to poor health-seeking behaviour (Dalhatu *et al.*, 2012; Heestermans *et al.*, 2016; Jobanputra *et al.*, 2015; Penot *et al.*, 2014). Nevertheless, different results were observed in

Zambia, where males and females aged 15–24 years had very similar suppression rates of 35.7% and 34.0%, respectively (Avert, 2016).

2.5 CLINICAL FACTORS

The median duration to suppress the VL from the initiation of ART to suppression of the VL below 1000 copies/ml range from one month to seven months (Howard *et al.*, 2002; Monforte *et al.*, 1998; Spacek *et al.*, 2006; Thiébaut *et al.*, 2000). The literature has indicated that clinical factors of high significance in viral suppression and treatment outcomes are baseline CD4 counts; WHO clinical stage at ART initiation and presence of opportunistic infections (Ayele *et al.*, 2015); pregnant at ART initiation (Hodgson *et al.*, 2014; Kriel, 2017, Wang *et al.*, 2011); history of TB (Bulage *et al.*, 2017); Cotrimoxazole Prophylaxis Treatment (CPT) (Mermin *et al.*, 2004); and Isoniazid Preventive Therapy (IPT) (Okonji *et al.*, 2021).

2.5.1 Baseline CD4 count

Baseline CD4 count levels have been found to be associated with VL as reported by Jobanputra *et al.* (2015). Individuals with CD4 counts between 350–499 cells/mm³ are considered as having mild immunosuppression; those with 200–349 cells/mm³ have advanced immunosuppression; and those with CD4 counts less than 200 cell/mm³ have severe immunodeficiency (WHO, 2007). Response to ART is affected by the immune stage at which it is started; for example, people commencing ART with advanced immunodeficiency (CD4 > 200–350 per mm^3) appear to have better virological outcomes than those who commence with more severe immunodeficiency (Bennett *et al.*, 2002; Bonnet *et al.*, 2005; Grabar *et al.*, 2005). Patients with CD4 counts less than 350 cells/mm³ and are under 20 years of age were significantly more likely to have unsuppressed viral loads (Jobanputra *et al.*, 2015). Desta *et al.* (2020) has also shown that adolescents and adults who had a baseline CD4 count of < 200 cells/mm^3 were 1.33 times (AOR = 1.33, 95% CI: 1.14, 1.54) more likely to have viral non-suppression compared to patients with ≥500 CD4 count at baseline

On the other hand, Phillips *et al.* (2001) who analysed data from the databases of three studies in the Swiss HIV Cohort Study (SHCS), found that lower CD4 cell count at baseline was not associated with poorer virological outcome of ART. Nevertheless, patients with low baseline CD4 cell counts (< 200 × 10^6/L) showed a slightly lesser tendency to achieve viral suppression;

but there was no apparent difference between the two higher CD4 cell count categories (< or equal to 350×10^6/L and 200-349 $\times 10^6$/L). The difference in virological load and the difference in baseline CD4 count was not statistically significant.

2.5.2 WHO Staging

The WHO Clinical Staging system has been shown to be a practical and accurate way to manage HIV-infected patients, with international studies showing agreement between clinical manifestations included in the WHO staging system and laboratory markers including CD4 cell count and total lymphocyte count (Kagaayi *et al.*, 2007; Kassa *et al.*, 2007; Lynen *et al.*, 2006; Malamba *et al.*, 1999). The WHO system categorises adults and adolescents' patients 15 years of age and older into one of four hierarchical clinical stages ranging from Stage I (asymptomatic) to Stage IV (AIDS). Patients are assigned to a particular stage when they demonstrate at least one clinical condition in that stage's criteria. Patients remain at a higher stage after they recover from the clinical condition which placed them in that stage (Malamba *et al.*, 1999). Stage I patients are asymptomatic or have persistent generalised lymphadenopathy (lymphadenopathy of at least two sites [not including inguinal] for longer than six months), where they may remain for several years (National Department of Health, 2010). In Stage II even in early HIV infection, patients may demonstrate several clinical manifestations. Clinical findings included in Stage II (mildly symptomatic stage) are unexplained weight loss of less than 10% of total body weight and recurrent respiratory infections (such as sinusitis, bronchitis, otitis media, and pharyngitis), as well as a range of dermatological conditions including herpes zoster flares, angular cheilitis, recurrent oral ulcerations, papular pruritic eruptions, seborrhoeic dermatitis, and fungal nail infections (WHO, 2005). Those encompassed by the WHO clinical Stage III (the moderately symptomatic stage) category are weight loss of greater than 10% of total body weight, prolonged (more than one month) unexplained diarrhoea, pulmonary tuberculosis, and severe systemic bacterial infections including pneumonia, pyelonephritis, empyema, pyomyositis, meningitis, bone and joint infections, and bacteraemia. Mucocutaneous conditions, including recurrent oral candidiasis, oral hairy leukoplakia, and acute necrotising ulcerative stomatitis, gingivitis, or periodontitis, may also occur at this stage (WHO, 2005). The WHO clinical Stage IV (the severely symptomatic stage) designation includes all of the AIDS-defining illnesses. Clinical manifestations for Stage IV disease that allow presumptive diagnosis of AIDS to be made based on clinical findings alone are HIV wasting syndrome, Pneumocystis pneumonia (PCP), recurrent severe or radiological bacterial

pneumonia, extrapulmonary tuberculosis, HIV encephalopathy, CNS toxoplasmosis, chronic (more than one month) or orolabial herpes simplex infection, esophageal candidiasis, and Kaposi's sarcoma (WHO, 2005).

Patients remain at a higher stage after they recover from the clinical condition which placed them in that stage (Malamba *et al.*, 1999). Jobanputra *et al.* (2015) who explored factors associated with virological detectability in Swaziland children and adults on ART reported that patients with WHO Stage III and IV disease and CD4 count less than 350 cells/mm^3, were significantly more likely to have unsuppressed viral loads.

Another study conducted in the Cape Metropole in South Africa that followed adolescents' data for two years found that WHO Stage IV at baseline had the most favourable VLS rates at months 12 and 24 and those with WHO Stage III at baseline had better suppression rates at month 4 (Kriel, 2017). Moreover, Desta *et al.'s* (2020) study found that the likelihood of developing viral non-suppression for patients in WHO Stage II was 1.31 times (AOR = 1.31, 95% CI: 1.10, 1.54) more likely when compared with patients in WHO Stage I (Desta *et al.*, 2020).

However, other studies revealed that the WHO stage was not associated with virological failure (Bayu *et al.*, 2017; Hailu *et al.*, 2018; Rangarajan *et al.*, 2016). These variations might be due to the use of different WHO definitions or variations in practice among the different health care providers (Desta *et al.*, 2020).

2.5.3 History of Tuberculosis

Tuberculosis (TB) infection remains a significant challenge for the immuno-compromised HIV patients. TB is the commonest opportunistic infection resulting in significant morbidity and is also the leading cause of mortality in HIV-infected individuals (WHO, 2017). Having an active opportunistic infection like TB was associated with low viral suppression across all age categories in Uganda (Bulage *et al.*, 2017). Another study evaluating factors associated with unsuppressed VL (VL > 400 copies/ml) in patients in care on first-line ART for ≥ six months attending South African public healthcare facilities, highlighted that youth/adolescents and patients on TB treatment had increased odds of not achieving viral suppression (Davey *et al.*, 2018).

2.5.4 Pregnant at initiation

Another clinical factor that was suggested to affect viral suppression was pregnancy (Hodgson *et al.*, 2014; Kriel, 2017; Wang *et al.*, 2011). Factors such as early sexual debut, and additional risk behaviours such as older and concurrent sexual partners and inconsistent contraception use among adolescent females (Hargreaves *et al.*, 2008; Idele *et al.*, 2014; Nyanzi *et al.*, 2001) resulted in an increased risk for both HIV infection and pregnancy during adolescence (Delany-Moretlwe, 2013). It was reported that HIV-infected pregnant women (younger than 30 years) had higher unsuppressed viral loads compared to men and non-pregnant women due to LTFU (Wang *et al.*, 2011) and poor adherence to ART (Hodgson *et al.*, 2014). A systematic review of factors affecting ART initiation, adherence, and retention of HIV-infected pregnant and postpartum women by Hodgson *et al.* (2014) found that reported barriers to initiation and adherence were poor understanding of HIV, ART, and the prevention of mother-to-child transmission (PMTCT) programme. Women expressed fears that ART may harm the developing foetus and also felt that it was unnecessary to initiate ART as they felt very healthy.

Kriel's (2017) study also showed a significantly greater proportion of non-pregnant compared to pregnant adolescents that were virologically suppressed at months 4 (67.6% vs 46.4%: $p = 0.002$), 12 (46.3% vs 29.8%: 0.015) and 24 (35.3% vs 8.3%: $p < 0.001$). In addition, Kriel (2017) also observed that pregnant females who initiated ART in their first trimester had significantly better VLS results in the first year post-ART initiation, i.e. 80.0% and 60.0% VLS at months 4 and 12 respectively. Early antenatal care can provide opportunities to educate the pregnant adolescent on HIV and ART and assist with any barriers to poor adherence to achieve favourable outcomes for her as well as the baby.

Furthermore, a cohort study conducted in Rio de Janeiro comparing epidemiological, clinical, and laboratory data between perinatally (PHIV) and behaviourally (BHIV) HIV-infected pregnant youth observed that, although not significantly different, there was a trend for PHIV (31%) to be more likely to achieve viral suppression at delivery than BHIV (21.3%) women (Lundberg *et al.*, 2018). This may be attributed to the fact that they were more likely to start ART prior to pregnancy or during the first trimester (Lundberg *et al.*, 2018).

The high viral loads in pregnant adolescent mothers have poor clinical outcomes for the mother and her child (Callahan *et al.*, 2017). While limited current evidence suggests that HIV-exposed infants of adolescent mothers have poorer HIV-related clinical outcomes than infants of older

women, one study found that a higher proportion of infants of adolescent mothers were infected with HIV than infants of adult mothers (10.8% vs. 6.1%, OR 1.7, 95% CI 1.2–2.4) (Ronen *et al.*, 2017), likely reflecting the suboptimal virologic suppression, service uptake, adherence and virologic suppression seen in adolescent populations (Woldesenbet *et al.*, 2015).

The sub-Saharan African region lacks PMTCT settings targeting HIV-infected pregnant adolescents with enhanced retention and follow-up activities, where the limited evidence available suggests that higher rates of mother-to-child HIV transmission among infants of HIV-infected pregnant adolescents (Callahan *et al.*, 2017).

2.5.3 Cotrimoxazole Prophylaxis Treatment

Cotrimoxazole is a fixed-dose combination of two antimicrobial drugs (sulfamethoxazole and trimethoprim) that covers a variety of opportunistic bacterial, fungal and protozoan infections in people living with HIV/AIDS (PLWHA) (Sisay *et al.*, 2018; WHO, 2013c). CPT is reported to be an inexpensive, well-tolerated intervention for people living with HIV to reduce HIV related morbidity and mortality (WHO, 2013c). In addition, cotrimoxazole is widely available in resource-limited settings (WHO, 2016). Cotrimoxazole prophylaxis reduces morbidity and mortality among people living with HIV in sub-Saharan Africa, regardless of age, degree of immunosuppression, disease stage or duration of ART (Suthar *et al.*, 2012; Walker *et al.*, 2010). A systematic review of cotrimoxazole prophylaxis along with the initiation of ART in HIV-infected adolescents (> 13 years of age) and adults in resource-limited settings showed a reduction in mortality of 58% (95% CI 39 to 71) (Suthar *et al.*, 2012).

The WHO recommends that cotrimoxazole prophylaxis must be implemented as an integral component of the HIV care package (WHO, 2016). The WHO (2016) recommends cotrimoxazole for adults (including pregnant women) with severe or advanced HIV clinical disease (WHO Stage III or IV) and/or with a CD4 count of ≤350 cells/mm^3; in settings where malaria and/or severe bacterial infections are highly prevalent, cotrimoxazole prophylaxis should be initiated and continued regardless of CD4 cell count or WHO stage; routine cotrimoxazole prophylaxis should be administered to all HIV-infected people with active TB disease regardless of CD4 cell counts (WHO, 2016). The WHO (2016) also stated that cotrimoxazole prophylaxis may be discontinued for adults (including pregnant women) with HIV infection who are clinically stable on ART, with evidence of immune recovery and viral suppression.

In addition, cotrimoxazole prophylactic effect prevents the development of a range of opportunistic infections such as PCP, toxoplasmosis, and bacterial infections. Some studies have also reported slowing down the decline in CD4 T-cells and lowering the annual rate of VL increase (Mermin *et al.*, 2004; Wiktor *et al.*, 1999). A 19-month follow-up cohort study of 509 people with HIV in Uganda, found that the mean annual rate of CD4 decline slowed during cotrimoxazole treatment, from 203 to 77 cells/mm^3 per annum and the mean annual rate of VL increase fell from 0.90 to 0.08 $\log_{10}$ per annum (Mermin *et al.*, 2004). Another study in Ethiopia found that baseline CPT had an effect on the duration of VLS. Patients with early initiation of CPT were two times more likely to suppress the VL earlier than those patients who had not initiated CPT.

Other studies on cotrimoxazole prophylaxis in Africa have produced conflicting results disregarding the benefits of cotrimoxazole on HIV-infected patients (Manyart *et al.*, 2001; Kalou *et al.*, 2005). A randomised controlled study in Senegal that assessed the efficacy and tolerance of chemoprophylaxis with cotrimoxazole (80 mg of trimethoprim and 400 mg of sulphamethoxazole) compared with placebo among HIV-1-infected adults showed that there is no beneficial effect of chemoprophylaxis with low-dose cotrimoxazole on survival or occurrence of opportunistic or non-opportunistic infections for HIV-1-infected patients (Manyart *et al.*, 2001). However, another study in Abidjan, Côte d'Ivoire found that levels of VL CD4+ T-cell counts, and markers of immune activation were not different for patients on the standard treatment of TB compared with those on standard and cotrimoxazole treatment (Kalou *et al.*, 2005).

2.5.5 Isoniazid Preventive Therapy

HIV is the strongest risk factor for developing TB disease in those with latent or new Mycobacterium tuberculosis infection. The risk of developing TB is between 20 and 37 times greater in people living with HIV than among those who do not have HIV infection (WHO, 2010). TB is responsible for more than a quarter of deaths among people living with HIV (Getahun *et al.*, 2010). In response to the dual epidemics of HIV and TB, WHO has placed interventions that reduce the morbidity and mortality from TB in people living with HIV, such as the provision of ART and the Three I's for HIV/TB: intensified case-finding of TB, infection control for TB and IPT (WHO, 2021).

It has been known for many years that IPT for PLHIV prevents TB. The WHO recommends that PLHIV who are unlikely to have active TB should receive at least six months of self-administered IPT (5mg per kg ((max 300mg)) as part of a comprehensive package of HIV care. Individuals should be seen monthly and given only one month's supply of medication at each visit (WHO, 2010; 2021). There is evidence that giving IPT for at least 36 months is beneficial in setting with a high prevalence of TB and a high likelihood of transmission. The effects of IPT augment the effects of ART on reducing the incidence of TB. Although IPT uptake is increasing, fewer than 25% of persons living with HIV and who are in care are receiving it (WHO, 2021).

The WHO (2021) recommends that IPT should be provided to Tuberculin Skin Test (TST) positive HIV individuals. However, operational difficulties in the provision of TST are sometimes perceived to be a barrier to the provision of IPT. Therefore, the WHO strongly recommends that in resource-constrained settings, TST should not be a requirement for initiating IPT and that PLHIV should be started on IPT following negative symptom-based screening. In addition, PLHIV who are household or close contacts of people with TB and who after an appropriate clinical evaluation are found not to have active TB should be treated for presumed latent TB infection (LTBI) with IPT. The WHO reported that PLHIV has demonstrated that IPT is more effective in those with a TST than those with an unknown or negative test (WHO, 2021). The WHO (2021) therefore recommends that the TST should be used where it is affordable and available. This was echoed in South Africa where the NDOH (2019) included these recommendations in the National ART Guidelines.

Another perceived barrier to commencing IPT is the fear that individuals may develop drug-resistant TB following IPT. Large trials, however, have shown that drug-resistant TB rates are not raised among those who develop TB following IPT, compared to those expected of people living with HIV (Fielding *et al.*, 2011).

In addition to effectively preventing TB in patients infected with HIV (Akolo *et al.*, 2010), IPT was also found to affect VL (Sultan *et al.*, 2019; Okonji *et al.*, 2021). A prospective follow-up study that investigated 3 927 adult PLWHIV on first-line ART in Ethiopia concluded that baseline IPT along with baseline CD4 count, baseline VL, CPT, IPT and adherence level are identified as the independent predictors of time to HIV VLS (Sultan *et al.*, 2019). This study depicts that the average time to VLS during the study period was three months (Sultan *et al.*, 2019). A retrospective study investigating VLS among adolescents on ART in Ehlanzeni

District, Mpumalanga, South Africa found that adolescents who started on IPT after ART initiation were more likely to attain viral suppression compared to those who did not (Okonji *et al.*, 2021).

2.6 ART REGIMEN

The goals of ART are to provide maximal and durable suppression of VL, restore and preserve immune function, reduce HIV related infectious and non-infectious morbidity, prolong life expectancy and improve quality of life, prevent onward transmission of HIV and minimise adverse effects of the treatment (Meintjes *et al.*, 2017). These goals can be achieved by suppressing viral replication completely for as long as possible, by using well-tolerated and sustainable treatment taken with good adherence. With prolonged viral suppression, the CD4+ lymphocyte count usually increases, which is accompanied by a restoration of the pathogen-specific immune function. It is still unclear whether the immune function ever returns to full normality (Meintjes *et al.*, 2017). However, long-term cohorts show that patients who adhere well to ART have a near-normal life expectancy (Johnson *et al.*, 2013).

Effective and suppressive ART regimens should be used in the treatment of HIV-infected individuals to obtain optimal results and to prevent resistance (Meintjes *et al.*, 2017). The most common drug classes used in South Africa that inhibit key HIV enzymes required by the virus for intracellular replication are reverse transcriptase inhibitors (reverse transcriptase is essential for the completion of early stages of HIV replication); integrase inhibitors, which are required for the integration of proviral DNA into the host chromosomal DNA; and protease inhibitors (PI) which are required for the assembly and maturation of infectious viral progeny (Meintjes *et al.*, 2017).

The most common and available drugs in southern Africa include Nucleoside and nucleotide reverse transcriptase inhibitors (NRTI), Tenofovir (TDF), Lamivudine (3TC), Emtricitabine (FTC), Abacavir (ABC), Zidovudine (ZDV) Stavudine (d4T), Didanosine (ddI), Efavirenz (EFV), Nevirapine (NVP), Rilpivirine (RPV) and Etravirine (ETR). PIs include Atazanavir (ATV), Lopinavir/ritonavir (LPV/r), Darunavir (DRV) and Saquinavir (SQV). Integrase inhibitors (also termed as integrase strand transfer inhibitors) are Raltegravir (RAL) and Dolutegravir (DTG) (Meintjes *et al.*, 2017).

The current South African National guidelines state that all people living with HIV (PLHIV) are eligible to start ART regardless of their age, CD4 cell count and clinical stage (NDOH,

2019). However, in some circumstances, ART treatment is deferred. Such circumstances include patients diagnosed with TB, as when TB treatment is initiated, ART is delayed. Starting time of ART will depend on the site of TB (neurological or non-neurological) and CD4 counts (more or less than 50 cells/μL). Moreover, pregnant women, infants and children under five years, and clients with advanced HIV disease should be prioritised for rapid ART initiation (NDOH, 2019).

The current preferred first-line ART regimen in previously untreated patients is: TDF + emtricitabine (FTC) (or 3TC) + efavirenz (EFV) or TDF + emtricitabine (FTC) (or 3TC) + dolutegravir (DTG) or TDF + emtricitabine (FTC) (or 3TC) + rilpivirine (RPV) provided VL < 100 000 copies/mL (Meintjes *et al.*, 2017; NDOH, 2019). A baseline resistance test is recommended to guide first-line regimen choice in only in two situations: pre-exposure prophylaxis (PrEP) received in the previous six months or a patient with history of sexual exposure to a person with known drug-resistant HIV or known to have failed an ART regimen (Meintjes *et al.*, 2017).

A fixed-dose combination (FDC) where two or more drugs are incorporated in a single dosage form, such as a capsule or tablet, allows a once-daily dosage and better adherence (Meintjes *et al.*, 2017). TDF is the favoured NRTI to use with 3TC, as it aligns with public sector programmes. It is also widely available as an FDC and is very well-tolerated. However, patients with a Creatine Clearance of < 50 mL/min should not start TDF and should rather start ABC. A meta-analysis showed that virological suppression is equivalent with ABC- and TDF-containing first-line regimens regardless of baseline VL (Sabin *et al.*, 2008).

The third drug in the first-line regimen is Efavirenz (EFV), dolutegravir or rilpivirine. The WHO guidelines currently recommend efavirenz-based first-line ART, with EFV 600 mg as the preferred option and EFV 400 mg as an alternative option. EFV 400 mg is currently not available in FDCs, and for this reason, it is not recommended as a first-line ART (Meintjes *et al.*, 2017). Dolutegravir is now available as an alternative for first-line ART in the private sector. It is included in the first-line regimen in the public sector in Botswana and is likely to be accessible in public sectors in other countries in the region when affordable generic options become available at scale. Dolutegravir has been shown to be superior to efavirenz-based ART in the single trial and also has a higher barrier to resistance (Walmsley *et al.*, 2015). Dolutegravir is preferred to the other integrase inhibitor available in Southern Africa because it has a higher barrier to resistance (Meintjes *et al.*, 2017).

After the patient receives his ART, the patient must be followed up after three months (this early VL is desirable to detect adherence problems early, before resistance develops), six months and then six-monthly. VL monitoring is key to the success of ART. Decisions to change ART made on the basis of virological failure, rather than on clinical or immunological failure alone, have been shown to result in better patient outcomes (Tucker *et al.*, 2014). Treatment success is defined by a decline in VL to < 50 copies/ mL within six months of commencing ART, and sustained thereafter (Meintjes *et al.*, 2017). Treatment failure is defined by a confirmed VL of > 1000 copies/mL on two measurements taken 2–3 months apart (NDOH, 2019). Several factors can influence the measurement of the VL. The decision to alter ART should, therefore, be based on the results of repeat testing after 2–3 months, following intensive adherence counselling. Inadequate patient adherence to the prescribed regimen remains the most common reason for treatment failure (Meintjes *et al.*, 2017).

Changing the first-line ART regimen to a second-line regimen is a major step. The drugs used in second-line regimens are often not as well-tolerated and are more expensive and generally require twice-daily dosing (Meintjes *et al.*, 2017). For this reason, clinicians tend to switch to second-line ART after a prolonged period of virological failure, causing a progressive increase in the accumulation of resistance mutations. If the patient is on an NNRTI-based first-line regimen, Meintjes *et al.* (2017) recommended switching to a second-line regimen without undue delay when two VL measurements have been > 1000 copies/mL, preferably with the measurements taken 2–3 months apart, with at least four weeks of an intensified adherence intervention in between. As for DTG, because of the high barrier to resistance of DTG, it is likely that many such patients will not have resistance and will merely require improved adherence on the same first-line regimen. For that reason, switching from first line dolutegravir-based ART to second line is only recommended if a resistance test is positive.

For the second-line ART regimen two NRTIs and a RTV-boosted (/r) PI are recommended (Meintjies *et al.*, 2017). Based on clinical trials demonstrating superior tolerability, the preferred PI in second-line therapy should be ritonavir-boosted atazanavir (ATV) 300 mg/RTV 100 mg daily. NRTI combinations advised for second-line regimens include either AZT + 3TC, or TDF + 3TC (FTC can be substituted for 3TC), depending on the likely mutational profile selected during the patient's first line NRTI combination.

Third-line ART is used when a patient has experienced virological failure on drugs from the NRTI, NNRTI and PI classes, and has documented PI resistance (Meintjes *et al*, 2015). Before

considering third-line therapy, adherence interventions should be intensified, and then checked. If there is still no viral suppression, then a resistance test should be performed to confirm the presence of resistance to the PI being used in second-line therapy. The decisions regarding treatment choices in third-line therapy are complex and need to be guided by resistance patterns found on resistance testing. It is essential that resistance tests are interpreted by an expert in conjunction with a full ART history. A number of drugs are available for use in third-line ART: InSTIs (DTG and RAL), the newer PI DRV and newer NNRTIs (ETR and RPV). These provide an opportunity for effective viral suppression with third-line therapy in the majority of patients, provided that adherence is optimal (Meintjes *et al.*, 2015; Yazdanpanah *et al.*, 2009).

Virological failure and development of viral drug resistance can result in reduced treatment options and disease progression (Meintjes *et al.*, 2017; Steegan *et al.*, 2009). Kriel (2017) investigated the VLS according to the different ART regimens at initiation among adolescents in South Africa. He found that ART regimen was significantly associated with VLS after 12- and 24-months post-ART initiation with highest rates of VLS found among adolescents on the Abacavir-based regimen which was the recommended first-line ART regimen for the younger adolescent, with suppression rates of 73.5% at month 4, 61.8% at month 12, and 64.7% at month 24. He claimed that this result may not be due to the actual regimen itself, but possibly linked to this regimen being the first-line ART regimen for younger adolescents. The Abacavir-based regimen given to the adolescent at initiation consists of three separate drugs, while older adolescents often receive an FDC of Tenofovir-based regimen at initiation (Kriel, 2017). The FDC has been shown to have definite benefits for programmes and patients particularly related to better adherence outcomes (Ramjan *et al.*, 2014). Therefore, the possible reason for better VL outcomes among young adolescents receiving Abacavir-based regimens compared to the older adolescent receiving the FDC of Tenofovir-based regimen is better retention in care (Kriel 2017; Van Wyk *et al.*, 2020). Most younger adolescents receive care in paediatric services and these services are often initiated and managed by outreach teams and support services (from non-profit organisations in conjunction with tertiary hospital collaboration), which vary from adult services. Moreover, young adolescents are also more likely to have a caregiver or treatment support people responsible for their treatment may all be contributing to more favourable retention rates as well as subsequent adherence benefits and VL monitoring efficiencies (Kriel, 2017; Van Wyk *et al.*, 2020).

A cross-sectional study on therapeutic regimen in adults, adolescents and children in Cameroon found that viral suppression appears higher in those treated with TDF (Tenofovir/nucleoside reverse transcriptase) + 3TC (Lamivudine/ nucleoside reverse transcriptase) + EFV (Efavirenz/non-nucleoside reverse transcriptase) (TLE) (83.2%) compared to other NNRTI-based or Protease inhibition based (PI/r-based) regimens (71.4%). In fact, this combination has been found to be equivalent or superior to its comparator arms (other nucleoside reverse transcriptase (NRTI)-backbone and/or NNRTI) in many studies (Keiser *et al.*, 2002; Mathews *et al.*, 2002; Nachega *et al.*, 2009; Tang *et al.*, 2012). Fokam *et al.* (2019) also found treatment failure rate at VS < 1000 copies/mL was higher among patients on second-line regimens compared to first-line patients (28.6% vs 20.1%, p = 0.037).

Desta *et al.*'s (2020) study among Ethiopian patients revealed similar results; where the likelihood of developing viral non-suppression in patients who were on a 1c (AZT-3TC-NVP) (Zidovudine-Lamivudine-Nevirapine) regimen was 1.32 times higher (AOR = 1.32, 95% CI: 1.22, 1.44) when compared with patients who were on a 1e (TDF-3TC-EFV) (Tenofovir)-Lamivudine -Efavirenze) regimen. A similar study in Nepal reported that a 1e (TDF - 3TC - EFV) (Tenofovir-Lamivudine-Efavirenze) regimen had a better virological response among Nepalese PLHIV (Ojha *et al*., 2016).

Moreover, other studies by Bain-Brickley *et al.* (2011) and Muri *et al.* (2017) demonstrated that adolescents on a Lopinavir/ritonavil (LPV/r) containing regimen had high viral suppression scores. Likewise, patients who were switched to second/third-line regimen had low risk of virological non-suppression (Bulage *et al.*, 2017).

However, other studies reported no association between the ART regimens used and viral non-suppression (Bayu *et al.*, 2017; Hailu *et al.*, 2018). This variation might be due to genetics and socio-demographic differences between study settings. All these variables may be associated with the observed viral non-suppression (Desta *et al.*, 2020).

A study from Uganda showed that second/third-line ART regimens were protective against non-suppression (Bulage *et al.*, 2017). However, the emergence of drug-resistant viruses limits the treatment options and increases the threat of morbidity and mortality.

In addition, the timeliness of switching to effective ART regimens after failure may also affect viral suppression. Adolescents with delayed switching from a failing ART regimen to an effective one experience virological failure and are at an increased risk of accumulating drug

resistance and mutations, resulting in fewer choices to active antiretroviral medications and a poor response to the new therapy (Salou *et al.*, 2016). In a study conducted in South Africa, Bernheimer *et al.* (2015) concluded that a large number of children did not achieve viral suppression due to a low rate of regimen changes despite failure of the first-line regimen.

2.7 BEHAVIOURAL AND SOCIAL FACTORS

HIV cure involves important behavioural and social processes that complement the domains of biomedicine (Grossman *et al.*, 2016). To move cure regimens through the translational research pathway, attention needs to be paid to both biomedical and socio-behavioural elements (Wilson *et al.*, 1995). While the behavioural and social sciences have made important contributions to HIV prevention (Tolley *et al.*, 2006) and treatment research, the HIV cure research field has yet to tap into the full potential of behavioural and social sciences research (BSSR). Behavioural and social factors include individual, interpersonal, community and structural factors that are relevant to HIV outcomes (Gaist *et al.*, 2017). Basic BSSR can provide the empirical foundation to understand values, beliefs, perceptions and lived experiences of key populations and communities of interest is vital to planning successful HIV cure and reduction in VL (Gaist *et al.*, 2017).

The next section highlights some behavioural factors that can affect viral suppression such as retention in care (Geng *et al.*, 2010), adherence (Flynn *et al.*, 2004; Murphy *et al.*, 2010) and alcohol use (Cruz *et al.*, 2014). Disclosure was also found to have a positive influence on viral suppression (Bain-Brickley *et al.*, 2011; Halperin *et al.*, 2013).

2.7.1 Retention in Care

Retention in care of HIV-infected patients on ART is critical for favourable clinical outcomes as it allows individuals to continue receiving ART without interruption (Geng *et al.*, 2010). Remaining engaged in care allows for the assessment of treatment success, for appropriate treatment adjustments, and allows patients to benefit from other services, support and prevention strategies offered by treatment programmes. Retention in care is not only of benefit to the individual but ultimately benefits the broader public as it contributes to effectiveness of ART programmes and controlling the epidemic as a whole. Suboptimal retention in care leads

to non-adherence to ART, which in turn, increases the risk to high viral loads, possible drug-resistant mutations, morbidity and mortality (Clouse *et al.*, 2013).

The WHO (2013b) defined retention in care as including all patients who are not registered as deceased, stopped treatment or loss to follow up for any reason. Patients retained in care are known to be alive and continuing to visit the clinic. The WHO retention in care definition translates into the following formula for measuring retention in care as equal to all patients ever started minus (death + stop + loss to follow up). LTFU is a term used to classify patients who fail to present to a clinic within a certain period of time. The WHO recommends using a period of 90 days since the last missed appointment as the criterion to classify a patient as LTFU. Patients who are less likely to be retained are more likely to have non-viral suppression,

Several studies demonstrated that adolescents seem to have lower retention rates than other age groups. A retrospective cohort study done in an American hospital outpatient HIV clinic compared outcomes of older HIV-infected adolescents and young adults (17–24 years) and HIV-infected adult controls (25–40 years) initiating ART in a programme, showed that adolescents and young adults demonstrated higher rates of LTFU compared with adults (Ryscavage *et al.*, 2011).

In the African context, similar results were observed in a retrospective cohort study on ART patients attending an ART clinic in a hospital in Ethiopia. The study found that being adolescent placed the patient at higher risk of LTFU (Berheto *et al.*, 2014). Another retrospective cohort study in a Zimbabwean public sector hospital clinic with an adolescent-focused service, compared outcomes of adolescents and adults and found that adolescents had rates of LTFU significantly higher than adults (Shroufi *et al.*, 2013). Ssali *et al.'s* (2014) study in Uganda also found that the risk of non-retention in adolescents was significantly greater among those who obtained their ART refills from a health facility than those accessing their refills at community drug distribution sites. This was found at 12-, 24-, and 36-months post-ART initiation.

Furthermore, when disaggregating younger and older adolescents van Wyk *et al.*'s (2020) study among South African patients found that older adolescents (15–19 years) were significantly less likely to be retained in care over the first 24 months, compared with younger adolescents. Likewise, an observational prospective cohort study in rural Zimbabwe demonstrated that LTFU was highest among the young adults (19.1–24 years), at 16.8 per 100

person years, and lowest in the young adolescent age group (10–15 years), at 4.2 per 100 person years (Bygrave *et al.*, 2012).

Studies investigating retention among adolescents' report trends of low retention in care (Kranzer *et al.*, 2017; Okoboi *et al.*, 2016). This trend is claimed to result from the transition of adolescents from paediatric to adult HIV programmes which is known to be a high-risk period for disengagement with care (Cervia, 2013; Dahourou *et al.*, 2017). This also highlights those variations in behaviour, risks and needs within the spectrum of adolescents need to be considered or further explored when considering programme planning (Van Wyk *et al.*, 2020).

Multiple studies indicate that patients retained in care are more likely to achieve viral suppression compared to those not engaged in regular care (Giordano *et al.*, 2007; Mugavero *et al.*, 2012; Tripathi *et al.*, 2011). Among 2 197 South Carolina HIV-infected residents entering care between 2004 and 2007, 50% were retained in care. Patients retained in care had a greater decrease in HIV VL from baseline compared to those with suboptimal retention in care (Tripathi *et al.*, 2011) Likewise, among 8 235 patients followed for 12 months at six HIV clinics, retention in care, regardless of the measure used, was significantly associated with viral suppression (Mugavero *et al.*, 2012). Yehia *et al.* (2014) further demonstrated that retention in care is even more strongly associated with viral suppression in patients with lower CD4 counts.

Tailoring of services for adolescents and integrating other health services may improve retention, as reported by Lamb *et al.* (2014) where youth (15–24 years) accessing ART at facilities that provided sexual and reproductive health services and adolescent support groups had significantly lower attrition rates. Massavon *et al.* (2014) also reported that the site of ART services impacts on retention rates, with higher retention in care rates found in the community home-based care approach than the facility-based/family-centred approach (94% vs. 84.7%, respectively).

2.7.2 Adherence

The WHO (2015) defined adherence as the extent to which a person's behaviour (e.g., taking medication, following a diet, or making lifestyle changes) corresponds with agreed recommendations from a health care provider. In the context of an ART programme, it is seen as the measure of how well a patient complies with taking the medication as well as complying with other prescripts of the treatment programme.

Measuring adherence is important in assessing the individual's chance of a successful treatment outcome. Direct measures of adherence include therapeutic drug monitoring or directly observing the consumption of the treatment. Indirect approaches include VL monitoring, counting prescription claims, electronic pill container devices, provider reporting, clinic attendance monitoring, pill-counts or client self-reporting (Ross-Degnan *et al.*, 2010; Stricker *et al.*, 2013).

Good adherence is strongly linked to having a reduced VL (Flynn *et al.*, 2004; Murphy *et al.*, 2010). A study conducted among adolescents and adults in Ethiopia found that patients who were poorly adherent to the ART drugs were 2.56 times (AOR = 2.56, 95% CI: 1.97, 3.33) more likely to have viral non-suppression compared with patients with good adherence. Other studies have also reported similar results where poor adherence to treatment is positively associated with virological treatment failure (Bayu *et al.*, 2017; Casado *et al.*, 1999; Kiweewa *et al.*, 2019). This is because, as the drug concentration decreases in the blood, HIV RNAs might not be suppressed which in turn leads to an increase in VL (Desta *et al.*, 2020).

Poor adherence to ART among adolescents was associated with the increased amount of medication expected to be taken (Belzer *et al.*, 1999; Murphy *et al.*, 2010). Furthermore, not having medication at hand when required to be taken was found to be another reason for poor adherence amongst adolescents (Murphy *et al.*, 2003). In the REACH cohort of adolescents, Murphy *et al.* (2010) found factors associated with poor adherence to include pill burden, alcohol use and side effects to medication.

Adherence may also be adversely affected by the daily activities of people with chronic illnesses such as HIV; for example, adolescents who expressed changes in their daily routines was a common reason for unsatisfactory adherence to medication (Murphy *et al.*, 2003). It was also found that a common reason for missing medication doses among HIV-infected adults was that they were too busy (Spire *et al.*, 2002). Forgetting to take medication was a common reason found for poor adherence not only among HIV-infected adolescents (Murphy *et al.*, 2003) but also HIV-infected adults (Spire *et al.*, 2002). In the REACH cohort of adolescents, Murphy *et al.* (2010) found factors associated with poor adherence to include dropping out of school and complications with day-to-day routines. The VL trends in the aforementioned studies indicate that adherence to ART amongst adolescents appears worse than that of adults and children and that a tailored approach to adolescent care and management could optimise the outcomes of this vulnerable group.

2.7.3 Disclosure

Disclosure is another factor considered to affect adolescents' adherence to ART. Sharing or disclosing one's HIV status to family and friends provides a support structure which helps to maintain retention (Halperin *et al.*, 2013) and adherence to ART treatment, resulting in greater levels of virological suppression (Hawkins, 2016). A systematic review reported that peer support therapy among adolescents has been associated with better viral suppression (Bain-Brickley *et al.*, 2011). Furthermore, a multicentre cohort study in South Africa demonstrated improved viral suppression in children on ART receiving community-based adherence support (Fatti *et al.*, 2014).

Other behavioural factors that may affect adherence to ART include alcohol use. It was reported that adherence to ART is affected by alcohol consumption by the caregiver or the adolescent. A study conducted by Cruz *et al*. (2014) reported that non-use of alcohol and lower caregiver anxiety were associated with better adherence and viral suppression in children and adolescents. A case control in Zimbabwe found that alcohol consumption by adolescents significantly increases the risk of virological failure (Sithole *et al.*, 2018).

2.8 SUMMARY

In summary, the reviewed studies presented conflicting findings on the association between age and gender and viral suppression. Some studies found that there was an association between viral suppressions and age and gender; others found out that there is no significant association between viral suppression and demographic factors. This study also explored the relationship of a number of clinical factors and VL, which include baseline CD4 count, WHO staging, history of TB and pregnancy. The literature revealed that patients on ART with high CD4 counts (200 – 499 cells/mm^3) had more viral suppression compared to those with CD4 counts of less than 200 cell/mm^3 which have severe immunodeficiency. However, other studies reported that lower CD4 cell count at baseline was not associated with poorer virological outcome of ART. Furthermore, advanced WHO stages at baseline were associated with poor viral suppression. However, other studies revealed that WHO stage was not associated with virological failure. These variations might be due to use of different WHO definitions or variations in practice among the different health care providers. Moreover, studies have also revealed that patients on TB at baseline have increased odds of not achieving viral suppression.

The association of pregnancy and viral suppression was also explored in the literature review. Most of the studies reported that HIV-infected pregnant women have higher unsuppressed viral loads compared to men and non-pregnant women. Some authors suggested that the reason behind that is due to LTFU.

In the review of ART regimen and prophylaxis factors, the literature revealed that adolescents receiving Abacavir-based regimen given to young adolescents at initiation and FDC of Tenofovir-based regimen at initiation were observed to have relatively good viral suppression outcomes. Moreover, viral suppression appears higher in patients treated with TDF (Tenofovir/nucleoside reverse transcriptase) + 3TC (Lamivudine/ nucleoside reverse transcriptase) + EFV (Efavirenz/non- nucleoside reverse transcriptase) (TLE) compared to other NNRTI-based or Protease inhibition based (PI/r-based) regimens. Furthermore. prophylaxis cotrimoxazole and isoniazid and their effect on viral suppression was also highlighted in the literature review. Cotrimoxazole prophylaxis in Africa has produced conflicting results: some studies demonstrated that baseline cotrimoxazole preventive therapy has a positive effect on the duration of VLS, while other studies found that cotrimoxazole had no positive effect on VL levels. Isoniazid was also reported to enhance viral suppression outcome. Furthermore, all reviewed articles agreed that patients retained in care are more likely to achieve viral suppression compared to those not engaged in regular care. Good adherence is also strongly linked to having a reduced VL. In addition, early disclosure reflected on good adherence which resulted in higher viral suppression.

CHAPTER 3: METHODOLOGY

3.1 STUDY DESIGN

A retrospective, quantitative cross-sectional study was chosen to determine the predictors of viral suppression among adolescents on antiretroviral therapy (ART) in Thabo Mofutsanyane District Municipality, Free State province, South Africa, using routinely collected programme data extracted from an electronic database, Tier.net. The study design took a snapshot of the predictors of viral suppression among adolescents in 2019 (Bonita *et al*., 2006). The design measured independent variables demographic, baseline clinical characteristics, treatment factors and behavioural factors (retention in care) and the dependent variable/ outcome viral suppression simultaneously. Therefore, both the occurrence of viral suppression and the factors causing an increase and decrease in VL at one point in time were measured.

This study design was used to unpack the research question as South Africa has relatively good records for HIV patients. An electronic database of patients initiated on ART already existed from which eligible patients and the facilities at which they initiated their ART could be identified very efficiently for this study design, which also allowed the abstraction of data from the clinical folders to be relatively easy. Moreover, this study used previously collected and stored records in a database which allowed the study to be relatively inexpensive and less time consuming compared to prospective study designs (Bonita *et al*., 2006).

3.2 STUDY SETTING

Thabo Mofutsanyana District Municipality is a Category C municipality located in the eastern part of the Free State Province and is a semi-arid region with a dispersed settlement pattern. In 2019, the total population of Thabo Mofutsanyane District Municipality was 739 305 (Cooperative Governance and Traditional Affairs, 2020).

Thabo Mofutsanyane District Municipality has a very large comparative advantage in the agriculture sector. Nevertheless, 52.1% of its population lived below the lower poverty line in 2019. This is lower than the provincial rate at 60% and national at 58.6% (Cooperative Governance and Traditional Affairs, 2020).

In terms of the human development index, Thabo Mofutsanyana fared better with illiteracy with 15% of the population being illiterate while the national rate is at 26% (Cooperative Governance and Traditional Affairs, 2020). Moreover, the overall municipal unemployment rate of Thabo Mofutsanyane district was found to be 32.0% (Cooperative Governance and Traditional Affairs, 2020). The female working age population had the highest unemployment rate across all municipalities in the district. In 2017, 39.1% of women were unemployed compared to men at 32.4% (Cooperative Governance and Traditional Affairs, 2020).

The health profile of the District Health Plan 2019/20–2021/22 demonstrates that the leading cause of death for the 5–64 age groups in Thabo Mofutsanyana was HIV/AIDS. The HIV and AIDS death trends are no different from those of other district municipalities in the Free State, an increasing HIV rate and decreasing AIDS deaths. The number of persons living with HIV increased from an estimated 94 000 in 2008 to 96 700 thousand in 2017, which represents 12.9% of the total population of Thabo Mofutsanyana. Declining AIDS mortality rates can be attributed primarily to an increase in the roll-out of the ART, PMTCT, the distribution of condoms and medical male circumcision (Cooperative Governance and Traditional Affairs, 2020).

Health services in the district are delivered through two regional hospitals, 9 district hospitals, 1 community health centre, 73 clinics and 24 mobile service units (Cooperative Governance and Traditional Affairs, 2020).

3.3 STUDY POPULATION AND SAMPLING

Total population sampling was used in this study. The study population included all adolescents, aged 10–19 years, receiving ART in 2019 in Thabo District, Free State (N = 6 300).

The study sample included all adolescents according to the set criteria indicated below:

Inclusion criteria

- Adolescents on ART for at least 6 months.
- Those who have at least one documented VL in the last 12 months.

Exclusion criteria

- Those who are on ART for less than 6 months.
- Those who are older than 19 years.
- Those with no VL documented in their record.

The minimum sample size to have sufficient power (80%) to detect statistical differences to a confidence level of 5% (alpha = 0.05) was calculated as **421**. This was calculated using ClinCalc (Kane, 2019) by taking into account the viral suppression rate of adolescents in one year from a literature study of a population with the same HIV patient age population in South Africa (68.8%) (Kriel, 2017), our predicted viral suppression rate of 75%. However, all routine records of adolescents who were on ART for the period of interest and met the inclusion criteria were included in the analysis as these were readily available from the electronic database. <provide a motivation why this choice is superior> (Crossman, 2020).

3.4 DATA COLLECTION

A retrospective chart review which is a specific type of data collection method as used (Lipowski *et al.*, 2008). Data was collected from an electronic database. After determining the sample of HIV-infected adolescent patients initiated on ART from all the facilities spread across Thabo Mofutsanyane District Municipality, Free State province, South Africa, data was extracted from the electronic database, Tier.net. The principal investigator extracted data from the electronic database. The electronic database was reviewed and a list of all the adolescents on ART in the last six months was generated. Adolescents with recorded VLs in the last 12 months were included in the study.

Once all the required data was extracted and completed in the abstraction forms, data was then entered into an excel spreadsheet and cleaned. Data was then imported into SPSS for analysis.

VL was the outcome variable. Individual-level viral load was the recommended measure of ART efficacy: it indicated treatment adherence and the risk of transmitting HIV. A viral load < 50 c/mL was categorised as fully suppressed; VL = 50–999 c/ml was categorised as transient suppression; and VL > 1000 c/ml was categorised as unsuppressed (NDOH, 2019).

Socio-demographic variables that were included in the study were the gender, the current age and age at ART initiation of the patient. Clinical characteristics that were included were the WHO clinical stage at initiation, CD4 count at ART initiation, pregnancy at ART initiation,

history of TB, IPT at ART initiation and Cotrimoxazole at baseline. ART information extracted from the database included ART regimen at initiation, current ART regimen and duration of treatment. The behavioural factor that was extracted from the data set was retention in care (patients who were not registered as deceased, stopped treatment or LTFU for any reason (in care at clinic), transferred or moved out or died).

3.5 DATA ANALYSIS

In this study possible covariates that can affect VLS were investigated, which was the outcome variable in this study. Viral load was categorised into Fully Suppressed VL < 50 c/mL, Transient Suppression VL 50–999 c/ml, Unsuppressed VL > 1000 c/ml and missing.

The covariates that were analysed were categorised into three characteristics: socio-demographic characteristics which included current age; age at ART initiation and gender; clinical characteristics, which included WHO clinical stage, CD4 counts, pregnant at ART initiation, history of TB, IPT at baseline, cotrimoxazole at baseline, ART regimen at initiation, current ART regimen and duration of treatment; and the behavioural characteristic, retention in care.

Descriptive frequency tables were created for categorical variables outlining the number of adolescents in the various categories and the proportions, using percentages. Continuous data was also presented with either means with standard deviations or medians with interquartile ranges.

Bivariate analysis was conducted to determine the significance and strength of associations between VLS and the exposure variables; gender; the current age and age at ART initiation of the patient; WHO clinical stage at initiation; CD4 count at ART initiation; pregnancy at ART initiation; history of TB; IPT at ART initiation and Cotrimoxazole at baseline; ART regimen at initiation; current ART regimen and duration of treatment; and retention in care. Statistical significance was tested using the chi-square test (with significance set at $p < 0.05$). Where significance was observed, the strength of the associations was calculated as risk ratios with 95% confidence interval, using SPSS v 26.

Multivariate logistic regression was used to identify factors independently associated with viral suppression. AOR and 95% confidence intervals were calculated.

3.6 VALIDITY AND RELIABILITY

To minimise selection bias, all adolescents who met the inclusion criteria were enrolled for the study. Operationalisation of variables in the study was performed to increase the reliability and validity of variables under investigation. Operationalisation refers to the act of "translating a construct into its manifestation" (Trochim & Donnelly, 2008:361).

In the study, the abstraction form was used to help ensure a consistency of measurement. This reduced errors in data collection. The abstraction form had a logical organisation similar to the flow and format of the data set.

Intra-rater reliability evaluates the differences when the same abstractor records the same set of variables. Intra-rater reliability of the data capturing was examined by allowing the rater to capture a number of patient folders from the database, then to capture the same data again for the same patients at a different time. The two final products of the data collection of the same rater were compared for any inconsistency (Matt & Matthew, 2013).

3.7 ETHICS CONSIDERATIONS

Ethics clearance was obtained from the University of the Western Cape Biomedical Research Ethics committee (Appendix 2: BM 20/10/10) and permission for access of the data from Tier.net was obtained from the Thabo Mofutsanyane District office.

This study followed the 1964 Helsinki guidelines, it is crucial to protect life, health, privacy, and the dignity of the research participants. In the study great care was put in place to protect the participants from harm. Moreover, this research was conducted because the importance of the research purpose outweighed the risk that might be attributed to the study either at present or in the future (WHO, 2001).

Data extraction excluded adolescents' unique identities, such as folder number, identity number, name and surname.

CHAPTER 4: RESULTS

4.1 INTRODUCTION

In this chapter, the results of the study are reported. It includes sections outlining the realisation of the study sample, the description of the socio-demographic and clinical characteristics of the adolescents in the study, the description of the VS of adolescents as well as the bivariate analysis of VS and socio-demographic and clinical characteristics. Multivariate analysis was also conducted to analyse whether socio-demographic and clinical variables were independently associated with viral suppression.

4.2 REALISATION OF SAMPLE

Data from 6 300 adolescent and young adults (18–24 years) patients on ART from facilities spread across the Free State province were obtained from the Provincial Tier.net register. Of the originally recruited 6 300 patients, those who were older than 19 years old and on ART for less than six months were excluded from the sample. Moreover, patients who did not have a documented VL were also excluded from the sample. The final sample size that was analysed was 4 520.

4.3 CHARACTERISTICS OF THE STUDY PARTICIPANTS

Table 4.1 describes the characteristics of the adolescents who were included in the study. It provides a deception of baseline demographic and clinical characteristics of the study participants.

4.3.1 Socio-Demographic Characteristics of Study Participants

The median age of adolescents in this study was 15 years (Interquartile Range [IQR] (13 – 18)). Most of the adolescents in this study were 15-19 years (68.21%) (n=3083) and female (56.17) (n=2359) (Table 4.1).

The median age at ART initiation in the current cohort was 8 years (IQR 5–12), with 22.23% (n=1005) (initiating ART below 4 years of age, 39.91% (n=1804) at the age of 5–9 years,

25.88% (n=1170) at the age of 10–14 years and a small proportion 11.97% (n=541) at the age of 15–19 years.

Table 4.1: Socio-demographic and clinical characteristics of adolescents on ART in the Thabo Mofutsanyane District, Free State province, 2019 (n=4 520)

		Frequency	Percentage (%)
Current age (in years)	10–14	1 437	31.79
	15–19	3 083	68.21
Gender	Male	1 981	43.83
	Female	2 539	56.17
Age at ART initiation (in years)	0–4	1 005	22.23
	5–9	1 804	39.91
	10–14	1 170	25.88
	15–19	541	11.97
Baseline CD4 count (cells/mm^3)	< 200	1 169	36.02
	200–500	1 298	40.00
	> 500	778	23.98
WHO stage at initiation	Stage I	2 007	56.09
	Stage II	794	22.19
	Stage III	660	18.45
	Stage IV	117	3.27
History of TB	Yes	320	10.59
	No	2 702	89.41
Pregnant	Yes	158	5.93
	No	2 508	94.07
Received IPT	Yes	906	26.31
	No	2 538	73.69
Cotrimoxazole	Yes	1 571	41.16
	No	2 246	58.84
Duration on ART	6–11	158	3.50
	1–2 years	371	8.21
	3–5 years	1 130	25.00
	6–10 years	2 252	49.82
	>10 years	609	13.47
ART regimen at baseline	3EA	1	0.02
	A3E	2252	50.72
	A3L	206	4.64
	AdE	1	0.02
	AFE	5	0.11
	ALZ	1	0.02
	S3E	845	19.03
	S3L	187	4.21
	S3N	18	0.41
	SdL	1	0.02
	T3E	45	1.01
	T3L	5	0.11
	T3N	1	0.02
	TFE	643	14.48
	TFL	1	0.02
	Z3E	133	3.00
	Z3L	72	1.62
	Z3N	12	0.27
	ZdL	5	0.11

	ZLA	1	0.02
	A3N	2	0.05
	Other	3	0.07
Current ART Regimen	3EA	0	0.00
	A3E	2 084	46.13
	A3L	340	7.53
	AdE	1	0.02
	AFE	11	0.24
	AFL	2	0.04
	ALZ	2	0.04
	S3E	253	5.60
	S3L	43	0.95
	S3N	6	0.13
	T3E	15	0.33
	T3L	18	0.40
	T3N	3	0.07
	TFE	1 070	23.68
	TFL	13	0.29
	Z3E	293	6.49
	Z3L	332	7.35
	Z3N	9	0.20
	ZdL	4	0.09
	A3N	11	0.24
	Other	8	0.18
Retention in care	In care	3 167	70.07
	Lost to follow up	523	11.57
	Transferred	736	16.28
	Died	94	2.08

Notes: 3EA (Lamivudine+ Efavirenz+ Abacavir), A3E (Abacavir+ Lamivudine + Efavirenz), A3L (Abacavir+ Lamivudine + Lopinavir/ritonavir), A3N (Lamivudine+ Efavirenz+ Nevirapine), AdE (Abacavir+didanosine+Efavirenz), AFE (Abacavir+ Emtricitibine+Efavirenz), AFL (Abacavir+ Emtricitibine+ Lopinavir/ritonavir), ALZ (Abacavir+ +Lopinavir/ritonavir+Zidovudine), S3E (Stavudine+ Lamivudine + Efavirenz), S3L (Stavudine + Lamivudine + Lopinavir/ritonavir), S3N (Stavudine+lamivudine+Nevirapine), SdL (Stavudine+didanosine+ Lopinavir/ritonavir), T3E (Tenofovir+Lamivudine+Efavirenz), T3L (Tenofovir + Lamivudine + Lopinavir/ritonavir), T3N (Tenofovir + Lamivudine + Nevirapine), TFE (Tenofovir+ Emtricitibine+ Efavirenz), TFL (Tenofovir+ Emtricitibine+ Lopinavir/ritonavir), Z3E (Zidovudine + Lamivudine + Efavirenz), Z3L (Zidovudine+ Lamivudine+ Lopinavir/ritonavir), Z3N (Zidovudine+ Lamivudine+Nevirapine), ZdL (Zidovudine+didanosine+ Lopinavir/ritonavir), ZLA (Zidovudine+ Lopinavir/ritonavir+ Abacavir).

4.3.2 Baseline Clinical Characteristics of Study Participants

The median CD4 count at ART initiation was 285 cells/ml (IQR (103 – 490). At ART initiation 36.02% (n=1169) of adolescents had a CD4 count less than 200 cell/mm³; a large number of adolescents 40% (1298) had a baseline CD4 counts between 200 – 349 cells/mm³; and 23.98% (n=778) had a baseline CD4 counts > 500 cells/mm³ (Table 4.1). Of those participants who had documented WHO staging ART initiation, 56.09% (n=2 007) were classified as WHO Stage I. 22.19% (n=794) were classified as WHO Stage II, 18.45% (n=660) were WHO Stage III and 3.27% (n=117) were WHO Stage VI (Table 4.1).

At the time of ART initiation, 10.59% (n=320) of the adolescents had a history of TB and were on TB treatment (Table 4.1). Only 5.93% (n=158) of the females in the study were pregnant (Table 4.1). Only 26.31% (n=906) of adolescents at ART initiation had been initiated on isoniazid at baseline. However, 41.16% (n=1571) of the 4 520 adolescents were on cotrimoxazole at ART initiation (Table 4.1).

The median duration on treatment was 6.58 years (IQR 3.58–8.75 years); 3.5% (n=158) of the adolescents had been on ART for 6–11 months; 8.21% (n=371) for one to two years; 25% (n=1130) for 3–5 years; almost half on the analysed population (49.82%) (n=1130) were on ART for 3–5 years; and 13.47% (n=609) were on ART for more than 10 years (Table 4.1).

Half of the sample of adolescents (50.72%, n=2252), had started ART with, A3E (Abacavir+ Lamivudine + Efavirenz) followed by S3E (Stavudine+ Lamivudine + Efavirenz), (19.03% n=845); TFE (Tenofovir+ Emtricitibine+ Efavirenz) (14.48% n=643), A3L (Abacavir+ Lamivudine + Lopinavir/ritonavir) (4.64% n=?); S3L (Stavudine + Lamivudine + Lopinavir/ritonavir), (4.21% n=206); Z3E (Zidovudine + Lamivudine + Efavirenz) (3.00% n=?); and Z3L (Zidovudine+ Lamivudine+ Lopinavir/ritonavir) (1.62% n=72) respectively (Table 4.1).

Most of the adolescents had A3E (Abacavir+ Lamivudine + Efavirenz) (46.13%, n=2084) as their current ART regimen; followed by TFE (Tenofovir+ Emtricitibine+ Efavirenz) (23.68% n=1070); A3L (Abacavir+ Lamivudine + Lopinavir/ritonavir) (7.5% , n=340); Z3L (Zidovudine Lamivudine+ Lopinavir/ritonavir) (7.35% n=332); Z3E (Zidovudine + Lamivudine + Efavirenz) (6.49%, n=293); and S3E (Stavudine+ Lamivudine + Efavirenz) (5.60%, n=243) (Table 4.1).

4.5 VIRAL SUPPRESSION OF ADOLESCENTS ON ART

The median VL for adolescents was 124 c/ml (IQR: 124–501). Most (68.74%; n=3107) of the participants were transient suppressed (between 50–999 c /ml); while 9.51% (n=430) were fully suppressed (< 50 c/ml) and 21.75% (n=983) were unsuppressed (≥1000 c/ml)) (Figure 4.1).

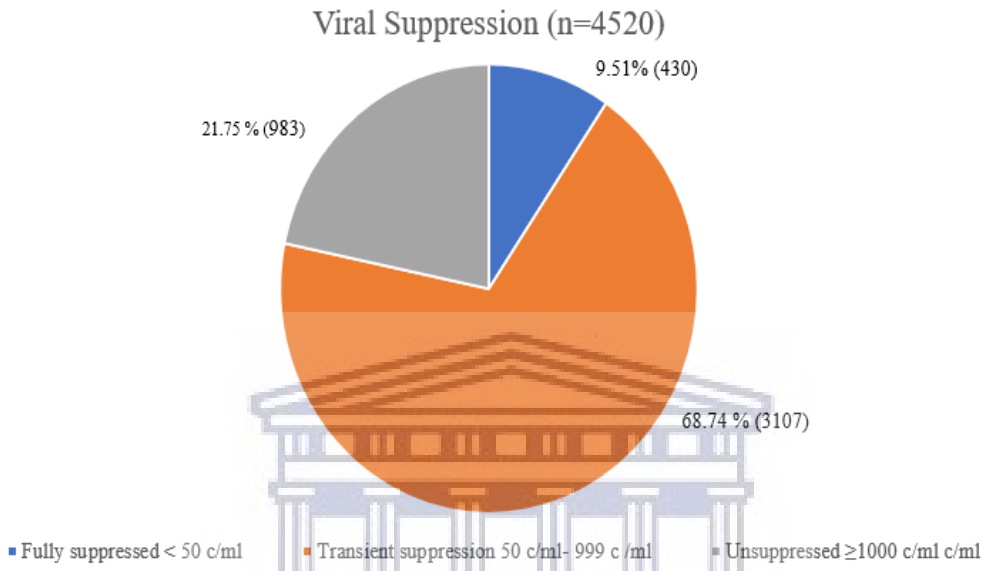

Figure 4.1: Levels of viral suppression of Adolescents initiated on ART in the Thabo Mofutsanyane District Municipality, Free State province, South Africa (N=4,520).

4.6 FACTORS ASSOCIATED WITH VIRAL SUPPRESSION

Table 4.2 represents the results of bivariate analysis of demographic and clinical factors associated with viral suppression.

Table 4.2: Viral suppression by demographic and clinical characteristics

		Viral Suppression		
		Yes n (%)	**No** n (%)	***p*-value**
Total		3 537 (78.25)	938 (21.75)	
Current age (in years)	10–14	1 160 (80.72)	277 (19.28)	0.006
	15–19	2 377 (77.10)	706 (22.90)	
Gender	Male	1 526 (77.03)	455 (22.97)	0.079
	Female	2 011 (79.20)	528 (20.80)	
Age at ART initiation (in years)	0–4	839 (83.48)	166 (16.52)	< 0.001*
	5–9	1 375 (76.22)	429 (23.78)	
	10–14	876 (74.87)	294 (25.13)	
	15–19	447 (82.62)	94 (17.38)	
Baseline CD4 count (cells/mm^3)	< 200	843 (72.11)	326 (27.89)	< 0.001*
	200–500	1 014 (78.12)	284 (21.88)	
	> 500	653 (83.93)	125 (16.07)	
WHO stage	Stage I	1 617 (80.57)	390 (19.43)	0.001*
	Stage II	591 (74.43)	203 (25.57)	
	Stage III	497 (75.30)	163(24.70)	
	Stage IV	95 (81.20)	22 (18.80)	
History of TB	Yes	228 (71.25)	92 (28.75)	0.003*
	No	2 121 (78.50)	581 (21.50)	
Pregnant	Yes	125 (79.11)	33 (20.89)	0.98
	No	1 986 (79.19)	522 (20.81)	
Received IPT	Yes	717 (79.14)	189 (20.86)	0.68
	No	1 992 (78.49)	546 (21.51)	
Cotrimoxazole	Yes	1 206 (76.77)	365 (23.23)	0.15
	No	1 768 (78.72)	478 (21.28)	
Duration on ART	6–11 months	135 (85.44)	23 (14.56)	0.045*
	1–2 years	297 (80.05)	74 (19.95)	
	3–5 years	891 (78.85)	239 (21.15)	
	6–10 years	1 728 (76.73)	524 (23.27)	
	> 10 years	486 (79.80)	123 (20.20)	
ART regimen at baseline	A3E	1 730 (76.82)	522 (23.18)	< 0.001*
	A3L	159 (77.18)	47 (22.82)	
	S3E	644 (76.21)	201 (23.79)	
	S3L	162 (86.63)	25 (13.37)	
	TFE	536 (83.36)	107 (16.64)	

	Z3E	102 (76.69)	31 (23.31)	
	Z3L	52 (72.22)	20 (27.78)	
	Other	86 (84.31)	16 (15.69)	
Current ART Regimen	A3E	1 688 (81.00)		< 0.001*
	A3L	230 (67.65)	396 (19.00)	
	S3E	196 (77.47)	110 (32.35)	
	S3L	33 (76.74)	10 (23.26)	
	TFE	868 (81.12)	57 (22.53)	
	Z3E	240 (81.91)	202 (18.88)	
	Z3L	217 (65.36)	53 (18.09)	
	Other	64 (62.14)	39 (37.86)	
Retention in care	Retained	2 579 (81.43)	588 (18.57)	< 0.001*
	Not retained	958 (70.81)	395 (29.19)	

*denotes statistical significance at p < 0.05

4.6.1 Demographic Characteristics

A chi-square test of independence was performed to examine the relation between current age and viral suppression. The relation between these variables was significant, with χ^2 (1, N =3537) = 7.56, and p = 0.006. There was also a statistical significance between age at ART initiation and viral suppression , χ^2 (3, N = 2698) = 34.47 p= < 0.001. There was no statistical significance found between viral suppression and gender (p=0.16).

4.6.2 Clinical Characteristics

In the bivariate analysis, statistical significance was observed between VLS and clinical characteristics such as of adolescents' baseline CD4 count, χ^2 (2, N =2510) = 37.98, p= < 0.001 and WHO stage, χ^2 (2, N = 3453) = 17.10, p= 0.001 (Table 4.2).

It was observed that viral suppression was the highest in those with CD4 counts > 500 cells/mm^3 (83.93%; n=653). Stage IV had the highest viral suppression (81.20%; n=95), followed by Stage I (80.57%; n=1 617). Furthermore, history of TB and viral suppression was also statistically significant, χ^2 (1, N = 2349) = 8.68, p=0.003 (Table 4.2).

There was no statistical association between viral suppression and received IPT, χ^2 (1, N = 2709) = 0.20 p=0.68, cotrimoxazole and viral suppression, χ^2 (1, N = 2974) = 2.05, p=0.15 and pregnancy and viral suppression, χ^2 (1, N =2111) = 0.0005, p=0.98 (Table 4.2).

4.6.3 Treatment factors

Duration on ART and viral suppression, χ^2 (4, N = 3537) = 9.67, p= 0.045, ART regimen at baseline and VLS, χ^2, (7, N =3471) = 26.33, p= < 0.001), current ART regimen and VLS, χ^2 (7, N = 3536) = 87.51, p= < 0.001 were statistically significant (Table 4.2).

Patients who were on S3L at baseline had the highest viral suppression (86.63%; n=162), TFE (83.36%; n=536), A3L (77.18%; n=159) and A3E (76.82%; n=1 730) had high viral suppression scores. Moreover, patients on the following current ART regimens had high viral suppression scores, Z3E (81.91%; n=240) TFE (81.12%; n=868), A3E (81%; n= 1 688) and S3L (76.74%; n=33).

4.6.4 Behavioural factors

Retention in care and VLS, were statistically significant, χ^2 (1, N =3537) = 62.92, p= < 0.001 (Table 4.2). Adolescents who were retained in care had higher viral suppression (81.43%; n= 2 579) compared to those who were not retained (70.81%; n= 958).

4.7 DETERMINANTS OF VIRAL SUPPRESSION AMONGST ADOLESCENTS ON ART

Table 4.3 presents the results of multivariate analysis which show the effect of variables on viral suppression after adjusting for other explanatory variables and possible confounders of demographic and clinical factors associated with viral suppression.

Table 4.3: Multivariate analysis of determinants of adolescents on ART in the Thabo Mofutsanyane District, Free State province, 2019 (n=4,520)

		Crude OR (95% CI)	Adjusted OR (95% CI)
Age (in years)	10 – 14	1	1
	15 – 19	0.80 (0.69–0.94)	1.32 (0.93–1.88)
Gender	Male	1	1
	Female	1.13 (0.99–1.30)	1.09 (0.86–1.37)
Age at ART initiation (in year)	0 – 4	1	1
	5 – 9	0.63 (0.52–0.77)	0.52 (0.34–0.80)
	10 – 14	0.59 (0.48–0.73)	0.41 (0.23–0.72)
	15 – 19	0.94 (0.71–1.24)	0.39 (0.17–0.93)
Baseline CD4 count (cells/mm^3)	< 200	1	1
	200 – 500	1.38 (1.14–1.66)	1.24 (0.96–1.62)
	> 500	2.02 (1.60–2.54)	1.77 (1.28–2.47)
WHO stage	Stage I	1	1
	Stage II	0.70 (0.58–0.85)	0.78 (0.59–1.03)
	Stage III	0.74 (0.60–0.91)	0.92 (0.68–1.26)
	Stage IV	1.04 (0.65–1.68)	1.75 (0.81–3.78)
History of TB	No	1	1
	Yes	0.68 (0.52–0.88)	0.78 (0.50–1.02)
Duration on ART	6 – 11 months	1	1
	1 – 2 years	0.68 (0.41–1.14)	1.07 (0.39–2.92)
	3 – 5 years	0.64 (0.40–1.01)	1.06 (0.41–2.75)
	6 – 10 years	0.56 (0.36–0.88)	1.03 (0.38–2.79)
	> 10 years	0.67 (0.41–1.09)	0.86 (0.28–2.62)
ART regimen at baseline	A3E	1	1
	A3L	1.02 (0.73–1.43)	1.81 (0.91–3.61)
	S3E	0.97 (0.80–1.16)	0.97 (0.66–1.41)
	S3L	1.96 (1.27–3.01)	**2.87 (1.01–8.16)**
	TFE	1.51 (1.20–1.90)	**2.07 (1.12–3.85)**
	Z3E	0.99 (0.66–1.50)	1.59 (0.64–3.97)
	Z3L	0.78 (0.46–1.33)	1.03 (0.37–2.93)
	Other	1.62 (0.94–2.79)	0.99 (0.43–2.28)
Current ART Regimen	A3E	1	1
	A3L	0.49 (0.38–0.63)	0.34 (0.21–0.55)
	S3E	0.81 (0.59–1.10)	1.19 (0.66–2.12)

	S3L	0.77 (0.38–1.58)	0.18 (0.04–0.74)
	TFE	1.01 (0.84–1.21)	0.76 (0.53–1.09)
	Z3E	1.06 (0.77–1.46)	1.27 (0.67–2.42)
	Z3L	0.44 (0.34–0.57)	0.36 (0.24–0.54)
	Other	0.38 (0.25–0.58)	0.27 (0.13–0.54)
Retention in care	Retained	1	1
	Not retained	0.55 (0.48–0.64)	0.45 (0.35–0.58)

Notes: **Bold** shows significance at 5% significance level
OR – odds ratio
95% CI – 95% confidence interval

Multivariate logistic regression analysis has shown that age at ART initiation, CD4 count at baseline, baseline ART regimen, current ART regimen and retention in care had a significant effect or were risk factors (or determinants) of viral suppression.

The odds of being virally suppressed reduced with increased age at ART initiation. When comparing other age groups to ART initiation at 0 to 4 years, it is evident that those who started ART between 5 and 9 years (AOR =0.52; CI: 0.34–0.80), between 10 and 14 years (AOR=0.41; CI: 0.23–0.72) and between 15 and 19 years (AOR=0.39; CI: 0.17–0.93) were less likely to be virally suppressed (Table 4.3).

Results from the multivariate analysis revealed that a higher CD4 count at baseline was associated with higher odds of viral suppression and adolescents who had a CD4 count greater than 500 cells/mm^3 (AOR=1.77; CI: 1.28–2.47) were 77% more likely to be virally suppressed compared to adolescents who had a CD4 count less than 200 cells/mm^3. Moreover, there was borderline significance for the association between TB and viral suppression and the results pointed towards lower chances of suppression in adolescents who had a history of TB (AOR=0.78; CI: 0.50–1.02) (Table 4.3).

Considering the baseline ART regimen, we found that adolescents who started on S3L (AOR=2.87; CI: 1.01–8.16) and TFE (AOR=2.07; CI: 1.12–3.85) regimens were more than two times likely to be virally suppressed compared to those who started on A3E (Table 4.3).

Moreover, when considering the current ART regimen, most of the regimens performed worse than the A3E regimen. Adolescents on A3L (AOR=0.34; CI:0.21–0.55), S3L (AOR=0.18; CI: 0.04–0.74), Z3L (AOR=0.36; CI: 0.24–0.54), and other regimens (AOR=0.36; CI: 0.24–0.54) had lower odds of being virally suppressed when compared to participants on A3E regimen (Table 4.3).

Retention in care proved to be an important factor for viral suppression as the odds of viral suppression were significantly lower amongst those who were not retained in care (AOR=0.45; CI: 0.35–0.58).

Results from multivariate analysis show that gender had an insignificant effect on viral suppression (Table 4.3). Moreover, although current age and viral suppression and duration on ART and viral suppression were statistically significant in bivariate analysis; however, results from multivariate analysis show that the two factors had an insignificant effect on viral suppression.

Viral suppression for adolescents falls short of global target of 90%. With a score of seventy eight percent (n=4,520) of the adolescents on ART achieving viral suppression. The results of the multivariate logistic regression analysis have shown that age at ART initiation, CD4 count at baseline, baseline ART regimen, current ART regimen and retention in care were determinants of viral suppression.

CHAPTER 5: DISCUSSION

5.1 INTRODUCTION

This chapter presents a discussion of the study findings in relation to the problem statement and the available literature review. The discussion is arranged into the following subsections: viral suppression, socio-demographic factors, clinical factors, treatment factors and behavioural factors influencing viral suppression among adolescents.

5.2 ADOLESCENTS THAT ATTAINED VIRAL SUPPRESSION FOLLOWING SIX OR MORE MONTHS ON ART

This study found that most participants were fully suppressed (< 50 c/ml) or transient suppressed (50–999 c/ml) at 9.5% and 68.7%, respectively. Our findings were low compared to Zanoni *et al. 's* (2016) meta-analysis of South African adolescents and young adults on ART, where 81% was virally suppressed. However, the findings of this study fall in the range of 28% to 89%, as reported by Ferrand *et al.* (2016) in their review of adolescents in care in countries in southern Africa, Uganda, South Africa, Rwanda, China, Brazil, Mexico, Argentina and 13 USA cities.

However, an analysis of clinical records in the Eastern Cape facilities, which is a setting reflecting poverty and healthcare similar to the Free State found 47.5% and 23.2% of adolescents were virally suppressed or fully virally suppressed respectively, within the past 12 months (Haghighat *et al.*, 2021). Another study in the Western Cape facilities reported much lower viral load suppression (< 1000 c/ml) of adolescents at 40.0% and 25.0% after one and two years on ART respectively (Kriel, 2017).

Findings suggest that South African adolescent progression to the final "90" of viral suppression in the UNAIDS 90-90-90 treatment goal remains low, at 78.25% for ART-initiated adolescents aged 10–19 years. Therefore, this study extends evidence on the need of an optimised adolescent HIV care cascade in South Africa for the adolescent population across healthcare facilities (Maskew *et al.*, 2019). This low rate of viral suppression in clinical records verifies previously published findings on the low ART adherence and ineffective adolescent adherence-promoting interventions among adolescents (Cluver *et al.*, 2016). These adherence-

promoting interventions can be instrumental in decreasing the high numbers of adolescents that were at transient suppression (68.74% n=3017) and converting them to fully suppressed (< 50 c/ml). Findings suggest that critical challenges persist in adolescent attainment of consistent ART adherence and viral suppression after treatment initiation.

5.3 SOCIO-DEMOGRAPHIC CHARACTERISTICS ASSOCIATED WITH VIRAL SUPPRESSION

In this study, current age and gender were an insignificant determinant of viral suppression. Moreover, although the duration on ART and viral suppression was statistically significant in the bivariate analysis, results from multivariate analysis have shown that duration of ART had an insignificant effect on viral suppression.

5.3.1 Current Age and Viral Suppression

In this study, adolescents were categorised as 10–14 years and 15–19 years and the differences in viral suppression between the two age groups was not significant. Our results were similar to a study conducted in Kenya examining the factors associated with viral suppression among adolescents in Hombay county which also concluded that there was no significant difference between current age and viral suppression (Mwangi *et al.*, 2019). On the other hand, data from clinical records in Eastern Cape Province, South Africa facilities found that there is a significant difference between viral suppression and current age and concluded that younger adolescents (AOR 1.39 [95% CI 1.06–1.82]) are more likely to be virally suppressed (Haghighat *et al.*, 2021). Further, a study that followed adolescents initiated on ART in public health facilities in the Metropole District Health Services of the Western Cape Province, South Africa revealed that younger adolescents (10–14 years) had better VLS rates at months 4, 12 and 24 compared to older adolescents (15–19 years); with significant differences at month 12 (63.4% vs 34.6%; p = 0.001) and month 24 (58.5% vs 17.3%; p < 0.001) (Van Wyk *et al.*, 2020). Van Wyk *et al.* (2020) demonstrated that better retention in care was observed in younger age groups (10–14 years) compared to the older group resulting in better VLS rates. In this study, the difference in the proportion of viral suppression between the two age groups was not statistically significant (80.7% for 10–14 years vs. 77.1% for 15–19 years). Many authors have associated viral suppression with retention in care (Adejumo *et al.*, 2015; Van Wyk *et al.* 2020) and claim that younger adolescents show better retention rates because they

depend on their adult caregivers to manage their ART regimen (Van Wyk *et al.*, 2020). However, this was not evident in this study.

5.3.2 Duration on ART and Viral Suppression

In this study, duration of ART and viral suppression was not associated, which contrasts with other studies. Results from Eastern Cape, South Africa revealed that adolescents on ART for ≥2 years were more likely to be fully viral suppressed (AOR 1.70 [95% CI 1.12–2.58]) (Haghighat *et al.,* 2021). Other studies in African countries such as Kenya found that adolescents who initiated ART at ages 5–9 years and 10–14 years were less likely to be virally suppressed (Mwangi *et al.*, 2019). These findings are similar to those from a study in Thailand where virological failure was higher among adolescents aged 10–16 years at ART initiation (Bunupuradah *et al.,* 2015), but contradicts Muri *et al.* (2017) and Makadzange *et al.* (2015) who associated older age at ART initiation with higher viral suppression rates in their studies in Tanzania and Zimbabwe, respectively.

5.3.3 Gender and Viral Suppression

In this study, gender was not associated with VLS, which contradicts Van Wyk *et al. 's* (2020) study in the Western Cape Province, where adolescent males were found to be significantly more likely to be virologically suppressed compared to females over the first two years after ART initiation. In Malawi, 51.9% of adolescent and young adult women had virological suppression compared to the 36.7% of males (Avert, 2016). Another retrospective cross-sectional study among adolescents and adults on ART in northern Ethiopia revealed that the likelihood of viral non-suppression for male patients was 30% more likely compared to female patients (AOR = 1.27, 95%; CI: 1.18, 1.37) (Desta *et al.*, 2020). Many authors suggest that males are more prone to viral non-suppression due to poor health-seeking behaviour (Dalhatu *et al.*, 2012; Heestermans *et al.*, 2016; Jobanputra *et al.*, 2015; Penot *et al.*, 2014).

5.4 CLINICAL FACTORS ASSOCIATED WITH VIRAL SUPPRESSION

Multivariate logistic regression shows that CD4 count at baseline, baseline ART regimen, current ART regimen and retention in care were risk factors (or determinants) of viral suppression. On the other hand, there was no statistical association between viral suppression and the following clinical characteristics: WHO stage, history of TB, received IPT, cotrimoxazole and pregnancy.

5.4.1 Baseline CD4 count

This study confirms the association between baseline CD4 counts levels and viral suppression. Results in this study revealed that a higher CD4 count at baseline was associated with higher odds of viral suppression and adolescents who had a CD4 count greater than 500 cells/mm^3 (AOR=1.77; CI: 1.28–2.47) were 77% more likely to be virally suppressed compared to adolescents who had a CD4 count less than 200 cells/mm^3. This study is in keeping with other studies that reported that people commencing ART with advanced immunodeficiency (CD4 > 200–350 per mm^3) appear to have better virological outcomes than those who commence with more severe immunodeficiency, less than 200 cell/mm³ CD4 count (Bennett *et al.*, 2002; Bonnet *et al.*, 2005; Graber *et al.*, 2005). Jobanputra *et al.* (2015) also reported that patients with CD4 counts less than 350 cells/mm³ and are under 20 years of age were significantly more likely to have unsuppressed viral loads (Jobanputra *et al.*, 2015). In addition, Desta *et al.* (2020) have also shown that adolescents who had a baseline CD4 count of < 200 cells/mm^3 were 1.33 times (AOR = 1.33, 95% CI: 1.14, 1.54) more likely to have viral non-suppression compared to patients with ≥500 CD4 count at baseline. A study in Tanzania also confirmed that having a high CD4 cell count at ART initiation was associated with better viral suppression (Muri *et al.*, 2017). This study is in line with the studies which showed that higher CD4 counts are associated with VLS (Bayu *et al.*, 2017; Rangarajan *et al.*, 2016). The reason could be that viral clearance might be slow in patients on ART with a low CD-4 T-cell count.

Contradictory results to this study were reported by Phillips *et al.* (2001) who analysed data from the databases of three studies in the SHCS and found that a lower CD4 cell count at baseline was not associated with poorer virological outcome of ART. Moreover, in the African region, a Kenyan study that explored the relationship between factors associated with adolescent viral suppression reported no significant effect between CD4 counts and viral suppression (Mwangi *et al.*, 2019)

5.4.2 WHO staging

In our study, multivariate analysis has shown no significant difference between WHO stage and viral suppression. Other authors in the literature contradict the results of this study such as Jobanputra *et al.* (2015) who explored factors associated with virological detectability in children and adults on ART in Swaziland and reported that patients with WHO Stage III and IV were significantly more likely to have unsuppressed viral loads.

Another study conducted in the Cape Metropole in South Africa also found that WHO stage at baseline had a statistically significant association with VLS but only at month 24 after ART initiation. Adolescents with WHO Stage IV at baseline had the most favourable VLS rates at months 12 and 24 after ART initiation, with those with WHO Stage III at baseline having the better suppression rates at month 4 after ART initiation (Kriel, 2017). Moreover, Desta *et al.* (2020) also reported that the likelihood of developing viral non-suppression for patients in WHO Stage II was 1.31 times (AOR = 1.31, 95% CI: 1.10, 1.54) more likely when compared with patients in WHO Stage I.

However, similar to our study, some studies revealed that WHO stage was not associated with virological failure (Bayu *et al.*, 2017; Hailu *et al.*, 2018; Rangarajan *et al.*, 2016). This variation of results between different studies might be due to use of different WHO definitions or variations in practice among the different health care providers (Desta *et al.*, 2020).

In the REACH cohort of adolescents, Murphy *et al.* (2010) found advanced HIV disease (CD4 count < 350 cells/mm^3) is usually associated with higher WHO clinical stages (WHO, 2007) which are associated with poor adherence. The health care system must aim to get people onto treatment at higher levels in the earlier stages of the disease and avoid the development of opportunistic infections. If this aim is achieved, relatively healthier people will be initiating ART resulting in the potential risk of healthier people not being motivated to remain in ART care (Ngarina *et al.*, 2013).

5.4.3 History of Tuberculosis

History of TB infection was not significantly associated with viral suppression. Though this study collected data on past history of TB infection, having an active opportunistic TB infection was associated with low viral suppression across all age categories in Uganda (Bulage *et al.* 2017). Another study evaluating factors associated with unsuppressed VL (VL > 400 copies/ml) in patients in care on first-line ART for ≥ 6 months attending South African public healthcare facilities, highlighted that youth/adolescents and patients on TB treatment had increased odds of not achieving viral suppression (Davey *et al.*, 2018). The difference in the findings could be explained by the fact that data was collected on past history of TB and not active TB or being on TB treatment. In addition, Davey *et al. 's* (2018) study measured viral load as unsuppressed VL (VL > 400 copies/ml) which is different from this study, where VL were measured as unsuppressed if it was ≥1000 c/ml. Ongoing HIV replication and high VL is

an important risk factor for TB (Fenner *et al.*, 2017). This could also explain the high VL in patients with active TB or on TB treatment.

5.4.4 Pregnant at Initiation

Another clinical factor that had no statistical association with viral suppression was pregnancy. Contradictory to this study, some authors reported that pregnancy can affect viral suppression (Hodgson *et al.*, 2014; Kriel, 2017, Wang *et al.*, 2011). It was reported that HIV-infected pregnant women (younger than 30 years) have higher unsuppressed viral loads compared to men and non-pregnant women due to LTFU (Wang *et al.*, 2011) and poor adherence to ART (Hodgson *et al.*, 2014). A systemic review of factors affecting ART initiation, adherence and retention of HIV-infected pregnant and postpartum women by Hodgson *et al.* (2014) found that reported barriers to initiation and adherence were poor understanding of HIV, ART and the PMTCT programme.

Furthermore, Kriel's (2017) study also showed a significantly greater proportion of non-pregnant compared to pregnant adolescents that were virologically suppressed at months 4 (67.6% vs 46.4%: $p = 0.002$), 12 (46.3% vs 29.8%: 0.015) and 24 (35.3% vs 8.3%: $p < 0.001$). In addition, Kriel (2017) also observed that pregnant females who initiate ART in their first trimester had significantly better VLS results in the first year post-ART initiation, i.e., 80.0% and 60.0% VLS at months 4 and 12 respectively. Early antenatal care can provide opportunities to educate the pregnant adolescent on HIV and ART and assist with any barriers to poor adherence to achieve favourable outcomes for the mother as well as the baby.

5.4.5 Cotrimoxazole Prophylaxis Treatment (CPT)

There was no statistical association between viral suppression and cotrimoxazole, the combination antimicrobial drug (sulfamethoxazole and trimethoprim) that covers a variety of opportunistic bacterial, fungal and protozoan infections in people living with HIV/AIDS (PLWHA) (WHO, 2013c; Sisay *et al.*, 2018). Some studies have reported that cotrimoxazole treatment slows down the decline in CD4 T-cells and lowers the annual rate of VL increase (Mermin *et al.*, 2004, Wiktor *et al.*, 1999). A 19-month follow-up placebo cohort study of 509 people with HIV in Uganda, found that the mean annual rate of CD4 decline slowed during cotrimoxazole treatment, from 203 to 77 cells/mm^3 per annum and the mean annual rate of VL increase fell from 0.90 to 0.08 $\log_{10}$ per annum (Mermin *et al.*, 2004) The cohort study authors suggested that VL and CD4 trends during cotrimoxazole treatment could be a consequence of

the effect of prophylaxis on the frequency of opportunistic infections. VL tended to rise during acute infections, which in turn could lead to more rapid CD4 cell decline, further weakening the immune system's response to infections (Mermin *et al.*, 2004). Another study in Ethiopia found that the baseline cotrimoxazole preventive therapy also had an effect on the duration of VLS. Patients with early initiation of CPT were two times more likely to suppress the VL earlier than those patients who were not initiated on CPT. The effect of CPT on time to VLS might be because early initiation of cotrimoxazole prophylaxis results in a significant reduction in serious bacterial infections and mortality. Given the high underlying risk of high viral replication and serious bacterial infection during the early period, this improvement in co-morbidity could correspond with a substantial success in early VLS (Sultan *et al.*, 2019).

Other studies in cotrimoxazole prophylaxis in Africa have produced similar results to the current study, thus disputing the benefits of cotrimoxazole on HIV-infected patients (Manyart *et al.*, 2001; Kalou *et al*, 2005). A study in Abidjan, Côte d'Ivoire investigating the changes in HIV RNA VL, CD4+ T-cell counts, and levels of immune activation markers associated with anti-tuberculosis therapy and cotrimoxazole prophylaxis among HIV-infected tuberculosis patients found that levels of VL, CD4+ T-cell counts, and markers of immune activation were not different for patients on standard treatment of tuberculosis compared with those on standard cotrimoxazole treatment (Kalou *et al.*, 2005).

5.4.6 Isoniazid Preventive Therapy

In this study there was no statistical association between viral suppression and IPT, the preventive therapy for TB among PLHIV (National Department of Health, 2010). However, some studies reported that, in addition to effectively preventing TB in patients infected with HIV (Akolo *et al.*, 2010), IPT was also found to affect VL (Okonji *et al.*, 2021; Sultan *et al.*, 2019). A retrospective follow-up study that investigated 3 927 adult PLWHIV on first-line ART in Ethiopia concluded that baseline IPT along with baseline CD4 count, baseline VL, CPT, IPT and adherence level were identified as the independent predictors of time to HIV VLS (Sultan *et al.*, 2019). This study showed that the average time to VLS during the study period was three months with 95% CI (2.68, 3.32) (Sultan *et al.*, 2019). Likewise, a retrospective study investigating VLS among adolescents on ART in Ehlanzeni District, Mpumalanga Province, South Africa found that adolescents who started on IPT after ART initiation were more likely to attain viral suppression compared to those who did not (p=0.038) (Okonji *et al.*, 2021).

5.4.7 ART Regimen

Considering the baseline ART regimen, this study found that adolescents who started on S3L (Stavudine + Lamivudine + Lopinavir/ritonavir) (AOR=2.87; CI: 1.01 – 8.16) and TFE (Tenofovir+ Emtricitibine+ Efavirenz) (AOR=2.07; CI: 1.12 – 3.85) regimens were more than two times likely to be virally suppressed compared to those who started on A3E (Abacavir+ Lamivudine + Efavirenz). Similar to the current study, other studies have revealed that Tenofovir-based regimens, especially T3E regimen, have high viral suppression rates. A cross-sectional study conducted in Cameroon investigating viral suppression levels according to a therapeutic regimen in adults, adolescents and children found that viral suppression appeared higher in those treated with TDF (Tenofovir/nucleoside reverse transcriptase) + 3TC (Lamivudine/ nucleoside reverse transcriptase) + EFV (Efavirenz/non- nucleoside reverse transcriptase) (TLE) (83.2%) compared to other NNRTI-based or Protease inhibition based (PI/r-based) regimens (71.4%). In fact, this combination has been found to be equivalent or superior to its comparator arms (other nucleoside reverse transcriptase (NRTI)-backbone and/or NNRTI) in many studies (Mathews *et al.*, 2002; Nachega *et al.*, 2009; Philips *et al.*, 2001; Tang *et al.*, 2012). Desta *et al.*'s (2020) study among Ethiopian patients revealed similar results, where patients on T3E (TDF(Tenofovir)-3TC (Lamivudine)-EFV (Efavirenez)) regimen had higher rates of viral suppression compared to other regimens such as the 1c (AZT(Zidovudine)-3TC (Lamivudine)-NVP (Nevirapine) (Z3N) regimen. A similar study in Nepal reported that the 1e (TDF (Tenofovir /3TC (Lamivudine)/EFV (Efavirenez)) regimen had a better virological response among Nepalese people living with HIV (PLHIV) (Ojha, Shakya,& Dumre, 1999). Tenofovir-based regimen is usually a FDC. FDC has been shown to have definite benefits for programmes and patients particularly related to better adherence outcomes (Ramjan *et al.*, 2014). Therefore, the possible reason for better VL outcomes among adolescents receiving Tenofovir-based regimes is better adherence to the ART.

Moreover, considering the current ART regimen in the current study, most of the regimens performed worse than the A3E (Abacavir + Lamivudine + Lopinavir/ritonavir) regimen. Adolescents on A3L (Abacavir + Lamivudine + Lopinavir/ritonavir), (AOR=0.34; CI:0.21 – 0.55), S3L (Stavudine + Lamivudine + Lopinavir/ritonavir), (AOR=0.18; CI: 0.04 – 0.74), Z3L (Zidovudine + Lamivudine + Lopinavir/ritonavir) (AOR=0.36; CI: 0.24 – 0.54), and other regimens (AOR=0.36; CI: 0.24–0.54) had lower odds of being virally suppressed compared to participants on A3E regimen. Kriel *et al.* (2017) investigated the VLS according to the different

ART regimens at initiation among adolescents in South Africa. They found that ART regimen was significantly associated with VLS after 12- and 24-months post-ART initiation with the highest rates of VLS found among adolescents on the Abacavir-based regimen which was the recommended first-line ART regimen for the younger adolescent, with suppression rates of 73.5% at month 4, 61.8% at month 12 and 64.7% at month 24. They claimed that this result may not be due to the actual regimen itself, but possibly linked to this regimen being the first-line ART regimen for younger adolescents. The Abacavir-based regimen given to the adolescent at initiation consists of three separate drugs, while older adolescents often receive a FDC of Tenofovir-based regimen at initiation (Kriel, 2017). The FDC has been shown to have definite benefits for programmes and patients particularly related to better adherence outcomes (Ramjan *et al.*, 2014). Therefore, the possible reasons for better VL outcomes among young adolescents receiving Abacavir-based regimens compared to the older adolescent receiving the FDC of Tenofovir-based regimen are better retention in care (Kriel, 2017; van Wyk *et al.*, 2020). The majority of younger adolescents receive care in paediatric services and these services are often initiated and managed by outreach teams and support services (from non-profit organisations in conjunction with tertiary hospital collaboration), which vary from adult services. Moreover, young adolescents are also more likely to have a caregiver or treatment support people responsible for their treatment. These interventions may all contribute to more favourable retention rates as well as subsequent adherence benefits and VL monitoring efficiencies (Kriel, 2017; van Wyk *et al.*, 2020).

On the other hand, the results of the current study conflict with other studies that reported no association between the ART regimens used and viral non-suppression (Bayu *et al.*, 2017; Hailu *et al.*, 2018). This variation might be due to genetics and socio-demographic variations among the different study settings. All these variables may lead to viral non-suppression (Desta *et al.*, 2020).

The odds of being virally suppressed reduced with increased age at ART initiation. This study compared different age groups to ART initiation at 0 to 4 years, this study revealed that those who started ART between 5 and 9 years (AOR=0.52; CI: 0.34–0.80), between 10 and 14 years (AOR=0.41; CI: 0.23–0.72) and between 15 and 19 years (AOR=0.39; CI: 0.17–0.93) were less likely to be virally suppressed. We believe that patients who were introduced to ART at a young age are more accustomed and aware of how to adhere to and maintain their ART regimens because of many years of experience. They, therefore, have a good adherence and

retention pattern which eventually allows them to be more virally suppressed compared to those who initiated ART at later stages.

5.5 RETENTION IN CARE

Several studies demonstrated that adolescents seem to have lower retention rates compared to other age groups (Ryscavage *et al.*, 2011). Optimal retention in care leads to good adherence to ART which results in decreasing the risk to high VLs among HIV patients (Clouse *et al.*, 2013). Low levels in viral load are not only of benefit to the individual decreasing HIV-related morbidity and mortality (Clouse *et al.*, 2013) but ultimately benefit the broader public as it contributes to effectiveness of ART programmes and controlling the epidemic.

In the current study, retention in care had a clear significant effect with viral suppression for all patients who ever started (– death + stop + LTFU). Those who were retained in care were more virally suppressed (81.43%) compared to those that were not retained in care (70.81%). The results from the current study are in line with multiple studies in the literature that indicate that patients retained in care are more likely to achieve viral suppression compared to those not engaged in regular care (Giordano *et al.*, 2007; Mugavero *et al.*, 2012, Tripathi *et al.*, 2011,). Among 2 197 South Carolina HIV-infected residents entering care between 2004 and 2007, 50% were retained in care. Patients retained in care had a greater decrease in HIV VL from baseline compared to those with suboptimal retention in care (Tripathi *et al.*, 2011). Likewise, among 8 235 patients followed for 12 months at six academic HIV clinics, retention in care, regardless of the measure used, was significantly associated with viral suppression (Mugavero *et al.*, 2012). Yehia *et al.* (2014) further demonstrated that retention in care is associated with viral suppression.

Tailoring an HIV programme targeting adolescents and attending to the location or sites where these intervention programmes take place may improve retention, as reported by Lamb *et al.* (2014) where youth (15–24 years) accessing ART at facilities that provided sexual and reproductive health services and adolescent support groups had significantly lower attrition. Moreover, Massavon *et al.* (2014) also reported that the site of ART services also impacts retention rates, with higher retention in care rates found in the community home-based care approach than the facility based/family-centred approach (94% vs. 84.7% respectively).

5.6 SUMMARY

This study found that most participants were fully suppressed (< 50c/ml) or transient suppressed (50–999 c/ml) at 9.5% and 68.7%, respectively. The findings were low compared to Zanoni *et al.*'s (2016) meta-analysis of South African adolescents and young adults on ART, where 81% was virally suppressed. However, our findings fall in the range of 28% to 89%, reported by Ferrand *et al.* (2016) in their review of adolescents in care in countries in southern Africa, Uganda, South Africa; Rwanda; China, Brazil, Mexico, Argentina and 13 USA cities, among them Washington, Baltimore and New York.

In the current study, current age and gender were an insignificant determinant of viral suppression. Data from clinical records found a significant effect between viral suppression in younger adolescents. Many authors suggested that viral suppression is higher in young adolescents because younger adolescents show better retention rates because they depend on their adult caregivers to manage their ART. In the current study, duration of ART was not associated with viral suppression which contrasts with other studies. Results from Eastern Cape, South Africa, revealed that adolescents on ART for ≥2 years were more likely to be fully viral suppressed, but this contradicts Muri *et al*. (2017) and Makadzange *et al.* (2015) who associated older age at ART initiation with higher viral suppression rates in their studies in Tanzania and Zimbabwe. In the current study, gender was not associated with VLS, Conflicting results were observed in the literature, with high viral suppression in males in some studies and higher viral suppression in females in others.

Results in our study revealed that a higher CD4 count at baseline was associated with higher odds of viral suppression and adolescents who had a CD4 count greater than 500 cells/mm^3. The results in this study are similar to many other results in the literature (Bennett *et al.,* 2002; Bonnet *et al.,* 2005; Grabar *et al.,* 2005). Contradictory results to this study were reported by Phillips *et al.* (2001) who analysed data from the databases of three studies in the SHCS and found that a lower CD4 cell count at baseline was not associated with poorer virological outcome.

In this study, multivariate analysis showed no significant difference between WHO stage and viral suppression. Conflicting results from the literature were observed regarding the effect of

WHO on viral suppression (Desta *et al.*, 2020; Kriel, 2017); some studies reported a significant effect and others did not (Bayu *et al.*, 2017; Hailu *et al.*, 2018; Rangarajan *et al.*, 2016).

History of TB in this study had no significant effect on viral suppression; however, having an active opportunistic TB infection was associated with low viral suppression across South Africa (Bulage *et al.*, 2017). African public healthcare facilities highlighted that youth/adolescents and patients on TB treatment had increased odds of not achieving viral suppression (Davey *et al.*, 2018). Ongoing HIV replication and high VL is an important risk factor for TB (Fenner *et al.*, 2017), this could also explain the high VL in patients with active TB or on TB treatment.

Another clinical factor that had no statistical association with viral suppression was pregnancy. Contradictory to our study, some authors reported that pregnancy can affect viral suppression (Hodgson *et al.*, 2014; Kriel, 2017, Wang *et al.*, 2011). It was reported that HIV-infected pregnant women (less than 30 years) have higher unsuppressed VLS. Kriel's (2017) study also showed a significantly greater proportion of non-pregnant compared to pregnant adolescents that were virologically suppressed.

A number of studies in the African region found no association between cotrimoxazole prophylaxis and viral suppression similar to the results in the current study (Kalou *et al.*, 2005; Manyart *et al.*, 2001). Other studies claimed that cotrimoxazole reduces viral load. The effect of CPT on time to VLS might be because early initiation of cotrimoxazole prophylaxis has a significant reduction in serious bacterial infections and mortality. Given the high underlying risk of high viral replication and serious bacterial infection during the early period, this improvement in co-morbidity could correspond to a substantial success in early VLS (Sultan *et al.*, 2019).

The current study did not find any relationship between IPT and viral suppression. However, some studies reported a relationship between IPT and viral suppression (Okonji *et al.*, 2021; Sultan *et al.*, 2019).

Tenofovir-based regimen is usually an FDC. FDC has been shown to have definite benefits for programmes and patients particularly related to better adherence outcomes (Ramjan *et al.*, 2014). Therefore, the possible reasons for better VL outcomes among adolescents receiving Tenofovir-based regimes is better adherence. Moreover, better VL outcomes among young adolescents receiving Abacavir-based regimens the majority of younger adolescents receive

care in paediatric services and these services are often initiated and managed by outreach teams and support services caregiver or treatment support people responsible for their treatment may all be contributing to more favourable retention rates as well as subsequent adherence benefits and VL monitoring efficiencies.

Similar tour study, several studies demonstrated that adolescents seem to have lower retention rates compared to other age groups (Ryscavage *et al.*, 2011).

The next chapter draws the study to a close and presents the conclusions and recommendations.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

6.1 CONCLUSION

Viral suppression among adolescents on ART in Thabo Mofutsanyane District is still below the target of 90%. Adherence support for adolescents on ART is critical for viral suppression. Targeted interventions are required to improve retention in care and VLS amongst adolescents on ART, with specific interventions tailored for them. Routine monitoring of adherence should be improved by formally including clinic attendance monitoring, pill-counts and client self-reporting, as well as POC VL testing to adolescent ART services.

6.2 LIMITATIONS

The major limitation of this study was that some of the records and variables were missing. Values that were missed were not included from each variable and the analysis conducted was based on the totals with complete records. This may have affected the analysis of variables associated with viral suppression.

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 that can also be explored such as social, cultural and economic factors that can also affect viral suppression.

The strength of this study was its large sample size (n=4 520) derived from health facilities across Thabo Mofutsanyane District Municipality, Free State Province, South Africa, and therefore the results provide a near true reflection of viral suppression among adolescents receiving ART in Thabo Mofutsanyane.

6.3 RECOMMENDATIONS

Further interventions should be implemented to improve and sustain retention in care and therefore adherence to ART which was found to be a very important factor associated with viral suppression. Moreover, policies must be put in place to optimise adherence and viral suppression among adolescents.

- Adherence is imperative for viral suppression and should be assessed at every visit to identify and address possible barriers to adherence for adolescents on ART.
- There is need for further investments in improving retention and adherence support for adolescents on ART such as trained adherence counsellors.
- Barriers to retention in care/adherence should be identified and addressed.
- Further studies that involve qualitative studies or mixed methods could be conducted to identify other determinants associated with viral suppression, such as cultural, economic and social factors.

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APPENDIX 1: ABSTRACTION TOOL

MEDICAL RECORDS ABSTRACTION TOOL

Data Abstraction Code: _____

VIRAL LOAD

- **Last ART Viral Load ----------**

	Viral load Suppression	Tick
1	Fully Suppressed VL < 50 c/mL	
2	Transient Suppression VL 50 -999 c/ml	
3	Unsuppressed VL > 1000 c/ml	
4	Missing	

DEMOGRAPHIC CHARACTERISTICS

- Current age (10-14 years / 15-19 years).
- Age at ART initiation (0-4 /5-9 / 10-14 years / 15-19 years).
- Gender: Male _____ Female _____

CLINICAL INFORMATION

- WHO Clinical stage at initiation

	WHO Stage	Tick
1	Stage 1	
2	Stage II	
3	Stage III	
4	Stage IV	
5	Unknown	

- CD4 counts at initiation (< 200 /200-500 / > 500 / Missing).
- Pregnancy at ART initiation (YES /NO /Missing).
- History of TB (YES /NO / Missing).
- IPT (YES / NO / Missing)

- On Cotrimoxazole at baseline (Yes / No /Missing)

ART INFORMATION

ART regimen at initiation	
1	3EA (Lamivudine+ Efavirenz+ Abacavir)
2	A3E (Abacavir+ Lamivudine + Efavirenz)
3	A3L (Abacavir+Lamivudine + Lopinavir/ritonavir)
4	AdE (Abacavir+didanosine+Efavirenz)
5	AFE (Abacavir+ Emtricitibine+Efavirenz)
6	AFL (Abacavir+ Emtricitibine +lopinavir)
7	ALZ (Abacavir+ +Lopinavir/ritonavir+Zidovudine)
8	S3E (Stavudine+ Lamivudine + Efavirenz)
9	S3L (Stavudine + Lamivudine + Lopinavir/ritonavir)
10	S3N (Stavudine+lamivudine+Nevirapine)
11	SdL (Stavudine+didanosine+ Lopinavir/ritonavir)
12	T3E (Tenofovir+Lamivudine+Efavirenz)
13	T3L (Tenofovir + Lamivudine + Lopinavir/ritonavir)
14	T3N (Tenofovir + Lamivudine + Nevirapine)
15	TFE (Tenofovir+ Emtricitibine+Efavirenz),
16	TFL (Tenofovir+ Emtricitibine+ Lopinavir/ritonavir)
17	Z3E (Zidovudine + Lamivudine + Efavirenz)
18	Z3L (Zidovudine+Lamivudine+Lopinavir/ritonavir)
19	Z3N (Zidovudine+ Lamivudine+Nevirapine)
20	ZdL (Zidovudine+didanosine+ Lopinavir/ritonavir)
21	ZLA (Zidovudine+ Lopinavir/ritonavir+ Abacavir)
22	A3N ((Lamivudine+ Efavirenz+ Nevirapine)
23	Other
24	Missing

Current ART regimen	
1	3EA (Lamivudine+ Efavirenz+ Abacavir)
2	A3E (Abacavir+ Lamivudine + Efavirenz)
3	A3L (Abacavir+Lamivudine + Lopinavir/ritonavir)
4	AdE (Abacavir+didanosine+Efavirenz)
5	AFE (Abacavir+ Emtricitibine+Efavirenz)
6	AFL (Abacavir+ Emtricitibine +lopinavir)
7	ALZ (Abacavir+ +Lopinavir/ritonavir+Zidovudine)

8	S3E (Stavudine+ Lamivudine + Efavirenz)
9	S3L (Stavudine + Lamivudine + Lopinavir/ritonavir)
10	S3N (Stavudine+lamivudine+Nevirapine)
11	SdL (Stavudine+didanosine+ Lopinavir/ritonavir)
12	T3E (Tenofovir+Lamivudine+Efavirenz)
13	T3L (Tenofovir + Lamivudine + Lopinavir/ritonavir)
14	T3N (Tenofovir + Lamivudine + Nevirapine)
15	TFE (Tenofovir+ Emtricitibine+Efavirenz),
16	TFL (Tenofovir+ Emtricitibine+ Lopinavir/ritonavir)
17	Z3E (Zidovudine + Lamivudine + Efavirenz)
18	Z3L (Zidovudine+Lamivudine+Lopinavir/ritonavir)
19	Z3N (Zidovudine+ Lamivudine+Nevirapine)
20	ZdL (Zidovudine+didanosine+ Lopinavir/ritonavir)
21	ZLA (Zidovudine+ Lopinavir/ritonavir+ Abacavir)
22	A3N ((Lamivudine+ Efavirenz+ Nevirapine)
23	Other
24	Missing

- Duration of treatment (6-11 months / 1-2 years / 3-5 years / 6-10 years and more than 10 years)

- Retention (Retained ((Patient who are not registered as deceased, stopped treatment or LTFU for any reason) / Not retained (stopped treatment or LTFU for any reason, lost to follow up, /Transferred or moved out, Died)

APPENDIX 2: ETHICAL CLEARANCE LETTER

UNIVERSITY of the WESTERN CAPE

60 YEARS of hope, action & knowledge

10 December 2020

Dr B Elashi
School of Public Health
Faculty of Community and Health Sciences

Ethics Reference Number: BM20/10/10

Project Title: Determinants of viral suppression among adolescents on antiretroviral therapy in Thabo Mofutsanyane District Municipality, Free State province, South Africa.

Approval Period: 09 December 2020 – 09 December 2023

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 annually by 30 November for the duration of the project.

Permission to conduct the study must be submitted to BMREC for record-keeping.

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

Director: Research Development
University of the Western Cape
Private Bag X 17
Bellville 7535
Republic of South Africa
Tel: +27 21 959 4111
Email: research-ethics@uwc.ac.za

NHREC Registration Number: BMREC-130416-050

FROM HOPE TO ACTION THROUGH KNOWLEDGE.

APPENDIX 3: CONFIRMATION OF PROFESSIONAL EDITING

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8 August 2021

Declaration of professional edit

Determinants of viral suppression among adolescents on antiretroviral therapy in Thabo Mofutsanyane District Municipality, Free State province, South Africa

Balsam Ahmed Yousif Elashi

I declare that I have edited and proofread this thesis. My involvement was restricted to language usage and spelling, completeness and consistency and referencing style. I did no structural re-writing of the content.

I am qualified to have done such editing, being in possession of a Bachelor's degree with a major in English, having taught English to matriculation, and having a Certificate in Copy Editing from the University of Cape Town. I have edited more than 200 Masters and Doctoral theses, as well as articles, books and reports.

As the copy editor, I am not responsible for detecting, or removing, passages in the document that closely resemble other texts and could thus be viewed as plagiarism. I am not accountable for any changes made to this document by the author or any other party subsequent to the date of this declaration.

Sincerely,

Dr J Baumgardt
UNISA: D. Ed. Education Management
University of Cape Town: Certificate in Copy Editing
University of Cape Town: Certificate in Corporate Coaching

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