Adherence, Retention in Care and Treatment Outcomes of Adolescents on Antiretroviral Therapy in the Western Cape Metropole in South Africa

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KEY WORDS

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Loss to Follow-up

Viral Load Suppression

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ABSTRACT

***Background*:** Approximately 6% of all people living with HIV in 2016 are adolescents aged 10-19 years. It is reported globally that adolescents on antiretroviral therapy (ART) are at increased risk for poor retention in care, adherence and viral load suppression, compared to children and adults.

***Aim*:** The current study described retention in care, treatment outcomes and indications of poor adherence amongst adolescent patients on ART in public health facilities in the Metropole District Health Services of the Western Cape Province between January 2013 and December 2014.

Methodology: A quantitative retrospective cohort analysis was done of adolescents initiated on ART in public primary health care facilities in the Metropole of the Western Cape Province in 2013, and followed up for 24 months. Data were extracted from the provincial Tier.net electronic database and clinical folders, and captured in Excel. SPSS statistical software was used for descriptive and inferential analysis.

Results: A sample of 220 adolescents was realised for this study. The retention in care declined over the study period, with rates of 68.6%, 50.5% and 36.4% at months 4, 12 and 24, respectively. In bivariate analysis, retention in care was significantly associated with younger age (10 – 14 years) at month 4 (risk ratio (RR) = 1.37; [95% confidence interval (CI) 1.17 – 1.60]), month 12 (RR = 1.85 [1.48 – 2.31]) and month 24 (RR = 2.35 [1.73 – 3.20]) after initiation on ART. Male adolescents were significantly more likely to be retained in care compared to females (month 4: RR = 1.29 [1.08 – 1.53]; month 12: RR = 1.39 [1.06 – 1.84]; and month 24: RR = 1.60 [1.11 – 2.30]). Pregnant adolescents were significantly less likely to be retained in care at month 4 (RR = 0.73 [0.59 – 0.90]); month 12 (RR = 0.60 [0.44 – 0.83]); and month 24 (RR = 0.47 [0.30 – 0.74]) compared to those who were not pregnant.

Viral load suppression also declined over the study period, with rates of 59.5%, 40.0% and 25.0% at months 4, 12 and 24, respectively. In bivariate analysis, viral load suppression was significantly associated with younger age (10 – 14 years) at month 12 (RR = 1.83 [1.35 – 2.49]; and month 24 (RR = 3.38 [2.24 – 5.10]) after ART initiation. Male adolescents were significantly more likely to be virologically suppressed compared to females (month 4: RR = 1.49 [1.22 – 1.81]; month 12: RR = 1.50 [1.07 – 2.12]; and month 24: RR = 2.33 [1.50 – 3.62]). Pregnant adolescents were significantly less likely to be virologically suppressed (month 4: RR = 0.69 [0.53 – 0.89]; month 12: RR = 0.64 [0.44 – 0.94]; and month 24: RR = 0.24 [0.11 – 0.50]) compared to adolescents who were not pregnant.

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The proportion of adolescents who had at least one indicator of poor adherence by months 4, 12 and 24 were 21.8%, 24.5% and 16.2%, respectively. However, this result needs to be treated with caution because reporting of adherence were not standardised, and based on the clinician's judgement.

Conclusion: Retention in care and viral load suppression of adolescents on ART declined significantly over 24 months following ART initiation, particularly amongst the older adolescent group aged 15 – 19 years. Targeted interventions are required to improve retention in care and viral load suppression amongst adolescents on ART, with specific interventions tailored for older adolescents as well as pregnant females. Routine monitoring of adherence should be improved by formally including clinic attendance monitoring, pill-counts and client self-reporting, as well as point-of-care viral load testing to adolescent ART services.

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DECLARATION

I declare that *Adherence, Retention in Care and Treatment Outcomes of Adolescents on Anti-Retroviral Therapy in the Western Cape Metropole in South Africa* is my work, 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.

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Date: 4 December 2017

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ABBREVIATIONS AND ACRONYMS

A3E	Abacavir, Lamivudine and Efavirenz
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Treatment
ARV	Antiretroviral
BMI	Body Mass Index
CD4	Cluster of Differentiation 4
CDC	Community Day Centre
CHC	Community Health Centre
CI	Confidence Interval
HAART	Highly Active Antiretroviral Therapy
HAST	HIV, AIDS, Sexually Transmitted Infections and TB
HIV	Human Immunodeficiency Virus
IPT	Isoniazid Preventive Therapy
IQR	Interquartile Range
LTFU	Lost to Follow-up
MSM	Men having Sex with Men
PEP	Post Exposure Prophylaxis
PHC	Primary Health Care
PMTCT	Prevention of Mother to Child Transmission
PrEP	Pre Exposure Prophylaxis
REACH	Reaching for Excellence in Adolescent Care and Health
RR	Risk Ratio
T3E	Tenofovir, Lamivudine and Efavirenz
T3L/rit	Tenofovir, Lamivudine and Lopinovir/ritonavir
TFE	Tenofovir, Emtricitibine and Efavirenz
TB	Tuberculosis
UNAIDS	Joint United Nations Programme on HIV and AIDS
UNICEF	United Nations International Children's Emergency Fund
VL	Viral Load
WHO	World Health Organization
Z3E	Zidovudine, Lamivudine and Efavirenz

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CHAPTER 1: INTRODUCTION

1.1 Background

In 2016 an estimated 2.1 million adolescents between the ages of 10 and 19 years were reported to be HIV infected globally - which approximates 6% of all people living with HIV (UNICEF, 2017). Sub-Saharan Africa is one of the regions with the highest number of HIV infected adolescents with about 1.7 million HIV infected adolescents. South Africa contributes 25% of the 24.7 million people living with HIV in sub-Saharan Africa (UNAIDS, 2014b). With over 400 000 new HIV infections occurring in 2012, South Africa ranks first in HIV incidence in the world (Shisana *et al.*, 2014). Nearly 3 million children aged between 0–14 years and 2.9 million young people aged between 15–24 years are living with HIV. The national HIV prevalence among adolescent girls aged 15–19 years was estimated at 5.6% compared to adolescent boys whose prevalence rate was estimated at one fifth of that of girls (UNAIDS, 2014b). Of the new HIV infections among adolescents worldwide, 2 out of 3 are female (UNICEF, 2017). Similar trends are observed in sub-Saharan Africa where adolescent and young adult women are up to two to three times more likely to be infected than the males of similar age.

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An alarming trend over the last decade is the increase in AIDS-related deaths amongst adolescents, which is in contrast to the decrease in deaths reported among all other age groups (UNICEF, 2017). Globally, AIDS-related deaths fell by almost 40% between 2005 and 2013 for all age groups except adolescents (aged 10–19 years) (UNICEF, 2014b). HIV is the leading cause of adolescent mortality in sub-Saharan Africa and the second highest worldwide (WHO, 2014b). In 2012 the leading cause of death in all ages in South Africa was HIV/AIDS: 50.7% among 5 – 14 year olds and 51.9% among 15 - 44 year olds (Msemburi *et al.*, 2016). It is argued that these statistics reflect, in part, the improvements in the response to paediatric HIV, with infected children now surviving into adolescence and early adulthood (Mofenson & Cotton, 2013).

The goal of ART programmes is to achieve sustained suppression of HIV replication, which would in turn, result in plasma levels of the virus (viral load) being reduced to the point of being undetectable to modern laboratory tests (Nachega *et al.*, 2009). This, in turn, signals the reconstitution of the patient's immune system, which results in improvements in general

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health and well-being, and thus contributes to the decline in morbidity and mortality. The success of ART programmes in achieving viral load suppression is dependent on good retention in care (Clouse *et al.*, 2013), displaying good adherence to their medication (Jaspan, Li, Johnson & Bekker, 2009) as well as lifestyle and behavioural changes that are conducive to general health and well-being (Kim, Gerver, Fidler & Ward, 2014). Lifestyle and behavioural changes such as avoiding risky sexual behaviour, consuming a balanced nutrition, and avoiding substance use and abuse are particularly challenging during adolescence.

Along with the challenges of having a chronic illness such as HIV, adolescence is associated with physiological, emotional, cognitive and socio-developmental changes which may influence the management and control of their chronic condition (Nglazi *et al.*, 2012). These developmental challenges accompany behavioural patterns such as increased risky behaviour, experimentation and pressures to conform, which may result in poor adherence to ART. Poor adherence, in turn, increase the risk of viral load rebound, possible drug resistance and the risk of morbidity and mortality. Adolescence is also a period of high risk for acquiring HIV as well as re-infection with other strains of HIV. Results from a South African national household survey suggest that risky sexual behaviour is on the rise - as indicated by an increase in the number of individuals with sexual debut before 15 years (Shisana *et al.*, 2014). The survey also highlighted that a third of young females aged 15–19 years had sexual partners who are five or more years older. Young women are particularly vulnerable to sexually acquired HIV (Cowan & Pettifor, 2009). In settings where heterosexual transmission drives the local epidemic as in sub-Saharan Africa, females are infected at younger ages than males through exposure to older males. The vulnerability of adolescents is also exacerbated through interaction with and membership to vulnerable groups associated with increased risk of acquiring HIV or possible increased risk of poor treatment outcomes, such as men who have sex with men (MSM), transgender persons, people who inject drugs, sex workers and prisoners (Lall, Lim, Khairuddin & Kamarulzaman, 2015).

South Africa initiated the national ART programme in 2004. The number of new people initiated on ART between 2010 and 2013 globally was 5.6 million; with SA contributing the highest proportion (33%) of this total (UNAIDS, 2014b). Results from comparisons of national HIV prevalence surveys SA carried out in SA in 2008 and 2012 reported an increase in HIV prevalence by 1.2 million - this can be partially explained by the massive expansion

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of the ART programme that has saved many lives (Shisana *et al.*, 2014). According to the 2012 National HIV Prevalence, Incidence and Behaviour Survey of SA more than 2 million of the estimated 6.3 million people living with HIV in SA were eligible for ART with an estimated 31.5% of those living with HIV being on ART. Findings from a national document on the millennium development goals reported that 70.8% of men, 87.3% of women and 56.2% of children in SA who were eligible for ART were on treatment in 2013 (Republic of South Africa, 2013). Of those above 15 years of age and were eligible for ART, 86% were initiated on treatment. South Africa has also adopted the "90-90-90" strategy which has set HIV and ART targets for 2020 in order to end HIV by 2030 (UNAIDS, 2014a). The targets of this strategy are that 90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy, and 90% of all people receiving antiretroviral therapy will have viral load suppression.

In South Africa, like in many countries in sub-Saharan African countries, the ART programme is differentially focused on adult and child populations (Livingstone *et al.*, 2014). Adolescents generally access care either in paediatric or adult services. Services designed for adolescents have shown good outcomes with regard to retention in care and mortality as seen in results from an adolescent-focused ART service in Zimbabwe (Shroufi *et al.*, 2013). Adolescent focused programmes have been developed in Western settings, but the availability of more resources in their context may not make their intervention amenable to implementation in sub-Saharan Africa (Bygrave *et al.*, 2013). The critical nature of the state of adolescents infected with HIV has resulted in UNICEF and UNAIDS commencing an initiative to end adolescent AIDS (UNICEF, 2014a). The "All In 2015" initiative is a collaborative effort which includes various partners and sectors, including adolescents, to work with countries to develop their response to urgently attempt to combat adolescent AIDS. Key to this process or any other intervention planning to improve outcomes is knowledge related to the local epidemic and how it relates to adolescents.

Initial evidence indicates that retention in care and adherence of adolescents are poorer when compared to younger or older age groups (Livingstone *et al.*, 2014). Even in an adolescent-focused service such as the service in Zimbabwe, adherence was found to be poor (Shroufi *et al.*, 2013). Furthermore, Shroufi *et al.* (2013) also makes reference to numerous studies reporting virological outcomes among HIV-infected adolescents being worse than those in adults.

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1.2 Problem Statement

As already mentioned, adolescents in the ART programme have unique challenges compared to other population groups. These challenges may result in unsatisfactory programmatic outcomes, threatening the success of ART programmes achieving the 2020 targets of the "90-90-90" strategy, adopted by South Africa, in order to contribute in ending HIV by 2030 (UNAIDS, 2014a).

According to Kim *et al.* (2014), Africa records the best adherence rates amongst adolescents on ART compared to other regions. Other studies, nevertheless, have reported that the adherence and viral load suppression amongst adolescents on ART remain unsatisfactory (Nglazi *et al.*, 2012; Nachega *et al.*, 2009). This could partly be attributed to the fact that the ART programmes of many countries focus on meeting the needs of the paediatric and adult populations on ART, with little to no specific attention being paid to the adolescent group. Addressing the challenges of adolescent ART adherence, viral load suppression and retention in care would require an understanding of the adherence, viral load suppression and retention in care trends, demographics and clinical characteristics of these adolescents.

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1.3 Aim and Objectives

Aim

The aim of the study was to describe adherence, retention in care and treatment outcomes of adolescent patients on ART in public health facilities in the Metropole of the Western Cape Province.

Objectives

- To describe the socio-demographic and baseline clinical characteristics of adolescents initiated on ART in public primary health care facilities in the Western Cape Metropole in 2013.
- To describe the adherence, retention in care and treatment outcomes of adolescents on ART at 4, 12 and 24 months after ART initiation.
- To determine risk factors for viral load suppression of adolescents on ART.
- To determine risk factors for retention in care of adolescents on ART.

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CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

Uninterrupted retention in care (Clouse *et al.*, 2013) and adherence to ART within the broader treatment programme (Jaspan *et al.*, 2009) are integral for sustaining positive health outcomes to HIV-infected patients on ART; including adolescents on ART. This literature review describes the concepts of retention in care and adherence of patients on ART as well as how it relates to adolescents in ART programmes. It also reviews empirical evidence on mortality among adolescents on ART and the factors associated with retention in care and adherence to on ART.

2.2 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). Furthermore, remaining engaged in care allows for the assessment of treatment success, for appropriate treatment adjustments, and also allows patients to benefit from other services, support and prevention strategies offered by treatment programmes. Retention in care and the benefits to the individual ultimately benefit the broader public as it contributes to effectiveness of ART programmes and controlling the epidemic as a whole. Sub-optimal retention in care leads to non-adherence to ART, which in turn, increases the risk of possible drug-resistant mutations, morbidity and mortality (Clouse *et al.*, 2013).

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2.2.1 Definitions of Retention in Care

Retention in care and related terms are used in HIV/ART programmes but has no uniform definition. Understanding the definition of these terms is critical when engaging data as well as evaluating the outcomes of ART programmes. Studies utilise definitions for retention in care as remaining alive and in care at a clinic (Clouse *et al.*, 2013), or refers to individuals still receiving care either on-site or at another site (Orrell, Kaplan, Wood & Bekker, 2011). The WHO defines 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) (WHO, 2013a). Loss to follow-up (or being lost to follow-up) is a term used to classify patients who fail to present to a clinic

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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 lost to follow-up.

2.2.2 Retention in Care Rates in Antiretroviral Therapy Programmes

A 2011 report describing data from 149 countries showed average retention in care rates of 81% at 12 months and 75% at 24 months (WHO, UNICEF & UNAIDS, 2011). Similar results were found in a systemic review of 33 studies describing the patient retention in care in ART programmes in 39 cohorts in sub-Saharan Africa: a median of 86.1% of clients remained in care at 6 months, 80.2% at 12 months, 70% at 24 months and 64.6% at 36 months (Fox & Rosen, 2010). In South Africa decentralised ART services aimed to make treatment accessible and decrease loss to follow-up. A study determining the 12 month loss to follow-up of patients at an ART primary healthcare clinic in South Africa found that attrition after ART initiation remained high at 25.0%, with most attrition occurring during first 6 months on ART (19.8%) and lowering between 6–12 months on ART (4.7%) (Clouse *et al.*, 2013).

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2.2.3 Retention in Care Rates in Adolescents

Studies assessing the rates of loss to follow-up in adolescents on ART report varying results. A systemic review and meta-analysis of adolescent HIV continuum of care in South Africa found that in a meta-analysis of six South African studies reported that 83% (95% CI 68% - 94%) of HIV-infected adolescents on ART were retained in care within the first 1 to 2 years of being on treatment (Zanoni, Archary, Buchan, Katz & Haberer, 2016). A Ugandan study reported overall retention of adolescents of 96% at 6 months, 90% at 12 months, 83% at 24 months, 76% at 36 months, and 71% at 48 months (Ssali *et al.*, 2014). In another study in Uganda involving 10 districts also supported by The AIDS Support Organization, Nabukeera-Barungi *et al.* (2015) reported that after one year post ART initiation, 90.0% of the 156 starters were retained in care. Okoboi *et al.* (2016) reported 65% were retained in care over a 5 year period.

Adolescents may differ with other age groups in relation to their retention in care. 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 not youth orientated. Adolescents and young adults demonstrated higher rates of loss to follow-up compared with

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adults (Ryscavage *et al.*, 2011). Similarly, a retrospective cohort study of ART patients attending an ART clinic in a hospital in Ethiopia found that being adolescent placed the patient at higher risk of loss to follow-up (Berheto, Haile & Mohammed, 2014). When disaggregating adolescents and young adults into narrower age bands, as seen in an observational prospective cohort study in rural Zimbabwe, loss to follow-up 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.*, 2013). Adolescents (16-19 years) also had a higher risk of loss to follow-up compared to young adolescents. This highlights the variations in behaviour, risk and needs within the spectrum of adolescents and may need to be considered or further explored when considering programme planning. In a study evaluating loss to follow-up amongst pregnant women it was found that younger patients were also at greater risk of loss to follow-up (Kaplan, Orrell, Zwane, Bekker & Wood, 2008). However, although there is a risk of loss to follow-up in adolescents it does not always differ from the other age groups within ART programmes. An observational prospective cohort study of HIV-infected adolescents (9-19 years) and young adults (20-28 years) at a large public sector community-based ART programme in Cape Town, South Africa reported similar rates of loss to follow up between the 2 groups (Nglazi *et al.*, 2012).

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2.3 Adherence

Adherence to ART and the prescripts of an ART programme are critical in controlling HIV replication, prevention of new infections, immune recovery and maintaining good health (Kim *et al.*, 2014). Sub-optimal adherence increases the risk of viral drug-resistance, reducing the efficacy of ART which leads to disease progression and increase the risk of acquiring opportunistic infections (Wiener, Riekert, Ryder & Wood, 2004). Furthermore, it results in reducing future drug options resulting from cross resistance (Chesney, 2003).

2.3.1 Definition of Adherence

Adherence is defined as the extent to which an individual's health-related behaviours correspond with outlined medical advice (Murphy, Belzer, Durako, Sarr, Wilson & Muenz, 2005). The WHO defines 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 (WHO, 2015). In the context of an ART

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programme it is seen as the measure of how well a patient complies with taking his/her medication as well as complying with other prescripts of the treatment programme.

2.3.2 Measurements of Adherence

Measuring adherence is important in assessing the individual's chance of successful treatment outcome or gauging the risk of possible treatment failure within the context of a treatment programme. Adherence can be monitored by direct or indirect means (Khan, Song, Williams, Bright, Sill & Rakhmanina, 2009). Direct measures of adherence include therapeutic drug monitoring or directly observing the consumption of the treatment. Indirect approaches include viral load monitoring, counting prescription claims, electronic pill-container devices, provider reporting, clinic attendance monitoring, pill-counts or client self-reporting (Stricker *et al.*, 2013; Ross-Degnan *et al.*, 2010). Khan *et al*. (2009) found that self-reported adherence was found to be a significant predictor of achieving an undetectable viral load; with those with those reporting to be always or mostly adherent being more likely to have an undetectable viral load than those reporting to be rarely or never adherent. However, the validity of self-reporting has been questioned by many studies (Belzer, Fuchs, Luftman & Tucker, 1999; Spire, Duran, Souville, Leport, Raffi & Moatti, 2002) as recall bias or manipulation of responses may affect this measurement. Similarly, the manipulation of pill-counts may also result in unreliable adherence assessments (Ross-Degnan *et al*., 2010) which have led to many facilities in the Western Cape Province ceasing to use this measure for adherence. Monitoring clinic attendance, prescription claims or assessing the general health status are other possible measures but these measures do not guarantee that medicine was consumed.

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2.3.3 Viral Load Monitoring

Viral load monitoring is an indirect measure of adherence often used in many ART programmes whereby the viral load acts as a proxy to assess adherence particularly in the case of viral load suppression which serves as a reasonably reliable marker of good adherence (Stricker *et al.*, 2013). A meta-analysis and systematic review by Kim *et al.* (2014) found that studies most often defined viral load suppression as less than 400 copies/ml. However, viral load suppression is also defined at lower thresholds, e.g. less than 50 copies/ml (Orrell *et al.*, 2011). *Virological breakthrough* is another term which refers to any individual whose viral load reached more than 1000 copies/ml after previous suppression, i.e. less than 50 copies/ml. *Virological failure* is defined as a plasma viral load of more than 1000 copies/ml

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based on 2 consecutive viral load measurements after 3 months with adherence support (WHO, 2013b). The patient must have taken ART for at least 6 months before it can be determined that the regimen had failed.

Although viral load suppression is a good indicator of adequate adherence to ART, an unsuppressed viral load is not necessarily always a good marker of poor adherence (Wiener *et al.*, 2004). Patients may be adherent to their medication but are infected with a resistant strain of HIV. Thus in resource limited settings where resistance testing is not easily accessible a comprehensive approach to assessing adherence and developing the management plan is required. Patients may also have unsuppressed viral loads due to malabsorption of medication or drug interactions between ART and other medication being taken for concurrent medical conditions, and this may result in lowering the levels of ARVs in the blood resulting in an increase in the viral load (WHO, 2014a). Despite these limitations, the WHO has recommended viral load monitoring as the preferred method of monitoring patients on ART (WHO, 2014c). The ART programme in the Western Cape has also endorsed viral load monitoring as its method of choice of monitoring response to treatment and as a proxy for adherence (Western Cape Government Health, 2015).

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Viral load 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 return on another date to the facility in order to obtain the result. Point-of-care (POC) viral load testing is another method of obtaining a viral load result while the patient is present (Phillips *et al.*, 2016). It is currently being used in resource-limited settings, research and technology development (Marcus, Ferrand, Kranzer & Bekker, 2017). Obtaining an immediate result gives the clinician a result which would immediately determine whether adherence support and interventions needs to be initiated. POC testing will also decrease amount of visits required to obtain and report the result to the patient, which patients would find more convenient.

2.3.4 Viral Load Outcomes in Adolescents

The dearth of quality studies and data on adolescents and viral load outcomes was stated as a major finding in a literature review conducted which aimed to evaluate the proportion of adolescents accessing ART in routine healthcare settings who achieved virological suppression (Ferrand *et al.*, 2016). In one of the first studies to specifically address the response to ART in HIV-infected adolescents , virological suppression was found to be lower

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than expected and was related to lack of adherence (Flynn *et al.*, 2004). Adherence to ART was the only predictor of achieving undetectable virus loads which led to subsequent recommendations for efforts to improve treatment outcomes to have a strong focus on adherence to medication. This was also promulgated in the REACH (Reaching for Excellence in Adolescent Care and Health) study in the USA by Murphy, Wilson, Durako, Muenz and Belzer (2001) who found a strong association between adherence and reduced viral load. Williams *et al.* (2006) also found a strong association between viral load and complete adherence to ART medications amongst children and adolescents from an American setting. 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 viral load suppression at time points reported that at one year post-ART initiation viral load suppression rates of adolescents varied considerably, ranging from 27% to 89%.

PEPFAR released statistics following national household surveys in three sub-Saharan African countries (Zimbabwe, Malawi and Zambia) which shed light on these countries' ART programmes in relation to viral load suppression figures among differing age groups (Avert, 2016). The average viral load suppression among adolescents and young adults from these countries was 42%.

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2.4 Factors Related to Retention in Care, Viral Load Suppression and Adherence amongst Adolescents on Antiretroviral Therapy

Numerous factors can impact on adherence and retention in ART care. These factors can be categorised as follows: individual-related factors (age, 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), socio-economic factors (poverty, family support, transport, food, stigma, discrimination), and socio-cultural factors (religion, traditional health-seeking behaviour) (Mukumbang, Van Belle, Marchal & Van Wyk, 2017). Andersen's Behavioural Model is an example of a framework designed to provide an understanding of how patient and environmental factors impact health behaviours and outcomes (Holtzman *et al.*, 2015). Hotlzman *et al.* (2015) identified 18 factors (barriers/facilitators) affecting retention and ART adherence from their

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qualitative study in the United States of America. Those common to both retention and adherence were mental illness, substance abuse, stigma, insurance, social support, housing, reminder strategies, competing life activities, symptoms, colocation of services, and provider factors. Factors unique to retention were appointment scheduling, clinic experiences, and transportation. Factors specific to adherence were pharmacy services, medication characteristics, health beliefs, and health literacy. There is a paucity of studies available examining the above factors in relation to adolescents on ART in the developing world. Results from studies conducted in developed countries are unlikely to be applicable to the sub-Saharan African context.

2.4.1 Patient Factors and Medication Regimen Factors

Age was found to be a significant factor in studies evaluating adolescents and retention in care in ART programmes in sub-Saharan African countries, with older adolescents aged 15-19 years having higher risk of not being retained in care than younger adolescents aged 10 to 14 years (Kranzer *et al.*, 2017; Okoboi *et al*., 2016; Ssali *et al*., 2014; Bygrave *et al*., 2013). Compared to other age groups, adolescents and young adults have shown higher rates of attrition, as seen in a cohort study conducted in clinics in Kenya, Mozambique, Tanzania, and Rwanda where attrition pre and post-ART initiation was substantially higher among the older adolescent and young adult group (youth aged 15-24 years) compared to other age groups (Lamb *et al*., 2014). This contrasts with the findings in an American study which found better retention to be associated with being younger than 21 years of age (Magnus *et al.*, 2010). However, the context of this study was that it was conducted among African American and Latino adolescent HIV-positive men having sex with men.

Sex as a discriminator of retention in care was found in studies such as a Ugandan cohort study where Ssali *et al*. (2014) found that at 24 and 36 months female adolescents had a higher risk of not being retained in care than male adolescents. However, Lamb *et al*. (2014) reported from a cohort study using data from clinics in Kenya, Mozambique, Tanzania, and Rwanda, that male youth (15 – 24 years) having higher post-ART attrition than pregnant as well as non-pregnant females. Contrary to the findings by Ssali *et al.* (2015) but in a different context, an American study that compared heterosexual males and MSM to females, and compared males and females using injectable drugs, found males had worse retention in care outcomes in both comparisons (Hall, Gray, Tang, Li, Shouse & Mermin, 2012).

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Immunity and levels of immunosuppression have been found to be associated with retention in care. Individuals with CD4 counts between 350 – 499 cells/mm³ are considered 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). The latter two ranges increases the risk of developing various opportunistic infections related to advanced (WHO stage III) to severe (WHO stage IV) HIV associated symptoms.

Reif et al. (2016) found that adolescent patients with a CD4 count less than 50 cells/mm³ had significantly higher attrition at 12 months after ART initiation compared to those with CD4 counts more than 350 cells/mm³. Okoboi *et al.* (2016) also reported from a Ugandan study that adolescents with higher CD4 counts (≥250cells/mm³) at the initiation of ART had a significantly lower risk of attrition. However, contrary to the above findings, Ssali *et al.* (2014) found that adolescents in their Ugandan study with higher CD4 counts had a significantly greater risk of non-retention in care at 24 and 36 months compared to those with lower CD4 counts at ART initiation. Massavon *et al.* (2014) also reported a risk of attrition in children and adolescents being significantly associated with mild immunosuppression. In relation to the WHO stage and retention in care, Ssali *et al*. (2014) found that the risk of non-retention in care of adolescents at 12 months was significantly greater among those with a WHO clinical stage III and IV compared to those with WHO stage I and II disease. Similarly, Massavon *et al. (*2014) also reported from Uganda that the risk of attrition in children and adolescents was significantly associated with WHO clinical stages III and IV. The association between WHO stage III and IV and the increased risk of mortality, as found in Bakanda *et al.* (2011) and Nglazi *et al*. (2011), may also result in lower retention in care rates due to increased deaths. With all HIV-infected individuals being eligible for ART irrespective of WHO stage or CD4 count, ART programmes are hoping to initiate ART prior when patients are relatively healthy and prior to them reaching advanced or severe immunosuppression. However, this may result in patients not being motivated to remain in care and take their treatment as they are either not ill or may even develop adverse effects which they did not suffer from in the first place (Ngarina, Popenoe, Kilewo, Biberfeld & Ekstrom, 2013).

Disclosure and its association with retention in care can be found on two fronts. Firstly, disclosing of one's HIV status to significant others may impact on retention in care as seen in a retrospective cohort study in the United States which reported disclosure of HIV status being strongly associated with improved retention in care (Halperin, Pathmanathan & Richey,

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2013). Secondly, adolescents being aware of their own status may influence health and social behaviours and impact on outcomes, as outlined in a retrospective study evaluating HIV disclosure in adolescents in West Africa which found that 28.8% of adolescents knew their HIV status, and that the retention in care at 36 months following ART initiation was 74.6% but was found to be significantly higher for those adolescents who knew their status (Arrive *et al*., 2012).

The ART delivery model may also impact retention in care and other outcomes of adolescents. A retrospective cohort study in a Zimbabwean public sector hospital clinic with an adolescent-focused service, compared outcomes of adolescents and adults, and found adolescents had rates of loss to follow-up significantly lower than adults (Shroufi *et al*., 2013). Ssali *et al.* (2014) 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. Tailoring of services for adolescents and integrating other health services may also 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. Massavon et al. (2014) also reported that the site of ART services also 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).

Age was found to be a discriminator of viral load suppression in various studies with the risk and vulnerability of HIV-infected adolescents infected becoming evident when comparing their viral load outcomes to those of other age groups. In the context of using viral load suppression as an indicator for good adherence, a descriptive study looking at viral load detectability in paediatric, adolescent and adult ART patients in Swaziland, reported that patients had a significantly higher likelihood of having a detectable viral load 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 (Nachega *et al.*, 2009; Nglazi *et al.*, 2012; Ryscavage *et al.*, 2011; Avert, 2016). Livingstone *et al.* (2014) also reported retention in care and adherence rates of adolescents in ART programmes being poorer than that of younger or older age groups, with Khan *et al*. (2009) reporting that adolescents were significantly less likely to reach undetectable viral loads than younger children. However,

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results reported from a systematic review and meta-analysis by Kim *et al.* (2014) on adherence to ART in HIV-infected adolescents had varying levels of agreement with the aforementioned studies. They reviewed studies which reported adherence based on adequate adherence of at least 85% on self-report or undetectable viral loads and when comparing adults and adolescents, the results of this study found adherence in adolescents comparable to that of adults in the regions of Africa and North America. Europe and South America showed adolescents adherence trends being worse than that of adults. Shroufi *et al.* (2013) also found that despite the clinic of study having an adolescent-focused service, results showed that among those who were followed for 5 years or more, 5.8% of adolescents switched to 2nd line regimen due to virological failure, compared with 2.1% of adults.

The viral load 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.

Sex as a factor associated with viral load suppression has shown varied results. This was evident in the PEPFAR statistics released from Zimbabwe, Malawi and Zambia (Avert, 2016). These statistics showed that in Zimbabwe suppression rates among the HIV-infected adolescents and young adult females (15 to 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 males. However, Zambian males and females aged 15 to 24 years had very similar suppression rates of 35.7% and 34.0%, respectively.

An association between the level of immunosuppression and viral load suppression has been described, as reported by Jobanputra *et al.* (2015) who explored factors associated with virological detectability in children and adults on ART. Patients with WHO stage III and IV disease, CD4 count less than 350 cells/mm^3 and being under 20 years of age were significantly more likely to have unsuppressed viral loads.

Good adherence has been strongly linked to having a reduced viral load (Flynn *et al.*, 2004; Murphy *et al.*, 2001) and in the context of a paucity of quality studies directly looking at adolescents and viral load outcomes (Ferrand *et al.*, 2016), adherence and factors impacting on adherence needs to be considered in conjunction with viral load outcomes.

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Age and sex are key factors associated with adherence to ART. Murphy *et al.* (2001) reported that non-adherence in HIV-infected adolescents on ART was worse than that of HIV-infected adults on ART. Nachega *et al.* (2009) found that not only are adolescents less adherent to ART than adults but that HIV-infected adolescents were more likely to be female compared to adults. This seems to be in keeping with results from a survey by Shisana *et al.* (2014) which highlighted the increased risk of adolescent women acquiring HIV due to young females (15-19 years) having sexual partners substantially older than them. The survey also found that a third of young females aged 15–19 years had sexual partners five or more years older than they were which places them at higher risk of acquiring HIV. The higher risk of adolescent females than males was also outlined by Singh *et al.* (2006) - who attributed this result to gender-power imbalances, amongst other issues.

Medication related factors also influence adherence patterns in adolescents. 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.*, 2001). Furthermore, not having medication at hand when required to be taken was found to be another reason for poor adherence amongst adolescents (Murphy, Sarr, Durako, Moscicki, Wilson & Muenz, 2003) as well as adults infected with HIV (Spire *et al.*, 2002). In the REACH cohort of adolescents Murphy *et al.* (2001) found factors associated with poor adherence to include pill burden, alcohol use, and side effects to medication. Ferrand *et al.* (2010) described that one of the most common issues affecting adolescents and their treatment as reported by health care workers in Zimbabwe was the erratic intake of 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 as 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 being 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.* (2001) found factors associated with poor adherence to include dropping out of school and complications of day-to-day routine.

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The negative impact of behavioural challenges and psychiatric illness on adherence are often undervalued and hence mismanaged. Murphy *et al.* (2005) reported that good adherence in the long term were associated with less alcohol use and being in school. Sub-optimal adherence was also significantly associated with younger age and depression. However, poor levels of adherence in adult patients were also significantly associated with higher levels of depression and with younger age (Spire *et al.*, 2002). Khan *et al.* (2009) found that factors affecting adherence in adolescents who acquired HIV peri-natally were related to changes in lifestyle involving growing independence, separation from parental involvement, increased peer pressure and fear of stigmatisation, increased risk-taking behaviour, psychiatric problems and substance abuse. Similarly, Jaspan *et al.* (2009) found poor adherence in adolescent patients being a result of peer pressure, risk-taking behaviour, but also rebelliousness and disease denial. Two of the common issues affecting adolescents and their treatment reported by health care workers in Zimbabwe included psychosocial problems (56%) and lack of disclosure of HIV status (21%) (Ferrand *et al.*, 2010). The main psychosocial stressors for adolescents were stigma, difficulty in identifying with HIV-negative adolescents, anxiety about sexual relationships and future planning, and low self-esteem. These stressors were compounded by having to care for ill relatives and siblings and by being the head of the family. Issues related to poor adherence were a desire to conform, attendance at boarding school, where it was not possible to supervise the taking of medicines from guardians.

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Socio-economic challenges also impact on adherence. Poor housing conditions and lack of social support were also found to be significantly associated with poor adherence in HIV-infected patients (Spire *et al.*, 2002).

2.4.2 Patient–healthcare Provider Relationship and the Health System

Services providers' attitudes play a significant role in patients' choosing to utilise services as seen in a qualitative study of homosexual youths which showed that primary-care providers exhibited judgmental behaviour, stereotyping and homophobia when administering care which resulted in patients avoiding the health service (Schilder, Buchner & Hogg, 1998 as cited by Chesney, 2000). Patients who are comfortable with or used to talking about personal problems during clinical interactions with HAART prescribing physicians were less likely to be non-adherent (Spire *et al.*, 2002).

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Many ART programmes do not have adolescent-tailored services to help adolescents remain engaged in care as reported by Shroufi *et al.* (2013). Health systems that tailor certain services towards adolescents may have favourable outcomes, as evidenced by results from an ecological study in an American HIV clinic where adolescents received individualised care and support from a multidisciplinary adolescent service (Davila, Miertschin, Sansgiry, Schwarzwald, Henley & Giordano, 2013). They were shown to have significantly fewer gaps in their care journey compared to adolescents not having access to such a service. The public health sector in the Western Cape does offer support services to patients, including adolescents, in the form of adherence counselling for ART patients entering the ART programme as well as those dealing with adherence issues whilst on ART (Dewing, Mathews, Schaay, Cloete, Louw & Simbayi, 2012). The Western Cape also routinely offers patients older who are 18 years and older and who are stable on ART the opportunity to enter a club system which provides efficient access to ART and continued adherence support (Wilkinson, 2013). Certain facilities have initiated teen or adolescent clubs which cater for youth. However, this is not offered as a standard service at all facilities and is driven by staff of individual clinics or initiated by non-profit organisation support (Nglazi *et al.*, 2012).

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The health system and the type of services it provides to adolescents may also be a factor in outcomes such as retention in care. Massavon *et al.* (2014) in Uganda reported higher attrition among HIV-infected children and adolescents in facility based compared to community home-based ART services after adjusting for other factors (HR [Hazard Ratio]: 0.29, 95% CI: 0.12–0.70).

2.5 HIV-infected Adolescents and Mortality

Despite HIV being the leading cause of adolescent mortality in Africa and the number two cause worldwide, the available evidence suggests that mortality among adolescents on ART is not significantly different compared to other age groups on ART (WHO, 2014b).

2.5.1 Mortality Rates in HIV-infected Adolescents

An observational cohort study of patients in Uganda showed that the crude mortality rate of adolescents (36.5 per 1000 person-years) was not significantly higher than that of children (22.8 per 1000 person-years) nor adults (37.5 per 1000 person-years) (Bakanda *et al.*, 2011). A retrospective cohort study in a public sector hospital clinic in Bulawayo in Zimbabwe with an adolescent-focused clinic showed trends in mortality rates for adolescents (6.4 per 100

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person years) being similar to that of adults (7.3 per 100 person-years) (Shroufi *et al.*, 2013). Similar results were found in an observational study comparing HIV-infected adolescents (9-19 years) and young adults (20-28 years) at a public sector community-based ART program in South Africa (Nglazi *et al.*, 2012). Overall mortality rates in adolescents (1.2 deaths per 100 person years) were slightly lower than that of young adults (3.1 deaths per 100 person-years). However, an observational prospective cohort study of young adolescents (10-15 years), adolescents (16-19 years), young adults (19.1-24 years) and adults (24.1-29.9 years) reported that the risk of death was highest in adults compared to young adolescents (Bygrave *et al.*, 2013).

2.5.2 Factors Associated with Mortality in Adolescents

An observational prospective cohort study of HIV-infected adolescents and adults at a community-based ART clinic in South Africa found the probability of death in the first year of ART to be 7.9% with cumulative probability of death after 6 years of 15.2% (Nglazi *et al.*, 2011). Furthermore, the findings outlined that being male, having lower baseline CD4 count, and/or having a WHO staging of III or IV was associated with higher mortality risk. These findings were similar to that of Bakanda *et al.* (2011) who also found that features that predicted mortality included having a shorter duration of time receiving ART, being male, as well as having advanced clinical disease (CD4 count < 100 cells/mm^3) and with a high WHO stage (i.e. WHO stage III or IV).

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Some patients who have died are not always known or confirmed by facilities and are classified as being lost to follow-up. This gives an inaccurate skewed picture of actual mortality rates. To account for these inaccuracies studies include assumptions to accommodate the influence of misclassification, as seen in Bakanda *et al.* (2011) where an assumption was made that 50% of those lost to follow-up had actually died.

TB/HIV co-infection remains a significant challenge for programmes managing those infected with HIV, with TB being the commonest opportunistic infection resulting in significant morbidity and also being the leading cause of mortality in HIV-infected individuals (WHO, 2017). Effectively preventing TB would assist in decreasing the risk of morbidity and mortality, and have positive effects on outcomes, including retention in care, for HIV-infected patients. In order to assist in preventing active TB disease in HIV-infected individuals, isoniazid preventive therapy (IPT) was introduced for which strong evidence

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exists outlining its effectiveness in preventing TB in those with HIV; evidence including a Cochrane meta-analysis of 12 randomised controlled trials of IPT in HIV-infected adults which showed a 62% reduction in TB in those with a positive tuberculin skin test (Akolo, Adetifa, Shepperd, & Volmink, 2010). The WHO and UNAIDS included IPT in their recommended essential package of care for HIV-infected individuals in 1998, and was reinforced in 2007 following the review of various trials and studies (WHO, 2010). Subsequent WHO IPT guidelines went on to recommend that tuberculin skin tests were not an essential requirement for IPT initiation (WHO, 2011). This was echoed in South Africa where the National Department of Health included these recommendations in the National ART Guidelines (Department of Health Republic of South Africa, 2013), as well as being adopted as part of the Western Cape's provincial ART guidelines where revised IPT guidelines were clarified via provincial circulars (Western Cape Government Health, 2014).

Co-trimoxazole is another medication that assists in markedly reducing morbidity and mortality by providing protection against harmful opportunistic infections including Pneumocystis Jiroveci, Toxoplasmosis, many bacterial infections, as well diarrhoea-causing infections such as Isospora Belli and Cyclospora species (National Department of Health, 2010a). Evidence outlining its effectiveness range from randomised controlled trials and cohort studies in sub-Saharan Africa (Nunn, Mwaba, Chintu, Mwinga, Darbyshire & Zumla, 2008; Zachariah *et al*., 2003) including South Africa (Grimwade, Sturm, Nunn, Mbatha, Zungu & Gilks, 2005), to Cochrane reviews (Grimwade & Swingler, 2003; Grimwade & Swingler, 2006). The WHO endorsed the use of co-trimoxazole which culminated in the release of co-trimoxazole guidelines such as the version released in 2006 (WHO, 2006). Co-trimoxazole also formed part of South Africa's Antiretroviral Programme of 2004 (National Department of Health South Africa, 2004), and has been included in numerous iterations of the Western Cape Antiretroviral Treatment Guidelines over the years including the most recent version (Western Cape Government Health, 2016).

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2.6 Pregnancy and Antiretroviral Therapy Outcomes

The diagnosis of HIV in the period of adolescence poses numerous challenges for adolescents with regard to initiation, retention and adherence to ART as well as the social and interpersonal challenges, which have been previously outlined (Nglazi *et al.*, 2012). Adolescents who are pregnant and HIV infected in the Western Cape are generally being managed at the PHC level in obstetric services (antenatal, peri-partum and post-partum) not

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tailored or routinely available to manage this unique patient group; hence no routinely available data is collected for this specific group.

Initiating HIV infected pregnant women need to be diagnosed and then initiated on ART timeously in order to effectively prevent HIV transmission from the mother to the child. However, all women who are eligible do not always initiate ART. This is evidenced by a systemic review of studies related to HIV infected pregnant women and their linkage to HIV care found that 38-88% of women who were known to be eligible for ART failed to initiate treatment (Ferguson, Grant, Watson-Jones, Kahawita, Ong'ech & Ross, 2012). Individual factors identified as needing to be addressed were the factor of stigma and the fear there of, as well as financial constraints of these women.

Wang *et al.* (2011) found that HIV-infected pregnant women initiating ART in the community clinic in a North West Province mining community in South Africa were significantly more likely to be lost to follow-up 6 month post initiation. Higher loss to follow-up rates were significantly associated in pregnant (HR=3.75, 95% CI 1.53 - 9.16) and younger (less than 30 years) women (HR=2.14, 95% confidence interval (CI) 1.05 - 4.38). Compared to men, pregnant women with baseline CD4 counts less than 200 cells/ml had a higher risk of loss to follow-up at 6 months (HR=6.06, 95% CI 2.20 - 16.71). A similar trend can be seen when comparing non-pregnant and pregnant women (HR=3.62, 95% CI 1.52 - 8.62). A retrospective cohort study assessing loss to follow-up and mortality rates for HIV infected women from a primary healthcare facility in Gugulethu, Cape Town, described a crude pre-treatment programmatic loss to follow-up among pregnant women of 19.8% compared to 17.1% among non-pregnant women (Kaplan *et al.*, 2008). The pre-treatment mortality was significantly lower amongst pregnant women than non-pregnant women (0.3% vs. 4.7%; $p<0.001$) while the pre-treatment loss to follow-up rate was significantly higher (13.2% vs. 6.0%; $p<0.001$). Age (< 25 years of age) and pregnancy were independently associated with loss to follow-up (Kaplan *et al*., 2008). Tenthani *et al.* (2014) also found that women in Malawi who initiated ART during pregnancy as part of the prevention of mother to child transmission (PMTCT) programme were 5 times more likely to be lost to follow-up compared to those women who initiated for general health reasons (adjusted OR 5.0, 95% CI 4.2-6.1).

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The PMTCT programme in the Western Cape stipulates that women who are pregnant and are diagnosed with HIV be initiated on ART on the same day, barring any clinical contra-indications. Tenthani *et al.* (2014) described that 35% of all HIV-infected pregnant women in this study initiated lifelong ART on the day of diagnosis, and found that these women were found to be twice as likely to be lost to follow-up compared to those who initiated later than the date of diagnosis.

A systemic review of factors affecting ART initiation, adherence and retention of HIV-infected pregnant and post-partum women by Hodgson *et al.* (2014) found that reported barriers to initiation, adherence, and retention were poor understanding of HIV, ART, and the PMTCT programme. Women expressed fears that ART may harm the developing fetus and also felt it unnecessary to initiate ART as they felt very healthy. The latter may have current relevance with current policy stating universal coverage for all HIV infected individuals irrespective of CD4 count or WHO stage. Other common individual-level problems affecting retention and adherence in pregnant and post-partum women were forgetting to take ART, losing/misplacing medication, or lack of access to medication when on travel. Hodgson *et al.* also found that disclosure of HIV infection to a spouse and the spouse being involved in the treatment process of the female partner were associated with improved initiation, adherence, and retention in ART care. However, multiple studies reported that women were reluctant to disclose their HIV status to partners because they feared significant negative consequences. Fear of stigma was also found as a critical barrier to ART initiation, adherence and retention among pregnant and postpartum women that was found in the abovementioned systemic review.

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CHAPTER 3: METHODOLOGY

3.1 Study design

A retrospective cohort study design was used to describe and analyse adolescents in the ART programme initiated in 2013 in public primary health care facilities in the Metropole of the Western Cape Province. The retrospective study design allowed for the collection of data elements that have already occurred and for the collection of various outcomes as well as baseline or possible exposure variables (Beaglehole, Bonita & Kjellstrom, 1997). In this study the primary outcomes were retention in care, viral load suppression and adherence. Furthermore, the study described the adolescents' socio-demographic and baseline characteristics, their programmatic and treatment outcomes at various points in time, and determined risk factors for selected outcomes. The use of this study design and the existence of a database of patients initiated on ART were beneficial in that the eligible patients and the facilities at which they initiated their ART could be identified very efficiently, assisted in sourcing the appropriate clinical folders more efficiently, as well as reduced the resources (financial and human) and time required compared to that of prospective study designs.

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3.2 Study Setting

The study took place in the Metropole of the Western Cape Province in South Africa. The Western Cape has a population of 5 822 734 with 64.2% of the population residing in the City of Cape Town Metropole with the remainder resident in the rural areas of the province (Western Cape Government Provincial Treasury, 2012). The proportions of the population by race group are 42.4% Coloured, 38.6% African, 15.7% White, 1.4% Asian/Indian and 1.9% other with 19.7% of people living in poverty. The Metropole is densely populated with numerous informal settlements in and around the formal urban areas. The rural part of the province is less densely populated and communities are often separated by vast distances with less than ideal access to various services. The top cause of years of life lost in the Western Cape in 2010 was HIV/AIDS (MRC, 2014). Results from the 2012 National Antenatal Sentinel HIV and Herpes Simplex Type-2 Prevalence Survey in South Africa found the Western Cape to have an HIV prevalence estimate among antenatal women of 16.9% (National Department of Health, 2012). The national antenatal HIV prevalence for 2012 is 29.5%.

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The Western Cape Government Health is responsible for public health services in the province. However, in the Metropole primary health care services are rendered by two health authorities, namely the Western Cape Government Health's Metro District Health Services (MDHS) as well as the City of Cape Town Health. This does improve access to health care services but does also present challenges with rolling out of new services, amendments to service packages, linkages to care, and certain facilities limited service packages with poor integration of services resulting in clients having to attend different facilities for different conditions.

The Western Cape ART programme has been in existence for over 10 years and the most recent ART guidelines have been updated in 2016, from the 2013 version, which have consolidated adult, adolescent and paediatric treatment guidelines as well as the PMTCT guidelines (Western Cape Government Health, 2016). In the Western Cape Province the majority of patients (adults and children) access ART services at primary health care facilities (clinics, community day centres and community health centres). At the end of June 2017, the Western Cape Province had 237 285 patients on ART (229 171 patients ≥ 15 years of age and 8 114 patients < 15 years of age). The Metropole accounts for 74.3% (167 833) of the total ART patients in the Western Cape (162 092 patients ≥ 15 years of age and 5 741 patients < 15 years of age) (Western Cape Government Health: HAST, 2017). ART services are rendered at the facility types in the Western Cape outlined in Table 3.1.

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Table 3.1: Facilities in the Western Cape rendering ART services

Facility Type	Rural	Metro	Total
Clinic (including satellite clinics)	138	26	164
Mobile Clinics	8	0	8
Community Day Centre	17	29	46
Community Health Centre	0	9	9
District Hospital	4	6	10
TB Hospitals	4	2	6
Regional Hospitals	0	4	4
Correctional Centres	8	1	9
Total	179	77	256

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However, services rendered at these facilities vary, with some facilities rendering only adult ART services and others offering both adult and paediatric services. Furthermore, some facilities offer ART services daily while others have outreach services offered only certain days of the week. Human resource capacity also varies, with some facilities not having medical officers or clinical nurse practitioners on their staff establishment; hence the need for outreach support. Capacity for adult ART services in the Western Cape has improved with the implementation of Nurse Initiated Management of Antiretroviral Treatment where by nurses are trained and receive authorisation to initiate first line ART following a structured mentorship and training programme. A challenge in the rural areas remains irregular access to competent and skilled clinicians to manage paediatric patients, and complicated adult and adolescent patients.

As previously stated, the majority of ART services is designated as paediatric or adult programmes. Adolescent-specific ART services are not part of the standard care being offered at all ART facilities, with those offering these services being limited to services initiated and/or supported by tertiary hospitals or non-profit organisations.

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Laboratory services in the Western Cape are accessible and relatively efficient, and are provided by the National Health Laboratory Service. The Western Cape also has a reliable and well monitored supply of medication which is generally only affected by national and global stock-outs. A central dispensing unit also operates in the Metropole which pre-packs chronic medication and delivers it to designated collection points. The availability of the fixed-dose combination of antiretroviral drugs has also decreased the pill burden on patients, mainly adults and late adolescents. In a systematic review and meta-analysis looking at the impact of fixed-dose combination antiretroviral therapy appear to offer multiple advantages for programmes and patients, particularly with respect to treatment adherence (Ramjan *et al.*, 2014).

The ART Programme also provides adherence support through facility based adherence counsellors as well as community based community health workers. These community health workers provide support to patients in their first few months on ART as well as to those who are at risk of treatment failure, have experienced treatment failure or have other challenges with adherence. Community health workers also play a critical role in tracing and recalling patients who have missed their appointments or who require urgent recall for clinical reasons.

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To assist chronic stable patients on ART with more efficient and structured access to treatment the Adherence Club Model has been rolled out which allows easier access to medication, decrease in waiting times and an opportunity for peer support. However, this service is currently only available for patients 18 years of age and older, as per the club guidelines. The Risk of Treatment Failure programme is another programme being offered within the ART programme which identifies those at risk of failing their treatment (identified as having an unsuppressed viral load) and entering them in a structured adherence support programme in order to improve adherence and manage any identified barriers to achieving viral load suppression (Medecins Sans Frontieres, 2012).

The release of circular H116 in August 2012 (Western Cape Government Health, 2012) outlined amendments to the preceding ART guidelines with the amendments eventually forming part of the Western Cape Antiretroviral Treatment Guidelines 2013 released in June 2013 (Western Cape Government Health, 2013). The eligibility criteria for initiating ART in adults and adolescents (10 to 19 years of age) included all patients with CD4 counts less than 350 cells/mm³ irrespective of their WHO stage, all types of TB irrespective of CD4 count, all pregnant/breast feeding HIV-infected women irrespective of CD4 count, or WHO stage III or IV irrespective of CD4 count. The guidelines also outlined the eligibility criteria for ART in infants and children (which would include adolescents younger than 15) which included all children less than 5 years of age irrespective of CD4 count, or children 5 years to 15 years with WHO clinical stage III or IV or those with a CD4 count less than or equal to 350 cells/mm³.

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The standardised 1st line ART regimen for adults and adolescents includes Tenofovir, Emtricitabine or Lamivudine, and Efavirenz to be taken once daily (Western Cape Government Health, 2013). These drugs are available in a fixed-dose combination translating into patients needing to take only one tablet daily. However, Tenofovir is only recommended for those 15 years and older of age 40kg and heavier, and with a glomerular filtration rate of 80 or more. The 1st line ART regimen for infants and children younger than 3 years (or weighing less than 10kg) included Abacavir, Lamivudine and Lopinavir/Ritonavir. 1st line for children older than 3 years (or weighing ≥10kg) who were not exposed to Nevirapine during PMTCT programme would receive Abacavir, Lamivudine and Efavirenz, whereas children older than 3 years (or weighing 10kg or more) who were exposed to Nevirapine during the PMTCT programme received Abacavir, Lamivudine and Lopinavir/Ritonavir. The

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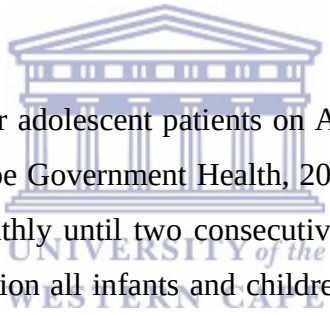
guidelines provide various options for adults, adolescents and children who have contra-indications to any drugs in the 1st line regimen or fail on 1st line.

To monitor response after initiating adults and all adolescents on, viral loads are to be taken at months 4, 12 and 12 monthly thereafter as long as the levels are lower than 400 copies/ml at each measure (Western Cape Government Health, 2013). Due to various associated risks, patients with drug resistant TB as well as those who are pregnant or breastfeeding have more viral loads done during their course of TB treatment or their pregnancy and breastfeeding period in addition to the routine viral loads done at months 4, 12 and 12 monthly bloods. The guidelines defines virological failure as having a viral load of more than 1000 copies/ml on two occasions taken 3 months apart despite intensive adherence counselling (and excluding/managing tolerability, drug-drug interactions and/or psychological issues). Confirmed virological failure should result in patients being changed to a 2nd line ART regimen.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The CD4 count of adult and older adolescent patients on ART should be done at 12 months post ART initiation (Western Cape Government Health, 2013). If the CD4 count is less than 200 cells/mm³ then repeat 6 monthly until two consecutive CD4 counts are more than 200 cells/mm³. Following ART initiation all infants and children should have a CD4 count done at months 4 and 12. However, for children older than 5 years of age, if the CD4 count is less than 200 cells/mm³ then repeat 6 monthly until two consecutive CD4 counts are more than 200 cells/mm³.

Co-trimoxazole prophylaxis remains an integral part of the Western Cape's ART programme (Western Cape Government Health, 2016). The criteria for administration of co-trimoxazole prophylaxis for adult and adolescent (including pregnant) patients are that the patients should have CD4 counts less than 200 cells/mm³, or be diagnosed as on WHO clinical stage II, III or IV. The eligibility criteria for prescribing co-trimoxazole for HIV-infected children 6 years of age and older include having a CD4 count less than 200 cells/mm³ or < 15%, or having WHO clinical stage III or IV (National Department of Health, 2010b).

District Hospitals provide ART services in their outpatient department. Older adolescents form part of their adult outpatient department services with the younger adolescents forming part. The District Hospitals also have birthing units. It is here where pregnant females are

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also initiated on ART. CDCs and CHCs offer additional services such as management of chronic diseases of lifestyles, TB services, paediatric services, women's health services, mental health services, and basic antenatal care services as well as midwife obstetric units at certain of the CHCs. The basic antenatal care and midwife obstetric unit services are also where pregnant HIV infected females are initiated on ART. Paediatric services are also where some younger adolescents get initiated on ART. It should be noted that not all CDCs and CHCs provide all the aforementioned services, e.g. offering ART services but not TB or basic antenatal care services. This fragmentation of services may impact negatively on retention in care and adherence to ART as well as other medication. Some of the CHCs and CDCs have stand-alone ART services as opposed to those who have ART services integrated in their general chronic disease management services. Some facilities' paediatric ART services are supported by tertiary facility outreach teams supported by non-profit organisations. Very few facilities have adolescent specific ART services, with majority of adolescents being managed either within adult services or within paediatric services. The District Hospitals, CDCs and CHCs all have non-profit organisation provided counsellors providing HIV testing services as well as adherence counselling services. They are also supported by non-profit organisation provided community health workers who provide adherence support at community level through home visits to patients who opt for this service. However, clients can either refuse home visits from community health workers or may be living outside of the area supported by the community health workers and therefore cannot be visited. Facilities also have access to nutritional supplementation products as well as access to nutritionist and/or dieticians if a patient has a low body mass index. The patients who have a raised body mass index or conditions that require diet optimisation also make use of these services. Facilities also have access to Mental Health services provided by facility-based psychiatric nurses and sub-district psychologist with some facilities having visiting psychiatrists (specialists and/or registrars) on specific days of the month.

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3.3 Study Population and Sampling

The study population constitutes HIV infected adolescents who fulfil the following inclusion criteria:

- Between 10-19 years at the start of the study
- Initiated on first line ART between January and December 2013; and

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- Receiving ART at a PHC facility or District Hospital under the MDHS in the Metropole of the Western Cape Province upon initiation.

Exclusion criteria

- Patients initiated on ART from PHC facilities outside of the Metropole of the Western Cape Province's MDHS, Tertiary Hospitals, Secondary Hospitals (including the Metro-TB complex) or the private sector that are transferred into MDHS PHC facilities in the Metropole for continued care will be excluded from the study.

The study participants were identified using the Provincial Tier.net electronic database using the inclusion and exclusion criteria. This database, which collates all the patients ever started on ART in the Province along with routinely captured data elements such as selected socio-demographic, baseline clinical and ongoing clinical data and outcomes, was used to identify adolescent patients who were initiated in 2013 and those who were initiated at another facility but transferred-in to the facility were excluded. Any patient who had no indication whether they were new initiations at the facility or whether they were transferred-in would have their folders drawn and assessed for eligibility. The participants were then listed in their facility where they were initiated ART and their clinical folder was accessed at the facility with the help of the facility clerk. Once the folders were found the data collection commenced using the data collection tool (Appendix 1) with unique identifiers being used for each study participant.

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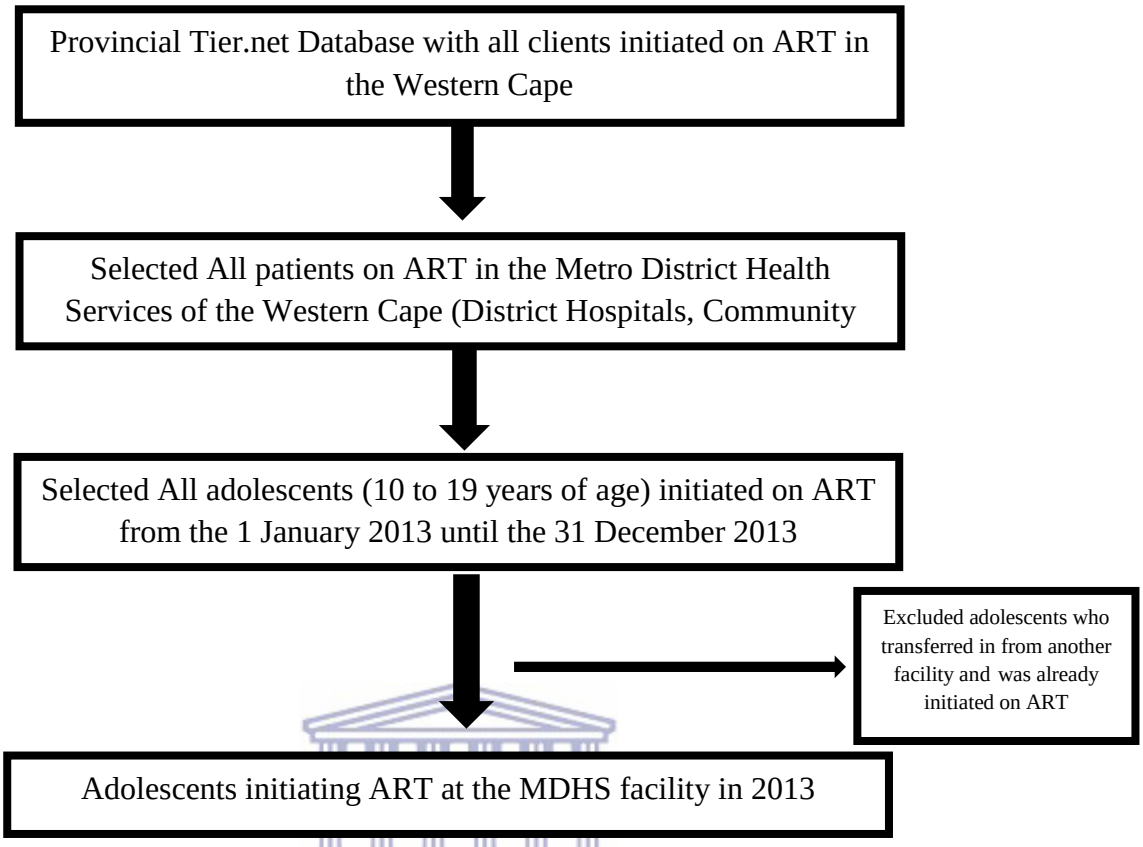

Figure 3.1: Diagram of sampling for the study:

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3.4 Data Collection

Data collection commenced after the pre-test and data collection tool was adapted. The adolescents who met the eligibility criteria were initiated across 31 facilities across the Cape Metropole. These included 6 District Hospitals, 10 CHCs and 15 CDCs. The completion of the data collection was delayed by the delay in response from substructures and facilities granting the researcher permission to access the facility and arrange logistics to retrieve the clinical folders. Other reasons for delay in completion was the postponement of scheduled visits to facilities due to unforeseen circumstances as well as the inability to find the folders requested to be drawn. Further dates needed to be arranged in order to repeat attempts to find folders. This resulted in data collection commencing in March 2017 and being completed in September 2017.

The variables contained in the data collection tool were largely limited by the content of the clinical folders which consisted of standardised HIV stationery and other forms of clinical and counsellor stationery. The standardised HIV stationery has undergone numerous

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revisions over time resulting in different versions being utilised at various facilities. However, the content of the various stationery versions were very similar. As expected, the completion of stationery, the capturing from the stationery into the electronic register, as well as the provision of adherence support strategies which formed part of the ART programme (such as the in facility individual and group counselling by adherence counsellors as well as home visits by community health workers) varied from facility to facility which led to certain variables being either not completed in the standardised stationery for a variety of reasons which ultimately impacted on the variables being extracted.

Variables to be extracted would include baseline socio-demographic characteristics, baseline clinical characteristics, and outcome data including retention in care, viral loads and indicators of poor adherence.

3.4.1 Baseline Socio-demographic Variables

The variables extracted within this category included the sex of the patient, the age at ART initiation, the next of kin identified by the patient at first visit to the ART facility, and the year of HIV diagnosis. This is usually completed partly by facility clerks and partly by clinicians (doctors or nurses). Other socio-economic variables are documented in the social history section of the HIV stationery. These variables are documented at baseline and include the type of dwelling the patient resides in, the number of rooms in the dwelling, the number of adults in living in the dwelling, if the dwelling contains a refrigerator, and the source of income of the patient at baseline. These provide an indication of the socio-economic status and living conditions of the patient. The social variables include the patient's awareness of his/her HIV diagnosis at ART initiation, the disclosure of the patient's HIV status to a significant other at ART initiation. In our study *significant other* included any person, other than the health care workers, that the adolescent disclosed his/her HIV status to. The use of alcohol and/or drugs by the client was also extracted.

3.4.2 Baseline Clinical Variables

The clinical variables included the history of treatment exposure prior to initiation of ART, CD4 count prior to ART initiation, WHO stage at ART initiation, patient has been initiated on co-trimoxazole at ART initiation, if the patient is on TB treatment at ART initiation, history of previous episodes of TB prior to ART initiation, pregnancy at ART initiation, and other chronic illnesses at ART initiation. The nutritional status at ART initiation (Body Mass

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Index, Mid Upper Arm Circumference, and the growth charts) will also be extracted. The body mass index is calculated using heights and weights and where the clinicians have not calculated the body mass index but weights and heights were available, the researcher has calculated the body mass index. Any documented chronic illness that the patient suffers from was also extracted.

3.4.3 Retention in Care

Retention in care in the ART programme is a major outcome being assessed. Variables that affect retention include loss to follow up and deaths. A patient is considered lost to follow up if the patient has not received treatment for 90 days or more and have not died or been transferred out to another facility. The lost to follow up date was determined from when the patient was last seen at the clinic where they were provided their last medication prior to the 90 day absence from the facility. Patient deaths and patients transferred out were also sort. Therefore, by using the intention-to-treat population in this study the retention in care definition was the proportion of HIV-infected adolescents alive and on ART at months 4, 12 and 24 post-ART initiation among the entire study sample of adolescents initiated on ART at the beginning of the study period (for example the retention in care at month 4 had a numerator being the number of adolescents in the study sample who are alive and on ART at month 4, and a denominator being the total number of adolescents study sample).

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3.4.4 Viral Load and Viral Load Suppression

The viral load is measure used in the ART programme as an indicator of treatment response to ART as well as a guide to identify possible issues with adherence. For this study viral load suppression was defined as a viral load less than 400 copies/ml. The proportion of adolescents who are virologically suppressed at month 4, 12 and 24 were also determined with the principle if intention-to-treat. Another quality of care indicator which was determined was the proportion of viral loads done at the time points in the adolescent's journey as proposed by the ART guidelines used in the Western Cape Province, i.e. months 4 and 12 post ART initiation, and annually thereafter. Therefore, for this study it translated into determining viral loads done at month 4, month 12 and month 24 post ART initiation. Furthermore, in this study viral load blood results were accepted for month 4 following ART initiation if bloods were drawn within a month earlier of the month 4 date or up 3 months after the month 4 date. Results of viral load bloods drawn up to 3 month prior or 3 months after the month 12 post-ART initiation date were also accepted. Similarly, results of viral

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load bloods drawn up to 3 month prior or 3 months after the month 24 post-ART initiation date were also accepted (the same principles would apply to bloods such as CD4 counts). Additional viral loads would be done on patients if their viral loads were not suppressed (viral load > 1000 copies/ml), i.e. 3 months after the last unsuppressed viral load and having had adherence support during this period. If the repeat viral load was still more than 1000 copies/ml then it constitutes virological failure and the adolescent will need to be assessed for changing to second line ART. The reason for selecting a viral load of less than 400 copies/ml as being suppressed is that a viral load between 400 and 1000 copies/ml will result in a programmatic response to assess adherence and assist with adherence support without the need for an earlier viral load as is the case with a viral load more than 1000 copies/ml (as proposed by the ART guidelines).

3.4.5 Indicators of Poor Adherence

Indicators of poor adherence were also collected. These indicators were assessed prior to and including month 4 post ART initiation, from month 5 up to and including month 12 post-ART initiation, and from month 13 up to and including month 24 post-ART initiation. If an adolescent had numerous episodes within these time periods it will only be documented once at the measuring points of month 4, 12 and 24. The denominator was taken as those who were retained in care at the end of each time point. The indicators of poor adherence included the following:

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- Patient self-report of poor adherence to ART
- Caregiver of adolescent reporting poor adherence to ART
- Health worker (counsellor or clinician) indicating poor adherence through pill-count
- Patient defaulting by missing appointment date by more than 2 weeks but less than 90 days with evidence in the folder that adherence may have been compromised

Some patients missed their appointment date but may have indicated that they obtained medication from another source, had enough medication to cover the period since their missed appointment, or have received medication from the facility as evidenced by a script being issued by pharmacy but notes were not made in the clinical stationery by any clinician.

3.5 Data Management and Analysis

Data extraction from folders at facilities were entered into data collection tools and once all available data was extracted the completed data collection tools were then entered into an

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excel spread sheet. The data was checked for accuracy of transfer from the data collection tools and arranged to facilitate the coding process which followed. Data was coded and transferred into SPSS statistical software which was used to compute summative and inferential statistics. Data that was imported into SPSS was also cross checked with the original excel sheet to exclude errors in data transfer.

Initially dummy tables and frequencies were run in order verify the suspected inadequacy of available data of certain variables. Some variables (such as Attends a Support Group, Patient/Caregiver Agreed to Home Visit, Treatment Buddy at Baseline) had too much missing data as a result of poor recording by clerks, counsellors or clinicians. Upon enquiry, for the same variable some facilities stated it was due to individual error or omission, while others stated that at their facility it was not expected to robustly document certain variables or parts of the HIV stationery. However, the reasons for the missing data were not explored as part of this study.

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To describe the study participants the researcher utilised SPSS to produce descriptive frequency tables created for categorical baseline variables outlining the number of adolescents in the various categories and the proportion (percentage was presented to one decimal place). Continuous data was firstly assessed for normality using the Shapiro Wilk Test for normality and then presented with either means with standard deviations or medians with interquartile ranges. Means, medians and interquartile ranges were presented to one decimal place while the standard deviation was presented to three decimal places.

Outcomes such as retention in care, viral load suppression and adherence were described at months 4, 12 and 24 using the principle of intention-to-treat (McMahon, Elliott, Bertagnolio, Kubiak & Jordan 2013). By using the intention-to-treat population the denominators for outcomes included the total number of adolescents in the study sample who initiated on ART in 2013 (including those adolescents who were lost to follow-up or died during the study period). By analysing using the intention-to-treat population one is able to expose factors at the individual or programme level that may impact on the risk of mortality and loss to follow up (McMahon *et al*., 2013). However, analysis of outcomes, such as viral load suppression, using the population who were retained in care (on treatment population) gives an indication of the effectiveness of antiretroviral therapy only for those receiving the medication (McMahon *et al*., 2013).

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To determine statistical significance and predictors for retention in care and viral load suppression Chi-square tests, bivariate analysis and risk ratios were conducted between independent and dependent variables with cut off for p value set at 0.05 (with p values reported to three decimal places) and for risk ratios 95% confidence interval was provided (risk ratios and 95% confidence intervals were reported to 2 decimal places).

Adolescents were also disaggregated into younger adolescents (10 – 14 years) and older adolescents (15 – 19 years) using their age at ART initiation, and the retention rates, viral loads done and viral load suppression rates describes at months 4, 12 and 24 and graphically illustrated. CD4 counts were also categorised into less than 200 cells/mm³, 200 to 349 cells/mm³, and more than or equal to 350 cells/mm³. Pregnancy at ART initiation was described and analysed by viewing pregnancy as a potential exposure for all adolescents. Therefore, adolescents were categorised into the response of *Yes* for adolescents who were pregnant and *No* for any adolescent who was not pregnant, be they female or male.

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3.6 Validity and Reliability

The use of standardised HIV stationery in the Western Cape ART programme gave the researcher guidance with regard to the possible data to be found in the study participants' clinical folder. This included the chosen outcome variables and other baseline social, economic and clinical variables. This not only assisted the researcher in refining the study aims, objectives, criteria and variables, it also assisted the researcher in the design of the data collection tool, with input from experienced colleagues involved in the management and governance of the Western Cape public sector HIV and ART programme.

Following the original design of the tool, validity and reliability was tested when it was pre-tested by the researcher at 4 facilities on 4 patients at each facility. The researcher and a HAST colleague completed the data collection process on the same clinical folders independently. They then repeated this process for a second time on the same folders but on a separate occasion. The final products of the various data collection processes were compared, i.e. the 2 products from the same individual were compared to each other, as well as a comparison between the products of the researcher and the HAST colleague were made. Consistency in the results was assessed and a discussion related to the understanding and interpretation of the variables being extracted was had, and based on these processes

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decisions were made on adjustments to the tool and collection processes. Despite the researcher being the only individual to conduct the data collection, the pre-testing process and discussions also identified certain misunderstandings and biases of the researcher which the researcher aimed to limit in the formal data collection process. Adjustments were also made after considering certain variations in the adult versus paediatric standardised HIV stationery.

The use of an inclusive sample minimised selection bias. However, the facilities' inability to find all the folders of the inclusive sample could have impacted on the outcomes measured. Not only were folders not found but duplicate folders were sometimes retrieved and the original folders that contained all the relevant baseline and treatment information were considered missing. Steps taken by the researcher minimise this impact was to re-visit facilities where the yield of folders found was not ideal. The researcher provided a revised list of the folders not found (or of the duplicate folders) to facility clerks as well as negotiating a suitable time for them to assist with the retrieval of folders. This process did result in many previous missing folders being found.

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The quality of data obtained was also influenced by numerous factors and processes. Programmatic and governance processes contribute to improving the validity of data, i.e. the extent to which measurements measure what it is intended to measure. Standardised HIV clinical stationery is used to document clinical and laboratory findings and data is captured into electronic registers like Tier.net which is designed in conjunction with the standard stationery. Clinicians, counsellors and facility clerks/data capturers are orientated and trained on the use of the stationery, which also has guidelines printed at the back of each standard continuation sheet to guide the user on how to complete the stationery. Clerks who capture data undergo rigorous baseline and refresher training on the electronic register and this is supported by a non-profit organisation and/or substructure information management. The capturing and data flow process is also guided by an ART Monitoring and Evaluation Standardised Operating Procedure document which outlines where and when data has to flow in order to ensure quality and valid data. The checking of data is done at multiple levels including at facility level (operational or facility managers), sub-district/substructure level (information management, HAST manager), and at the provincial level (HAST information management, HIV treatment programme deputy director and HAST director). Facilities are also supported and audited by sub-district/substructure HAST managers with clinical stationery, Tier.net and data quality on their agenda. However, the use of the Tier.net

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database as a source of data for completion of the collection tool was not possible as various fields in the database had missing fields. The use of the database was therefore limited to identifying the study population and eliminating those who did not meet the eligibility criteria. Hence, the clinical folder was chosen as the main source from which data would be extracted from. Despite the use of standardised and stationery and the accompanied training, the completion of the various fields by clinicians and support staff, e.g. counsellors and clerks, was variable and inconsistent resulting in missing data for certain variables. The variation in adhering to ART guidelines especially related to blood/laboratory monitoring of patients was also noted. It was unclear whether it resulted from a lack of training and knowledge related to clinical and operational/programmatic guidelines and practices or just unjustified omissions.

The reliability of data is enhanced by the processes discussed above and also the manner in which many of the variables of interest are measured. Laboratory tests are carried out on body fluid or tissue specimens to obtain CD4 counts, viral loads, TB results, etc. and these are carried out by the National Health Laboratory Services which is a reputable service provider with high quality equipment and rigorous quality processes in place. They also do regular support visits to the offices of their health partners to improve on the quality of specimens sent from facilities, turn-around time of processing and reporting results of specimens, flagging of abnormal results, data flow, etc. Blood results that were not clearly captured in the folder but were documented to have been done sourced by the facility and included in the data collection.

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Other clinical variables measured at the facility level, such as weights and heights, are done using standardised equipment ordered and calibrated through strict supply chain processes. Socio-demographic data are obtained from patients by trained clerks and captured into Tier.net. Dates of birth are corroborated by identification documents which patients are encouraged to produce when utilising health facilities for the first time.

3.7 Generalisability

With the facilities involved in the study being from numerous facilities in the Western Cape Metropole the results of this study could not only to the study population but possibly similar patient group (HIV infected adolescents on ART) being cared for by other health authorities in the primary health care setting in the Western Cape Metropole as they share the same

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guidelines (treatment and adherence guidelines) and receive similar adherence support in the form of counselling and community adherence support from funded non-profit organisations.

3.8 Ethics Considerations

Following approval of the study for degree purposes by the University of the Western Cape Senate Higher Degrees Committee, and approval of scientific methodology and ethics clearance from the Biomedical Science Research Ethics Committee of the University of the Western Cape (Appendix 2), an application for study approval and permission to use data sources was made to the Western Cape Provincial Health Department; specifically to the Health Impact Assessment Unit (Appendix 3 is an example of one of the letters received from the Health Impact assessment which approved access to the health facilities mentioned in the letter).

No direct contact with patients was required for this study. Patient and facility data was anonymised through the use of unique identifiers during analysis and reporting of study findings. The following processes were utilised in order to protect patient and facility information. The initial collection of data had the patient's name, folder number, facility name, and a unique identification number of each patient. This draft was saved in case the patient data needs to be traced in the future. Another draft was saved without the name and folder number and only the unique identification number was used. This draft was used in the data analysis procedure with no patient or facility identifiers used in the reporting or study write up phases. The various data drafts were saved in password protected storage devices and be in the possession of the primary researcher. All completed data collection tools were stored in a box which was locked up in a cupboard situated in a room only accessed by the primary investigator in order to maintain the patient and facility confidentiality and safety during the study.

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CHAPTER 4: RESULTS

4.1 Introduction

In this chapter the results of the study will be reported. It will include sections outlining the realisation of the study sample, the description of the baseline socio-demographic and clinical characteristics of the adolescents in the study, the description of the retention in care of adolescents as well as the bivariate analysis of retention in care and baseline characteristics, the description of viral load suppression of adolescents as well as the bivariate analysis of viral load suppression and baseline characteristics, and the description of the indicators of poor adherence.

4.2 Realisation of Sample

Data from 332 adolescent patients on ART from 29 facilities spread across the Western Cape Metropole were obtained from the Provincial Tier.net register. As outlined in Figure 4.1, the realised sample size was 220. Of the originally recruited 332 patients, 28 patients were incorrectly captured as new patients (actually transferred in from other facilities); four patients who were not adolescents (dates of birth incorrectly captured); and 12 patients had been incorrectly captured as having initiated ART in 2013. A further 68 folders could not be found despite numerous attempts at tracing these documents at the various facilities.

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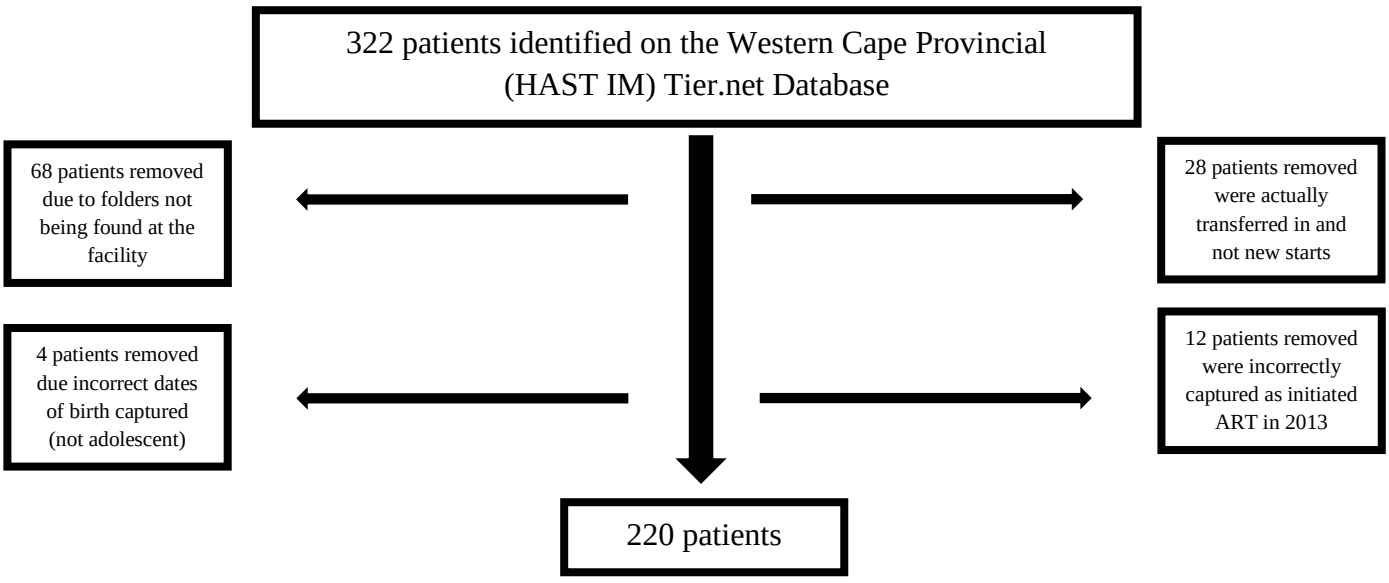

Figure 4.1: Realisation of Sample

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4.3 Baseline Socio-demographic Characteristics of Study Participants

The median age of adolescents initiating ART was 17.0 years (Interquartile Range [IQR] 15.0 - 18.0). The majority of adolescents in this study were 15-19 years (81.4%) and female (82.7%) (Table 4.1).

Most adolescents included in the study were financially supported by their families and friends (58.6%); with only 6.8% being employed and 7.3% receiving a grant as their (family's) source of income. However, 27.3% of the study participants did not indicate what their source of income was. More than half of study participants reported that they lived in a formal house (52.7%); while 31.4% lived in informal dwellings, and 2.7% lived in hostels and other forms of housing.

Most (82.7%) adolescents disclosed their serostatus to a person other than a health care worker. Only 12.3% of adolescents admitted to using alcohol and/or drugs. 18.2% had no record of their substance use being assessed.

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4.4 Baseline Clinical Characteristics of Study Participants

The median CD4 count at ART initiation was 292.5 cells/ml (IQR 228.8 - 391.3). Only 2 participants had no CD4 count recorded at baseline. At ART initiation nearly 20% of adolescents had a CD4 count less than 200 cell/mm^3, with half (49.5%) of adolescents having baseline CD4 counts between 200 – 349 cells/mm^3 (Table 4.2).

Of those participants who had WHO staging done at ART initiation, 66.8% were WHO stage I and II, with 23.2% and 6.8% being WHO stage III and IV respectively (Table 4.2).

At the time of ART initiation, 14.1% of the adolescents were on TB treatment.

Just under half (46.2%) of all females were pregnant at the time of ART initiation. The mean gestational age at ART initiation was 23.4 weeks (Standard Deviation 7.727). The majority of pregnant adolescents initiated ART in the 2nd trimester (59.5%); followed by 32.1% in the 3rd trimester and only 6% within the 1st trimester of their pregnancy.

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Only 8.3% of adolescents who were eligible for IPT at ART initiation had actually been initiated on isoniazid at baseline. However, 62.2% of the 135 adolescents who were eligible for co-trimoxazole at ART initiation were prescribed co-trimoxazole at baseline.

Most adolescents were initiated on the fixed-dose combination consisting of Tenofovir, Emtricitibine and Efavirenz (71.4%); while 12.3% received Tenofovir, Lamivudine and Efavirenz, which entails taking three separate tablets. The proportion of adolescents who were initiated on Abacavir, Lamivudine and Efavirenz (15.5%) were all in the 10 – 14 years age category - which was the recommended first line regimen for children in this age category (Western Cape Government Health, 2013).

Table 4.1: Baseline Socio-demographic Characteristics of Adolescents Initiated on ART in 2013 at MDHS Facilities in the Western Cape

		Frequency	**Percentage (%)**
Age	10 – 14 years	41	18.6
	15 – 19 years	179	81.4
Sex	Male	38	17.3
	Female	182	82.7
Source of Income	Employed	15	6.8
	Family and Friends	129	58.6
	Grant	16	7.3
	Missing	60	27.3
Type of Dwelling	Informal Dwelling	69	31.4
	Formal House	116	52.7
	Hostel	4	1.8
	Other	2	0.9
	Missing	29	13.2
Disclosure to Significant Other	Yes	182	82.7
	No	27	12.3
	Missing	11	5.0
Reported Alcohol and/or Drug use	Yes	27	12.3
	No	153	69.5
	Missing	40	18.2

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Table 4.2: Baseline Clinical Characteristics of Adolescents Initiated on ART in 2013 at MDHS Facilities in the Western Cape

		Frequency	Percentage (%)
CD4 Count (copies/ml)	< 200	42	19.1
	200-349	109	49.5
	≥ 350	67	30.5
	Missing	2	0.9
WHO Stage	I	99	45.0
	II	48	21.8
	III	51	23.2
	IV	15	6.8
	Missing	7	3.2
On TB treatment	Yes	31	14.1
	No	189	85.9
Pregnant	Yes	84	38.2
	No	136	61.8
Gestational Age	1st Trimester	5	6.0
	2nd Trimester	50	59.5
	3rd Trimester	27	32.1
	Missing	2	2.4
IPT	Yes	15	6.8
	No	165	75.0
	NA	40	18.2
Co-trimoxazole	Yes	84	38.2
	No	51	23.2
	NA	85	38.6
ART Regimen Initiated	TFE	157	71.4
	T3E	27	12.3
	A3E	34	15.5
	Z3E	1	0.4
	T3L/rit	1	0.4

TFE (Tenofovir+Emtricitibine+Efavirenz)
T3E (Tenofovir+Lamivudine+Efavirenz)
A3E (Abacavir+Lamivudine+Efavirenz)
Z3E (Zidovudine+Lamivudine+Efavirenz)
T3L/rit (Tenofovir+Lamivudine+Lopinovir/ritonavir)

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4.5 Retention in Care of Adolescents Initiated on ART

Retention in care decreased over time as shown in the overall levels at months 4, 12 and 24 being 68.6%, 50.5% and 36.4%, respectively.

4.5.1 Age and Retention in Care

Compared to older adolescents (15 – 19 years), younger adolescents (10 – 14 years) had significantly better rates of retention in care at months 4 (87.8% vs 64.2%; p = 0.003), 12 (80.5% vs 43.6%; p < 0.001) and 24 (68.3% vs 29.1%; p < 0.001) post-ART initiation (Figure 4.2). At month 4 the younger adolescents were 37% more likely to be retained in care than the older adolescents (Risk Ratio (RR) = 1.37 [95% Confidence Interval (CI) 1.17 – 1.60]). At month 12 younger adolescents were 85% more likely to be retained in care than the older adolescents (RR = 1.85 [1.48 – 2.31]). The probability for retention in care at month 24 was more than double for younger adolescents compared to older adolescents (RR = 2.35 [1.73 – 3.20]).

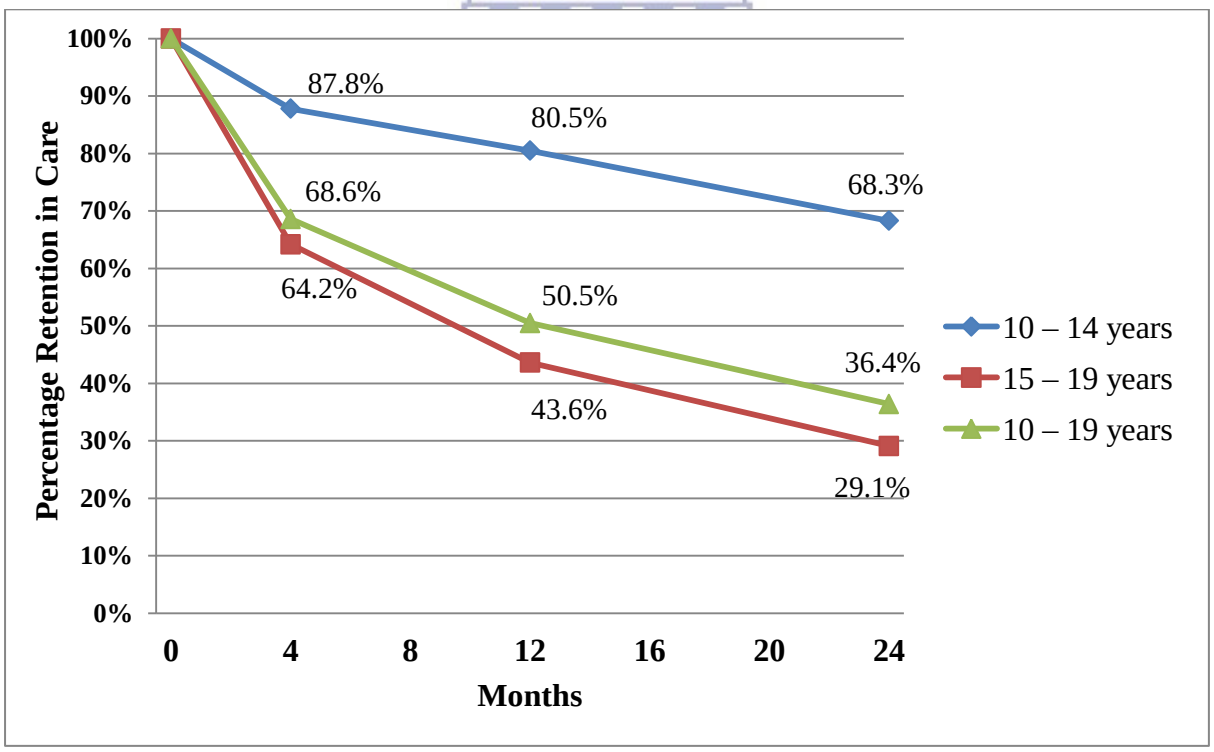

Figure 4.2: Retention in Care of Adolescents at Months 4, 12 and 24 Post-ART Initiation

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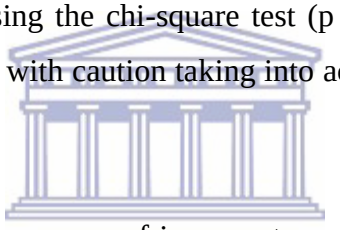
4.5.2 Sex and Retention in Care

Males were found to have significantly better rates of retention than females at months 4 (84.2% vs 64.2%; p = 0.023); 12 (65.8% vs 47.3%; p = 0.038); and 24 (52.6% vs 33.0%; p = 0.022) post-ART initiation (Table 4.3). Males were found to be nearly 30% more likely to be retained at month 4 than females (RR = 1.29 [1.08 – 1.53]). At month 12 males were 39% more likely to be retained compared to females (RR = 1.39 [1.06 – 1.84]) and 60% more likely than females to be retained at month 24 (RR = 1.60 [1.11 – 2.30])

4.5.3 Disclosure and Retention in Care

Adolescents who disclosed their HIV status to a significant other around the time of ART initiation were retained significantly better at month 12 (p = 0.008) and were twice as likely to be retained than those not disclosing at baseline (RR = 2.06 [1.07 – 3.95]). Retention in care at month 24 was also better for those who disclosed their status and just about met the level of statistical significance using the chi-square test (p = 0.044). However, the level of significance should be interpreted with caution taking into account the RR being 2.08 (0.92 – 4.68) (Table 4.5).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Socio-demographic factors such as source of income, type of dwelling and reported alcohol and/or drug use were not statistically associated with retention in care (Table 4.3).

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Table 4.3: Baseline Socio-demographic Characteristics and Retention in Care of Adolescents Initiated on ART

	Month 4		Month 12		Month 24	
	n (%)	p value	n (%)	p value	n (%)	p value
Age						
10 – 14 years	36 (87.8%)	0.003*	33 (80.5%)	<0.001*	28 (68.3%)	<0.001*
15 – 19 years	115 (64.2%)		78 (43.6%)		52 (29.1%)	
Sex						
Male	32 (84.2%)	0.023*	25 (65.8%)	0.038*	20 (52.6%)	0.022*
Female	119 (65.4%)		86 (47.3%)		60 (33.0%)	
Source of Income						
Employed	12 (80.0%)	0.063	6 (40.0%)	0.077	5 (33.3%)	0.052
Family and Friends	80 (62.0%)		60 (46.5%)		41 (31.8%)	
Grant	14 (87.5%)		12 (75.0%)		10 (62.5%)	
Type of Dwelling						
Informal Dwelling	47 (68.1%)		34 (49.3%)		23 (33.3%)	
Formal House	76 (65.5%)	0.243	54 (46.6%)	0.817	39 (33.6%)	0.395
Hostel	1(25.0%)		1 (25.0%)		0	
Other	2 (100%)		1 (50.0%)		0	
Disclosure to Significant Other		0.272		0.008*		0.044*
Yes	127 (69.8%)		97 (53.3%)		70 (38.5%)	
No	16 (59.3%)		7 (25.9%)		5 (18.5%)	
Reported Alcohol and/or Drug Use		0.059		0.401		0.279
Yes	22 (81.5%)		10 (37.0%)		6 (22.2%)	
No	96 (62.7%)		70 (45.8%)		50 (32.7%)	

**indicates statistical significance*

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4.5.4 WHO Stage and Retention in Care

The WHO staging at ART initiation was significantly associated with retention in care at months 4 (p = 0.021), 12 (p = 0.024) and 24 (p = 0.008). Adolescents with WHO stage I at baseline demonstrated the poorest retention rates with 59.6% at month 4, 39.4% at month 12 and 24.2% at month 24. Adolescents with WHO stage IV at baseline were slightly better retained in care with two thirds retained at month 4 and 60.0% and 40.0% being retained at month 12 and months 24 respectively. Best retention rates at month 4 were among adolescents with baseline WHO stages III (84.3%), with retention rates at month 12 being just over 60% for those with baseline WHO stage II and III. Half of adolescents with WHO stage II at baseline were retained in care at month 24. At month 4 adolescents who were WHO stage III at baseline were nearly 30% more likely to be retained in care compared to those being WHO stage I (RR = 1.29 [1.14 – 1.42]). At month 12 adolescents who were WHO stage II at baseline were 35% more likely to be retained than those who were WHO stage I at baseline (RR = 1.35 [1.09 – 1.53]). Similarly, at month 12 adolescents who were

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WHO stage III at baseline were 35% more likely to be retained than those who were WHO stage I at baseline (RR = 1.35 [1.10 – 1.53]). Those who were WHO stage II at baseline were 1.5 times more likely to be retained at month 24 than WHO stage I (RR = 1.52 [1.24 – 1.69]); with those adolescents at WHO stage III at baseline were 46% more likely to be retained in care compared to WHO stage I (RR = 1.46 [1.15 – 1.66]).

4.5.5 Pregnancy and Retention in Care

Adolescents who were pregnant at ART initiation had significantly lower retention rates than non-pregnant adolescents at months 4 (56.0% vs 76.5%; p = 0.001), 12 (35.7% vs 59.6%; p = 0.001) and 24 (21.4% vs 45.6%; p < 0.001). Being pregnant at baseline decreases the likelihood of retention by 27% (RR = 0.73 [0.59 – 0.90]), 40% (RR = 0.60 [0.44 – 0.83]) and 53% (RR = 0.47 [0.30 – 0.74]) at months 4, 12 and 24, respectively (Table 4.5). Significant associations were also found between gestational age at ART initiation and retention in care at months 4 (p < 0.001), 12 (p = 0.004) and 24 (p = 0.002). Nearly one third of adolescents initiated on ART in the third trimester of pregnancy were retained at month 4, with better retention rates for women initiating ART in the first trimester (80.0%) and second trimester (68.0%) (Table 4.4).

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4.5.6 Co-trimoxazole and Retention in Care

At month 24, adolescents who were on co-trimoxazole at ART initiation were retained significantly better than those who were eligible but not started on co-trimoxazole at baseline (45.2% vs 38.5%; p = 0.035). However, despite those being on co-trimoxazole at baseline having better retention in care rates at month 4 (73.8% vs 63.5%, p = 0.398) and month 12 (57.1% vs 48.1%, p = 0.282) post-ART initiation compared to those eligible but not started on co-trimoxazole, these results were not statistically significant (Table 4.4).

4.5.7 ART Regimen and Retention in Care

The ART regimen that adolescents were initiated on was significantly associated with retention in care at months 4 (p = 0.010), 12 (< 0.001) and 24 (p < 0.001). The best retention rates was found among adolescents who were initiated on A3E, i.e. month 4 (94.1%), month 12 (85.3%) and month 24 (73.5%). Those who were initiated on Tenofovir-based regimen showed similar trends in retention rates when comparing those on the fixed-dose combination (TFE) and those on three separate drugs (T3E) at month 4 (63.7% vs 63.0%), month12 (41.4% vs 55.6%) and month 24 (28.0% vs 37.0%) (Table 4.4).

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Baseline clinical variables including CD4 count, being on TB treatment at baseline, and being on IPT were not statistically associated with retention in care (Table 4.4).

Table 4.4: Baseline Clinical Characteristics and Retention in Care of Adolescents Initiated on ART

	Month 4		Month 12		Month 24	
	n (%)	**p value**	**n (%)**	**p value**	**n (%)**	**p value**
CD4 Count						
< 200	30 (71.4%)	0.742	23 (54.8%)	0.634	18 (42.9%)	0.218
200 – 349	77 (70.6%)		57 (52.3%)		43 (39.4%)	
≥ 350	44 (65.7%)		31 (46.3%)		19 (28.4%)	
WHO Stage						
I	59 (59.6%)		39 (39.4%)		24 (24.2%)	
II	34 (70.8%)	0.021*	29 (60.4%)	0.024*	24 (50.0%)	0.008*
III	43 (84.3%)		31 (60.8%)		23 (45.1%)	
IV	10 (66.7%)		9 (60.0%)		6 (40.0%)	
On TB Treatment						
Yes	25 (80.6%)	0.120	20 (64.5%)	0.091	13 (41.9%)	0.487
No	126 (66.7%)		91 (48.1%)		67 (35.4%)	
Pregnant						
Yes	47 (56.0%)	0.001*	30 (35.7%)	0.001*	18 (21.4%)	<0.001*
No	104 (76.5%)		81 (59.6%)		62 (45.6%)	
Gestational Age						
1st Trimester	4 (80.0%)	<0.001*	2 (40.0%)	0.004*	2 (40.0%)	0.002*
2nd Trimester	34 (68.0%)		20 (40.0%)		10 (20.0%)	
3rd Trimester	8 (29.6%)		7 (25.9%)		5 (18.5%)	
On IPT						
Yes	9 (60.0%)	0.346	7 (46.7%)	0.407	4 (26.7%)	0.658
No	111 (67.3%)		80 (48.5%)		60 (36.4%)	
On Co-trimoxazole						
Yes	62 (73.8%)	0.398	48 (57.1%)	0.282	38 (45.2%)	0.035*
No	33 (63.5%)		25 (48.1%)		20 (38.5%)	
ART Regimen						
TFE	100 (63.7%)	0.010*	65 (41.4%)	<0.001*	44 (28.0%)	<0.001*
T3E	17 (63.0%)		15 (55.6%)		10 (37.0%)	
A3E	32 (94.1%)		29 (85.3%)		25 (73.5%)	
Z3E	1 (100%)		1 (100%)		0	
T3L/rit	1 (100%)		1 (100%)		1 (100%)	

**indicates statistical significance*
TFE (Tenofovir+Emtricitibine+Efavirenz)
T3E (Tenofovir+Lamivudine+Efavirenz)
A3E (Abacavir+Lamivudine+Efavirenz)
Z3E (Zidovudine+Lamivudine+Efavirenz)
T3L/rit (Tenofovir+Lamivudine+Lopinovir/ritonavir)

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Table 4.5: Baseline Socio-demographic and Clinical Characteristics and Retention in Care of Adolescents Initiated on ART

	Month 4 RR (95% CI)	Month 12 RR (95% CI)	Month 24 RR (95% CI)
Age			
10 – 14 years	1.37 (1.17 - 1.60)	1.85 (1.48 - 2.31)	2.35 (1.73 - 3.20)
15 – 19 years	1.00	1.00	1.00
Sex			
Male	1.29 (1.08 - 1.53)	1.39 (1.06 - 1.83)	1.60 (1.11 – 2.30)
Female	1.00	1.00	1.00
Disclosure to Significant Other			
Yes	1.18 (0.85 – 1.63)	2.06 (1.07 – 3.95)	2.08 (0.92 – 4.68)
No	1.00	1.00	1.00
WHO Stage			
I	1.00	1.00	1.00
II	1.16 (0.93 – 1.34)	1.35 (1.09 – 1.53)	1.52 (1.24 – 1.69)
III	1.29 (1.14 – 1.42)	1.35 (1.10 – 1.53)	1.46 (1.15 – 1.66)
IV	1.11 (0.68 – 1.40)	1.34 (0.94 – 1.60)	1.39 (0.77 – 1.70)
Pregnant			
Yes	0.73 (0.59 – 0.90)	0.60 (0.44 – 0.83)	0.47 (0.30 – 0.74)
No	1.00	1.00	1.00

RR: Risk Ratio
CI: Confidence Interval

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4.6 Viral Load Suppression of Adolescents Initiated on ART

The viral loads suppression rates of the intention-to-treat population were 59.5% at month 4, 40.0% at month 12 and 25.0% at month 24 (Figure 4.3).

4.6.1 Age and Viral Load Suppression

The younger adolescents (10 – 14 years) had higher viral load suppression rates than the 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%; $p < 0.001$). Younger adolescents were 83% more likely to be virologically suppressed at month 12 than older adolescents (RR = 1.83 [1.35 – 2.49]); with younger adolescents being 3.4 times more likely to be retained at month 24 (RR = 3.38 [2.24 – 5.10]). No significant association was found between age and viral load suppression at month 4 (70.7% vs 57.0%; $p = 0.106$).

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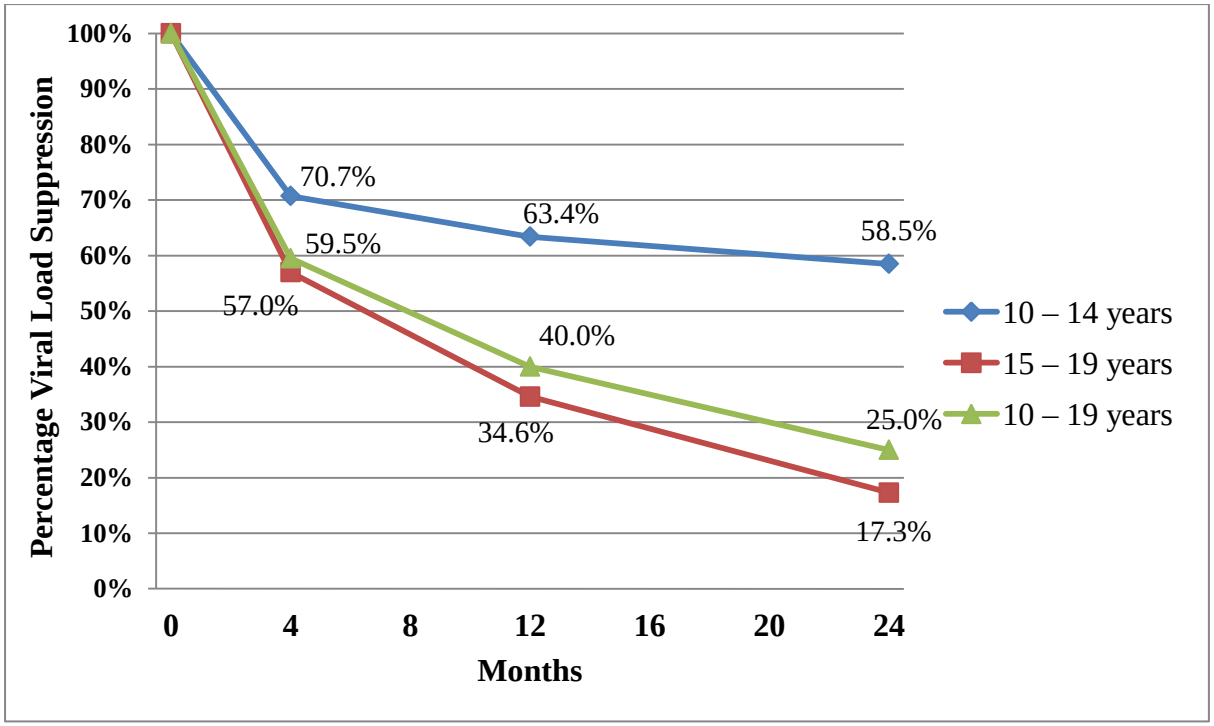

Figure 4.3: Viral Load Suppression of Adolescents at Months 4, 12 and 24 Post-ART Initiation

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4.6.2 Sex and Viral Load Suppression

Males were found to be significantly more likely to be virologically suppressed at months 4 ($p = 0.002$), at month 12 ($p = 0.035$) and at month 24 ($p< 0.001$). Males were 1.5 times more likely to be virologically suppressed than females at months 4 (RR = 1.49 [1.22 – 1.81]), and 12 (RR = 1.50 [1.07 – 2.12]), and 2.3 times more likely at month 24 (RR 2.33 [1.50 – 3.62]) (Table 4.8).

4.6.3 Source of Income and Viral Load Suppression

Despite source of income producing a statistically significant result at month 24 ($p = 0.003$), one should remain cautious when interpreting this result as the findings could be affected by the high number of dropouts prior to month 24, along with the fact that the associations between source of income and viral load suppression not being statistically significant at months 4 and 12 (Table 4.6).

Baseline socio-demographic characteristics including type of dwelling, disclosure to significant other and reported alcohol and/or drug use were not statistically associated with viral load suppression (Table 4.6).

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Table 4.6: Baseline Socio-demographic Characteristics and Viral Load Suppression of Adolescents Initiated on ART

Baseline Socio-Demographic Characteristics	Month 4		Month 12		Month 24	
	n (%)	p value	n (%)	p value	n (%)	p value
Age						
10 – 14 years	29 (70.7%)	0.106	26 (63.4%)	0.001*	24 (58.5%)	<0.001*
15 – 19 years	102 (57.0%)		62 (34.6%)		31 (17.3%)	
Sex						
Male	31 (81.6%)	0.002*	21 (55.3%)	0.035*	18 (47.4%)	<0.001*
Female	100 (54.9%)		67 (36.8%)		37 (20.3%)	
Source of Income						
Employed	10 (66.7%)	0.141	5 (33.3%)	0.365	2 (13.3%)	0.003*
Family and Friends	73 (56.6%)		51 (39.5%)		25 (19.4%)	
Grant	13 (81.3%)		9 (5.6%)		9 (5.6%)	
Type of Dwelling						
Informal Dwelling	42 (60.9%)		27 (39.1%)		14 (20.3%)	
Formal House	64 (55.2%)	0.288	43 (37.1%)	0.454	27 (23.3%)	0.589
Hostel	1 (25.0%)		0		0	
Other	2 (100%)		1 (50%)		0	
Disclosure to Significant Other		0.709		0.117		0.076
Yes	108 (59.3%)		76 (41.8%)		49 (26.9%)	
No	15 (55.6%)		7 (25.9%)		3 (11.1%)	
Reported Alcohol and/or Drug Use		0.721		0.913		0.510
Yes	16 (59.3%)		10 (37.0%)		4 (14.8%)	
No	85 (55.6%)		55 (35.9%)		31 (20.3%)	

**indicates statistical significance*

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4.6.4 Pregnancy, Gestational Age and Viral Load Suppression

Significantly greater proportions of non-pregnant compared to pregnant adolescents were virologically supressed 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). Pregnant adolescents at baseline were 31% less likely to be virologically suppressed (RR = 0.69 [0.53 – 0.89]) at month 4, 36% less likely at month 12 (RR = 0.64 [0.44 – 0.94]) and 76% less like at month 24 (RR = 0.24 [0.11 – 0.50]). Gestational Age was also significantly associated with viral load suppression at months 4 (p < 0.001), 12 (p = 0.033) and 24 (p < 0.001) (Table 4.7). Those initiated in the first trimester had significantly better viral load suppression rates of 80.0% and 60.0% at months 4 and 12 respectively, compared to those initiating in the second and third trimesters. However, by month 24, none of those who initiated in the first trimester had achieved viral load suppression, with those initiating in the second trimester having 10.0% virological suppression at month 24 and those initiating in the third trimester fairing slightly worse (7.4%) (Table 4.7).

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4.6.5 ART regimen and Viral Load Suppression

ART regimen at initiation was significantly associated with viral load suppression at month 12 ($p = 0.019$) and month 24 ($p < 0.001$). The highest rates of virological suppression were found with those initiated 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 (Table 4.7).

4.6.6 WHO Stage and Viral Load Suppression

WHO stage at baseline had a statistically significant association with viral load suppression at month 24 ($p = 0.020$), but not at months 4 ($p = 0.081$) and 12 ($p = 0.441$). Adolescents with WHO stage III at baseline had the most favourable suppression rates at month 4 (72.5%), with those having WHO stage IV at baseline displaying the best virological suppression rates at months 12 and 24 (53.3% and 40.0% respectively). Adolescents who were found to have WHO stage I at baseline had the poorest suppression rates at months 4 (51.5%), 12 (35.4%) and 24 (15.2%). At month 4 adolescents with WHO stage III at baseline were 29% more likely to be virologically suppressed than those who were WHO stage I (RR = 1.29 [1.08 – 1.45]), which was statistically significant. Being WHO stage II, III or IV made adolescents more likely to be suppressed at month 12 relative to being WHO stage I at baseline, but the results were not statistically significant (Table 4.8). However, month 24 suppression rates of those with baseline WHO stage II, III and IV were significantly higher compared to the reference WHO stage I; with adolescents having a baseline WHO stage II being 52% more likely to be suppressed than adolescents at WHO stage I (RR = 1.52 [1.09 – 1.74]) and WHO stage III were 55% more likely to be suppressed than WHO stage I (RR = 1.55 [1.17 – 1.75]). Being WHO stage IV at baseline resulted in a 62% better likelihood of viral load suppression at month 24 (RR = 1.62 [1.18 – 1.83]).

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4.6.7 Co-trimoxazole and Viral Load Suppression

At month 24 adolescents who were started on co-trimoxazole at baseline had significantly better viral load suppression rates than those who were eligible but not commenced on co-trimoxazole at baseline (35.7% vs 23.1%; $p = 0.010$). Those on co-trimoxazole at baseline had better viral load suppression rates than those eligible but not on co-trimoxazole at baseline at both months 4 (65.5% vs 50.0%; $p = 0.203$) and 12 (45.2% vs 38.5%; $p = 0.437$), but these results were not statistically significant.

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Baseline clinical characteristics such as CD4 count, TB treatment and on IPT were not significantly associated with viral load suppression (Table 4.7).

Table 4.7: Baseline Clinical Characteristics and Viral Load Suppression of Adolescents Initiated on ART

	Month 4		Month 12		Month 24	
	n (%)	p value	n (%)	p value	n (%)	p value
CD4 Count						
< 200	24 (57.1%)	0.703	18 (42.9%)	0.816	14 (33.3%)	0.262
200 – 349	64 (58.7%)		45 (41.3%)		28 (25.7%)	
≥ 350	43 (64.2%)		25 (37.3%)		13 (19.4%)	
WHO Stage						
I	51 (51.5%)		35 (35.4%)		15 (15.2%)	
II	30 (62.5%)	0.081	22 (45.8%)	0.441	15 (31.3%)	0.020*
III	37 (72.5%)		20 (39.2%)		17 (33.3%)	
IV	10 (66.7%)		8 (53.3%)		6 (40.0%)	
On TB Treatment						
Yes	23 (74.2%)	0.073	15 (48.4%)	0.304	11 (35.5%)	0.146
No	108 (57.1%)		73 (38.6%)		44 (23.3%)	
Pregnant						
Yes	39 (46.4%)	0.002*	25 (29.8%)	0.015*	7 (8.3%)	<0.001*
No	92 (67.6%)		63 (46.3%)		48 (35.3%)	
Gestational Age						
1st Trimester	4 (80.0%)	<0.001*	3 (60.0%)	0.033*	0	<0.001*
2nd Trimester	29 (58.0%)		15 (30.0%)		5 (10.0%)	
3rd Trimester	5 (18.5%)		6 (22.2%)		2 (7.4%)	
On IPT						
Yes	8 (53.3%)	0.492	5 (33.3%)	0.826	2 (13.3%)	0.184
No	96 (58.2%)		66 (40.0%)		39 (23.6%)	
On Co-trimoxazole						
Yes	55 (65.5%)	0.203	38 (45.2%)	0.437	30 (35.7%)	0.010*
No	26 (50.0%)		20 (38.5%)		12 (23.1%)	
ART Regimen						
TFE	88 (56.1%)		54 (34.4%)		25 (15.9%)	
T3E	16 (59.3%)	0.296	11 (40.7%)	0.019*	7 (25.9%)	<0.001*
A3E	25 (73.5%)		21 (61.8%)		22 (64.7%)	
Z3E	1 (100%)		1 (100%)		0	
T3L/rit	1 (100%)		1 (100%)		1 (100%)	

**indicates statistical significance*
TFE (Tenofovir+Emtricitibine+Efavirenz)
T3E (Tenofovir+Lamivudine+Efavirenz)
A3E (Abacavir+Lamivudine+Efavirenz)
Z3E (Zidovudine+Lamivudine+Efavirenz)
T3L/rit (Tenofovir+Lamivudine+Lopinovir/ritonavir)

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Table 4.8: Baseline Socio-demographic and Clinical Characteristics and Viral Load Suppression of Adolescents Initiated on ART

	Month 4 RR (95% CI)	Month 12 RR (95% CI)	Month 24 RR (95% CI)
Age			
10 – 14 years	1.24 (0.98 – 1.57)	1.83 (1.35 – 2.49)	3.38 (2.24 – 5.10)
15 – 19 years	1.00	1.00	1.00
Sex			
Male	1.49 (1.22 – 1.81)	1.50 (1.07 – 2.12)	2.33 (1.50 – 3.62)
Female	1.00	1.00	1.00
WHO Stage			
I	1.00	1.00	1.00
II	1.18 (0.90 – 1.38)	1.23 (0.84 – 1.49)	1.52 (1.09 – 1.74)
III	1.29 (1.08 – 1.45)	1.10 (0.61 – 1.42)	1.55 (1.17 – 1.75)
IV	1.23 (0.84 – 1.49)	1.34 (0.86 – 1.62)	1.62 (1.18 – 1.83)
Pregnant			
Yes	0.69 (0.53 – 0.89)	0.64 (0.44 – 0.94)	0.24 (0.11 – 0.50)
No	1.00	1.00	1.00

RR: Risk Ratio
CI: Confidence Interval

Viral load suppression rates can also be presented as a proportion of the number of adolescents retained in care, which fits the proposed third 90 of the "90-90-90" UNAIDS strategy, i.e. 90% of all people receiving antiretroviral therapy will have viral suppression (UNAIDS, 2014a). The viral load suppression figures for adolescents retained in care were 86.8% at month 4, 79.3% at month 12 and 68.8% at month 24 for adolescents aged 10 – 19 years (Table 4.9).

Table 4.9: Proportion of Adolescents Retained in Care with Viral Load Suppression

	Month 4	Month 12	Month 24
Age			
10 – 14 years	80.6% (29/36)	87.9% (26/33)	85.7% (24/28)
15 – 19 years	88.7% (102/115)	79.5% (62/78)	59.6% (31/52)
10 – 19 years	86.8% (131/151)	79.3% (88/111)	68.8% (55/80)

A comparison of the viral load suppression rates of the intention-to-treat population and the on treatment (retention in care) population can be seen graphically in Figure 4.4.

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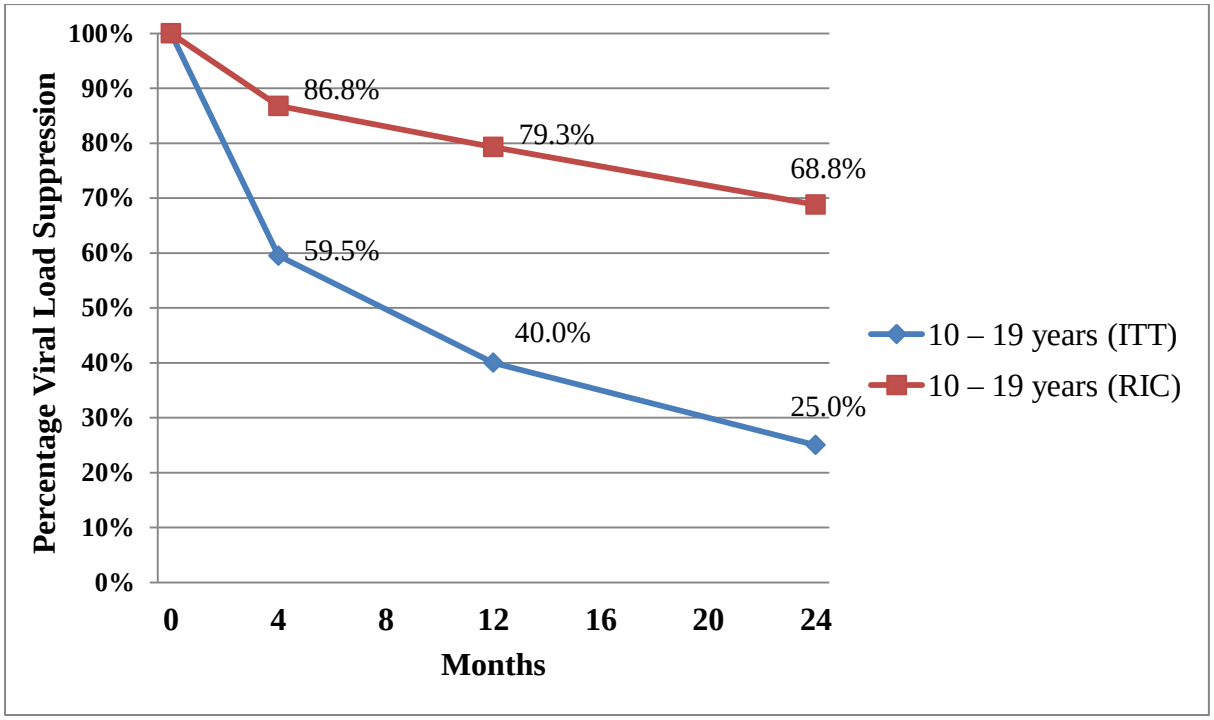

Figure 4.4: Viral Load Suppression of Adolescents: Comparison of ITT Population and On Treatment (Retention in Care) Population

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4.7 Indicators of Poor Adherence

Each patient's clinical record was assessed for indicators of poor adherence and reported at months 4, 12 and 24 as a proportion of the total number of patients remaining in care at the beginning of the various periods. If a patient had one or more indicators of poor adherence in the period in question (e.g. month 0 to month 4), then it will only contribute once.

By month 4 21.8% of the 220 adolescents started on ART had at least one indicator for poor adherence. After month 4 up to month 12, 24.5% of the 151 retained in care at month 4 had an indicator of poor adherence; with 16.2% of the 111 that were still in care at month 12 having an indication of poor adherence.

Table 4.10: Indicators of Poor Adherence

	Month 4 n (%)	**Month 12 n (%)**	**Month 24 n (%)**
Yes	48 (21.8%)	37 (24.5%)	18 (16.2%)
No	172 (78.2%)	114 (75.5%)	93 (83.8%)

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CHAPTER 5: DISCUSSION

5.1 Introduction

The description of retention in care, viral load suppression rates and adherence trends of adolescents on ART will provide valuable insight into whether adolescents are achieving satisfactorily with regard to these outcomes as seen in adolescents in other contexts. The analysis in this study could potentially assist in identifying baseline factors that may indicate those at increased risk in this already vulnerable population group.

5.2 Retention in Care

The current study found low retention in care rates of 68.6%, 50.5% and 36.4% at months 4, 12 and 24 post-ART initiation, respectively. These rates are considerably lower than those observed in other studies on the continent. For instance, a Ugandan study reported an overall retention of adolescents on ART of 96%, 90% and 83% at 6, 12 months, and 24 months, respectively (Ssali *et al.*, 2014). Nabukeera-Barungi *et al.* (2015) also reported that 90.0% of adolescents (N= 156) were retained in care one year post-ART initiation in Uganda. A meta-analysis of six South African studies also reported a relatively higher retention rate of 83% (95% CI 68% to 94%) of HIV-infected adolescents within the first 2 years on ART (Zanoni *et al.*, 2016).

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In our study, the results were reported using the intention to treat population as the denominator at every time point (months 4, 12 and 24), and did not exclude transfer-outs, and patients lost to follow-up and the numerator being those alive and on ART. The above-mentioned studies did not measure retention in care in the same manner. Nabukeera-Barungi *et al.* (2015) determined retention in care by dividing those still active in care by the total that started, after subtracting those who died and transferred out from both numerator and denominator. Ssali *et al*. (2014) calculated retention in care by using a numerator consisting of the total started on ART less those who died, stopped ART and lost to follow-up. The denominator was the total adolescents who started ART. Okoboi *et al*. (2016) defined retention as a patient who had a clinic visit in the 6 months before June 2013 and were alive at the end of June 2013, excluding deaths, stopped ART and lost to follow-up. Zanoni *et al*. (2016) also reported that diverse methods were used to measure retention in care in the studies included in their meta-analysis.

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The heterogeneity in the methods of measuring retention in care makes direct comparisons challenging. The use of the intention-to-treat population results in the retention rates in our study being inferior compared to the rates obtained in the studies discussed above. However, the intention-to-treat approach may be a preferred approach because very few facilities have a networked registry which means facilities are unable to be sure that those who transferred out are linked to care, are unsure of patients we assume are lost to follow-up are definitely not in care, are unsure whether those lost to follow-up are actually accessing care elsewhere, or if they have actually died. Thus, reporting results using the intention-to-treat principles gives a pragmatic and realistic view of what facilities actually know and experience.

5.2.1 Baseline Characteristics Associated with Retention in Care

The statistically significant baseline characteristics associated with retention in care included age, sex, disclosure, WHO staging, pregnancy, gestational age, on co-trimoxazole and ART regimen.

5.2.1.1 Age and Retention in Care

Age at ART initiation was found to be significantly associated with retention in care with younger adolescents (10 – 14 years) being retained better than the older group (15 – 19 years). This finding is congruent with trends reported in other studies that reported poor retention rates or higher attrition among older adolescents on ART compared to the younger adolescents (Kranzer *et al.*, 2017; Okoboi *et al.*, 2016; Bygrave *et al*., 2013; Ssali *et al*., 2014).

The better results observed among the younger adolescents could be explained by the fact that most younger adolescents receive ART care in paediatric services in the primary care setting, which are often operated by tertiary institutions or non-profit organisations. These services are also supplemented by extra clinical and non-clinical support (counsellors, occupational therapy, social workers, etc.) and these younger adolescents are expected to be accompanied by an older caregiver or treatment supporter. Paediatric services designed to manage children into early adolescents, often adapt their services to accommodate for young adolescents as part of their general paediatric service.

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The older adolescents on the other hand, often access ART care in adult ART services and do not received similar preferential services as the younger age group. Adult services are often overfilled with adult ART-tailored services including standard pre-ART and adherence counselling, which are not suited to meet the unique needs of adolescents. This could partly explain the trends with retention in care in adolescents.

5.2.1.2 Sex and Retention in Care

Males were found to have significantly better rates of retention than females at months 4, 12 and 24 post-ART initiation. Ssali *et al.* (2014) also showed that at 24 and 36 months, the risk of non-retention in care was significantly lower among male adolescents compared to female adolescents. However, in an American study involving adolescents and adults, males had worse retention in care outcomes compared to females (Hall *et al.,* 2012). The study population included heterosexual males and MSM males who were compared to females, as well as males and females using injectable drugs. This indicates the importance of context of the population of interest and being aware of the characteristics of the region's key populations and drivers of the epidemic, which may require unique targeted interventions. For example, MSM or adolescents using injectable drugs will require different interventions compared to female heterosexual adolescents.

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Many health services are accessed by females directly, through obstetric services or family planning services, or indirectly through the paediatric services. Males often enter services due to reasons such as ill health or injury, with very little opportunity to enter health care for other routine health services. Therefore, males enter services out of choice and are thereby possibly driven to remain in care as they move from a state of ill health to improved health, as opposed to women who enter ART services as a secondary reason. For example, in antenatal services a pregnant female's primary reason for accessing health services is related to her pregnancy. Health services thus often initiate the drive towards the need for ART services. The motivation to be retained in care for obstetric reasons could be stronger than for other health reasons such as HIV, as patients may feel they are otherwise in good health (Ngarina *et al.,* 2013).

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5.2.1.3 Disclosure and Retention in Care

Failure to disclose may negatively influence retention in care as many patients, particularly women, are often reluctant to disclose their HIV status for fear of negative consequences such as stigma (Hodgson *et al.*, 2014). However, disclosure could result in positive outcomes such as improved retention and adherence (Hodgson *et al*, 2014). Halperin *et al*. (2013) also identified that disclosure of HIV status is strongly associated with increased retention in care.

The likelihood of disclosure being a discriminator for retention in care in our study is slim, as most adolescents indicated having disclosed their status at baseline. The results of our study indicate that adolescents who disclosed their HIV status were better retained at months 4, 12 and 24, and particularly at month 12.

The impact of baseline disclosure to a significant other is not being maximised as the assessment is often done as a programmatic requirement and not a directed assessment in order to identify gaps in disclosure of the patient's status to relevant parties, e.g. household members, partners, parents, etc. Patients are asked about disclosure at baseline and positive responses are documented. However, significant individuals such as household members or partners whom the patient had not disclosed to are not documented or rechecked by health workers at a later stage. Challenges to disclosure are only re-assessed when patients are identified as being at-risk of failing treatment, e.g. after an unsuppressed viral load is picked up. Opportunities need to be sought to assess disclosure challenges prior to the routine measurement of viral loads particularly taking into account the increased length of time between routine blood monitoring (viral load taken 12 months after the last normal viral load result) (Western Cape Government Health, 2016).

Adolescents are a mobile and dynamic population whose change in circumstance (moving in with other family members, change in partner, school or employment circumstances, etc.) may necessitate further attempts at disclosure other than those done at baseline.

Disclosure of the diagnosis of HIV to the adolescent patient was not thoroughly assessed in this study as the capturing of this information was not robustly done in the clinical folders.

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5.2.1.4 WHO Staging and Retention in Care

Adolescents with baseline WHO staging II or III had better rates of retention than those with WHO stages I or IV; with those initiating at WHO stage I having the worst retention rates. Patients with WHO stage 1 are often well and asymptomatic or may only have persistent generalised lymphadenopathy (National Department of Health, 2010a). Their motivation to remain in care and take lifelong treatment may not be driven by the need to get healthy as possibly other patients who were not feeling sick (Ngarina *et al.,* 2013). Similarly, being clinically well but suffering subsequent adverse effects of treatment or having to endure long waiting times at health facilities may potentially lead to patients choosing to opt out of care. Approximately 40% of adolescents initiating ART having WHO stage I at baseline were not retained by month 4, with a further 20% dropping out of care by month 12. By month 24 only 24.2% of those initiating ART who were WHO stage I at baseline were still in care (intention to treat population). Those who were at WHO stage II at baseline had a 30% reduction in retention in care from initiation until month 4 post ART initiation, and then 10% decline in retention in care from month 4 (70.8%) to month 12 (60.4%) as well as from month 12 to month 24 (50%).

Contrary to the results in our study, a Ugandan study found that the risk of non-retention in care of adolescents at 12 months was significantly greater among those with a WHO clinical stage III and IV compared to those with WHO stage I and II (Ssali *et al*., 2014). Other studies also reported retention rates being negatively affected by higher mortality risk associated with WHO stage III and IV related diseases (Bakanda *et al.*, 2011; Nglazi *et al*., 2011). Similarly, Massavon *et al*. (2014) also reported that the risk of attrition in children and adolescents was significantly associated with WHO clinical stages III and IV.

Adolescents may enter ART services at WHO stage I or II, or with more advanced immune suppression coinciding with WHO stages III or IV. A further look into which adolescents may fall into these categories and the association with retention rates will possibly assist in managing the risk. Intuitively, children who acquired HIV through mother-to-child transmission and have survived into adolescence may present with late WHO staging while the adolescents who are behaviourally infected may be diagnosed and initiated prior to their immunity reaching an advanced state of suppression.

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5.2.1.5 Pregnancy, Gestational Age and Retention in Care

Retention rates of adolescents who were pregnant at baseline were significantly lower at months 4, 12 and 24 than non–pregnant adolescents; with levels being as low as 56.0% at month 4. Gestational age at baseline was also significantly associated with being retained in care with only 29.6% of those initiating in the third trimester being retained at month 4, compared to retention rate of 80.0% of those initiating in the first trimester (Table 4.4). Other South African studies have also found that pregnant women initiating ART were significantly more likely to be lost to follow-up (Kaplan *et al.*, 2008; Wang *et al*., 2011). The Western Cape has a structured PMTCT programme with formalised guidelines, part of which states that HIV-infected pregnant women should be targeted to initiate ART on the same day of diagnosis or fast tracked as soon as possible. Despite the implementation of the PMTCT programme, there seem to be a sustained low retention rates. Results from a Malawian study found that women initiating ART during pregnancy as part of their PMTCT programme were five times more likely to be lost to follow-up than non-pregnant women (Tenthani *et al.*, 2014).

For an adolescent, with a confirmed pregnancy and positive HIV diagnosis, being fast-tracked onto treatment may seem an overwhelming experience. Inadequate pre-ART preparation to improve the patient's knowledge and insight into HIV and its treatment as well as insufficient attention given to issues such as stigma and disclosure may explain the challenges faced by this population. Women initiating on the same day of HIV diagnosis have been found to be more likely to be lost to follow-up than those initiating ART on a day other than the same day of their initial HIV diagnosis (Tenthani *et al*., 2014). Not having an adequate understanding of HIV and the PMTCT programme may have dire effects on retention and adherence to ART (Hodgson *et al*., 2014). However, delays in initiation may risk women not initiating at all as seen in a systemic review examining HIV-infected pregnant women which reported that between 38 - 88% of eligible women failing to initiate ART (Ferguson *et al*., 2012).

5.2.1.6 ART Regimen and Retention in Care

ART regimen at initiation was also significantly associated with retention in care with those started on the regimen of Abacavir, Lamivudine and Efavirenz (three separate medications) showing superior retention rates even compared to the fixed dose combination tablet

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requiring one dose per day. However, the Abacavir-based regimen is the first line for younger adolescents who generally get managed in a paediatric setting and benefit from paediatric services and are being supported by a caregiver to access on-going care and adhere to medication.

Many older adolescents who were eligible to use Tenofovir-based ART regimen were initiated on the three separate medications of Tenofovir, Lamivudine and Efavirenz because of initial stock challenges with the fixed dose combination. Currently, consistent supplies of the fixed dose combination makes it available to all eligible patients barring any contra-indications and could assist in attaining favourable adherence and retention outcomes such as those found in a systematic review and meta-analysis, which identified associations between being on a fixed dose combination and better rates of looking adherence and viral load suppression (Ramjan *et al.*, 2014).

5.3 Viral Load Suppression

Achieving and sustaining viral load suppression are major goals of ART programmes in order reconstitute the immune system as sustained viral load suppression decreases morbidity and mortality related to HIV (Nachega *et al.*, 2009). Nevertheless, achieving viral load suppression requires other aspects of the treatment cascade, such as initiation, adherence and retention, to be optimised in order to make a broader impact on the epidemic.

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In our study, the viral loads suppression rates of the intention-to-treat adolescent population were 59.5% at month 4, 40.0% at month 12 and 25.0% at month 24. These figures are much lower than suppression rates found in other studies. In a meta-analysis of eight studies, it was identified that 81% of South African adolescents and young adults on ART had virological suppression, with no differences observed when compared to timing or different age bands (Zanoni *et al.,* 2016). In a literature review by Ferrand *et al*. (2016) six studies that assessed viral load suppression at time points reported that 12 months after ART initiation viral load suppression rates of adolescents were varying from 27% to 89%. Similar rates were found in studies not stratified by time. In other sub-Saharan African contexts, statistics released by PEPFAR following national household surveys in Malawi, Zambia and Zimbabwe revealed an average of 42% viral load suppression among adolescents and young adults who were on ART (Avert, 2016).

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Facilities and ART programme managers are often unable to account for the patients who leave their services, be they formally transferred out or patients who have been lost to follow-up. Those formally transferred out as well as those labelled lost to follow-up may or may not be accessing care elsewhere, or may even have demised. Resources such as a networked registry, which is currently not available to all ART sites, may allow facilities as well as districts to more accurately measure the success of their ART programmes. One can appreciate the levels of uncertainty when comparing the viral load suppression rates of the intention-to-treat population versus the on treatment population (retention in care population) at months 4 (59.5% vs 86.8%), 12 (40.0% vs 79.3%) and 24 (25.0% vs 68.8%). Most facilities in our study utilise stand-alone ART data collection systems, which are not networked, therefore, tracking patients in real-time is challenging. To minimise the uncertainty facilities will have to maximise efforts to retain their patients in care and subsequently ensure timeous viral load measurement in order to get a more accurate picture of their populations viral load suppression rates. The Provincial Department of Health is currently taking steps towards designing and implementing an integrated and networked health data capturing system but the actual date of completion and implementation is uncertain.

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5.3.1 Baseline Characteristics Associated with Viral Load Suppression

The statistically significant baseline characteristics associated with viral load suppression included age, sex, source of income, WHO staging, pregnancy, gestational age, on co-trimoxazole and ART regimen.

5.3.1.1 Age and Viral Load Suppression

Results from our study found that younger adolescents (10 – 14 years) had better viral load suppression rates at months 4, 12 and 24 compared to older adolescents (15 – 19 years); with significant differences at months 12 and 24. This is in keeping with other studies, such as Spire *et al*. (2002) that found older adolescents to be significantly less likely to achieve an undetectable viral load than younger adolescents and children. Age was found to be a significant factor when comparing adults and adolescents with the latter having lower rates of suppression (Nachega *et al*., 2009; Nglazi *et al*., 2012; Ryscavage *et al*., 2011). Adolescents and young adults (15 – 24 years) on ART in Zambia, Malawi and Zimbabwe were also found to have poorer retention rates than older patients in care in these countries (Avert, 2016)

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The younger adolescents in our study were also shown to have better retention in care (as previously discussed) and the conditions that assist in this favourable outcome would probably translate into better potential to support adherence and possibly culminating in better viral load suppression rates.

5.3.1.2 Sex, Pregnancy, Gestational Age and Viral Load Suppression

In our study, males were found to be significantly more likely to be virologically suppressed at months 4, 12 and 24 compared to females. This is not consistent with results from PEPFAR statistics from two of the three sub-Saharan African countries' (Zimbabwe, Malawi and Zambia) national household surveys (Avert, 2016). In Zimbabwe and Malawi virological suppression were higher amongst women compared to males. However, in Zambia males had slightly better suppression rates than their female counterparts.

Pregnancy mainly affected the older adolescents in our study and despite the availability a structured PTMCT programme non-pregnant adolescents had better retention in care adherence rates than those who were pregnant at baseline. In our study, pregnant females who initiate in their first trimester have significantly better viral load suppression results in the first year post-ART initiation; i.e. 80.0% and 60.0% viral load suppression at months 4 and 12 respectively. Early antenatal care booking provides opportunities to support the pregnant adolescent to achieve favourable outcomes for her as well as the baby. These opportunities include having a longer time period to educate the patient on HIV and ART, as well as identify and assist with any barriers to poor adherence including disclosure or socio-economic challenges. Early antenatal care booking becomes increasingly important in the context of the Western Cape ART guidelines encouraging same-day ART initiation for pregnant HIV-infected women (Western Cape Government Health, 2016). Hence, the services are encouraged to promote antenatal booking at the earliest gestational age possible. Owing to the lower retention in care rates among pregnant adolescents, their adherence to medication is consequently affected.

5.3.1.3 ART Regimen and Viral Load Suppression

ART regimen at initiation was significantly associated with viral load suppression after 12 and 24 months post-ART initiation with highest rates of viral load suppression found among

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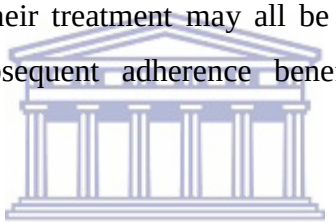
adolescents on the Abacavir-based regimen. However, this may not be due to the actual regimen itself, but possibly linked to this regimen being the first line ART regimen for younger adolescents. The Abacavir-based regimen consists of three separate drugs, which is more than the number of tablets required to be consumed with the fixed dose combination Tenofovir-based regimen, which older adolescents often receive at initiation. The fixed-dose combination 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 viral load outcomes among those initiated on Abacavir-based regimens may relate to similar reasons discussed in the ART regimen section of retention in care. 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. 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 viral load monitoring efficiencies.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5.3.1.4 WHO Stage and Viral Load Suppression

WHO stage at baseline had a statistically significant association with viral load suppression but only at month 24. Adolescents with WHO stage IV at baseline had the most favourable viral load suppression rates at months 12 and 24, with those with WHO stage III at baseline having the better suppression rates at month 4. However, in a descriptive study in Swaziland which explored factors associated with virological detectability in children and adults on ART, Jobanputra *et al*. (2015) reported that patients with WHO stage III and IV disease, CD4 count less than 350 cells/mm^3 and being under 20 years of age were significantly more likely to have unsuppressed viral loads. In the REACH cohort of adolescents Murphy *et al.* (2001) found advanced HIV disease (CD4 count < 350 cells/mm^3), usually associated with higher WHO clinical stages (WHO, 2007), to be associated with poor adherence. With the advent of universal coverage for HIV-infected individuals irrespective of WHO staging or CD4 count (Western Cape Government Health, 2016), the aim is to get people onto treatment at higher in the earlier stages of the disease and avoid the development of opportunistic infection. If this aim is realised, 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).

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Therefore, the ART services need to scale up efforts to motivate patients to remain in care and continue taking their medication to achieve viral load suppression.

5.4 Adherence

Due to the strong association between retention in care and adherence to medication, factors affecting retention in care are most likely going to influence adherence to medication, and ultimately viral load suppression. The Western Cape ART programme relies mainly on viral loads as a means to assess adherence among patients with unsuppressed viral loads. It should be noted that although viral load suppression is a good indicator of adequate adherence to ART, an unsuppressed viral load is not necessarily always a good marker of poor adherence (Wiener *et al*., 2004). Unsuppressed viral loads could result from medication resistance (Wiener *et al.,* 2004), drug interactions or malabsorption of drugs (WHO, 2014). Often, a result of an unsuppressed viral is the only time when patients are identified as having adherence challenges and when steps are taken to identify the adherence problem, its cause and possible steps taken to reverse the trend.

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The Risk of Treatment Failure programme is one such intervention being rolled out at ART sites in the Western Cape. This programme aims to achieve viral load suppression in patients with unsuppressed viral loads through structured adherence support to patients directed at their identified barriers to adherence (Medecins Sans Frontieres, 2012). Intervals between viral load monitoring are relatively wide with patients with suppressed viral loads at month 4 post-ART initiation having their next viral load measurement at month 12 and if suppressed, then annually thereafter (Western Cape Government Health, 2016). Patient adherence behaviours are dynamic and may fluctuate due to changes in patient's contexts, particularly in a vulnerable group such as adolescents. The relatively wide intervals between viral load measurements may require a structured adherence screening mechanisms in order to identify and manage those with adherence challenges earlier than the next viral load measurement, which may be up to 12 months later,

Although methods such as pill-counts have historically been used, currently it is inconsistently being utilised with many facilities opting to omit pill-counts and only assessing adherence following the identification of risks of poor adherence or treatment failure, e.g. having an unsuppressed viral load or missing appointments. This is a departure from previously recommended routine measurements of adherence such as formalised pill-counts

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or pharmacy records, facility attendance monitoring, and self-report measures (Ross-Degnan *et al.*, 2010). The ART programme does not implement robust and routine methods of measuring adherence, other than viral load monitoring. Point-of-care (POC) viral load testing, which is currently being utilised in poorly resourced settings in sub-Saharan Africa and in certain research settings, may be considered in a high risk population such as adolescents on ART (Marcus *et al.*, 2017).

In our study, the levels of adherence to ART were not measured, but indicators of poor adherence were captured from the data source, i.e. the clinical folder. By month 4 post ART initiation, 21.8% of the 220 adolescents at the start of the study had at least one indicator of poor adherence. By month 12, 24.5% out of the 151 adolescents who were still in care after month 4 had at least one indicator of poor adherence. Poor adherence by month 24 was reported in 16.2% of the 111 adolescents who were still in care after month 12.

Assessing adherence in this retrospective folder review was not ideal. No standard approach to assessing or measuring adherence is being exercised across all ART service points, which results in high risk of information bias due to the inconsistent methods of gathering and reporting adherence. In the past pill-counts were routinely used to assess adherence but recently, facilities choose to use it at their own discretion. Clinicians and support staff such as counsellors also contribute by making notes in the folder when they encounter possible issues related to adherence but there is no standard manner in which this is done. Another practice among certain counsellors is that they keep their own notes related to patients they see, including patients with adherence issues, because some facilities do not allow the entry of notes in the clinical stationery other than clinicians notes. Recently, new counsellor stationery has been developed and is currently being rolled out. This new stationery provides counsellors adequate space to document their encounters with patients.

Patients who missed appointments were also being managed in a variety of ways as observed during the review of folders in the data collection phase. Clinicians would document either good or poor adherence in conjunction with the acknowledgement of the patient missing their appointment date. Some clinicians would also report good adherence despite patients missing appointments and there being no evidence of patient's accessing medication to make up for the days they were without medication. Clinicians would also make no documentation of the patient missing their appointment and no comment on adherence, and just proceed to re-write

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the ART prescription. However, even if clinicians question patients on their adherence and missing appointments, the likelihood exists that patients' responses are influenced by social desirability bias and recall bias.

5.5 Quality of Care

TB remains the most prevalent opportunistic infection among people living with HIV and is the leading cause of morbidity and mortality among HIV-infected individuals (WHO, 2017). The evidence strongly suggests that IPT is an effective approach to preventing active TB disease among HIV-infected individuals. Findings from a Cochrane meta-analysis of 12 randomised controlled trials of IPT in HIV-infected adults showed a 62% reduction in TB in those with a positive tuberculin skin test (Akolo *et al.*, 2010). In 1998, the WHO and UNAIDS recommended IPT as part of the essential package of care for people living with HIV, and reinforced this recommendation in 2007 following the review of various clinical trials and studies corroborating IPT's effectiveness (WHO, 2010). However, in 2011 the WHO revised the IPT guidelines, which included that tuberculin skin tests were not a requirement for IPT initiation (WHO, 2011).

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The South African National Department of Health accepted the IPT strategy recommended by the WHO and included it in the National Antiretroviral Guidelines (Department of Health Republic of South Africa, 2013). The IPT strategy was also adopted by the Western Cape Government Health and adaptations and policy clarification was done via the release of official circulars (Western Cape Government Health, (2014). In our study, IPT at baseline was not significantly associated with retention in care and viral load suppression. However, the results indicated that 180 of the 220 adolescents met the eligibility criteria for IPT at baseline, but only 8.3% of the 180 that were eligible for IPT were started on IPT at baseline.

The low number of patients prescribed IPT at baseline does not allow for robust analyses related to outcomes on ART. However, the low proportion of eligible patients eventually initiated on IPT highlights quality of care issues related to uptake of IPT. Reasons for this have not formally been established. However, clinicians and programme managers have anecdotally postulated various reasons for the tardiness in IPT role out, including tuberculin skin tests stock outs, training on tuberculin skin testing, and confusion surrounding IPT's effectiveness for patients other than those with positive tuberculin skin tests.

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There is extensive evidence supporting the effectiveness of co-trimoxazole prophylaxis to prevent serious opportunistic infections and decreasing morbidity and mortality in people living with HIV, as seen in Cochrane reviews (Grimwade & Swingler, 2006; Grimwade & Swingler, 2003), studies conducted in sub-Saharan Africa (Nunn *et al*, 2008; Zachariah *et al*., 2003) including studies conducted in South Africa (Grimwade *et al.,* 2005). The WHO issued guidelines for co-trimoxazole prophylaxis for HIV-infected children, adolescents and adults in 2006 (WHO, 2006). Co-trimoxazole prophylaxis also formed part of South Africa's National Antiretroviral Treatment Guidelines in 2004 (National Department of Health South Africa, 2004), as well the Western Cape Antiretroviral Treatment Guidelines including the latest edition (Western Cape Government Health, 2016).

Despite the results indicating that being on co-trimoxazole at baseline was significantly associated with being retained in care as well as being virologically suppressed at month 24, it is challenging to find clinical or programmatic relevance to this result. However, as a quality of care indicator co-trimoxazole at baseline can provide useful information. Of the 220 patients at the start of the study, 135 were eligible to start co-trimoxazole, nevertheless, only 84 (62.2%) of the 135 eligible adolescents were started on co-trimoxazole at baseline. The 37.8% of patients who should have received co-trimoxazole and benefitted from the preventative advantages of this medication. Our study merely reported on the number of adolescents on co-trimoxazole at baseline and did not aim to investigate the reasons behind those eligible for co-trimoxazole not receiving the intervention.

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CD4 count at baseline has been shown to have varying association with retention in care and outcomes that affect retention rates and related outcomes such as mortality and attrition. Ssali *et al.* (2014) reported non-retention in care was greater among adolescents with higher CD4 counts (100 - 249 cells/mm³ and ≥ 250 cells/mm³) than those with CD4 counts less than 100 cells/mm³. Okoboi *et al.* (2016) found that the risk of attrition in Ugandan adolescents was significantly lower with higher CD4 counts (≥250cells/mm³) at the initiation of ART. However, Reif *et al.* (2016) found that adolescent patients with lower CD4 count <50 cells/mm³ had higher attrition than those with CD4 count >350 cells/ mm³. Lower baseline CD4 counts in adolescents and adults was associated with increased risk of mortality (Bakanda *et al.,* 2011; Nglazi *et al*., 2011). Adolescents with lower CD4 counts were also found to be associated with having an unsuppressed viral load (Jobanputra *et al*., 2015), as well as being associated with poor adherence (Murphy *et al.*, 2001).

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Our study did not yield results finding CD4 count at baseline as a discriminator of retention in care or viral load suppression. However, what is of concern is that nearly 20% of adolescents started ART with severe immunodeficiency (CD4 count < 200 cells/mm³) placing them at high risk of acquiring opportunistic infections, with nearly half of the adolescents initiating ART with advanced immunosuppression (CD4 count 200 – 349 cells/mm³) which also carries a certain risk of opportunistic infections. With current guidelines stating that all HIV-infected adolescents are eligible for ART irrespective of CD4 count or WHO stage, the aim to is initiate ART at lower WHO stages and higher CD4 counts which places patients at decreased risk of poor outcomes (Western Cape Government Health, 2016). Therefore, the proportion of adolescents initiating at lower CD4 counts is of vital concern, and could be due to a variety of reasons including issues related to access to HIV testing services, access to ART services, access to age-appropriate services, disclosure, or stigma. Despite the results of our study not being statistically significant, a low CD4 count carries a significant amount of risk for opportunistic infections and also mortality which if detected at baseline may be a potential alert to clinicians and support staff of the risk of these particular patients and the necessary clinical and programmatic actions could be taken.

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5.6 Limitations of the Study

We adopted a retrospective cohort study design, which have various inherent limitations. We were unable to control the exposures and the outcomes to be assessed and are limited to the routine data expected to be documented as part of the ART services rendered.

The data source includes the patient's clinical folder as well as the Provincial Tier.net data registry. In our study we depended on the accuracy and completeness of documentation in clinical folders and electronic registers which is dependent on the behaviours of others stakeholders in services (clinicians, clerks and information management). Inconsistencies in documentation and capturing have resulted in missing data of certain variables of interest and have limited the ability of the study to describe and analyse the study population.

The sample size which is constrained by the criteria outlined has been further limited by folders of eligible patients not being found. The small sample size has also limited the ability to conduct analyses including multivariate logistic regression and assess for confounders.

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CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

Globally, it is reported that adolescents on ART are at increased risk for poor retention in care, adherence and viral load suppression, compared to children and adults. The Western Cape ART programme manages most adolescents on ART in either paediatric or adult ART services, with no standard adolescent-specific services or indicators to measure outcomes of adolescents on ART. Hence, the objectives of the study were to describe retention in care, treatment outcomes and adherence of adolescent patients on ART in public health facilities in the Metropole District Health Services of the Western Cape Province between January 2013 and December 2014. Our study found retention in care rates for adolescents on ART to be 68.6%, 50.5% and 36.4% at months 4, 12 and 24 respectively, Viral load suppression rates were found to be 59.5%, 40.0% and 25.0% at months 4, 12 and 24, respectively. This poor retention in care and viral load suppression rates, which are congruent with global trends, require a programmatic focus on this vulnerable population group with tailored interventions in order to avoid the negative individual and public health impact of these poor outcomes.

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The objectives of our study also included the description of baseline socio-demographic and clinical characteristics and analysing these characteristics to determine risk factors for retention in care and viral load suppression in adolescents on ART. Retention in care was found to have relevant significant associations with the following baseline characteristics: younger age (10 – 14), being male, having disclosed to a significant other, being WHO stage II and III, not being pregnant, and younger gestational age. Significant associations were found between viral load suppression and the following baseline characteristics: younger age, being male, being WHO stage II, III and IV, not being pregnant, and younger gestational age. These associations may be considered in the processes of adolescent ART programme design and any tailored interventions. However, the nature of our retrospective study design had inherent limitations as to the extent of the variables assessed for associations with the outcomes of interest and may require further research using study designs suited to expanding the capacity to identify further barriers to retention in care and viral load suppression in order to inform targeted interventions and programme design.

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In the Western Cape ART programme viral loads are being used to assess adherence to ART with other measures of adherence, such as pill-counts and self-reports, no longer being part of standard practice at all ART facilities. Hence, apart from using viral loads, our study was unable to measure adherence or even robustly report on indicators of poor adherence. However, because of the strong association between retention in care and adherence the factors affecting retention in care will likely affect adherence to ART. Therefore, the interventions and recommendations aimed at improving the poor retention in care rates found in our study will likely result in positive effects on adherence.

6.2 Recommendations

The recommendations to follow are aimed at improving the poor rates of retention in care and viral load suppression reported in our study. These recommendations include improvements in the monitoring and evaluation of adolescents on ART, addressing baseline factors associated with both retention in care and viral load suppression, and programmatic recommendations to optimise adherence and retention in care.

6.2.1 Improving the Monitoring and Evaluation of Adolescents on ART

To improve retention in care of adolescents, facilities and those involved in managing ART services must be able to monitor and evaluate adolescent outcomes, hence the need for adolescent specific indicators and outcome measures. Indicators and outcome measures for adolescents on ART would assist in identifying not only challenges but also provide a means of assessing improvements resulting from any improvement initiatives that were implemented. Current indicators used in the ART programme such as retention in care, viral loads done and viral load suppression can be disaggregated so that adolescent specific data can routinely be reported on. These indicators could be implemented in the presence or absence of adolescent-tailored ART services.

A networked electronic patient registry would provide localised and real-time assistance to ART sites and programme managers in accounting for patients not retained in care at their facilities. Patients who are lost to follow-up but have sought care elsewhere will be able to be traced to other facilities. Confirmation of linkage to care of those formally transferred out can also be done. This would also improve accuracy with the monitoring and evaluation of the ART programme relating to district and provincial retention in care rates. Electronic registers

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have the capacity to produce lists of defaulters which can used to trace defaulters. Defaulter tracing can either be done telephonically by facility staff or through home visits by community health workers. Strengthening the identification and the tracing of defaulters is critical in improving retention in care.

6.2.2 Disclosure

Disclosure should be assessed at baseline as well as be screened at every interaction with clinicians or counsellors. The disclosure needs at baseline may change with time and circumstance, especially considering the dynamic nature of an adolescent's social context, i.e. change in schools, changes in partners, changing of place of residence, etc. Disclosure should also be directed at individuals that may influence the health behaviour of the patient, such as partners and household members. Random disclosures to individuals not playing a significant role in the life of the adolescent should be interrogated in order to mitigate the negative impact of inadequate and inappropriate disclosure on outcomes.

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6.2.3 Pregnancy and Gestational Age

In our study, HIV-infected adolescents who were pregnant at baseline were found to be at particular high-risk of poor retention in care and adherence to medication. Tailored collaborative interventions should be considered to assist in HIV/ART education, adherence support, disclosure and support with challenges related to schooling and employment during this period. Programmes should set targets for retention of this key population group within the PMTCT programme. Formally measuring retention in care of this vulnerable population group would ensure that facilities and programme managers treat these patients as a priority.

Despite the primary focus of our study not being pregnant HIV-infected adolescents, our findings revealed that adolescents initiated at early gestational ages had better retention in care and viral suppression rates. However, further studies focused on pregnant HIV-infected adolescents are recommended to shed further light on associations between gestational age at ART initiation and outcomes such as retention in care and viral load suppression. In the context of a resource-limited health service, studies aimed at identifying gestational ages of highest risk could direct service design efforts to identify and manage the most at risk adolescents.

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6.2.4 Exploring Barriers to Retention in Care and Viral Load Suppression

The retrospective study design of our study limited the extent to which the barriers to retention in care and viral load suppression could be explored. Further studies (qualitative or mixed methods) could be conducted in the Western Cape to identify local barriers to retention in care and viral load suppression, with the findings to be taken into consideration to design targeted programmes and interventions.

6.2.5 Programmatic Recommendations to Improve Adherence and Retention in Care

The existing Western Cape ART guidelines include clinical guidelines for adolescents on ART, with specific clinical guidelines for younger as well as older adolescents. The ART programme needs to supplement the clinical guidelines with structured tailored adolescent service guidelines catering for the unique social and behavioural needs of adolescents, which also accounts for the specific needs for the younger as well as older adolescents. These guidelines should include tailored counselling and adherence strategies (e.g. peer groups and adolescent clubs), and integration of other health services (e.g. mental health, family planning, antenatal/obstetric services, occupational therapy, and TB services). Part of the preparation any adolescent-specific intervention should include sensitivity training to all cadres of facility staff regarding adolescents, their unique needs and how they should be engaged and managed when accessing services at a health facility.

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The Risk of Treatment Failure programme has been adopted by the Western Cape ART programme to manage ART patients with unsuppressed viral loads in order to improve adherence and achieve viral load suppression. This intervention is being used in adult ART services. A recommendation would be to adapt this intervention to make it suitable for younger as well as older adolescents on ART. A further recommendation would be to expand the criteria for entry into this programme to include other indicators of poor adherence other than unsuppressed viral loads; other indicators such as adolescents who are pregnant or those who have returned to care after a period of missing clinic appointments and/or poor adherence to medication.

In the absence of more frequent laboratory viral load testing, the high risk of poor adherence in adolescents may necessitate the recommendation of formally re-introducing traditional adherence measures including clinic attendance monitoring, pill-counts or client self-reporting. However, the unreliability and biases associated with particularly the latter two

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measures may jeopardise the success of these interventions. The need for measures of adherence other than viral load monitoring may be obviated if POC viral load testing is used for adolescents on ART. The clinical benefits include having results available immediately, which enables clinicians to initiate adherence interventions at the same visit. The other benefits include decreasing the number of visits to facilities, which may be attractive to the adolescent. The mobile nature of an adolescent, the fluctuant nature of their adherence patterns and their high risk for poor viral load outcomes makes the immediacy of POC viral load testing an attractive prospect. POC may also be used to screen adolescents in the periods between the routine 12-monthly viral load testing as outlined in the ART guidelines. POC can also allow for adolescent-tailored services to be rendered outside of the traditional health facility setting (Marcus *et al.,* 2017). POC testing may also be useful in communities where access to health facilities is a challenge. POC viral load testing may contribute in decreasing the number of routine viral load bloods being missed as finger prick testing may be favoured over the often undesired venepuncture (Turner, Anderson, Slater, Quigley, Dyck & Guiang, 2013 as cited by Marcus *et al.,* 2017). The initial use of POC testing may form part of research or pilot projects related to adolescents on ART, which will allow for the feasibility assessments of this recommendation.

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In keeping with the Department of Health encouraging integration of services, an adherence campaign strategy could be implemented at primary health care and community level for all chronic medication including ART. This should aim at modifying adherence behaviour by reinforcing messages of the importance of adherence in managing chronic diseases. However, with adolescents on ART being at high risk of having poor adherence and viral load suppression rates, every opportunity that health care workers engage these adolescents should be used to re-emphasize and educate around the importance of adherence to ART. This can be done by clinicians and counsellors at facility level, as well as by community health workers at a community level.

In conclusion, our study results indicate that reaching the last 90 of the 90-90-90 goal is still a far way off for adolescents on ART, and that this requires specific (disease focused), rather than a generalised (integrative) approach by the public health care system to advance the health of adolescents to safer waters of adulthood.

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APPENDICES

Appendix 1: Data Collection Tool

Data Collection Tool No:_____		Folder No:_____
	Criteria Questions	
1	Date of HIV Diagnosis	/ /
2	ART start date	/ /
3	Date of Birth	/ /
4	Age at ART start date	10◯ 11◯ 12◯ 13◯ 14◯ 15◯ 16◯ 17◯ 18◯ 19◯
5	ARVs prior to above ART start date	◯ No (Naïve) ◯ HAART ◯ PMTCT ◯ PEP ◯ PrEP ◯ Other ◯ Missing
	If 'No' or 'Blank' to question 4 then continue	
	Socio-demographic Details	
6	Male or Female	◯ Male ◯ Female
7	Relation of primary caregiver/next of kin to client	◯ Mother ◯ Father ◯ Brother ◯ Sister ◯ Spouse ◯ Partner (Bf or GF) ◯ Grandmother ◯ Grandfather ◯ Uncle ◯ Aunt ◯ Friend ◯ Guardian ◯ Other _____ ◯ Missing
8	Client aware of own status	◯ Yes ◯ No ◯ Unsure
9*	Disclosed status to person/s (other than healthcare workers)	◯ Yes ◯ No ◯ Missing
10	Drug or Alcohol Abuse in the household	◯ Yes (◯ A ◯ D) ◯ No ◯ Missing
11	Alcohol or Drug use by client	◯ Yes (◯ A ◯ D) ◯ No ◯ Missing
12	Source of Income	◯ Employed (client) ◯ Grant ◯ Pension ◯ Family or Friends ◯ Blank ◯ Missing
13	Mother's HIV status at time of birth of client	◯ HIV+ ◯ HIV- ◯ Unknown
14	Other Household Members HIV+	◯ Yes ◯ No ◯ Missing
15	Own children in household	◯ Yes ◯ No ◯ NA ◯ Missing

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16	Number of own children HIV+ in household	_____ ◯ NA ◯ Missing	
17	Number of own children HIV- in household	_____ ◯ NA ◯ Missing	
18	Number of own children status unknown	_____ ◯ NA ◯ Missing	
19	Other children in household	◯ Yes ◯ No ◯ Missing	
20	Number of other children HIV+ in household	_____ ◯NA ◯ Missing	
21	Number of other children HIV- in household	_____ ◯NA ◯ Missing	
22	Number of other children HIV status unknown in household	_____ ◯NA ◯ Missing	
23	Agreed on a home visit	◯ Yes ◯ No ◯ Missing	
24	Attends a support group	◯ Yes ◯ No ◯ Missing	
25	Lives in what sort of dwelling	◯ Informal Dwelling ◯ Formal House ◯ Hostel ◯ Other (specify_____) ◯ Missing	
26	Number of Rooms	◯1 ◯2 ◯3 ◯4 ◯5 ◯6 ◯7 ◯8 ◯9 ◯10 ◯>10 ◯ Missing	
27	Does the dwelling have a refrigerator	◯ Yes ◯ No ◯ Missing	
28	Number of Adults in Household	◯ 0 ◯1 ◯2 ◯3 ◯4 ◯5 ◯6 ◯7 ◯8 ◯9 ◯10 ◯>10 ◯ Missing	
29	Number of adults HIV+ in household	_____ ◯ NA ◯ Missing	
30	Number of adults HIV- in household	_____ ◯ NA ◯ Missing	
31	Number of adults HIV status unknown in household	_____ ◯ NA ◯ Missing	
32	Current Partner in Household	◯ Yes ◯ No ◯NA ◯ Missing	
33	Current partner Husband/Wife (spouse) of client	◯ Yes ◯ No ◯NA ◯ Missing	
34	Current Partner Tested for HIV	◯ Yes ◯ No ◯NA ◯ Missing	
35	Current Partner HIV status	◯ HIV+ ◯ HIV- ◯ Unknown ◯NA ◯ Missing	
36	Current Partner aware of the status of the client (partner)	◯ Yes ◯ No ◯NA ◯ Missing	
37	Desire to have children in the future	◯ Yes ◯ No ◯ Missing	
Baseline Clinical Characteristics			
38	Baseline CD4 count	_____ cells/mm³ ◯ Missing	
39	Baseline WHO staging	◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ Missing	
40	Baseline Nutritional Status	Weight: _____ Height: _____ Body Mass Index: _____ ◯ Underweight (<18.5)	Mid Upper Arm Circumference:_____ ◯ Missing

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		◯ Normal (18.5-24.9) ◯ Overweight (25-29.9) ◯ Obese (≥30) ◯ Missing	Z-score/Growth Chart_____ ◯ Height _____ ◯ Weight _____ ◯ Missing
41	On TB treatment at ART start	◯ Yes ◯ No ◯ Missing	
42	Type of TB	◯ Drug sensitive ◯ N/A ◯ Drug resistant ◯ Missing	
43	Previous History of TB (other than current)	◯ Yes (Year/s:) ◯ No ◯ Missing	
44	Pregnant at ART start	◯ Yes ◯ No ◯ NA ◯ Missing	
45	Gestational Age (GA)/Trimester at ART initiation	GA: Trimester: 1st◯ 2nd◯ 3rd◯ ◯ NA ◯ Missing	
46	Other chronic illnesses at baseline	◯ Yes ◯ No ◯ Missing If yes, then name	
47	On IPT at baseline	◯ Yes ◯ No ◯ NA ◯ Missing	
48	On Co-trimoxazole at baseline	◯ Yes ◯ No ◯ NA ◯ Missing	
49	ART Start Regimen Tenofovir + Emtricitabine + Efavirenz = 1, Abacavir + Lamivudine + Efavirenz = 2, Tenofovir + Lamivudine + Efavirenz = 3, Stavudine + Lamivudine + Efavirenz= 4, Didanosine + Lamivudine + Efavirenz = 5, Zidovudine + Lamivudine + Efavirenz = 6, Zidovudine + Lamivudine + Lopinavir/ritonavir = 7, Stavudine + Lamivudine + Lopinavir/ritonavir = 8, Abacavir + Zidovudine + Lopinavir/ritonavir = 9, Abacavir + Lamivudine + Efavirenz = 10, Zidovudine + Lamivudine + Efavirenz = 11, Stavudine + Lamivudine + Efavirenz = 12, Tenofovir + Emtricitabine +Nevirapine = 13, Tenofovir + Lamivudine + Nevirapine = 14, Tenofovir + Emtricitabine + Lopinavir/ritonavir = 15, Tenofovir + Lamivudine + Lopinavir/ritonavir = 16, Tenofovir + Zidovudine + Lamivudine + Lopinavir/ritonavir = 17, Tenofovir + Zidovudine + Emtricitabine + Lopinavir/ritonavir = 18, Stavudine + Lamivudine + Lopinavir/ritonavir = 19, Abacavir + Lamivudine + Lopinavir/ritonavir = 20, Stavudine + Lamivudine + Atazanavir/ritonavir = 21, Abacavir + Lamivudine + Atazanavir/ritonavir = 22, Tenofovir + Zidovudine + Emtricitabine + Atazanavir/ritonavir = 23, Tenofovir + Zidovudine + Lamivudine + Atazanavir/ritonavir = 24, Tenofovir + Emtricitabine + Atazanavir/ritonavir = 25, Tenofovir + Lamivudine + Atazanavir/ritonavir = 26,Other=27	_____	
	Clinical Outcomes		
50	VL at M4	◯ Month 4 (__): _____ (___/___/___) ◯ NA ◯ Missing	
51	Subsequent viral load if previous viral load was > 400 copies/ml at either M4	◯ VL after raised VL Month 4: _____ Date: _____ ◯ NA ◯ Missing	
52	Virological Failure M4	◯ Yes ◯ No ◯ NA	
53	CD4 Count M4	◯ Month 4 (__): _____(___/___/___) ◯ NA ◯ Missing	
54	VL at M12	◯ Month 12 (__): _____ (___/___/___) ◯ ND ◯ Missing	
55	Subsequent viral load if previous viral load was > 400 copies/ml at either M12	◯ VL after raised VL Month 12: _____	

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		Date: _____ ◯ NA ◯ Missing
56	Virological Failure M12	◯ Yes ◯ No ◯ NA
57	CD4 Count M12	◯ Month 12 (__): _____ (___/___/___) ◯ NA ◯ Missing
58	VL at M24	◯ Month 24 (__): _____ (___/___/___) ◯ NA ◯ Missing
59	Subsequent viral load if previous viral load was > 400 copies/ml at either M24	◯ After raised viral load Month 24: _____ Date: _____ ◯ NA ◯ Missing
60	Virological Failure M24	◯ Yes ◯ No ◯ NA
61	CD4 Count M24	◯ Month 24 (__): _____ (___/___/___) ◯ NA ◯ Missing
62	Virological Failure at other month	M____ Date:_____
63	Defaulting > 1 week but < 90 days (Month) and subsequent return to care prior to M4	◯ Yes (M___ / Date: ____/___/____) ◯ No ◯ NA
64	Defaulting > 1 week but < 90 days (Month) and subsequent return to care prior to M12	◯ Yes (M___ / Date: ____/___/____) ◯ No ◯ NA
65	Defaulting > 1 week but < 90 days (Month) and subsequent return to care prior to M24	◯ Yes (M___ / Date: ____/___/____) ◯ No ◯ NA
66	Any reported poor adherence other than VL by M4	◯ Yes ◯ No ◯ NA
67	If yes to 65, then was it:	Self-report = 1 (M____) Reported by caregiver = 2 (M____) Pill count = 3 (M____) Other = 4: details_____ ◯ NA
68	Any reported poor adherence other than VL between M5 and M12	◯ Yes ◯ No ◯ NA
69	If yes to 67, then was it:	Self-report = 1 (M____) Reported by caregiver = 2 (M____) Pill count = 3 (M____) Other = 4: details_____ ◯ NA
70	Any reported poor adherence other than VL between M12 and M24	◯ Yes ◯ No ◯ NA
71	If yes to 69, then was it:	Self-report = 1 (M____) Reported by caregiver = 2 (M____) Pill count = 3 (M____) Other = 4: details_____ ◯ NA
72	Any reported adverse effects of ART M0-M4	◯ Yes M__ (Date: ____/___/____) ◯ No ◯ NA
73	Any changes in regimen	◯ Yes ◯ No ◯ NA
74	Date of regimen change	____/____/____ M___ ◯ NA
75	Reason for change	◯ Adverse Drug Reaction ◯ Side Effects ◯ Drug Interaction

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		◯ Virological Failure ◯ Virological Resistance (Resistance Testing) ◯ Decrease Pill Burden ◯ Contra-indication ◯ Drug Discontinued ◯ Drug out of stock ◯ Other ◯ NA
76	Changed regimen M0-M4 Tenofovir + Emtricitabine + Efavirenz = 1, Abacavir + Lamivudine + Efavirenz = 2, Tenofovir + Lamivudine + Efavirenz = 3, Stavudine + Lamivudine + Efavirenz= 4, Didanosine + Lamivudine + Efavirenz = 5, Zidovudine + Lamivudine + Efavirenz = 6, Zidovudine + Lamivudine + Lopinavir/ritonavir = 7, Stavudine + Lamivudine + Lopinavir/ritonavir = 8, Abacavir + Zidovudine + Lopinavir/ritonavir = 9, Abacavir + Lamivudine + Efavirenz = 10, Zidovudine + Lamivudine + Efavirenz = 11, Stavudine + Lamivudine + Efavirenz = 12, Tenofovir + Emtricitabine +Nevirapine = 13, Tenofovir + Lamivudine + Nevirapine = 14, Tenofovir + Emtricitabine + Lopinavir/ritonavir = 15, Tenofovir + Lamivudine + Lopinavir/ritonavir = 16, Tenofovir + Zidovudine + Lamivudine + Lopinavir/ritonavir = 17, Tenofovir + Zidovudine + Emtricitabine + Lopinavir/ritonavir = 18, Stavudine + Lamivudine + Lopinavir/ritonavir = 19, Abacavir + Lamivudine + Lopinavir/ritonavir = 20, Stavudine + Lamivudine + Atazanavir/ritonavir = 21, Abacavir + Lamivudine + Atazanavir/ritonavir = 22, Tenofovir + Zidovudine + Emtricitabine + Atazanavir/ritonavir = 23, Tenofovir + Zidovudine + Lamivudine + Atazanavir/ritonavir = 24, Tenofovir + Emtricitabine + Atazanavir/ritonavir = 25, Tenofovir + Lamivudine + Atazanavir/ritonavir = 26, Other = 27, NA = 28	_____ ◯ NA
77	Any reported adverse effects of ART M5-M12	◯ Yes M__ (Date: ____/___/____) ◯ No ◯ NA
78	Any changes in regimen	◯ Yes ◯ No ◯ NA
79	Date of regimen change	____/____/____ M___ ◯ NA
80	Reason for change	◯ Adverse Drug Reaction ◯ Side Effects ◯ Drug Interaction ◯ Virological Failure ◯ Virological Resistance (Resistance Testing) ◯ Decrease Pill Burden ◯ Contra-indication ◯ Drug Discontinued ◯ Drug out of stock ◯ Other ◯ NA

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81	Changed regimen M5-M12 Tenofovir + Emtricitabine + Efavirenz = 1, Abacavir + Lamivudine + Efavirenz = 2, Tenofovir + Lamivudine + Efavirenz = 3, Stavudine + Lamivudine + Efavirenz= 4, Didanosine + Lamivudine + Efavirenz = 5, Zidovudine + Lamivudine + Efavirenz = 6, Zidovudine + Lamivudine + Lopinavir/ritonavir = 7, Stavudine + Lamivudine + Lopinavir/ritonavir = 8, Abacavir + Zidovudine + Lopinavir/ritonavir = 9, Abacavir + Lamivudine + Efavirenz = 10, Zidovudine + Lamivudine + Efavirenz = 11, Stavudine + Lamivudine + Efavirenz = 12, Tenofovir + Emtricitabine +Nevirapine = 13, Tenofovir + Lamivudine + Nevirapine = 14, Tenofovir + Emtricitabine + Lopinavir/ritonavir = 15, Tenofovir + Lamivudine + Lopinavir/ritonavir = 16, Tenofovir + Zidovudine + Lamivudine + Lopinavir/ritonavir = 17, Tenofovir + Zidovudine + Emtricitabine + Lopinavir/ritonavir = 18, Stavudine + Lamivudine + Lopinavir/ritonavir = 19, Abacavir + Lamivudine + Lopinavir/ritonavir = 20, Stavudine + Lamivudine + Atazanavir/ritonavir = 21, Abacavir + Lamivudine + Atazanavir/ritonavir = 22, Tenofovir + Zidovudine + Emtricitabine + Atazanavir/ritonavir = 23, Tenofovir + Zidovudine + Lamivudine + Atazanavir/ritonavir = 24, Tenofovir + Emtricitabine + Atazanavir/ritonavir = 25, Tenofovir + Lamivudine + Atazanavir/ritonavir = 26, Other = 27, NA = 28	_____ ◯ NA
82	Any reported adverse effects of ART M13-M24	◯ Yes M__ (Date: ____/___/____) ◯ No ◯ NA
83	Any changes in regimen	◯ Yes ◯ No ◯ NA
84	Date of regimen change	____/____/____ M___ ◯ NA
85	Reason for change	◯ Adverse Drug Reaction ◯ Side Effects ◯ Drug Interaction ◯ Virological Failure ◯ Virological Resistance (Resistance Testing) ◯ Decrease Pill Burden ◯ Contra-indication ◯ Drug Discontinued ◯ Drug out of stock ◯ Other ◯ NA
86	Changed regimen M13-M24 Tenofovir + Emtricitabine + Efavirenz = 1, Abacavir + Lamivudine + Efavirenz = 2, Tenofovir + Lamivudine + Efavirenz = 3, Stavudine + Lamivudine + Efavirenz= 4, Didanosine + Lamivudine + Efavirenz = 5, Zidovudine + Lamivudine + Efavirenz = 6, Zidovudine + Lamivudine + Lopinavir/ritonavir = 7, Stavudine + Lamivudine + Lopinavir/ritonavir = 8, Abacavir + Zidovudine + Lopinavir/ritonavir = 9, Abacavir + Lamivudine + Efavirenz = 10, Zidovudine + Lamivudine + Efavirenz = 11, Stavudine + Lamivudine + Efavirenz = 12, Tenofovir + Emtricitabine +Nevirapine = 13, Tenofovir + Lamivudine + Nevirapine = 14, Tenofovir + Emtricitabine + Lopinavir/ritonavir = 15, Tenofovir + Lamivudine +	_____ ◯ NA

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	Lopinavir/ritonavir = 16, Tenofovir + Zidovudine + Lamivudine + Lopinavir/ritonavir = 17, Tenofovir + Zidovudine + Emtricitabine + Lopinavir/ritonavir = 18, Stavudine + Lamivudine + Lopinavir/ritonavir = 19, Abacavir + Lamivudine + Lopinavir/ritonavir = 20, Stavudine + Lamivudine + Atazanavir/ritonavir = 21, Abacavir + Lamivudine + Atazanavir/ritonavir = 22, Tenofovir + Zidovudine + Emtricitabine + Atazanavir/ritonavir = 23, Tenofovir + Zidovudine + Lamivudine + Atazanavir/ritonavir = 24, Tenofovir + Emtricitabine + Atazanavir/ritonavir = 25, Tenofovir + Lamivudine + Atazanavir/ritonavir = 26, Other = 27, NA = 28	
87	Outcome M4	◯ Retained in Care: Date: _____ ◯ Transfer Out: Date: _____ ◯ LTFU: Date: _____ ◯ Died: Date: _____ ◯ Stopped Treatment: Date: _____ ◯ NA
88	Outcome M12	◯ Retained in Care: Date: _____ ◯ Transfer Out: Date: _____ ◯ LTFU: Date: _____ ◯ Died: Date: _____ ◯ Stopped Treatment: Date: _____ ◯ NA
89	Outcome M24	◯ Retained in Care: Date: _____ ◯ Transfer Out: Date: _____ ◯ LTFU: Date: _____ ◯ Died: Date: _____ ◯ Stopped Treatment: Date: _____ ◯ NA
90	Months in care prior to LTFU	_____ months ◯ NA
91	Returned to care following outcome of LTFU	◯ Yes (Date: ____/___/____) ◯ No ◯ NA

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Appendix 2: Ethics Approval

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OFFICE OF THE DIRECTOR: RESEARCH
RESEARCH AND INNOVATION DIVISION

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South Africa
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19 January 2017

Dr E Kriel
School of Public Health
Faculty of Community and Health Sciences

Ethics Reference Number: BM/17/1/15

Project Title: Adherence, retention in care and treatment outcomes of adolescents on antiretroviral therapy in the Western Cape Metropole in South Africa.

Approval Period: 15 December 2016 – 15 December 2017

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

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

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

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

PROVISIONAL REC NUMBER -130416-050

FROM HOPE TO ACTION THROUGH KNOWLEDGE

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Appendix 3: One of the Research Approval Letters from the Western Cape Government Health: Health Impact Assessment

Western Cape Government
Health

STRATEGY & HEALTH SUPPORT
Health.Research@westerncape.gov.za
tel: +27 21 483 6857; fax: +27 21 483 9895
5th Floor, Norton Rose House., 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za)

REFERENCE: WC_2017RP58_418
ENQUIRIES: Ms Charlene Roderick

University of Western Cape

Robert Sobukwe Road

Bellville

Cape Town

7535

For attention: Dr Ebrahim Kriel, Prof Brian Van Wyk, Mr Ferdinand Mukumbang

Re: Adherence, retention in care and treatment outcomes of adolescents on antiretroviral therapy in the Western Cape Metropole in South Africa.

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.

Please contact following people to assist you with any further enquiries in accessing the following sites:

Strand CDC	**Sr Christa Lubbe**	**021 853 8210**
Gustrouw CDC	**Sr Aisha Salie**	**021 845 5594**
Kleinvlei CHC	**Sr Volente Jonkers**	**021 904 4410**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final feedback (**annexure 9**) within six months of

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completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

3. In the event where the research project goes beyond the *estimated completion* date which was submitted, researchers are expected to complete and submit a progress report (**Annexure 8**) to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

4. The reference number above should be quoted in all future correspondence.

Yours sincerely

DR A HAWKRIDGE

DIRECTOR: HEALTH IMPACT ASSESSMENT

DATE: 28/7/2017

CC: **M PHILLIPS** **DIRECTOR: KESS**

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