RESEARCH REPORT

FACTORS ASSOCIATED WITH VIROLOGICAL FAILURE IN ADOLESCENTS IN A RURAL HIV PROGRAMME IN KWAZULU-NATAL

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DECLARATION

I, Nicoletta Mabhena (Student Number 562150) declare that this research report is my own work. I am submitting it in partial fulfilment of the requirements of the Master of Science in Epidemiology in the Field Of Population-Based Field Epidemiology at the University of the Witwatersrand, School of Public Health, Johannesburg. This report had not been submitted before for any degree at any other university. Acknowledgements and required referencing conventions have been adhered to where I have used thoughts and ideas of others.

Signed:

Date:

DEDICATION

I dedicate this work to my late niece Maxine Tatenda Kesha who succumbed to this illness as an adolescent. To my daughters Ruvarashe and Anashe Mabhena, thank you for being patient whilst I pursued my studies, you are both my inspiration.

ABSTRACT

Background

In 2010, 2.2 million adolescents were living with HIV (Human Immunodeficiency Virus) worldwide. This study aimed to describe the socio-demographic and clinical characteristics of the adolescents (10-19 years old) initiating anti-retroviral treatment (ART) and to investigate characteristics that are associated with virological failure in adolescents on ART.

Methods

This was an analysis of adolescents initiating ART from June 2004-2010 at the Hlabisa Treatment and Care Programme in KwaZulu-Natal, South Africa. Data was collected from two datasets at Africa Centre for Health and Population Studies. Time to outcomes of death and lost to follow up (LTFU) were quantified using Kaplan-Meier estimates. The outcome was virologic response (< 70copies/ml) after at least 6 months on ART and the associations with an unsuppressed viral load were investigated using multivariable logistic regression.

Results

543 adolescents, median age 15 years (IQR 12-18), initiated ART; 67.8% (368) were females. Age at treatment initiation showed a bimodal distribution, with a peak at 11 years and another at 17-19 years; 61 females aged 16-19 years initiated ART whilst pregnant. At baseline, median CD4 count was 152 cells/µl (IQR 72-251), 392 (72.2%) had prior TB and 129 (23.8%) a weight-for-age z-score ≤ -2 (i.e. were under-nourished). Numbers of adolescents starting ART increased from 53 in the years 2004-2006 to 196 in 2010. Overall mortality was 36.5 per 1000 person years (95% CI 27.2 - 48.8); LTFU 98.8 per1000 person years (95% CI 82.8-118). Adjusting for age and gender, LTFU was significantly higher in females initiating in late adolescence (15-19 years) ($p<0.001$) and 24 (39.3%) of those

initiating ART whilst pregnant were LTFU. The first viral load after initiation was taken at a median time of 11.25 months (IQR 7.78-16.20). Of the 364 adolescents with a viral load result after at least 6 months of ART, 119 (32.7%) had an unsuppressed viral load (95% CI 27.9- 37.5). Adolescents who initiated in the year 2010 were found to have less odds of an unsuppressed viral load compared to those who initiated between 2004 and 2006 [adjusted Odds Ratio (aOR) 0.29 (95% CI 0.11-0.79)]. Those who had the first viral load test done after > 30 months of ART had higher odds of an unsuppressed viral load compared to those tested after 6-12 months of ART [aOR 6.88 (95% CI 1.29-36.66)].

Conclusion

Despite the yearly increase in adolescents initiating ART, good virological responses can be obtained through increased ART support to both individuals and health care providers. Timely viral load monitoring identifies those in need of increased adherence support on ART and may result in good virological responses.

Recommendations

Adolescents on ART are a vulnerable group that requires special attention to improve clinical and virological outcomes. Adolescent friendly ART clinics may be useful in providing this service and mitigate the high attrition rates of those on treatment for HIV. Public health awareness campaigns on HIV and its treatment may have a positive impact on virological response to ART and therefore campaigns targeting adolescents must be intensified. Early virological testing after 6 months on ART to monitor treatment responses helps to identify those with sub-optimal response to ART and reduce the progression to virological failure and drug resistance to anti-retroviral drugs.

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ABBREVIATIONS

AC	Africa Centre for Health and Population Studies
ACDIS	Africa Centre Demographic Information System
AIDS	Acquired Immunodeficiency Syndrome
aOR	Adjusted Odds Ratio
ART	Antiretroviral Treatment
ARTemis	Antiretroviral Treatment Evaluation Monitoring Information System
AZT	Zidovudine
CI	Confidence Interval
DOH	Department of Health
DSA	Demographic Surveillance Area
EFV	Efavirenz
EGPAF	Elizabeth Glaser Pediatric AIDS Foundation
FTC	Emtricitabine
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IQR	Inter quartile range
LFTU	Lost to follow up
LPVr	Lopinavir
MDR	Multiple Drug Resistant
NVP	Nevirapine
OR	Odds Ratio
PACTG	Peadiatric Aids Clinical Trial Group
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PLWHIV	People living with HIV

PMTCT	Prevention of Mother to Child Transmission
REACH	Reaching for Excellent Adolescent Care and Health
SSA	Sub-Saharan Africa
TB	Tuberculosis
TDF	Tenofovir
USAID	United States Agency for International Development
WAZ score	Weight-for-age Z-score
WHO	World Health Organisation
XDR	Extremely drug resistant

CHAPTER 1: INTRODUCTION

The chapter begins with an overview of the Human Immunodeficiency Virus (HIV) disease burden in the world, sub-Saharan Africa (SSA) and South Africa. The impact of virological failure on both an individual's HIV treatment and public health HIV programmes are highlighted. Reasons that make the adolescents on antiretroviral treatment (ART) an important group for research are explored and this is followed by a review of the published literature on virological failure on ART. The chapter ends with a description of the objectives of the study.

1.1 Background

The HIV pandemic has entered its third decade with little prospect of a cure [1, 2]. By the end of 2010, an estimated 34 million people were infected with HIV worldwide, an increase of 17% from 2001 [3]. This has resulted in an increased need for, and uptake of, HIV treatment. In low and middle income countries, 47% of the 14.2 million people eligible for treatment were on ART at the end of 2010 (CD4 $\leq$ 200), compared to 39% at the end of 2009 [3]. The World Health Organization (WHO) defines an adolescent as an individual between the ages of 10-19 years inclusive [4] and this is the definition used in this report. In 2010, 2.2 million (2.0-2.5 million) adolescents were living with HIV worldwide and 60% (1.3 million) were females [5].

SSA, a region that has 12% of the global population, has the greatest burden of HIV (68% worldwide in 2010) and it remains the epicentre of the pandemic [3]. In 2010, there were an estimated 1.87 million adolescents infected with HIV in SSA (85% worldwide) [5].

In 2010, an estimated 5.6 million South Africans were living with HIV of whom 280 000 were children aged between 0 and 14 years. South Africa had an overall HIV prevalence of

17.9% in 2010 [3, 6, 7] and the prevalence amongst those aged 15-19 years was 7% and 3% in females and males respectively [5]. There is variation in the prevalence of HIV in the provinces of South Africa with KwaZulu-Natal having the highest disease burden with an estimated 39.5% among antenatal clinic attendees in 2010 [8]. The prevalence amongst those aged 15-19 years was 20.5% in this province as estimated in the same survey [8]. According to the KwaZulu-Natal Department of Health (DOH), overall ART coverage in the province was 81% between 2010 and 2011 [9].

The study setting is the Africa Centre for Health and Population Studies (AC) which is based in the Hlabisa sub-district of the Umkhanyakude district of KwaZulu-Natal (www.africacentre.com). Since 2000, the AC has collected data twice-yearly through interviews with key-household informants and annual household socio-economic surveys in its 438 square kilometre Demographic Surveillance Area (DSA) which is home to 85 000 individuals. The DSA is within the Hlabisa sub-district. The area has a high disease burden of HIV with an imputed based prevalence estimate of 27.3% in 2011 [10]. The overall HIV incidence in the area was 3.4 per 100 person-years (95% CI 3.1-3.7) with no sign of decline between 2003 and 2007 [11]. In 2004, as a response to the Comprehensive HIV and AIDS Care Management and Treatment Plan, the AC partnered with the DOH to initiate the Hlabisa HIV Treatment and Care Programme [12]. The programme was funded from 1 August 2004 to 31 December 2006 by the Elizabeth Glaser Paediatric AIDS Foundation (EGPAF) and since 1 May 2005 by the President's Emergency Plan for AIDS Relief (PEPFAR) and United States Agency for International Development (USAID) [12]. Between June 2004 and July 2011, a total of 667 adolescents were initiated on ART (personal communication senior database scientist, Africa Centre) [13].

WHO recommends that suppressed plasma viral loads should be reached within the first 6 months of ART [14]. Virological failure is defined by the South African DOH as two consecutive viral loads >1000 copies/ml at least 3 months apart after having been on ART for at least 6 months [15]. Though the DOH recommends using 1000 copies/ml as the threshold to determine if viral loads are suppressed, the Hlabisa HIV Treatment and Care programme used lower thresholds (25 copies/ml, 40 copies/ml and 70 copies/ml) during the study period. This was due to the different laboratory viral load test kits with different undetectable thresholds that were used. The DOH recommends viral load monitoring of individuals who have initiated ART after 6 months, 12 months and yearly thereafter if viral load is suppressed. After 6 months on treatment, a raised viral load indicates poor response to treatment and is used to identify individuals who need intense adherence counselling. For these individuals, a second test is done after 3 months to reassess virological suppression [15].

Due to the lack of the second viral load used to ascertain virological failure, the outcome in this study was an unsuppressed viral load to assess response to ART after at least 6 months of treatment. This study used the highest of the viral load thresholds at the Hlabisa HIV Treatment and Care programme (70 copies/ml) to determine if individuals had a suppressed viral load or not.

1.2 Statement of the Problem

With the expansion of ART programmes and coverage, monitoring of individuals on ART poses a great challenge in the public sector where there are resource limitations, particularly healthcare worker shortages [16, 17]. As survival on treatment has increased and HIV has become a chronic disease, ART demands good adherence to achieve long term virological suppression which is key to minimising drug resistance and preventing treatment failure [14,

18, 19]. With high patient to health caregiver ratios, an increased number of individuals are likely to have ART failure as monitoring of those on treatment becomes less intense. After treatment failure, an individual needs to switch to another ART regimen [15]. In resource-limited settings where genotyping for HIV drug resistance is unaffordable, switching to another ART regimen is done without distinguishing if failure is due to poor adherence alone or to drug resistance. The human and financial implications of ART failure are significant with the average annual cost of alternate ART regimens reaching up to eight times that of a first-line ART regimen [14]. The regimens may be more complex and more difficult to take than the initial treatment combinations. In resource-limited settings, second line treatment may not be available resulting in an increase in HIV morbidity and mortality [14, 20]. Adolescents on ART face many challenges related to treatment adherence, which will be discussed below, hence the importance of describing the factors associated with virological failure in this age group to identify potential cases of treatment failure. This will also aid healthcare workers in the early identification of those requiring intense adherence support with the aim of reducing those requiring treatment regimen switches.

1.3 Justification

Poor adherence to treatment regimens is the most common cause of detectable plasma viral loads in individuals after 6 months of ART initiation [21]. This is due to suboptimal viral suppression by insufficient plasma anti-retroviral drug levels [14]. Reinforcing the importance of adherence is vital in improving long-term ART outcomes. Research in southern Africa using pharmacy refills as an outcome measure, suggests that adolescents (11-19 years old) may have less adherence to ART compared to adults aged over 20 years (20.7% and 40.5% after 6 months of ART respectively; $p< 0.01$) [22].

Adolescence is a challenging period in which the individual undergoes physiological and psychological changes characterized by exceptionally rapid growth and development leading to puberty and sexual development [23]. Adolescents can be grouped according to their stages of development into early (10-14 years) and late (15-19 years) adolescence [23, 24]. Compared to those who are HIV negative, adolescents on ART have an extra burden of being on daily lifelong treatment. During adolescence, an individual's capacity for abstract and critical thinking also develops [23, 24] and those with HIV may have cognitive impairment and mental health problems such as anxiety, depression, attention-deficit or hyperactivity disorder and post-traumatic stress disorder [25]. The stigma of living with HIV, especially from peers who are not mature enough to understand, has a strong impact on the psychological and emotional development of HIV positive adolescents [26, 27]. As social relationships become more important, peer pressure may result in risky behaviour and hence adherence on treatment may reduce [27, 28]. Koenig et al reported that three behavioural health challenges are associated with adolescents on ART: a decreased adherence to treatment; earlier sexual debut and accompanying pregnancy and transmission risk; mental health problems [28]. All these challenges may have a negative impact on adherence to ART leading to treatment failure; identifying early warning predictors of failure in this group is therefore extremely important.

Literature on the factors associated with treatment failure in adolescents on ART is sparse even though they are a vulnerable group. A search in the PubMed database on the factors associated with virological failure in adolescents on ART, retrieved only 8 articles. With ART increasing the survival of HIV-positive individuals and HIV now a chronic disease, an increased number of children are surviving into adolescence emphasising the need for more research in this group to improve their quality of life and adherence to drugs [18, 19].

With the United Nations Millennium Development Goal number 6 of combating HIV by 2015 [29] , adolescent monitoring for early warning signs of failure should be intensified to prevent drug resistance to anti-retroviral drugs [14]. This report adds to the knowledge base of the management of adolescents on ART in public health HIV programmes in rural South Africa.

1.4 Literature Review

1.4.1 Characteristics of adolescents initiating ART

In a study in Cape Town analysing the treatment outcomes of adolescents (9-19 years of age) between 2002 and 2009, the median age at ART initiation was 11.5 years (IQR 10.0-17.3) [30]. Of those initiating ART, 67.7% were in early adolescence, 12.3% in middle adolescence and 20.3% in late adolescence [30]. In a study analysing pooled data from nine countries in southern Africa in the Aid for AIDS treatment programme, the median age at initiation of non-perinatally infected adolescents was 16.4 years (IQR 11.9-18.8) [22]. The majority of individuals who initiated ART in the Hlabisa HIV treatment and Care Programme between 2004 and 2008 were females (73%) [12]. This was the same for adolescents initiating in other programmes, Cape Town (66.2%) and southern Africa (72.7%) and their baseline median CD4 cell counts were 134 (IQR 41-198) and 144 (27-246) respectively [22, 30]. The median change in CD4 cell count from baseline to week 32 was 195 (IQR 136-439). Mortality rates for adolescents initiating ART were 2.9 per 100 person years (95% CI 2.3-3.7) and 5% for the programme in Cape Town and Aids for AIDS respectively [22, 30]. LTFU of adolescents in the Cape Town programme was 10 per 100 person years (95% CI 8.8-11.4) [22].

1.4.2 Virological criteria as a measure of treatment failure

There is no standard definition of ART failure but it can be defined by clinical, immunological or virological criteria. Immunological and clinical criteria are more appropriate for ruling out than for confirming virological failure. Immunological criteria have low sensitivity and positive predictive values (17.1% (95% CI 6.6–33.6%)) and (9.5% (95% CI 3.6–19.6%)) respectively compared to virological criteria [31, 32]. Due to this poor correlation between immunologic and virologic criteria, treatment failure may remain unnoticed in settings where HIV-RNA testing is not available for monitoring. A comparison of outcomes of ART in South Africa, where viral load monitoring is routine, with those in Malawi and Zambia, where monitoring is based on CD4 cell counts showed that the risk for death after 3 years of follow up (after adjusting for age, sex, first-line regimen and CD4 cell count) was 42% lower in South Africa (95% CI 0.50-0.66) [33]. Explanations of this finding may include the availability of viral load monitoring in South Africa resulting in early detection of failure, adherence counselling and timely switching of treatment regimens [33].

1.4.3 Virological failure at ART programmes

One viral load is used to determine viral suppression for individuals on ART [22, 34-37]. When two consecutive viral loads are available, virological failure can be concluded [15, 30]. A report on the outcomes of children ≤ 15 years old initiating ART between 2004 and 2008 in the Hlabisa HIV treatment and care programme in KwaZulu-Natal reported a 73.5% viral suppression (<25 copies/ml) after 6-12 months on ART [34].

Another study in Cape Town analysing treatment outcomes of adolescents (9-19 years of age) initiating ART, reported 27.5% viral suppression (<400 copies/ml) at 32 weeks of ART ($p<0.001$) [30]. The same study found a rate of virological failure of 8.2% (95% CI 4.6- 14.4)

when using an outcome of two consecutive viral load > 1000 copies/ml after 48 weeks of ART [30].

An observational cohort study in nine southern African countries reporting viral suppression (≤ 400 copies/ml) for adolescents (11-19 years old) initiating ART between 1999 and 2006 found a viral suppression rate of 63% after at least 6 months of treatment [22].

The IeDEA Southern Africa Collaboration analysed pooled data from children in 7 South African treatment programmes using an outcome of two consecutive unsuppressed viral loads with the second being > 1000 copies/ml, after 24 weeks of therapy. The objective of the study was to evaluate the probability of virological failure in children less than 16 years of age who initiated treatment between June 1999 and February 2008. Results showed that the 3 year probability for failure was 19.3% (95% CI 17.6%-21.1%) [38].

The Peadiatric AIDS Clinical Trials Group 381 (PACTG) was an observational cohort study of 120 adolescents (11-22 years old) on ART between March 1999 and October 2001 at 28 sites in the United States of America (USA). It reported that 59% of the cohort had achieved virological suppression (< 400 copies/ml) at week 16-24 of ART [37].

1.4.4 Factors associated with virological failure

Factors associated with virological failure in adolescents have been investigated in a few studies including data from PACTG that was analysed at 24 weeks [39] and then at 60 weeks [37]. At 24 weeks, logistic regression was used to analyse the predictors of virological failure and neither immunologic nor demographic characteristics were found to be predictors, only adherence to ART influenced virological outcomes ($p<0.001$) [39]. At week 60, analysis was done using Cox proportional hazards models and only immunological factors (T cell markers) and adherence were shown to be associated failure [37].

The Reaching for Excellence in Adolescent Care and Health (REACH) project was an observational study in the USA that analysed predictors of sub-optimal virological response in 154 adolescents (12-19 years old) initiating ART between 1996 and 2000 at 16 academic medical centres [40]. After at least 12 months on treatment, predictors of sub-optimal virologic response were adequate ART adherence (odds ratio (OR) 0.40 (95% CI 0.2-1.0)) and a history of prior ART use (i.e. prior use of single or dual ARV drugs before using a triple combination) (OR 2.90 (95% CI 1.10-5.70)) [40].

These studies on adolescents had small sample sizes and therefore might have low statistical power. This may explain the lack of significant predictors compared with studies in adults and children. Table 1 below summarises some of the factors associated with virological failure found in studies conducted in adults and children.

Some studies have shown an association between the age of ART initiation and virological failure [41-44]. An adult cohort study in Europe with 52 clinical centres reported that the risk of failure reduced 14% with each one year increase of age (p=0.04) [42]. Children (0-18 years of age) who initiated ART in Uganda and were followed up from April 2004 to June 2005 showed that males had more than twice the odds of virological failure compared to females (95% CI 1.20-4.93) [41]. Adherence on treatment may increase with age [22] resulting in better virological outcomes.

Table 1: Factors associated with virological failure in adults and children in the literature

Factors	Association with virological failure	Reference and country of study population
Baseline age	Children ≤ 18 years have increased risk for failure compared to those aged more than 18 years	Kamya et al., 2007 (Uganda) [41] Paredes et al., 2000 (Europe) [42] Parienti et al., 2004 (France) [43] Tuboi et al., 2005 (Brazil) [44]
Gender	Males had higher odds for failure compared to females	Kamya et al., 2007 (Uganda) [41]
Baseline CD4 count	Baseline CD4 counts less than 50 cells/µl have increased risk for failure compared to those greater than 150 cells/µl	Datay et al., 2010 (South Africa) [45] Kamya et al., 2007 (Uganda) [41] Paredes et al., 2000 (Europe) [42] Tuboi et al., 2005 (Brazil) [44]
Baseline viral load	One log increase of viral load increased the risk for failure	Paredes et al., 2000 (Europe) [42] Tuboi et al., 2005 (Brazil) [44] Davies et al.,2011 (South Africa) [38]
Orphans at baseline	Those with no parents had higher risks of failure compared to those with at least one parent	Janseens et al.,2007 (Cambodia) [46]
Baseline treatment regimen	Both Nevirapine and Ritonavir (as a single drug) based regimes had increased risk for failure compared to Efavirenz based regimes	Davies et al.,2011 (South Africa) [38] Datay et al., 2010 (South Africa) [45] Kamya et al., (Uganda) [41]
Exposure to prevention of mother to child transmission regimens	Those exposed to at least one drug at PMTCT increased risk for failure than those who were not exposed	Davies et al.,2011(South Africa) [38]
Baseline Haemoglobin Baseline MCV	No significant association with failure	Kamya et al., 2007 (Uganda) [41]
Baseline Weight	No significant association with failure	Davies et al.,2011 (South Africa) [38]
Baseline WHO stage	No significant association with failure	Davies et al.,2011 (South Africa) [38]

Baseline CD4 counts have been investigated as factors associated with treatment failure and some studies have shown that lower baseline CD4 counts have increased risk for failure [41, 42, 44, 45]. A case-control study in the Western Cape of South Africa reported that an individual with a baseline CD4 count less than 50 cells/µl was six times more likely to have virological failure compared to those with a baseline CD4 count of more than 150 cells/µl (95% CI 2.3-18.8) [45]. Though there have been debates whether the baseline CD4 count can

be predictive of disease progression, those who initiate with lower CD4 counts are more immunocompromised and might have more opportunistic infections and are sicker hence adherence to ART may be less.

The EuroSIDA study in Europe reported that having a higher baseline viral load was marginally significant in predicting virological failure. With every log increase in baseline viral load the risk of failing increased by 18% (95% CI 0.99-1.40) [42]. Higher levels of baseline viral loads have been shown to be predictive of disease progression [47] and may result in poorer treatment outcomes. Other baseline laboratory tests such as Haemoglobin and Mean Corpuscular Volume (MCV) have not been shown to have a significant association with failure [41].

The associations between drug regimens at initiation of treatment and virological failure have been explored. Initiating treatment with a Nevirapine (NVP) based versus an Efavirenz (EFV) based treatment regime was shown to be associated with virological failure (OR 2.46 (95% CI 1.23-4.90)) in Uganda [41]. In the IeDEA study, NVP based and Ritonivar (RTV) (alone) based regimens had significant increased risks for failure compared to EFV based regimens (HR 1.77 (95% CI 1.11-2.83), HR 2.39 (95% CI 1.57- 3.64) respectively) [38]. This analysis also reported that the children exposed to Prevention of Mother to Child Transmission (PMTCT) drug regimens had a 40% increased risk for failure as compared to those who were not exposed (95% CI 1.02 to 1.92) [38]. Regimens that were used for the PMTCT include single dose NVP alone or in combination with Zidovudine (AZT) from 34 weeks gestation [38]. NVP has been used widely as a single dose in PMTCT and NVP resistance may result in the poor virological responses in those who initiate on an ART combination that includes this drug.

A “drug holiday” of greater than 48 hours as a measure of adherence to treatment was evaluated in 71 HIV infected adults greater than 18 years in a cohort study in France (1996-1997); virological failure was associated with repeated drug holidays (HR 3.3 (95% CI 1.3–8.3)). The study also concluded that depression was an important predictor of failure (HR 2.5 (95% CI 1.0–6.4)) [43]. Poor adherence results in suboptimal viral suppression resulting in poor virological outcomes [22].

In a study at a resource limited setting in Cambodia including 212 children less than 13 years, being an orphan had 3.8 times more risk of virological failure (95% CI 1.80–8.00) compared to those with at least one parent [46]. Orphaned children may have poor adherence support leading to a higher risk of treatment failure.

Factors which have not been found to be associated with virological failure include weight at initiation, WHO stage at initiation (1/2 vs. 3/4) and year of initiation (before 2005 as compared to after 2005) [38].

Predictors of virological failure can be modelled to develop a simple prognostic tool which uses scores to identify patients at increased risk of virologic failure. A model was derived from data obtained at Massachusetts General Hospital USA from patients who were virologically suppressed (viral load ≤ 400 copies/ml) on ART during the period 1 January 2005 to 31 December 2006. Multivariable logistic regression was used to derive a one year failure predictive rule. A risk score based on seven predictors was used; suboptimal adherence, CD4 cell count < 100 cells/µl, drug and/or alcohol abuse, highly ART experienced, missed ≥ 1 appointment, prior virologic failure and virologically suppressed for ≤ 12 months. The model was validated at Brigham and Women's Hospital and showed good discrimination (C statistic, 0.79) and calibration (chi (2) = 1.9, p= 0.93). It was concluded that the model could be used as an intervention to improve outcomes in ART management [48].

1.4.5 Conclusion

Treatment failure on ART is best determined by using virological criteria. The rates of virological failure in adolescents differ in ART programmes. Factors that are associated with virological failure in adolescents in the USA were adherence, a history of prior ART use and T cell markers. The baseline factors that are associated with virological failure in children and adults include age, gender, CD4 count, viral load, initial treatment combination, poor treatment adherence and being an orphan. Factors associated with virological failure can be used to develop prognostic tools to identify adolescents at high risk of treatment failure.

This study seeks to investigate the factors associated with virological failure in adolescents in a nurse and counsellor-led rural ART programme in KwaZulu-Natal.

1.5 Objectives

1.5.1 Main Objective

To describe and investigate the characteristics associated with virological failure(using an unsuppressed viral load as proxy) in adolescents (individuals aged 10-19 years inclusive) who initiated ART between June 2004 and December 2010 in the Hlabisa HIV Treatment and Care Programme, KwaZulu-Natal, South Africa.

1.5.2 Specific Objectives

1. To describe the clinical and socio-demographic characteristics of those who initiated ART as adolescents.
2. To determine the prevalence of virological failure (using an unsuppressed viral load as proxy) after 6 months on ART in those who initiated treatment as adolescents.

3. To investigate the clinical and socio-demographic characteristics that are associated with virological failure (using an unsuppressed viral load as proxy) after 6 months on ART in those who initiated treatment as adolescents.

CHAPTER 2: MATERIALS AND METHODS

This chapter gives a description of the materials and methodology used in conducting the study. It starts with an outline of the study design followed by a description of the study setting, population and selection criteria for the participating individuals. The data sources together with the datasets used to investigate the factors associated with virological failure are presented. This is followed by a description of the data management for the study which includes data measurement, definitions of the study variables and methods used to process and analyse the data. The chapter closes with a presentation of the ethical considerations for the study.

2.1 Study Design

The study is an analysis of data that were collected from a cohort of adolescents on ART at the AC as part of their routine surveillance and clinical care in the Hlabisa sub-district of KwaZulu-Natal.

2.2 Study Setting

2.2.1 Study Site

The AC, established in 1997 and funded by the Wellcome Trust, is a population-based research centre at the University of KwaZulu-Natal. It conducts policy relevant health and population research in partnership with the local community and the local departments of health and education. It collects data twice a year from 85 000 individuals in the DSA which is 438 square kilometres [49] within the Hlabisa sub-district.

The Hlabisa HIV Treatment and Care Programme is a decentralised programme which operates from 17 nurse-led primary health-care (PHC) clinics in the rural Hlabisa sub-district. Six of these PHC clinics and 40% of the programme individuals fall within the DSA. By

February 2012, 20 442 individuals had been initiated on ART in the programme, 66% (13492) of whom were females.

The programme follows South African guidelines for the management of those infected by HIV. Until August 2011 eligibility for ART in adolescents were a CD4 count ≤ 200 cells/µl irrespective of clinical stage and a CD4 count ≤ 350 cells/µl in pregnant women and those with TB [15]. Those with WHO stage IV and those with multiple drug resistant/ extremely drug resistant (MDR/XDR) TB irrespective of their CD4 cell count were also eligible for ART [15]. The South African guidelines were revised in August 2011 in line with the WHO guidelines for eligibility [50]. The first line regimen for ART in adolescents in those > 15 years old is Tenofovir (TDF) + (Lamivudine (3TC) or Emtricitabine (FTC)) + (EFV or NVP) [15] and those ≤ 15 years old use Abacavir (ABC) instead of TDF due to renal and bone side effects. Protease inhibitors are reserved for second line regimens. Individuals on ART are monitored monthly with viral loads and CD4 counts being done at 6 and 12 months after ART initiation and then yearly thereafter unless clinically indicated. The programme initiated psychological services for HIV care and support in 2008 for people living with HIV (PLWHIV) and their carers [51]. This included support for the formation of support groups and developing the skills of healthcare givers through ART clinical and counselling training [51].

The study site was chosen as it has databases that contain both the clinical and socio-demographic characteristics of adolescents who initiated ART.

2.2.2 Data Sources at the study site

Data for the study were extracted from two databases. The first database, the Antiretroviral Treatment Evaluation and Monitoring Information System (ARTemis), was established in 2007 and includes clinical information on all HIV infected individuals managed in the

Hlabisa treatment and care programme from 2004. It captures both clinical and laboratory data at initiation, monthly follow up attendance and laboratory monitoring results (CD4 and viral loads) of participants. This database was used to obtain clinical data for all the adolescents (543) who initiated ART in the treatment programme.

The second database, the Africa Centre Demographic Information System (ACDIS), contains twice yearly surveillance data collected from the DSA since the year 2000. Data are collected based on interviews with key-household informants and annual household socio-economic surveys. This database was used to obtain the baseline socio-demographic data for the adolescents (153) residing within the DSA at ART initiation.

Though age and gender are viewed as demographic characteristics, they are described in this study under clinical characteristics because they were obtained from the ARTemis database for clinical characteristics.

2.3 Study Population

The study population included all individuals who initiated ART as adolescents at the Hlabisa Treatment and Care Programme in KwaZulu-Natal from 1 June 2004 to 31 December 2010. During this period, 543 individuals initiated ART as adolescents.

2.4 Study Sample

The programme started providing ART in June 2004 and 31 December 2010 was selected as the end date for inclusion in the analysis to allow at least 6 months of follow-up of individuals after ART initiation. This also allowed time for a viral load test to be done after at least 6 months of ART as the database closure was 31 October 2011.

2.4.1 Clinical characteristics dataset

To investigate the clinical characteristics, the following criteria were used:

Exclusion Criteria:

- Those with less than 6 months follow up from the date of ART initiation
- Those who did not have at least one viral load test result after 6 months of ART

Out of the 543 adolescents who initiated treatment in the programme; 23 (4.2%) died, 54 (9.9%) were lost to follow up and 7 (1.3%) transferred out of the programme before achieving 6 months follow up after ART initiation. Of the 459 who were still in the programme after 6 months from the date of initiation, 95 (20.7%) had no viral load test result. This resulted in a sample of 364 adolescents who had a viral load result after 6 months of treatment.

2.4.2 Socio-demographic characteristics dataset

To investigate the socio-demographic characteristics, the following criteria were used:

Exclusion criteria

- Those who did not reside in the DSA at the time of ART initiation
- Those with less than 6 months of follow up from the date of ART initiation
- Those who did not have at least one viral load test result after 6 months of treatment

Of the 543 who initiated treatment, 390 (71.8%) did not reside in the DSA at ART initiation. Only 101 (66%) of the 153 residing in the DSA at initiation had at least 6 months follow up and had a viral load result.

2.5 Data Management

2.5.1 Measurement

A multiple clerk and single entry system were used in both databases. For the ACDIS database, data were entered by clerks after questionnaires were barcode verified during the surveillance. Data entry for each individual was done twice yearly according to the surveillance schedule.

Data for the ARTemis were collected as part of the routine monitoring of individuals who attend the Hlabisa Treatment and Care programme by health care workers. Data were entered by clerks into the database after the initiation visit. Thereafter laboratory results for monitoring were imported into the ARTemis directly from the relevant reference laboratories databases. Monthly clinic attendance as recorded by the healthcare givers was also entered into the database. Missing information including laboratory results were followed up at the 17 clinics by the student and data missing from the database that were available in the clinic files were recorded on paper forms and subsequently entered into the database.

The data was extracted by the senior database scientist from both databases using SQL Server 2005. The datasets included the linked ACDIS and ARTemis data for those who resided in the DSA at initiation.

2.5.2 Study Variables

2.5.2a Outcome Variable

The outcome was analysed as a dichotomous variable. It was defined as suppressed if the viral load was ≤ 70 copies/ml or unsuppressed if the viral load was >70 copies/ml.

2.5.2b Exposure Variables

Clinical Variables

- Age was defined and calculated as the time between the date of birth and date of ART initiation. To allow for comparisons of the characteristics of adolescents at the different levels of development, age was also analysed as a categorical variable. It was categorized as early (<15 years old) and late (≥15 years old) adolescent stages.
- Gender was defined as the sex of the adolescent either male or female.
- Age and gender are described as clinical variables as they were obtained from the ARTemis database for clinical characteristics
- Clinical WHO stage was dichotomised, Stage 1 and 2 were combined as were stage 3 and 4. It was the clinical stage recorded closest to the date of ART initiation.
- Sex adjusted weight-for-age z-score (WAZ) were used to analyse weight at initiation as the weight varies with age, gender and stages of development. The use of body mass indices was precluded by the large number of missing data in the height variable. WAZ scores were calculated from the baseline weight and age observations using Microsoft Access 2007, the 1978 CDC/WHO growth reference curves and Epi Info Nutrition version 3.5.1 software. WAZ charts have an age range of 0 to 18 years therefore computation for those who were more than 18 years old at initiation was done using the age reference point of 18 years.

  It was categorised by whether the adolescent was malnourished (WAZ score ≤ 2) or not (WAZ score >2) [52]
- The clinics of initiation were categorised by whether they were in the DSA or not.
- Exposure to Tuberculosis (TB) was analysed as two variables and these were both dichotomised (Yes/No). The first variable was whether the adolescent had TB before

ART initiation and the second was whether the adolescent was on TB treatment at initiation of ART.

- Year of initiation variable was analysed as a categorical variable with the initial years of ART roll-out 2004-2006 combined as there were low number of adolescents initiated during this early period of the ART roll-out.
- Baseline CD4 cell counts were taken before initiation and were analysed as both a continuous and categorical variable. Categories were ≤100 cells/µl, 101-200 cells/µl and >200 cells/µl. The CD4 cell counts recorded closest to the ART initiation date were used as the baseline counts.
- All other baseline laboratory test results (Haemoglobin, Creatinine, Albumin, Alanine transaminase and Platelets) were dichotomised depending on the normal ranges of the test. All tests were done before initiation and the test results closest to the ART initiation date were used as the baseline results.
- Drug regimens at initiation were categorised according to the drug included in the first line regime (EFV, NVP or Lopinavir (LPVr)).
- Time to viral load test was used to adjust for the different times at which the individuals had their first viral load tests done after 6 months of treatment. The different times for viral load testing were mostly due to health care provider reasons. The variable was categorised as 6-12 months, 13-18 months, 19-24 months, 25-30 months and > 30 months.

Socio-demographic variables

- Education level was defined as the school grade the adolescent was in at initiation of treatment. This was categorised as primary or secondary/tertiary.
- School attendance was dichotomised according to whether the adolescent was currently attending school or not at ART initiation.

- "Mother and father dead at initiation" were analysed as categorical variables according to whether the mother/father was alive, dead or it was unknown at initiation.
- Distance from nearest clinic was analysed as a continuous variable in kilometres. It was calculated to be the distance from the homestead at ART initiation to the nearest clinic.

2.5.3 Data Quality Control

To identify inconsistencies in the data, consistency checks were done e.g. whether dates of births were less than date of ART initiation. Range checks using histograms and box plots for continuous variables were done to check for outliers. Duplicate checks were performed and if found these were removed.

2.5.4 Data Processing Methods and Analysis

STATA version 11 (STATA Corporation, College Station, TX) software package was used for all statistical analysis. A significance level of 5% was used except for the univariable analysis where a significance level of 20% to ascertain inclusion into the multivariable model was used.

To achieve the first objective of the study, frequencies were used to describe the categorical variables such as gender and TB at initiation. Continuous variables were tested for the assumption of normality using histograms, normal quantile plots and standardised normal probability plots (Appendix 1). Medians and interquartile ranges were used to summarize all the continuous variables as none of them were normally distributed. Graphs were also used to describe the study population. Kaplan Meier estimates for time from ART initiation to death and lost to follow up (LFTU) were used to describe the attrition rates of the group.

The prevalence of an unsuppressed viral load (>70 copies/ml) was calculated as a proportion of those with a viral load result after at least 6 months on treatment.

To investigate the association between an unsuppressed viral load and the categorical clinical and socio-demographic characteristics, Chi-square test of proportions were used. For testing the association between the continuous variables and an unsuppressed viral load, the Wilcoxon rank-sum test was used.

The multivariable method of analysis used to investigate the characteristics associated with an unsuppressed viral load was logistic regression because the outcome was dichotomous. Due to low numbers in the socio-demographic characteristics and the large proportions of missing data, they were only analysed using Chi-square test of proportions and Wilcoxon rank-sum test. To analyse the clinical characteristics, univariable logistic regression models were used to ascertain if the factors were statistically significant. These were added to the multivariable model starting with the one with the smallest p-value. The Mantel-Haenzsel test and interaction terms between variables were used to explore and to investigate effect modification. During the multivariable model building, a likelihood ratio test was used to assess improvement of the model after each addition of a new variable. The final multivariable model obtained was assessed using the Pearson chi-square goodness-of-fit test.

Missing data were followed up at the clinics in the treatment programme by the student and those found were added to the analysis (Appendix 2). Analyses using Chi-square and Wilcoxon rank-sum tests were done to investigate characteristics associated with the individuals who were on ART for at least 6 months and did not have a viral load result compared to those on ART for at least 6 months and had viral load results (Appendix 3). Missing data in the exposure variables were included as a category in the logistic regression analysis to find their trends and associations with an unsuppressed viral load.

2.6 Ethical Considerations

This study was performed anonymously using ARTemis and ACDIS identification numbers. Any potential individual identifiers were removed from the dataset by the senior database scientist. Storage of the datasets was in a password restricted laptop. Guardian consent and assent from individuals less than 18 years of age and individual consent from those above 18 years of age was obtained for the use of their information in both the treatment programme and the surveillance. Data use agreements were obtained by the student from AC (Appendix 6). Ethical approval to conduct the study was obtained from the University of Witwatersrand Ethics Committee on Human Research on 28/10/2011, clearance certificate number M111131 (Appendix 4). A change of title for the research from "Predictors of virological failure in adolescents at a rural HIV programme in Kwazulu-Natal" to "Factors associated with virological failure in adolescents in a rural HIV programme in Kwazulu-Natal" was granted by the Faculty of Health (Appendix 7). The study was also conducted adhering to the ethics requirements of the University of KwaZulu-Natal. The AC had permission from the Biomedical Ethics Committee of the University of KwaZulu-Natal for linkage of data from ARTemis to the data from ACDIS, current ethics number for the linkage is E134/06 (renewable annually). All results were given to the Africa Centre for Health and Population Studies as per the Africa Centre policy to be used in the improvement of the management of HIV positive adolescents especially in KwaZulu-Natal.

CHAPTER 3: RESULTS

This chapter presents the results of the study with the main aim of achieving the objectives of the research. A description of the baseline cohort clinical characteristics of the study sample opens the chapter followed by a description of the socio-demographic characteristics of those who initiated ART whilst residing in the DSA. The prevalence for the period 2004 to 2011 of an unsuppressed viral load after 6 months on ART is reported. The associations between an unsuppressed viral load and baseline clinical and socio-demographic characteristics are explored. The chapter closes with an identification and report of the characteristics that were associated with an unsuppressed viral load after the adjusted multivariable analysis.

3.1 Cohort characteristics

A total of 543 individuals were initiated on ART as adolescents at the Hlabisa Treatment and Care programme between June 2004 and December 2010 and these were followed up to 31 October 2011. Figure 1 shows the flow chart of adolescents who were included in the final analysis for investigating clinical characteristics that were associated with an unsuppressed viral load. Figure 2 shows the flow chart of adolescents who were included in the final analysis for investigating the association between household socio-demographic characteristics and an unsuppressed viral load. 28.2% (153) of the adolescents initiated treatment whilst residing in the DSA.

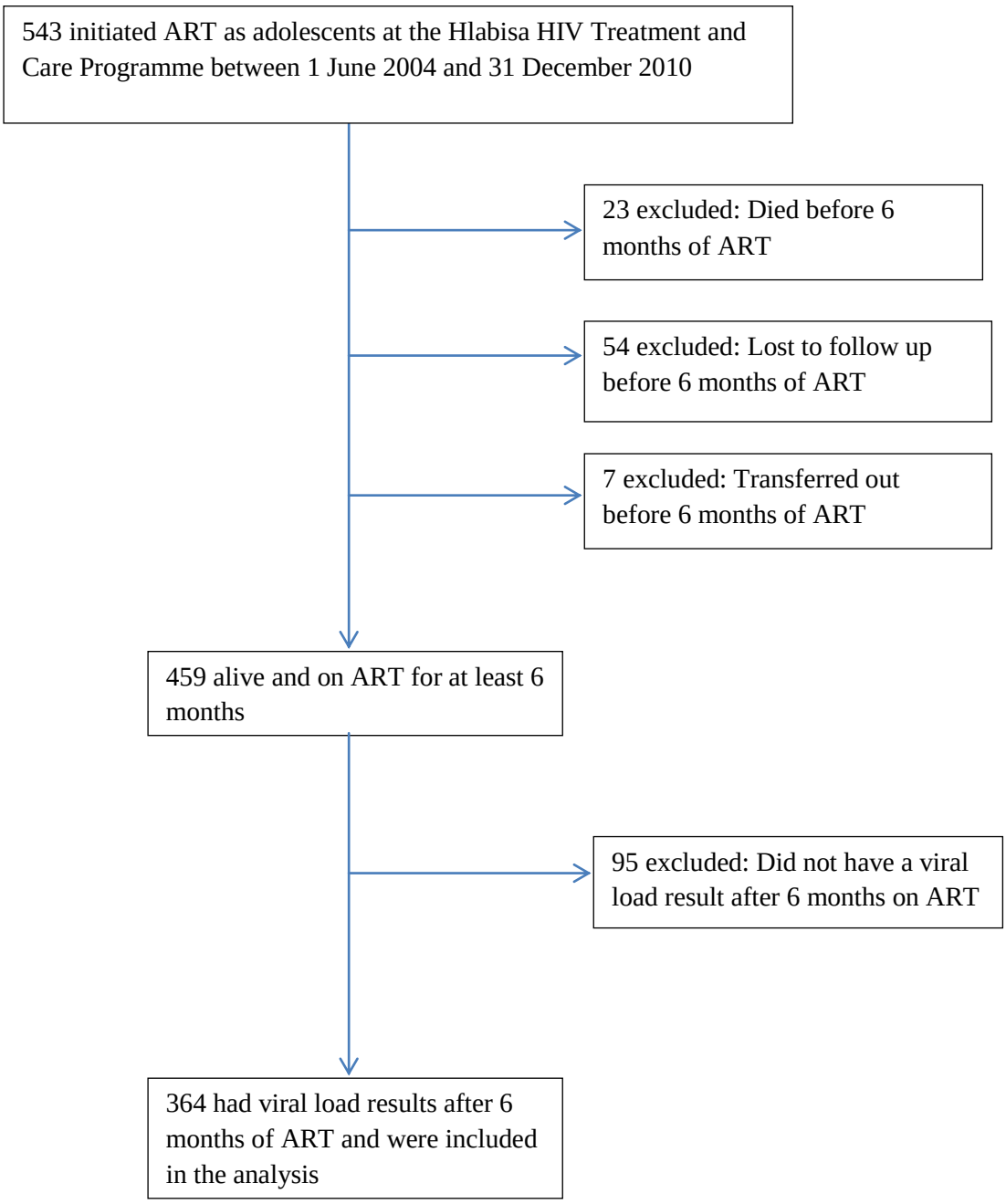

Figure 1: Flow chart of adolescents included in the study to investigate the clinical factors that were associated with an unsuppressed viral load

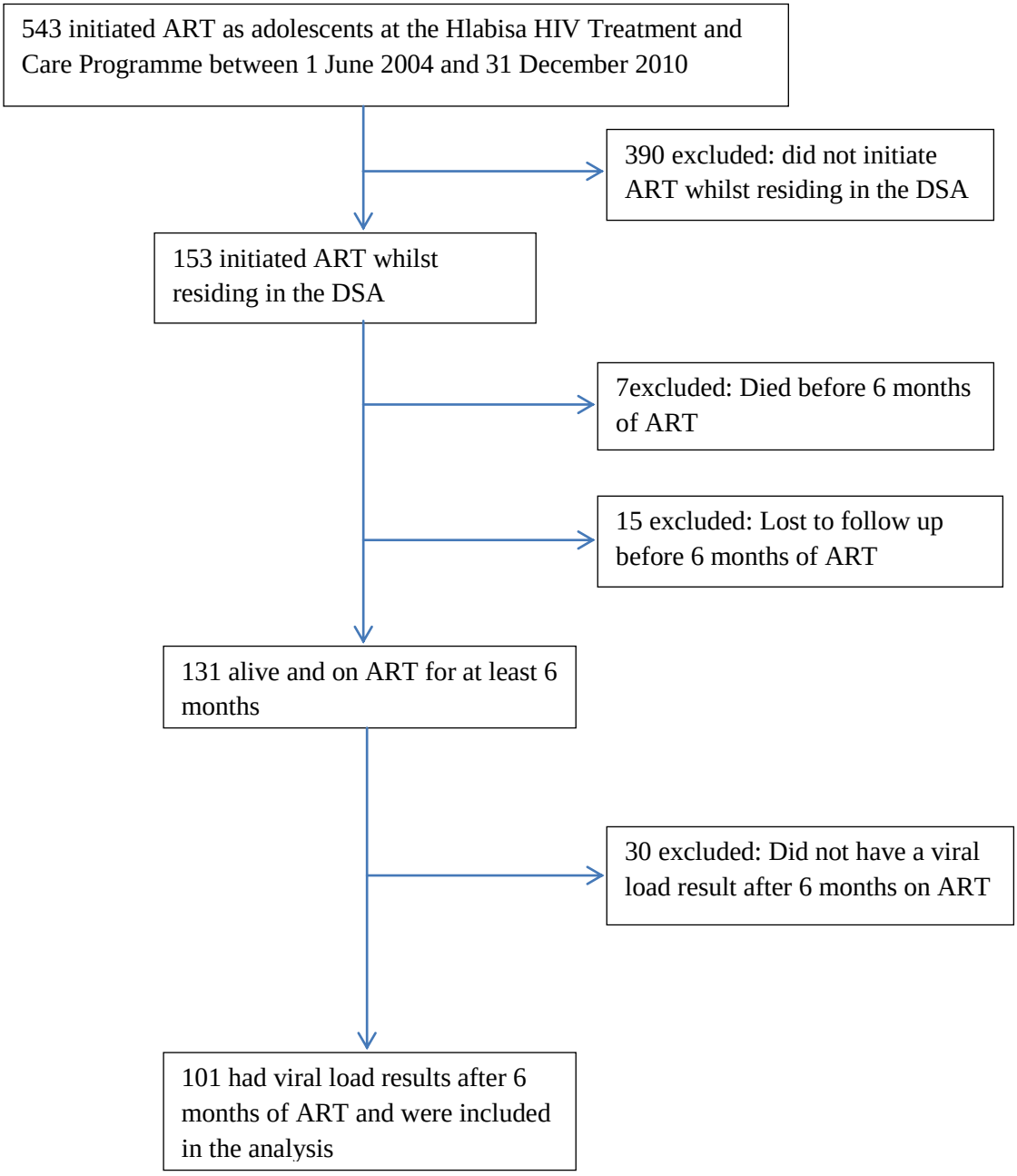

Figure 2: Flow chart of adolescents included in the study to investigate the socio-demographic factors associated with an unsuppressed viral load

3.1.1 Baseline Clinical Characteristics

Figure 3 shows the yearly number of adolescents initiating ART at the Hlabisa Treatment and Care Programme. There was a steady increase in the number of adolescents who initiated ART over the period 2004-2009 with a total of 53 in 2004-2006 and 129 in 2009. From 2009 to 2010 there was a steep increase in ART initiation.

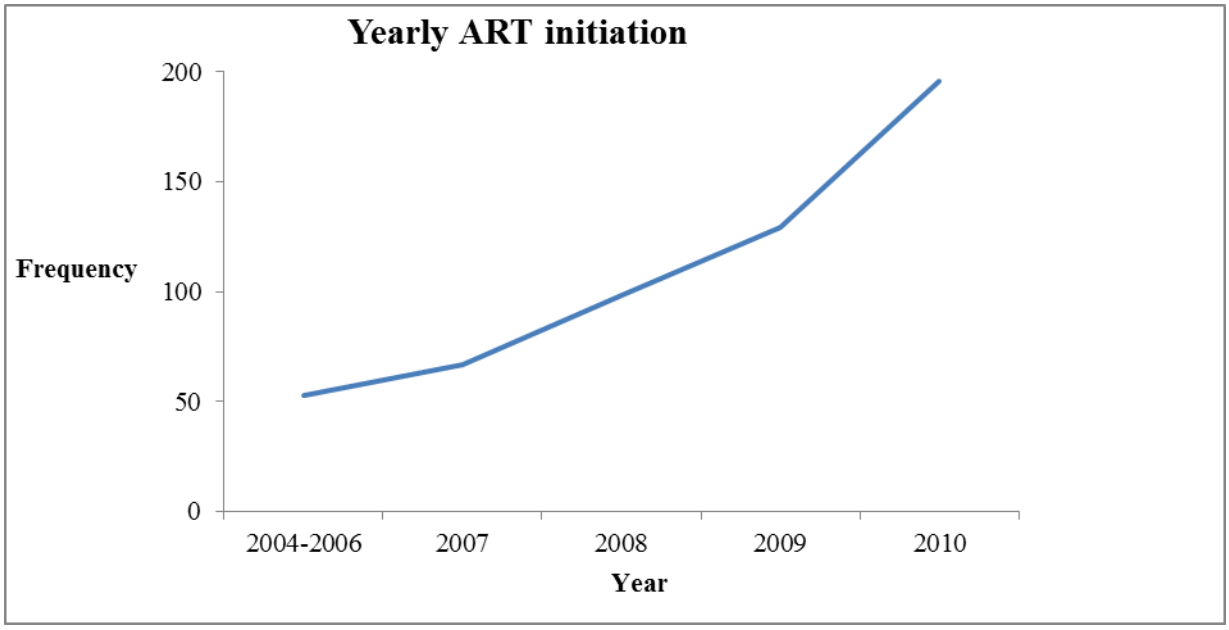

Figure 3: Frequency of ART initiation by year

Table 2 below summarises the baseline cohort clinical characteristics of the study population and this includes the proportion of missing data for each variable. The median age for ART initiation was 15 years (IQR 12-18) and 271 (49.9%) initiated whilst they were in early adolescence (aged 10-14 years). The adolescents in this study had a bimodal distribution of age at initiation with a peak between 10-12 years and a steep increase after 17 years (Figure 4). More females (368, 67.8%) than males initiated on ART in this cohort. Of the females 16-19 years old (222), 61 (27.5%) initiated ART whilst pregnant. Out of the 543 who initiated ART, 129 (23.8%) were malnourished with a WAZ score of -2 or less at initiation. The majority of the adolescents initiated treatment at a relatively advanced disease stage (WHO stage 3/4) though 147 (27.1%) of them had missing data. The median CD4 cell count at

initiation was 152cells/µl (IQR 79-251) and 163 (30%) initiated with a CD4 cell count of ≤ 100. Most of the adolescents (408) initiated ART on EFV containing regimes. At initiation, 103 (19%) were on TB treatment and 151 (27.8%) had been diagnosed with TB before treatment initiation. The majority of those who initiated had normal blood laboratory results of Heamoglobin, Platelets, ALT, Creatinine and Albumin.

Table 2: Baseline clinical characteristics of adolescents initiating on ART

Characteristic (n=543)	n	%
Age (years)		
Median (IQR)	15 (12-18)	
10-14 (early adolescence)	271	49.9
15-19 (late adolescence)	272	50.1
Gender		
Female	368	67.8
Male	175	32.2
WHO Stage		
1/2	130	23.9
3/4	266	49.0
Data missing	147	27.1
WAZ score		
Median (IQR)	-1.2 (-2.0 to -0.1)	
>-2	368	67.8
≤-2	129	23.8
Data missing	46	8.4
Initiation Clinic		
Clinics in the DSA	213	39.2
Clinics not in the DSA	316	58.2
Data missing	14	2.6
Prior TB		
No	392	72.2
Yes	151	27.8
On TB treatment		
No	409	75.3
Yes	103	19.0
Data missing	31	5.7

CD4 cell count		
Median (IQR)	152 (79-251)	
≤100 cells/µl	163	30.0
101-200 cells/µl	187	34.4
>200 cells/µl	178	32.8
Data missing	15	2.8
Haemoglobin		
>7g/dl	419	77.2
≤7g/dl	43	7.9
Data missing	81	14.9
Creatinine		
≤120 µmol/L	454	83.6
>120 µmol/L	5	0.9
Data missing	84	15.5
ALT		
≤60 IU/L	438	80.6
>60 IU/L	21	3.9
Data missing	84	15.5
Platelets		
>150 000 per µl	415	76.4
≤150 000 per µl	33	6.1
Data missing	95	17.5
Albumin		
>25 g/L	337	62.1
≤25 g/L	108	19.9
Data missing	98	18.0
Drug regime		
EFV containing	408	75.1
NVP containing	132	24.3
LPVr containing	3	0.6

Figure 4 shows the distribution by age and gender of the adolescents initiating ART. The distribution of ART initiation by gender was equal in early adolescence but in late adolescence the majority were females (236, 86.8%). There was a sharp increase in the number of females who initiated ART after 15 years of age whereas there was a decrease in males initiating ART after this age.

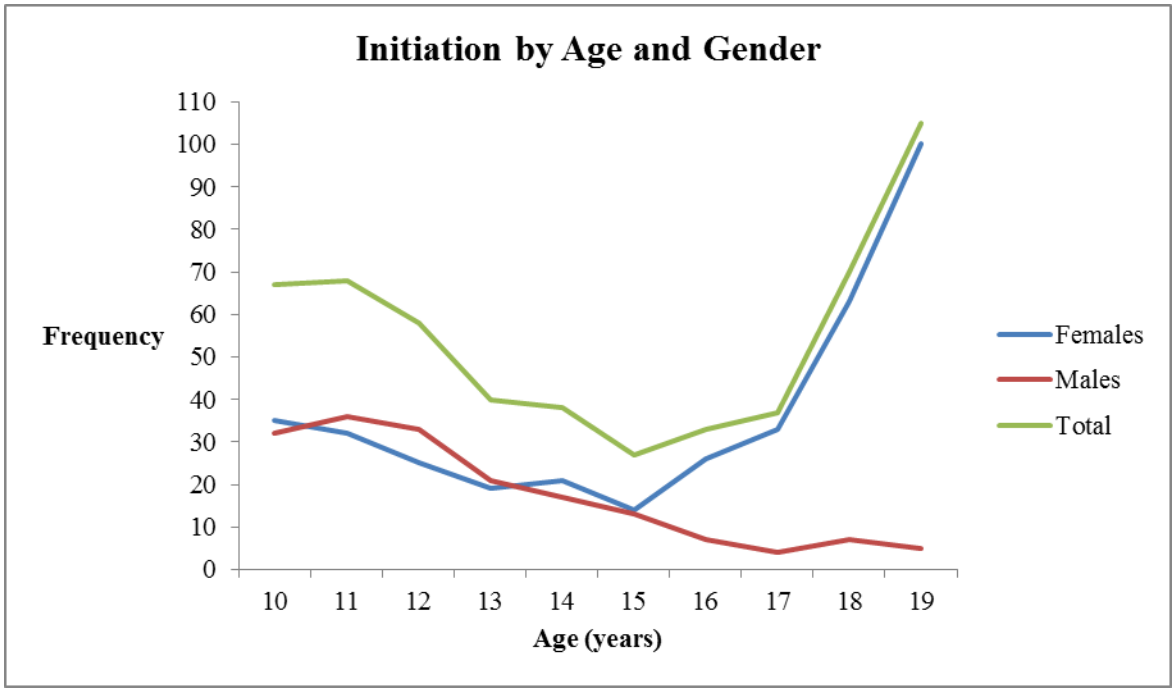

Figure 4: Frequency of ART initiation by Age and Gender

Figure 5 below shows the median WAZ score at initiation by gender and age. According to the WHO, WAZ scores of ≤ -2 are indicative of malnourishment [52]. The lower the WAZ score the more malnourished the individual. The overall median WAZ scores at initiation were generally >-2 reaching > 0 for those 19 years old. After the age of 14, the females had better nutritional status (WAZ scores >-2) compared to the males (WAZ scores ≤-2). This shows that those who initiated ART in late adolescence had better nutritional status than those in early adolescence ($p<0.001$). The females had better nutritional status than males at ART initiation ($p<0.001$).

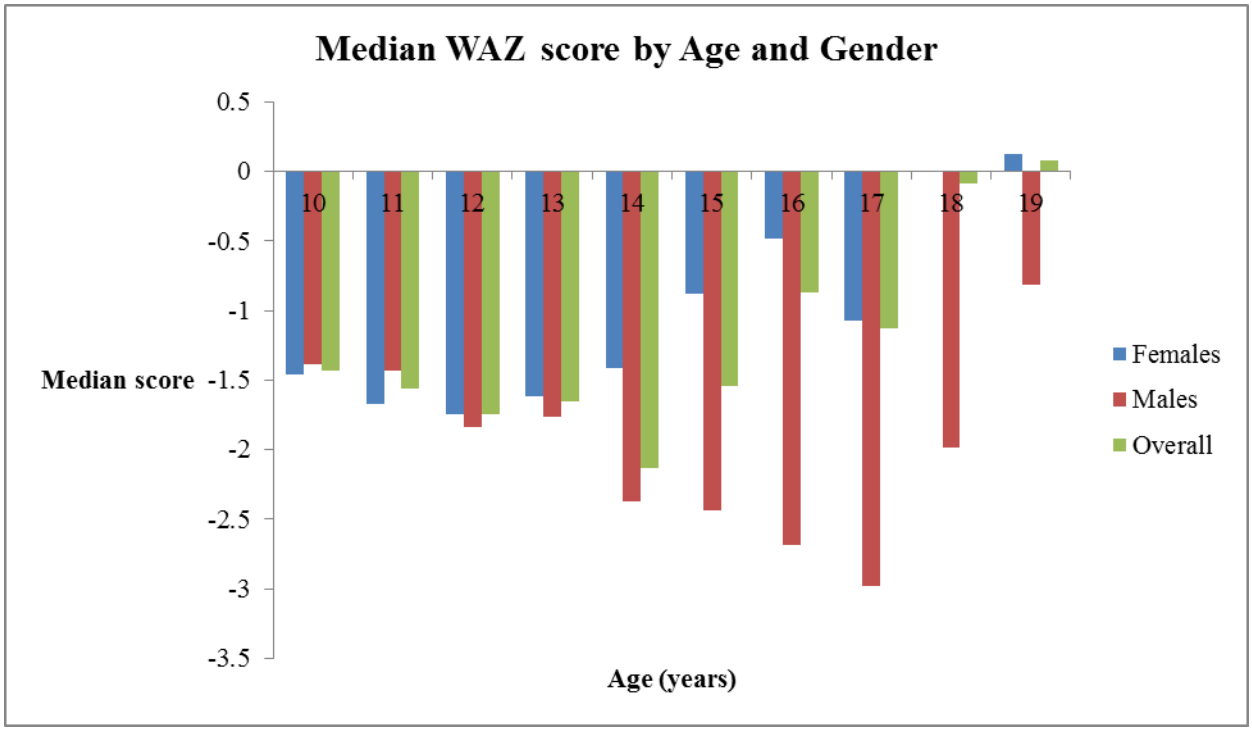

Figure 5: Median WAZ score at initiation by Age and Gender

3.1.2 Baseline socio-demographic characteristics

Those who initiated ART whilst residing in the DSA constituted 28.2% (153) of the cohort. Table 3 below summarises the socio-demographic characteristics of adolescents who initiated ART whilst residing in the DSA. Of the 153 who initiated whilst residing in the DSA, 61 (39.9%) had primary education as the highest education level at initiation though 50 (32.6%) had missing data. A total of 70 (45.8%) were attending school at initiation. Mothers were alive at initiation for 78 (51%) of the adolescents. It was not known whether the mother and father were dead or alive for 48 (31.3%) and 106 (69.2%) respectively of those who initiated whilst residing in the DSA. The median distance between the homestead at initiation and the nearest clinic was 2.2km (IQR 1.28-3.46).

Table 3: Socio-demographic characteristics of adolescents initiating on ART

Characteristic (n=153)	n	%
Highest Education level		
Primary	61	39.9
Secondary/Tertiary	42	27.5
Data missing	50	32.6
Attending school		
No	34	22.2
Yes	70	45.8
Data missing	49	32.0
Mother dead		
No	78	51.0
Yes	27	17.7
Unknown	48	31.3
Father dead		
No	29	19.0
Yes	18	11.8
Unknown	106	69.2
Distance from Clinic (km)		
Median (IQR)	2.20 (1.28-3.46)	
Data missing	37	24.2

3.1.3 Cohort Clinical Outcomes

The overall attrition rate for the study period was 38.3% (95% CI 34.2-42.4). After 6 months of follow up, the attrition rate was 15.5% (95% CI 12.3-19.2); 23 (4.2%) had died, 54 (9.9%) were LTFU and 7 (1.3%) had transferred out to other programmes.

The adolescents contributed a total of 1234.39 person years, with a median follow up time of 2 years (IQR 1.2-3.2). The median CD4 cell count increase from ART initiation to the first CD4 cell count test after 6 months was 211 cells/µl (IQR 71-359). LTFU was defined as the adolescent having no contact with the ART programme for more than 6 months before 31 October 2011 and was not known to have died or transferred out [33]. The overall incidence of LTFU was 98.8 per 1000 person years (95% CI 82.8-118). The unadjusted LTFU rates

were significantly different between females (122.0 per 1000 person years (95% CI 99.7-149.4)) and males (60.3 per 1000 person years (95% CI 41.7- 87.4)). The unadjusted LTFU rates were also significantly different between those initiating in early and late adolescence, 37.2 per 1000 person years (95% CI 25.7- 53.8) and 195.4 per 1000 person years (95% CI 159.6- 239.2) respectively. After adjusting for the adolescent developmental stage and gender, LTFU was highest in the females who initiated in late adolescence ($p<0.001$) (Appendix 5). Of those who initiated whilst pregnant (61), 39.3% (24) were LTFU. Those initiating in late adolescence contributed 83.5% of the LTFU before 6 months of ART.

The overall mortality rate was 36.5 per 1000 person years (95% CI 27.2 - 48.8). Mortality was not significantly different by gender and age category (Appendix 5). Assuming that 50% of those LTFU died, the mortality would be 85.9 per 1000 person years (95% CI 71.0-103.9). Of the 43 known to have died during the study period, 22 (51%) did so during the first 6 months of ART. Of the adolescents who died before 6 months, 12 (52.2%) initiated whilst severely immunocompromised (CD4 cell count $\leq$ 100 cells/µl).

3.2 Prevalence of an unsuppressed viral load

Of the 543 adolescents in the cohort, 459 were at least 6 months on ART and 364 (79.3%) of these had a viral load test result. The median time for the first viral load to be taken after initiation was 11.25 months (IQR 7.78-16.20). At the end of the study period, out of the 95 without a viral load; 43 (45.2%) were alive, 28 (29.5%) were LTFU, 9 (9.5%) died and 15 (15.8%) transferred out of the programme. There were significant differences by gender, adolescent developmental stage at initiation, drug regime at initiation and ART initiation by year between adolescents with no viral load results compared to those with a result (Appendix 3).

Of the 364 adolescents with a viral load result, 119 were not suppressed resulting in an overall prevalence of an unsuppressed viral load of 32.7% (95% CI 27.1- 39.1). Male adolescents had a higher prevalence of an unsuppressed viral load than female adolescents, 37.2% (95% CI 28.0- 48.6) and 29.7% (95% CI 22.9- 37.8) respectively though this is not statistically significant.

Figure 6 shows the prevalence of an unsuppressed viral load by the age of ART initiation. Those who initiated whilst aged 12 had the highest prevalence of an unsuppressed viral load (45.7%). Those aged 15 and 19 had the lowest prevalences 23.5% and 23.3% respectively.

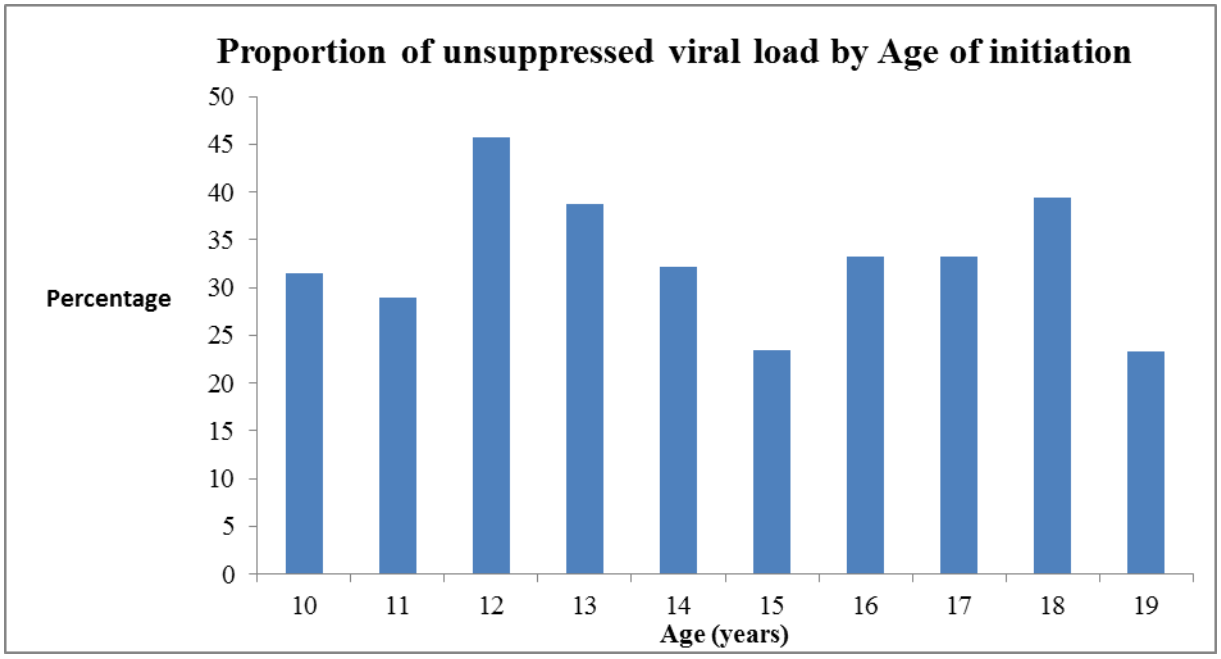

Figure 6: Age Specific Prevalence of an unsuppressed viral load

3.3 Characteristics associated with an unsuppressed viral load

Table 4 summarises the clinical and socio-demographic characteristics associated with an unsuppressed viral load. Of those who initiated with WHO stage 1/2, 25.3% (24) had a suppressed viral load. The association between baseline WHO stage and an unsuppressed viral load was significant (p=0.05). Having prior TB at ART initiation was significantly associated with an unsuppressed viral load (p=0.027). Of those who had TB before ART

initiation, 41.1% (44) had an unsuppressed viral load compared to 29.2% (75) of those who had not had TB. The year of ART initiation and time taken for a viral load to be taken were associated with an unsuppressed viral load. No socio-demographic characteristic was associated with an unsuppressed viral load.

Table 4: Associations between baseline clinical and socio-demographic characteristics and an unsuppressed viral load (n=364)

Characteristic n (%)	Viral Load				p value
	Suppressed		Unsuppressed		
Age (n=364)					
Median (IQR)	13 (11-18)		13 (11-17)		0.503
10-14 years	144	(65.2)	77	(34.8)	
15-19 years	101	(70.6)	42	(29.4)	0.277
Gender (n=364)					
Female	154	(70.3)	65	(29.7)	
Male	91	(62.8)	54	(37.2)	0.132
WAZ score (n=342)					
Median (IQR)	-1.3 (-2.0 to -0.2)		-1.4 (-2.2 to -0.3)		0.407
>-2	172	(69.1)	77	(30.7)	
≤-2	58	(68.2)	35	(37.6)	0.239
WHO Stage (n=285)					
Stage 1/2	71	(74.7)	24	(25.3)	
Stage 3/4	120	(63.2)	70	(36.8)	**0.050**
Initiation clinic (n=353)					
In DSA	91	(62.8)	54	(37.2)	
Not in DSA	147	(70.7)	61	(29.3)	0.119
Prior TB (n=364)					
No	182	(70.8)	75	(29.2)	
Yes	63	(58.9)	44	(41.1)	**0.027**
On TB treatment (n=353)					
No	192	(67.6)	92	(32.4)	
Yes	44	(63.8)	25	(36.2)	0.544
CD4 cell count (n=352)					
Median (IQR)	152 (78-246)		164 (68-302)		0.838
≤100 cells/µl	74	(67.3)	36	(32.7)	
101-200 cells/µl	78	(66.7)	39	(33.3)	
>200 cells/µl	84	(67.2)	41	(32.8)	0.944

Year of initiation (n=364)					
2004-2006	27	(62.8)	16	(37.2)	
2007	37	(69.8)	16	(30.2)	
2008	42	(59.2)	29	(40.8)	
2009	49	(53.9)	42	(46.1)	
2010	90	(84.9)	16	(15.1)	**<0.001**
Haemoglobin (n=316)					
>7g/dl	198	(67.4)	96	(32.6)	
≤7g/dl	14	(63.6)	8	(36.4)	0.721
Platelets (n=305)					
>150 000 per µl	190	(67.4)	92	(32.6)	
≤150 000 per µl	15	(65.2)	8	(34.8)	0.832
ALT (n=323)					
≤60 IU/L	210	(68.2)	98	(31.8)	
>60 IU/L	8	(53.3)	7	(46.7)	0.231
Albumin (n=316)					
>25 g/L	167	(66.8)	83	(33.2)	
≤25 g/L	43	(65.2)	23	(34.8)	0.801
Drug Regime (n=361)					
EFV containing	196	(67.1)	96	(32.9)	
NVP containing	46	(66.7)	23	(33.3)	
LPVr containing	3	(100)		(0)	0.478
Time to viral load test (n=364)					
6-12 months	147	(72.8)	55	(27.2)	
13-18 months	60	(64.5)	33	(35.5)	
19-24 months	23	(57.5)	17	(42.5)	
25-30 months	13	(65.0)	7	(25.0)	
> 30 months	2	(22.2)	7	(77.8)	**0.010**
Highest Education level (n=73)					
Primary School	33	(64.7)	18	(35.3)	
Secondary School	14	(63.6)	8	(36.4)	0.930
Attending school (n=72)					
No	12	(66.7)	6	(33.3)	
Yes	34	(63.0)	20	(37.0)	0.778
Mother dead (n=101)					
No	30	(62.5)	18	(37.5)	
Yes	14	(63.6)	8	(36.4)	
Unknown	19	(61.3)	12	(39.7)	0.985

Father dead (n=101)					
No	15	(88.3)	3	(11.7)	
Yes	4	(40.0)	6	(60.0)	
Unknown	44	(60.3)	29	(39.7)	**0.052**
Distance from Clinic (n=80)					
Median (IQR)	2.35	(1.26-3.16)	2.20	(1.47-3.52)	0.467

3.4 Clinical factors associated with an unsuppressed viral load after logistic regression

Both the univariable (unadjusted) and multivariable (adjusted) logistic regression models used to investigate the associations of characteristics with an unsuppressed viral load are included in Table 3.5. The odds ratio (OR) for each variable is shown together with the 95% CI. The final multivariable model had a Pearson chi-square goodness-of-fit of p=0.3396 indicating that the model has a good fit for the data used in this study.

Having had TB before initiation was significantly associated with an unsuppressed viral load in the unadjusted analysis. The odds of having an unsuppressed viral load were 69% more in those who had TB before initiation than those who did not (95% CI 1.06-2.71). The univariable model for the year of initiation was significant (p<0001). Also in the unadjusted analysis, adolescents who initiated in 2010 were 70% less likely to fail than those who initiated in 2004-2006 (95% CI 0.13-0.68). Those who had a baseline WHO Stage 3/4 were 73% more likely to have an unsuppressed viral load than those with a baseline WHO Stage 1/2 (95% CI 1.00-2.99) in the unadjusted model. In the unadjusted model, those who had greater than 30 months before the first viral load was done were more than 9 times more likely to have an unsuppressed viral load than those who had a viral load between 6 and 12 months though the CI is very wide (95% CI 1.89-46.40).

The variables gender, WHO stage and clinic of initiation were significant at the 20% level and were included in the multivariable model. The variables age (as a continuous variable),

categorised CD4 at initiation and the initial treatment regime were included in the final multivariable model as they have been previously shown to be associated with virological failure in children and adults. There was no significant univariable association of an unsuppressed viral load with categorised age at initiation, having been on TB treatment at initiation, baseline Haemoglobin, Platelets, ALT and Albumin.

Adjusting for the other variables, in the multivariable model, adolescents who initiated ART in 2010 had 68% less odds of having an unsuppressed viral load as compared with those initiating in 2004-2006 (95% CI 0.13-0.82). Adolescents whose viral load test was done after 30 months of ART were more than 7 times more likely to have an unsuppressed viral load compared to those done after 6-12 months although the CI is wide and therefore imprecise (95% CI 1.50-41.04).

Though not statistically significant, the trends in the adjusted model of the other characteristics are important to report. With each yearly increase of age at ART initiation, there was a 2% increase of having an unsuppressed viral load. The males were 58% more likely to have an unsuppressed viral load than the females. Initiating whilst in WHO stage 3/4 was associated with 11% odds of an unsuppressed viral load compared to those initiating in WHO stage 1/2. Initiating ART outside the DSA had a protective effect on an unsuppressed viral load. The individuals who had TB before ART were 54% more likely to have an unsuppressed viral load than those who did not have prior TB. No trend was found in the CD4 cell count variable. Those who initiated ART on NVP were 14% more likely to have an unsuppressed viral load than those who initiated on EFV. All missing data were not associated with an unsuppressed viral load.

Table 5: Logistic regression: Factors associated with an unsuppressed viral load (n=364)

Characteristic	OR (95% CI)	Adjusted OR (95%CI)
Age (years)**	0.97 (0.91-1.04)	1.02 (0.93-1.13)
Age group		
10-14 years	1	
15-19 years	0.78 (0.49-1.22)	
Gender		
Female	1	1
Male	1.41 (0.90-2.19)*	1.42 (0.82-2.46)
WAZ score		
>-2	1	
≤-2	1.35 (0.82-2.22)	
Missing data	1.04 (0.41-2.66)	
WHO Stage		
Stage 1/2	1	1
Stage 3/4	1.73 (1.00-2.99) *	1.11 (0.56-2.19)
Missing data	1.37 (0.71-2.66)	1.25 (0.60-2.60)
Initiation clinic		
In the DSA	1	1
Not in the DSA	0.70 (0.45-1.10)*	0.63 (0.39-1.04)
Missing data	0.96 (0.27-3.44)	0.65 (0.14-3.05)
Prior TB		
No	1	1
Yes	1.69 (1.06-2.71)*	1.46 (0.81-2.63)
On TB treatment		
No	1	
Yes	1.19 (0.68-2.06)	
Missing data	0.46 (0.10-2.19)	
CD4 cell count**		
≤100 cells/µl	1	1
101-200 cells/µl	1.03 (0.59-1.79)	1.00 (0.54-1.83)
>200 cells/µl	1.00 (0.58-1.73)	1.00 (0.55-1.86)
Missing data	0.69 (0.17-2.69)	0.64 (0.13-3.11)
Year		
2004-2006	1	1
2007	0.73 (0.31-1.71)	0.57 (0.22-1.49)
2008	1.17 (0.53-2.54)	1.08 (0.45-2.61)
2009	1.44 (0.69-3.04)	1.44 (0.63-3.32)
2010	0.30 (0.13-0.68)*	0.32 (0.13-0.82)**§**

Haemoglobin		
>7g/dl	1	
≤7g/dl	1.18 (0.49-2.91)	
Missing data	0.94 (0.49-1.81)	
Platelets		
>150 000 per µl	1	
≤150 000 per µl	1.10 (0.45-2.69)	
Missing data	0.98 (0.54-1.79)	
ALT		
≤60 IU/L	1	
>60 IU/L	1.88 (0.66-5.32)	
Missing data	1.11 (0.56-2.21)	
Albumin		
>25 g/L	1	
≤25 g/L	1.08 (0.61-1.90)	
Missing data	0.75 (0.38-1.49)	
Drug Regime**		
EFV containing	1	1
NVP containing	1.02 (0.58-1.78)	1.17 (0.55-2.49)
Time to viral load test		
6-12 months	1	1
13-18 months	1.47 (0.87-2.49)	1.41 (0.79-2.50)
19-24 months	1.98 (0.98-3.98)	1.60 (0.74-3.44)
25-30 months	1.44 (0.55-3.80)	0.89 (0.31-2.54)
> 30 months	9.35 (1.89-46.4)*	7.84 (1.50-41.04)§

***** p <0.2 included in the multivariate logistic regression model

**Variables included in the multivariable model as they were significantly associated with virological failure in the literature

§ p <0.05 in the adjusted model

CHAPTER 4: DISCUSSION

This chapter discusses the results that were found in this study. The study's main objective was to describe the characteristics of adolescents who initiated ART and to identify characteristics that are associated with ART failure in this population. It opens with the discussion of the results obtained in respect of each objective which is followed by the discussion of possible limitations of the study. The chapter closes with a discussion of the generalizability and external validity of the research results.

4.1 Cohort Characteristics

4.1.1 Clinical and Socio-demographic Characteristics

In keeping with goal 6 of the South Africa National Strategic Plan for HIV/AIDS and STI 2007-2011 of scaling up ART coverage [53], the numbers of adolescents who initiated ART increased nearly fourfold from the early years of ART roll out (2004-2006) to 2010. The steep increase in ART initiation from 2009 is a reflection of the improved identification of HIV positive people through the provider initiated HIV testing in the programme [12]. The median age at initiation was 15 years, slightly younger than those in a study of 154 adolescents with non-perinatally acquired HIV infection where the median age was 16.4 years [22] but older than another study where 72.3% of the adolescents had acquired HIV perinatally, where the median age at initiation was 11.5 years [30]. The median age for sexual debut obtained from the 2006 AC sexual behaviour and HIV surveillance for adolescents 15-19 years in the DSA was 16 years and 17 years for males and females respectively and this research also reported strong evidence that death of a mother for females was associated with increased vulnerability to earlier sexual debut and HIV infection [54]. This may indicate that those who initiated ART in late adolescence may have acquired HIV sexually. With the

reports of the clinical latency of HIV infection ranging from 4 years in rapid progressors [55] to 15 years in long term non-progressors [56, 57], differentiation of whether those initiating ART in late adolescence had perinatally or sexually acquired HIV infection is difficult. The females in this cohort may have been infected sexually and progressed rapidly with a short clinical latency period. They may also have been infected through breastfeeding and were long term non-progressors with a long clinical latency of HIV. Further analysis to distinguish the two is needed as they have different characteristics [58] which may result in different responses to ART and therefore virological failure.

This study reports that two thirds of those initiating ART as adolescents at the Hlabisa HIV Treatment and Care Programme were females, this is similar to the gender distribution in other ART programmes [12, 22, 30] where more females than males are registered. In early adolescence the proportion of males and females who initiated ART are similar. This differs from late adolescence where more females than males initiate ART- only 13.2% of those who initiated in late adolescence were males. This could be a reflection of the Hlabisa HIV Treatment and Care Programmes PMTCT initiatives where testing for HIV is high, 95.6% of women attending the antenatal clinic are tested and are referred for ART if eligible [59].

The median WAZ score distribution by age indicates that those who initiated in late adolescence had better nutritional status. This could further support the argument that those who initiated in late adolescence were sexually infected rapid progressors rather than perinatally infected long term non-progressors who often present with poor nutritional status from years of chronic illnesses. After 13 years of age the females had better nutrition than their male counterparts at ART initiation. Prevalence of obesity is higher amongst females than males in the DSA [60, 61] and this explains why females have better nutrition than boys at ART initiation. Nutritional status has been associated with clinical outcomes on ART [62] though it has not been found to be associated with virological failure [38].

About 40% of the adolescents who initiated ART did so whilst residing in the DSA, this is similar to results found on the overall analysis of the Hlabisa Treatment and Care programme [12]. The ART programme is decentralised and individuals collect their drugs at the clinic nearest to their homesteads. The median distance (2.2 km) from the homestead to the nearest clinic is relatively short compared to distances from clinics in the earlier years [63] and this may result in good pick up rates of drugs and therefore good ART adherence and virological outcomes. The number of adolescents without knowledge of whether the father is dead or alive is very high (69.2%) and this may be a reflection on the low marriage rates amongst women African women in KwaZulu-Natal [64]. Absence of a father has been shown to influence adolescent sexual behaviour [54] and their absence may also impact on adherence to ART and hence virological outcomes.

4.1.2 Clinical Outcomes

The mortality rate of 36.5 per 1000 person years for adolescents initiating ART at the Hlabisa HIV Treatment and Care programme is similar to that at other ART programmes in southern Africa [22, 30]. As in other programmes mortality is high in the first months of ART initiation [30, 65] and this is probably caused by initiating ART whilst severely immunocompromised, emphasising the need to seek medical care and start ART early. Overall LTFU (98.8 per 1000 person years) is similar to that for 9-19 year olds at a Cape Town programme (10.0 per 100 person years). The unadjusted LTFU rates between June 2004 and October 2011 were significantly different between the adolescent developmental stages with those initiating in late adolescents having a higher LTFU rate. This is similar to results from a study in Malawi which concluded that LTFU was higher in those 15-24 years old than those 6-14 years [66]. During late adolescence, an individual becomes more independent and distances themselves from guardian supervision and there is greater chance of becoming lost to follow up [67]. Social groups and the need for acceptance by peers

become important during this phase and the stigma of being HIV positive may result in the high rates of LTFU [67]. The unadjusted LTFU rate by gender was significantly higher for females than males and this could be because of cultural and social reasons of gender roles, marriage and pregnancy. The rate of LTFU in those initiating whilst pregnant is high and this poses a public health concern as the HIV status of their infants needs to be determined so as to initiate them on ART if necessary. This highlights the need for intense adherence counselling and active follow up of adolescents on ART. The attrition rate for the adolescents after 6 months of ART was 15.5% and it is greater than that of children ≤ 15 years (6%) in the same programme [34]. This is mostly due to those in late adolescence who contributed 83.5% of those LTFU before 6 months of ART. This high attrition rate may result in survival bias as those who died and were LTFU may have had poor virological response to ART.

4.2 Prevalence of an unsuppressed viral load

The proportion of an unsuppressed viral load in this study (32.7%) is lower than that reported for adolescents in other studies [22, 30, 39, 68]. Despite the lower threshold (≤ 70 copies/ml) used to determine viral suppression in this study compared to a threshold of ≤ 400 copies/ml in these other studies, adolescents in this cohort had a better virological outcome after 6 months of ART. This result might indicate better adherence and lower rates of baseline ARV drug resistance compared to the adolescents in other studies. Though males had a higher prevalence of an unsuppressed viral load than females, it was not statistically significant.

4.3 Factors associated with an unsuppressed viral load

This study did not find any association between baseline age, gender, baseline weight, WHO stage, baseline CD4 cell count, baseline treatment regime and other baseline laboratory variables with an unsuppressed viral load. This is similar to previous studies done in adolescents which only showed that prior exposure to ART, T-cell immunological markers

and adherence to treatment to be associated with virological failure [37, 39, 40]. Studies done in children and adults showed that baseline age, gender, baseline CD4 cell count, baseline treatment regime were associated with virological failure. The small sample size in this study could be a limitation in finding significant clinical and socio-demographic characteristics that are associated with an unsuppressed viral load as were found in children and adults. The associations of a missing viral load, despite being eligible for testing, with gender, adolescent developmental stage at initiation and initial treatment regime may also explain these findings as these individuals may have had poor virological outcomes. LTFU is a marker of poor adherence and it was greatest in females who initiated in late adolescence.

Adolescents who initiated ART in 2010 had less odds of an unsuppressed viral load than those who initiated in 2004-2006. In 2004, South Africa initiated the roll-out of ART with a lot of recruitment campaigns to identify and initiate as many individuals on ART possible. In 2008, psychological support in the Hlabisa health sub-district was initiated for those on ART, their caregivers and health care workers [51]. This support included provision of individual psychological support for those on ART and training on HIV patient management for health care workers [51]. Since 2009, the sub district has benefited from home and mobile counselling and testing (HMCT) services and HIV Community Education and Awareness campaigns [51]. The adolescents who initiated ART in 2010 may have had increased awareness of HIV, its management and the importance of adherence to ART resulting in having less likelihood of an unsuppressed viral load compared to those who initiated in 2004-2006. This further emphasises the reports that good clinical outcomes can be observed despite rapid scale up of ART treatment programmes [65, 69].

Though the CI was wide, individuals who had a viral load taken > 30 months after ART initiation had higher odds of failure compared to those who had it 6-12 months. The small number in this category resulted in the wide but significant CI. The individuals who had their

viral load done after 30 months had more exposure to ARV drugs which may have resulted in drug resistance from an increased risk of poor adherence and hence higher odds of an unsuppressed viral load [40]. This indicates the importance of timely viral load monitoring to identify those in need of increased adherence support on ART.

Though not significant, the males had higher odds of an unsuppressed viral load than females and this is similar to the association found in children in Uganda [41], this may show that males are less adherent to ART than females. The insignificant trend of age in this study could echo the reports that as adolescents grow older there is increased independence with peer groups becoming important and these factors may reduce adherence to ART and therefore an increased odds for an unsuppressed viral load [28]. Unlike in other studies in adults and children [41, 42, 44, 45], CD4 cell count was not found to be associated with an unsuppressed viral load.

4.5 Limitations of the study

This study was a secondary data analysis and did not allow analysis of variables that were not collected as part of the programmes patient management. Adherence and prior exposure to ART have been found to have important associations with virological failure in previous studies and data on these were not available in this study.

Data was entered into the database through a multiple clerk single entry and this may have resulted in erroneous data. The amount of missing data in the analysis was high and this could have masked possible associations of some variables with an unsuppressed viral load. Of the adolescents eligible for the analysis, 20.7% did not have viral loads. This resulted in a low sample size. Imputations of these data would have helped to reduce possible bias.

The attrition rate due to death, LTFU and transfer out before 6 months of ART was high and may have resulted in survival bias.

A time-to-event analysis would have been the most appropriate method for investigating the factors associated with virological failure in these adolescents but due to the absence of serial viral load blood sampling from initiation, this method of analysis was precluded.

4.6 Generalisability

The Hlabisa HIV Treatment and Care programme is a decentralised public health programme which is in the rural area. It is a nurse/counsellor driven programme with limited physician input and is similar to other ART programmes in rural South Africa. The programme has additional human resources and infrastructural support from the AC [12] and this may result in it differing from other South African DOH programmes. Due to this, caution must be taken when generalising the results obtained from this study to other ART programmes.

CHAPTER 5: CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

This study demonstrates that a bimodal distribution of age of adolescents initiating on ART in a rural programme in KwaZulu-Natal exists. Mortality rates and LTFU rates in this cohort are similar to those of adolescents at other ART programmes in southern Africa and after adjusting for adolescent developmental stage and gender, LFTU is greatest in females initiating in late adolescence. The prevalence of an unsuppressed viral load after 6 months of ART in the adolescents in this study is lower than that of adolescents in other treatment programmes and this may indicate better adherence and lower baseline drug resistance in the adolescents at the Hlabisa HIV Treatment and Care Programme.

Significant associations with an unsuppressed viral load in this cohort were the year the adolescents initiated ART and the time taken before the first viral load test was done after the adolescents initiated ART. Though not significant; males, initiating in late adolescence, WHO stage 3/4, prior TB, initiating on NVP containing regimens were associated with increased likelihood of an unsuppressed viral load.

Despite the yearly increase in adolescents initiating ART, good virological responses can be obtained through the increased support of both individuals on ART and their health care providers. Timely viral load monitoring identifies those in need of increased adherence support on ART and may result in good virological responses.

5.2 Recommendations

The bimodal distribution of age of adolescents initiating on ART raises the question when these individuals were infected by HIV. It has been shown that those infected perinatally and sexually have different characteristics and these may influence virological outcomes on ART

therefore more research is recommended to answer this question. Females ≥ 15 years of age and those initiating whilst pregnant are more likely to become LTFU. This indicates that they are an important group of adolescents who need to be targeted by strategies to reduce LTFU and hence increase adherence to ART. Further research is recommended in this group to investigate factors associated with LTFU.

Adolescent friendly clinics to manage this cohort are recommended as these individuals have different needs to adults or children. This may help improve adherence to treatment and therefore result in lower rates of an unsuppressed viral load. Continued HIV awareness and treatment campaigns and other psychological support services are also recommended. Viral load testing to monitor response to ART is important and should be done early to prevent progression to virological failure and drug resistance.

Further research in this cohort using both qualitative and quantitative methods to understand the factors surrounding HIV and its treatment in adolescents is recommended.

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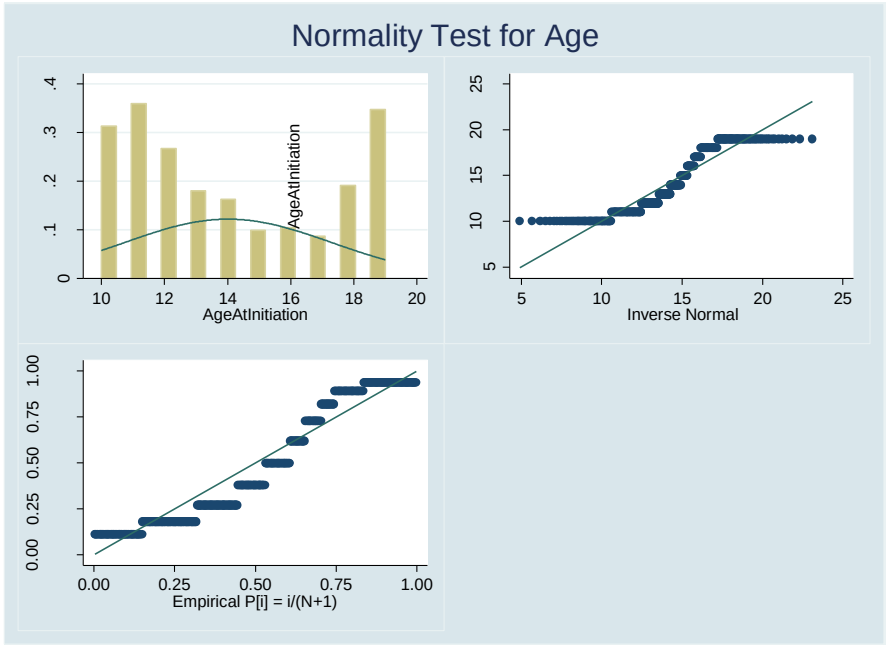
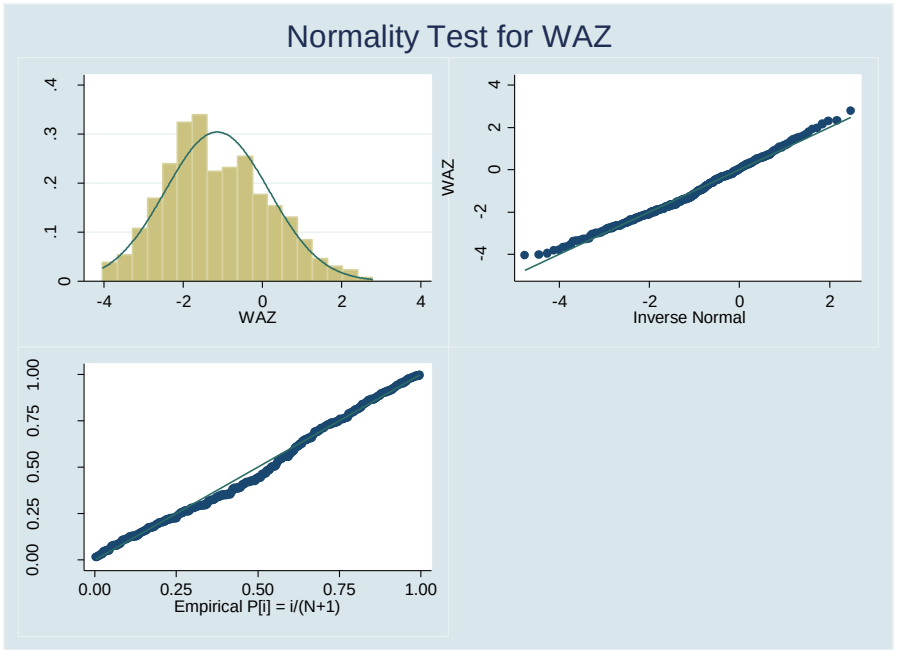
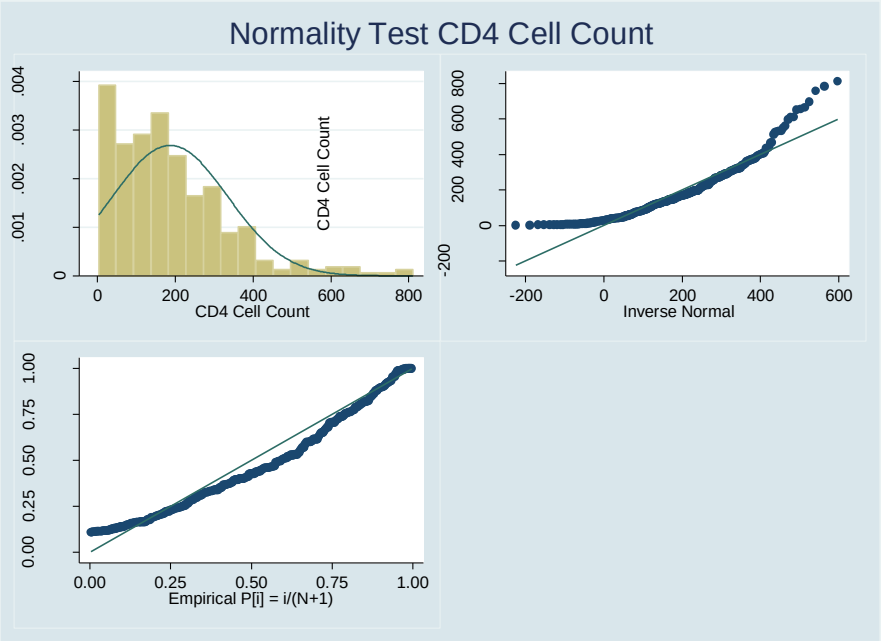
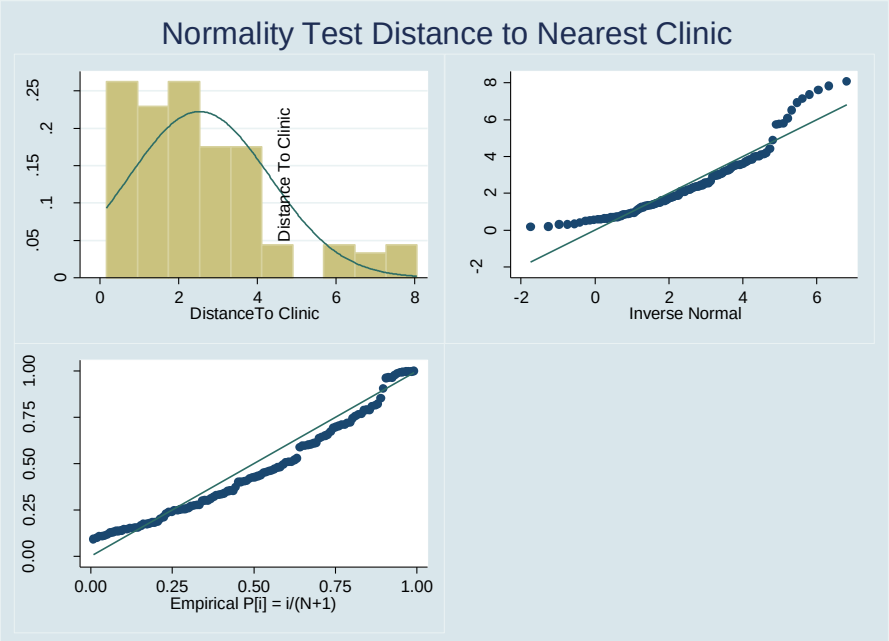
APPENDICES

APPENDIX 1: Testing Normality Assumptions






Normality Test CD4 Cell Count
CD4 Cell Count
CD4 Cell Count
Inverse Normal
Empirical P[i] = i/(N+1)


Normality Test Distance to Nearest Clinic
Distance To Clinic
DistanceTo Clinic
Inverse Normal
Empirical P[i] = i/(N+1)

APPENDIX 2: Missing data added into the analysis

Variable	Missing	Found (%) *
Weight	73	21 (29%)
WHO stage	182	25 (14%)
TB treatment	70	28 (40%)
CD4	28	9 (32%)
Haemoglobin	120	27(23%)
Creatinine	122	23 (19%)
ALT	118	21 (18%)
Platelets	130	22 (17%)
Albumin	136	22 (16%)
Viral load after 6 months	137	45 (33%)

* Data found in the clinic files and added to the analysis

APPENDIX 3: Characteristics associated with adolescents without viral load results

Characteristics associated with individuals eligible for viral load test with no results (n=459)

Characteristic	without viral load (n=95)		with viral load (n=364)		p value
Age (years)					
Median (IQR)	17 (14-18)		13 (11-19)		**<0.001**
10-14	28	29.5	221	60.7	
15-19	67	70.5	143	39.3	**<0.001**
Gender					
Females	78	82.1	219	60.2	
Males	17	17.9	145	39.8	**<0.001**
WAZ score					
>-2	71	74.7	249	68.4	
≤ -2	16	16.8	93	25.6	
Missing data	8	8.4	22	6.0	0.175
WHO Stage					
Stage 1/2	27	28.4	95	26.1	
Stage 3/4	37	39.0	190	52.2	
Missing data	31	32.6	79	21.7	**0.037**
Initiation Clinic					
In DSA	40	42.1	145	39.8	
Not in DSA	54	56.8	208	57.1	
Missing Data	1	1.1	11	3.0	0.545
Prior TB					
No	74	77.9	257	70.6	
Yes	21	22.1	107	29.4	0.158
On TB treatment					
No	69	72.6	284	78.0	
Yes	16	16.8	69	19.0	
Missing data	10	10.5	11	3.0	**0.008**
CD4 cell count					
≤ 100	25	26.3	110	30.2	
101-200	44	46.3	117	32.1	
> 200	23	24.2	127	34.9	
Missing data	3	3.2	10	2.8	0.061
Drug Regime					
EFV containing	66	69.5	292	80.2	
NVP containing	29	30.5	69	19.0	
LPVr containing	0	0	3	0.8	**0.036**

Year of initiation					
2004-2006	3	3.2	43	11.8	
2007	9	9.5	53	14.6	
2008	13	13.7	71	19.5	
2009	17	17.8	91	25.0	
2010	53	55.8	106	29.1	**<0.001**
Haemoglobin					
> 7g/dl	77	81.1	294	80.8	
≤ 7g/dl	7	7.4	22	6.0	
Missing data	11	11.6	48	13.2	0.835
Platelets					
>150 000 per µl	76	80.0	282	77.5	
≤150 000 per µl	7	7.4	23	6.3	
Missing data	12	12.6	59	16.2	0.666
ALT					
≤60 IU/L	81	85.3	308	84.6	
>60 IU/L	1	1.1	15	4.1	
Missing data	13	13.6	41	11.3	0.299
Albumin					
>25 g/L	57	60.0	250	68.7	
≤25 g/L	23	24.2	66	18.1	
Missing data	15	15.8	48	13.2	0.265

APPENDIX 4: Ethics Clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Ms Nicoletta Mabhena

CLEARANCE CERTIFICATE	M111131
PROJECT	Predicators of Virological Failure in Adolescents at a Rural HIV Programme in Kwa-Zulu-Natal
INVESTIGATORS	Ms Nicoletta Mabhena.
DEPARTMENT	School of Public Health
DATE CONSIDERED	28/10/2011
M1111310DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

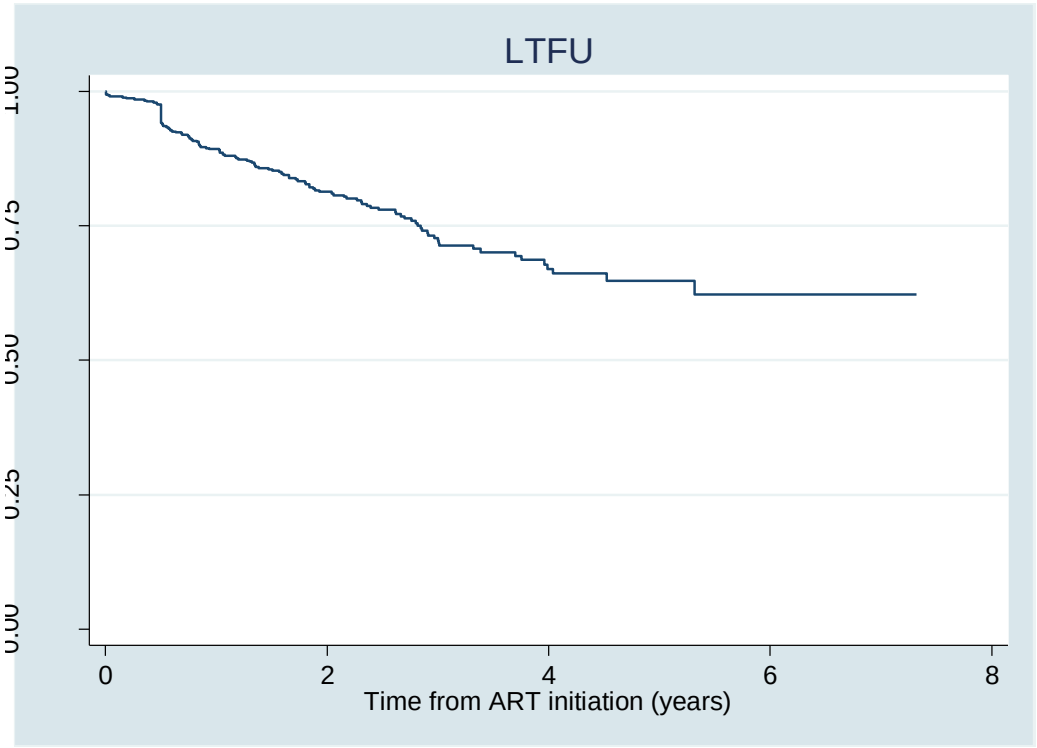
DATE 28/10/2011 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr Tobias Chirwa

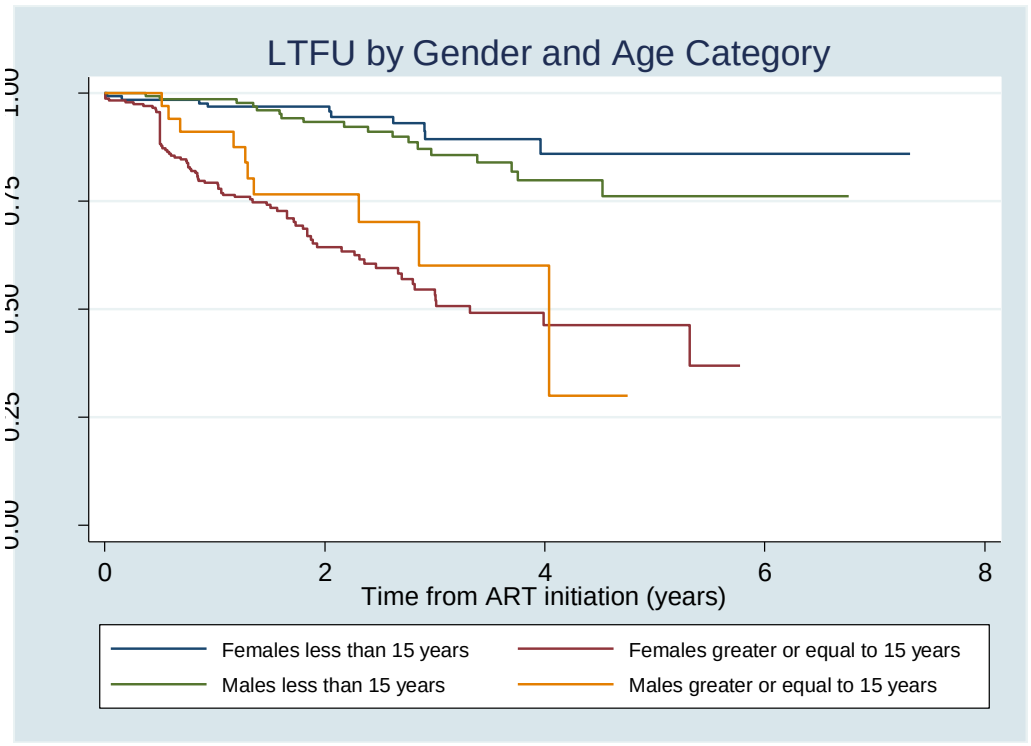
DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**
PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

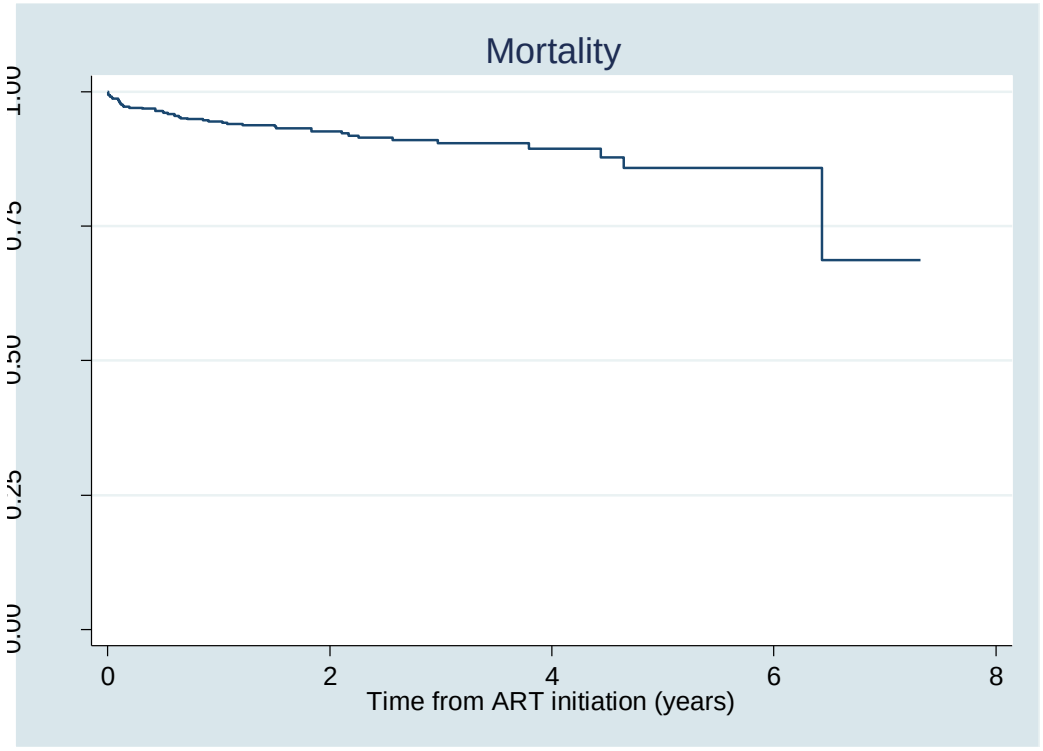
APPENDIX 5: Kaplan Meier Estimates



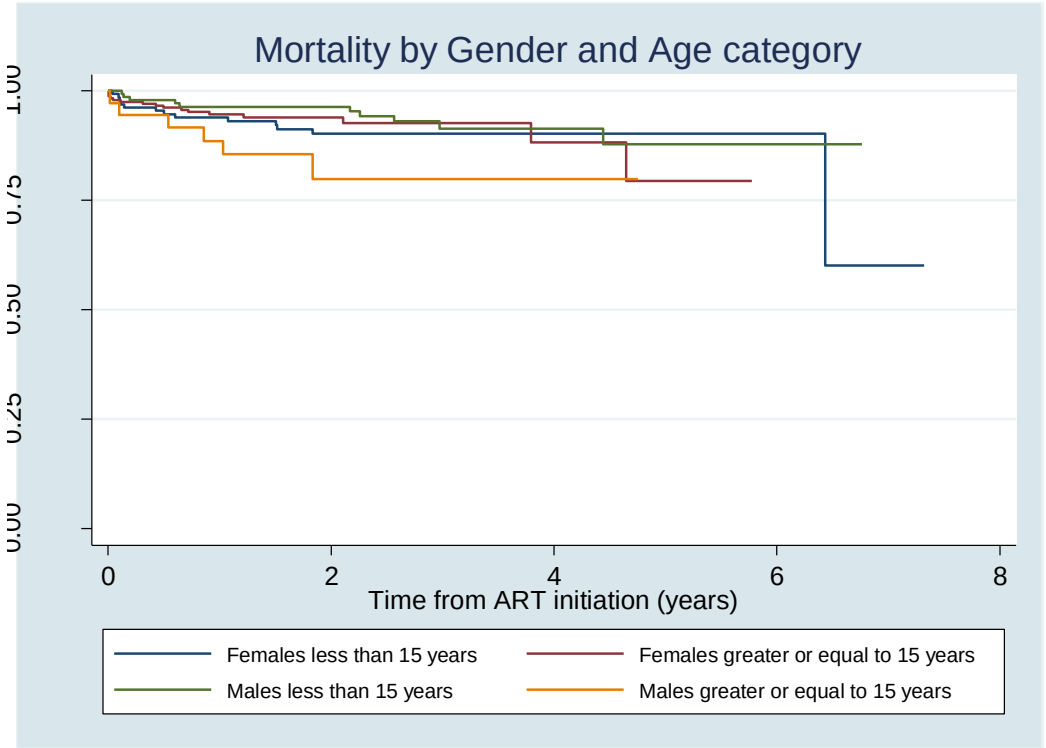
Kaplan Meier Estimates for LTFU



Kaplan Meier Estimates of LTFU by Gender and Age Category (p< 0.001)



Kaplan Meier Estimates for Overall Mortality



Kaplan Meier Estimates of Mortality by Gender and Age category (p=0.145)

APPENDIX 6: Data Use Agreements

AFRICA CENTRE FOR HEALTH AND POPULATION STUDIES

Africa Centre Demographic Information System (ACDIS)

Data Use Agreement

It is hereby agreed with : NICOLETTA MABHENA (The "Data User")
of UNIVERSITY OF WITWATERSRAND (Affiliation) on 28/09/2011 (date)
that s/he will have access to the following ACDIS dataset(s) :

1. DATA ON PEOPLE WHO INITIATED TREATMENT AS ADOLESCENTS
2. BETWEEN 10 and 19 YEARS BETWEEN 2004 - 2011 AND
3. THE FINAL DATA VARIABLES ARE STILL TO BE FINALISED
4. .....
5. .....

The following conditions will apply:

1. The Data User will neither release nor permit others to release the files or data therein to any person (including media and subcontractors) except with the written approval of the ACDIS Project Leader;
2. The Data User will neither use nor permit others to use the data in any way other than listed in the original application (Analysis Plan) for access to the dataset;
3. The Data User will ensure that the data are kept in a secured environment and that only authorized users have access to the data.
4. Every publication or report based on the data must carry an acknowledgement of the form:

   This Analysis is based on data collected by the Africa Centre Demographic Information System
5. The Data User will not release or permit others to release any data that identifies persons, directly or indirectly;
6. Once the dataset has served its indicated purpose it must be disposed of;

All datasets remain the property of the Africa Centre and the Africa Centre reserves the right to request the return of any datasets should any of the above conditions be violated;

The following documents **must** accompany this agreement:

1. A short description of the intended purpose and method of analysis of the data (Analysis Plan)
2. A list of the names and organizational affiliations of all those who will engage in this analysis. In the case of students, a statement by their supervisor that they will ensure that the student abides by these conditions.
3. A description of the means by which the Data User will restrict access to confidential Africa Centre data.

Signed:

..... Date: 28/09/2011
Data User

..... Date: 6/10/2011
Prof Marie-Louise Newell (Director)

..... Date: 29/9/2011
Dr AJ Herbst (ACDIS Project Leader)

IN COLLABORATION WITH THE UNIVERSITY OF KWAZULU-NATAL AND THE SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

Postal: PO Box 198, Mtubatuba 3935, South Africa **Physical:** Africa Centre, R618 en route to Hlabisa, Somkhele
Tel: +27 (0)35 550 7500 Fax +27 (0)35 550 7565 E-mail: info@africacentre.ac.za
Website: www.africacentre.ac.za

AFRICA CENTRE FOR HEALTH AND POPULATION STUDIES

UNIVERSITY OF KWAZULU-NATAL

Hlabisa HIV Treatment and Care Programme
Data Use Agreement

It is hereby agreed with: Nicoletta Mabhena ..... (The "Data User")

of University of Witwatersrand..... (Affiliation) on 28/09/2011..... (date)

that s/he will have access to the following ART Programme dataset(s) :

1. Data on people who initiated treatment as adolescents (10-19 years) between 2004-2011 and the final data variables are still to be finalised.

2. .....

3. .....

4. .....

5. .....

The following conditions will apply:

1. The Data User will neither release nor permit others to release the files or data therein to any person (including media and subcontractors) except with the written approval of the Africa Centre Director.
2. The Data User will neither use nor permit others to use the data in any way other than listed in the original application (Analysis Plan) for access to the dataset;
3. The Data User will ensure that the data are kept in a secured environment and that only authorized users have access to the data.
4. Every publication or report based on the data must carry an acknowledgement of the form:

   This analysis uses data collected by the Hlabisa HIV Treatment and Care Programme, made possible by the generous support of the American people through the United States Agency for International Development (USAID) and the President's Emergency Plan (PEPFAR) under the terms of Award No. 674-A-00-08-0001-00. The opinions expressed herein are those of the author(s) and do not necessarily reflect the views of USAID or the United States Government. The Africa Centre receives core funding from the Wellcome Trust (grant number 082384/Z/07/Z).

5. The Data User will not release or permit others to release any data that identifies persons, directly or indirectly;
6. Once the dataset has served its indicated purpose it must be disposed of;

All datasets remain the property of the Hlabisa HIV Treatment and Care Programme and we reserve the right to request the return of any datasets should any of the above conditions be violated;

The following documents **must** accompany this agreement:

1. A short description of the intended purpose and method of analysis of the data (Analysis Plan)
2. A list of the names and organizational affiliations of all those who will engage in this analysis. In the case of students, a statement by their supervisor that they will ensure that the student abides by these conditions.
3. A description of the means by which the Data User will restrict access to the data.

Signed:

..... Date: 28/09/2011

Data User

..... Date: 6/10/2011

Prof Marie-Louise Newell (Director)

..... Date: 28/09/2011

Dr Hilary Thulare (ART Programme Leaders)

Postal: PO Box 198, Mtubatuba 3935, South Africa
Physical: Africa Centre, R618 en route to Hlabisa, Somkhele
Tel.: +27 (0)35 550 7500
Fax: +27 (0)35 550 7565

wellcome trust

APPENDIX 7: Change of Research Title Approval

Faculty of Sciences
Medical School, 7 York Road, Parktown, 2193
Fax: (011) 717-2119
Tel: (011) 717-2108

Reference: Mrs Mathikhui Moshabesha
Email: Mathikhui.moshabesha@wits.ac.za
26 June 2012
Person No: 562150
TAA

Dr Nicoletta Mabhena
Postnet suite 698
P/Bag X 9
Benmore
South Africa
2010

Dear Dr Mabhena

Master of Science in Epidemiology in the field of Population-based Field Epidemiology: Approval of change of title

We have pleasure in advising that your proposal entitled "Factors associated with virological failure in adolescents in a rural HIV programme in KwaZulu-Natal" has been approved. Please note that any changes to this title has to be endorsed by the Faculty's Higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences