

**A RETROSPECTIVE COHORT ANALYSIS OF
ANTIRETROVIRAL TREATMENT MODIFICATIONS
AT THE REFERRAL HIV CLINIC
IN MBABANE, SWAZILAND**

by

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DECLARATION

I, Dr Simbarashe G Takuva, hereby declare that the dissertation which I hereby submit for the degree Master of Science in Epidemiology at the University of Pretoria is my own work and has not previously been submitted by me for a degree at another university.

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This work is dedicated to the patients of the Mbabane Government Hospital Antiretroviral Therapy Unit, Swaziland. This is where my passion for HIV medicine and clinical epidemiology was born and I have been fortunate to be part of this special establishment since its formal inception in 2004.

ABSTRACT

Background: Optimizing initial antiretroviral therapy (ART) regimens is of paramount importance in improving the durability of treatment efficacy and patient prognosis. We evaluated the reasons for and risk factors relating to ART modifications in an outpatient cohort in Mbabane, Swaziland.

Methods: Retrospective cohort analysis of data for 782 patients who started first-line ART between 1 March 2006 and 31 March 2008. Multivariate piecewise Cox regression models were used to identify potential predictors of treatment modification.

Results: Over a median follow-up period of 21 months, 17.5% of patients modified their regimen. Drug toxicity was the commonest reason (77 %) while drug contra-indications, namely tuberculosis (13.1%) and pregnancy (6.6%) accounted for 20% of the modifications. In the adjusted multivariate Cox piecewise regression model; after 11 months on ART, baseline CD4 cell count < 200cells/mm³ (HR = 4.42; 95% CI: 1.62 – 12.1), having Stavudine (d4T) in the initial regimen (HR = 2.64; 95% CI: 1.56 – 4.46) and baseline weight > 60kg (HR = 2.40; 95% CI: 1.43 – 4.04) significantly increased the hazards for modification.

Conclusions: Initiating HAART at higher CD4 counts, avoiding drugs with poor safety profiles, such as Stavudine (d4T), and identifying individuals who may require therapy for tuberculosis or who may become pregnant could reduce modification rates.

Keywords: first line ART; regimen durability; ARV modifications; Swaziland.

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ABBREVIATIONS

3TC	Lamuvudine
95% CI	95% confidence interval
ABC	Abacavir
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Transaminase
ART	Antiretroviral Therapy
ARV	Antiretroviral drug
AST	Aspartate Transaminase
AZT	Zidovudine
CD4	Cluster of differentiation
CI	Confidence interval
CNS	Central Nervous System
d4T	Stavudine
DART	Development of Anti-retroviral Therapy in Africa
DHS	Demographic Health Survey
EFV	Efavirenz
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HR	Hazards ratio
IQR	Interquartile range
LPV/rt	Ritonivir-boosted Lopinivir
LR	Log-rank
LTFU	Lost to follow up
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
PI	Protease inhibitor
PMTCT	Prevention of Mother to Child Transmission of HIV
RR	Relative Risk
SQV-rt	Ritonivir boosted Saquinavir
TDF	Tenofovir
WHO	World Health Organization

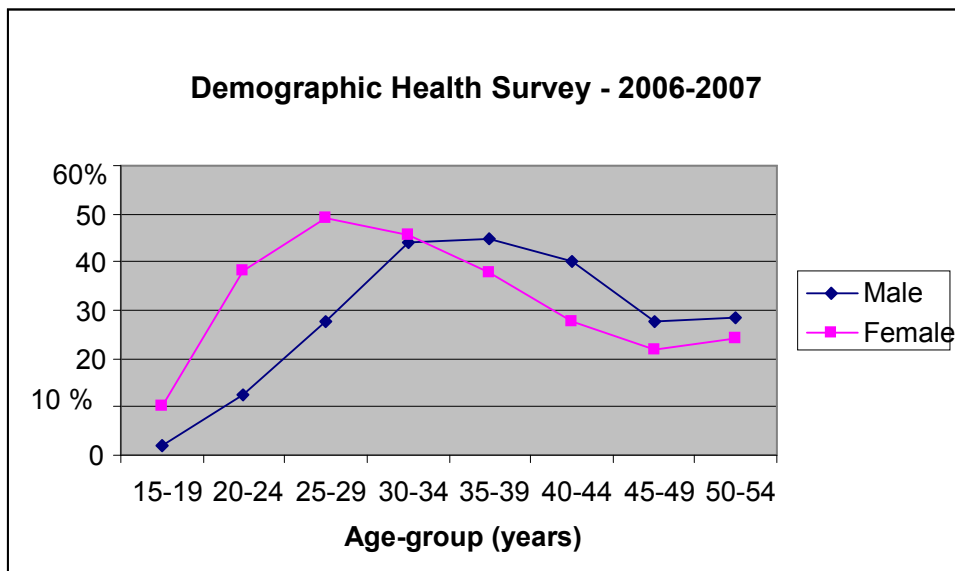
CHAPTER 1

INTRODUCTION

1.1 BACKGROUND

Sub-Saharan Africa is the region that is most affected globally by the burden of the Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS). An estimated 22.4 million children and adults were living with HIV infection in Sub-Saharan Africa by the end of 2008. This represents about 67% of world-wide HIV infections ¹. Swaziland, where this study was done, currently has one of the highest HIV prevalence rates in the world, as more than one in four adults between the ages of 15 and 49 is infected with HIV ². Figure 1 illustrates the age-group distribution of the pandemic in Swaziland.

Figure 1: HIV prevalence among the Swaziland population 15 years and older



Source: Swaziland Demographic Health Survey Report 2008. Ministry of Health and Social Welfare/Measure DHS Project, 2008.

The advent of Highly Active Antiretroviral Therapy (HAART) has resulted in a major reduction of AIDS and AIDS-related mortality ³. In 2005, the World Health Organization (WHO) advocated the 3 x 5 initiative, which led to a rapid scaling up in antiretroviral service provision in areas afflicted by the pandemic ⁴. In Swaziland, Antiretroviral Therapy (ART) provision has expanded to involve the primary healthcare set-up. As a result, more patients can access treatment. By the end of 2008, a total of 32 000 people were on ART treatment in Swaziland. This represented about 55% of the population in need of ART ². This increase was facilitated by the increased availability of, funding for and the reduced cost of ART.

The WHO's adapted treatment guidelines for Swaziland are used to guide HAART initiation and chronic care for HIV-infected patients ⁴. Patients who start HAART and those who are not yet eligible are followed up on in terms of the Swaziland Ministry of Health's HIV treatment guideline pre-ART protocol ⁵. The majority of the patients identified for initiation do start their treatment regimens. However, there are no quantitative data to show whether all the patients who start treatment are able to tolerate their initial treatment regimes.

A number of studies in Europe have shown that most patients tolerate their initial treatment regimens well for up to 24 to 36 months after initiation ^{6,7}. However, a significant number of patients need to have their treatment regimens modified for various important reasons, including poor tolerability of the drugs, drug toxicities, drug-to-drug interactions (for example, there are contra-indications for the use of HAART when it coincides with tuberculosis (TB) treatment or pregnancy) and treatment failure.

1.2 RATIONALE FOR THIS STUDY

Optimizing initial HAART regimens in terms of their durability and efficacy is vital for the prognosis of patients starting HAART. In a clinical setting where drug options are very limited, it is also important to understand conditions that may lead to any modifications (modifications can either be a single drug substitution or a regimen switch) to a HAART regime and the risk factors that may be associated with such modifications or the poor tolerability of HAART. Such an understanding will help us to design drug regimes that

are better tolerated among our patient populations. This would contribute to the running of safe, efficient and cost-effective treatment programmes.

Data from this study will provide baseline information for the introduction of a pharmacovigilance system in Swaziland, a project which is already in progress. This study will provide initial data on the incidence and burden of the antiretroviral drug-related toxicities and the optimal time to monitor for such toxicities. Knowing when a drug change is most likely to occur (in this case, because of toxicity) will help clinicians to anticipate such clinical events. Such information would enable clinicians to time examination visits and laboratory test schedules to coincide as closely as possible with such potential clinical events. This will help to avoid unnecessary costs and examinations.

1.3 RESEARCH QUESTIONS

1.3.1 Aim of the study

The aims of the study were

- to identify reasons why physicians make drug modifications; and
- to describe the time before specific first time ARV drug modifications and the associated risk factors.

1.3.2 Specific research objectives

The study had four main research objectives that flowed from the aims of the research set out above:

- to identify different reasons for ART regime modifications
- to determine the incidence rate of modification for each individual ARV per person in terms of years of follow-up required;
- to determine the time before specific ARV drug modification are needed; and
- to determine whether or not demographic characteristics such as sex and age, and clinical characteristics such as the CD4 cell count at initiation, weight at initiation, type of treatment regimen and period of drug or treatment exposure are determinants for treatment modification.

CHAPTER 2

LITERATURE REVIEW

2.1 INTRODUCTION

Most of the data presented in the existing literature are derived from clinical trials. This implies that such data are not an accurate reflection of what actually happens in routine care, especially in the developing world. Reports from clinical trials which aim to measure efficacy are different to those that follow routine programme cohorts. In clinical trials, typically, it is reported that 5% to 10% of patients stop their randomized treatment due to toxicities or problems with adherence to the regimen. However, few studies have looked into reasons for drug changes during ART in a routine clinical setting.

Most of the prior studies that were identified were done either in Europe or in North America. No such study has ever been conducted in Swaziland. In addition, most of the research done on this topic has looked at observational cohorts in Europe. One of the major differences between cohorts in developed and developing countries is the use of individualised treatment as opposed to standardized regimens, as well as the use of more expensive regimens that include protease inhibitors as first-line. It should be noted that observational cohorts of HIV-infected patients have reported higher rates of discontinuation and failure than cohorts observed in clinical trials⁶⁻⁹.

Preferred treatment regimes differ, depending on the environment in which patients live. In well-resourced settings, the preferred first-line therapy is a combination of a Protease Inhibitor (PI) plus two nucleoside reverse transcriptase inhibitors. By contrast, locally and in other limited-resource settings, non-nucleoside-based therapy is preferred¹⁰⁻¹¹. Triomune (a fixed dose combination of nevirapine, lamuvidine and stavudine) was extensively used in number of limited-resource countries like Malawi, Swaziland, Lesotho and Zimbabwe.

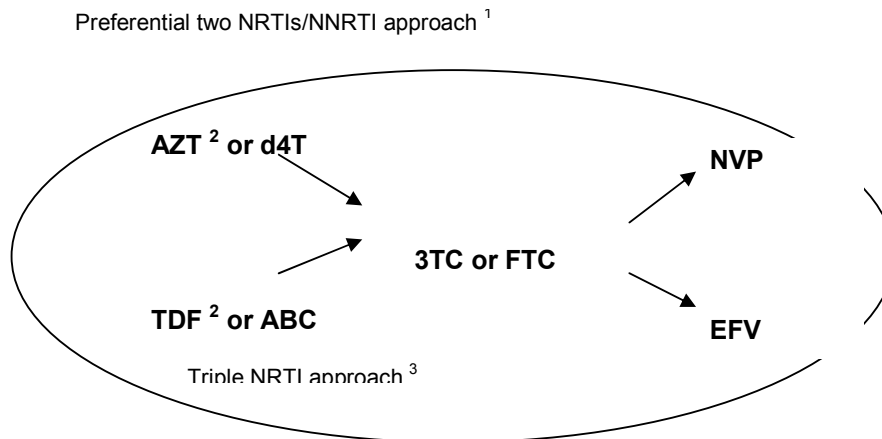
2.2 ANTIRETROVIRAL THERAPY REGIMENS IN RESOURCE-LIMITED SETTINGS

The scaling-up of ART provision in Africa has been impressive, rising from about 100 000 patients reached at the end of 2003 to about 810 000 patients at the end of 2005 ¹. ART is now considered an integral part of the comprehensive approach to HIV care and treatment. Studies clearly show that ART efficacy rates in Africa match those in the developed world ¹².

In limited-resource settings, treatment options are consolidated into two sequential potent regimens, which are called first-line and second-line ART. Guidance on simplified monitoring of treatment is readily available. The WHO has developed a standardized approach to treatment recommendations for resource-limited areas. In the standardized formula, first-line and second-line ART are emphasized. In the standard first-line approach, one non-nucleoside reverse transcriptase inhibitor (NNRTI) and two nucleoside reverse transcriptase inhibitors (NRTIs) are used, whereas in second-line ART, the PI class is used, plus two NRTIs ⁴. Simplified patient and laboratory monitoring algorithms to indicate when to initiate therapy, when to substitute/switch or stop therapy have been made readily available.

First-line ART is mainly NNRTI-based, with nevirapine (NVP) or efavirenz (EFV) as the preferred drugs. Stavudine (d4T) has been an essential part of the NRTI class, but, due to concerns over long-term toxicities, d4T is no longer a preferred drug. Zidovudine (AZT) is now recommended as an essential part of first-line ART, together with lamuvidine (3TC). Recently at the end of 2009, the WHO has added to its current recommendations, tenofovir (TDF), abacavir (ABC) and emicitrabine (FTC) as alternate first-line NRTI agents in resource limited settings. TDF is included because of its excellent safety profile and dosing schedule, as it can be taken once daily. Abacavir has been added to harmonize adult and paediatric treatment guidelines in order to facilitate a comprehensive family approach. However, because of the pricing of drugs, national HIV treatment programmes are allowed to be flexible enough to adapt their guidelines to accommodate the affordability of a given drug per country. PIs are generally reserved for second-line ART. Figure 2, below, shows the different first line drugs to start within resource-limited settings.

Figure 2: First Line Drugs for Adults and Adolescents



1 Preferential two NRTIs/NNRTI approach is based upon a combination of three drugs: two NRTIs combined with either NVP or EFV as the NNRTI.

2 Preferred NRTI to be combined with 3TC or FTC in standard first-line regimens.

Also a triple NRTI approach (i.e. three NRTI drugs selected only from the options shown within the dotted circle) can be considered as an alternative for first-line regimens in situations where NNRTI options provide additional complications (e.g. women who have CD4 counts between 250 and 350 cells/mm³, viral hepatitis coinfection, TB coinfection, severe reactions to NVP or EFV, and HIV-2 infection) as discussed above.

In resource-limited settings, the decision to start ART is mainly based on clinical and immunological criteria. Patient readiness to commence therapy is also an integral part of this process. Where CD4 cell monitoring or results are not available, the WHO's clinical staging is used after HIV infection is confirmed by antibody testing. Table 1 below shows the 2009 WHO recommendations for initiating ART ¹⁰.

Table 1: WHO Recommendations for ART Initiation

	Treatment recommendation
CD4 < 350 cells/mm ³	Treat irrespective of clinical stage
TB / HIV co-infection	Treat irrespective of CD4 count
W.H.O stage III or IV	Treat irrespective of CD4 count

Drug toxicity is a significant challenge that limits the use of ART. First-line drug toxicities usually fall into two categories: early and late toxicities. Early toxicity is usually experienced with hypersensitivity to NVP or EFV and central nervous system toxicities (CNS) due to EFV (usually transient psychotic episodes and dizziness after beginning EFV). These toxicities typically present in the first few weeks of therapy. Hypersensitivity is mostly seen with NVP and may result in a rash and if severe may lead to the development of a Steven Johnson syndrome requiring discontinuation of the offending drug. The CNS effects seen with EFV usually resolve after the first 2 weeks but if persistent and severe may require discontinuation of EFV. Most initial regimens used in resource-limited countries have included NVP or EFV and 3TC with d4T or AZT. Anaemia, neutropenia, lactic acidosis, lipodystrophy and peripheral neuropathy have been the most frequently reported late toxicities encountered with ART use. AZT-related anaemia and neutropenia typically present in the first few months after starting ART¹³⁻¹⁴. Table 2 shows common ART drug toxicities. Mitochondrial related toxicities (lipodystrophy, peripheral neuropathy, lactic acidosis, myopathy etc) are seen frequently with d4T use and still continue to contribute significantly to the burden of toxicity among patients on first line ART¹⁹⁻²⁰.

Table 2: Common ART toxicities, recommended tests at initiation and recommended drug substitutions

Drug	Recommended tests (if available)	Common associated toxicity	Suggested substitute
ABC	HLA-B*5701 genetic susceptibility screening	Hypersensitivity reaction / rash	AZT or TDF or d4T
AZT	Haemoglobin Neutrophil count	Severe anaemia / neutropenia / gastrointestinal intolerance Lactic acidosis	ABC or TDF or d4T TDF or ABC
d4T		Lactic acidosis / lipoatrophy / metabolic syndrome Peripheral neuropathy	TDF or ABC AZT or TDF or ABC
TDF	Renal function tests (creatinine clearance, urea , electrolytes)	Renal toxicity (renal tubular dysfunction)	AZT or ABC or d4T
EFV	Liver function tests (Alanine transferase, Aspartate)	Persistent and severe central nervous system toxicity Potential teratogenicity	NVP or any PI NVP or any PI
NVP	Liver function tests (Alanine transferase, Aspartate transferase)	Hepatitis Hypersensitivity reaction / Rash	EFV or any PI Any PI

2.3 EXPERIENCES WITH REASONS AND RISK FACTORS FOR ANTIRETROVIRAL DRUG CHANGES IN THE LITERATURE

Experiences with antiretroviral drug changes or modifications recorded in the literature are based on the types of regimen patients are receiving. Hence, these experiences are different in resource-limited settings from those in non-resource constrained settings. In

most North American and European cohorts, patients receive PI-based HAART, whereas in Sub-Saharan Africa, NNRTI-based HAART is the first-line regimen of choice.

When a single antiretroviral drug is stopped and replaced with another usually for toxicity and intolerance related reasons, this is called a substitution. With treatment failure, usually the whole regimen is completely changed and this is called a switch.

2.3.1 STUDIES ON PATIENT POPULATIONS ON MAINLY PI-BASED THERAPY

The most cited study on this topic is from the multi-centre Italian Cohort of Antiretroviral Naïve Patients (ICONA) study. In this study, during the follow-up period of median 45 months, 36.2% (312 out of 862 patients) discontinued therapy¹⁵. Drug toxicity (21.1%) was identified as the main reason, followed by non-adherence (7.1%). A further 5.1% discontinued therapy due to treatment failure, and the remainder had other reasons. The majority (84%) of this cohort initiated a PI-based regimen. Gastrointestinal side-effects were the main cause for toxicity-related discontinuations. Sex (women were twice as likely to have treatment changes than men), time spent on treatment, and the type of regimen started were risk factors independently associated with the probability of discontinuing HAART because of toxicity. A key strength of the ICONA study was that it recruited a large hospital-based cohort, hence providing a cohort that was more representative of patients seen in routine clinical practice than most cohorts enrolled into clinical trials. However, the relatively short follow-up period of median 45 weeks did not allow for an evaluation of long-term reasons, in other words, long-term toxicity.

The key findings of the ICONA observational study were similar to those of clinical studies conducted in large clinics in Europe¹⁵⁻¹⁷. In a United Kingdom cohort study, high rates of HAART modifications of up to 45% were observed, and in this same cohort, 26 % of the patients discontinued therapy. The study used a follow-up period of a median duration of 14 months¹⁷. More than 75% of this cohort had started a PI-based HAART regimen. Risk factors resulting in increased risk for discontinuation included old age, being treatment naïve when starting HAART, using nelfinavir as part of HAART, initiating on at least four antiretrovirals drugs, ritonavir use and virological failure. However, a major limitation of this study was that the patients were predominantly white

homosexual men, which may limit the extent to which the results can be generalized to other groups of patients.

In another study, in which the majority of patients were homosexual males of Dutch origin and 50% were treatment experienced, toxicity was also the most frequent reason for substitution; and the commonest types of drug substitutions were those of one PI with another PI. The one-year cumulative incidence of toxicity-driven modifications of this second regimen was 24%, mostly because of gastrointestinal side-effects and neuropathy¹⁸. The overall one-year cumulative incidence of modifying a second line HAART regime was 53%, indicating that half of these modifications were attributable to toxicity. A further sub-group analysis (10% of the studied cohort) showed that patients who had previously modified their regimen due to toxicity were also more likely to have their treatment modified during second-line treatment than those who had not modified due to toxicity: the relative risk (RR) was 2.5; the 95% confidence interval (95% CI) was 1.7-3.5). Other factors identified to be associated with toxicity-driven modifications were sex (women had a higher risk than men), the risk to modify treatment reduced as the calendar year increased and, interestingly, the type of switch – switching from a PI to NVP without changing the NRTI appeared to reduce the likelihood of a subsequent modification for toxicity reasons (RR 0.2; 95% CI: 0.1 - 0.6).

2.3.2 STUDIES ON PATIENT POPULATIONS BEING GIVEN MAINLY NNRTI-BASED THERAPY

Thus far, patterns and reasons for ART drug substitutions are poorly described in resource-limited settings. The studies discussed above were done in Europe and the drug combinations were mainly PI-based. This may not give a true reflection of patient populations in limited-resource settings who use NNRTI-based combinations.

Researchers in South Africa have looked at the reasons for drug substitution that were recorded in treatment-naïve adults receiving ART in two primary care treatment programmes in Cape Town¹⁹. Analysis included 2 679 individuals, followed for a median of 11 months. The predominant regimen (followed by more than 60% of the subjects) was EFV/3TC/d4T. At 3 years, 7.6% of the patients had been substituted off NVP, 7.8% were substituted off AZT, whereas only 1.9% had been substituted off EFV.

However, most substitutions were due to d4T, and these occurred in 21% of patients by the end of three years of follow-up. The main reasons for d4T substitution were symptomatic hyperlactataemia in 5% of the patients, lipodystrophy in 9% of the patients and peripheral neuropathy in 6% of the patients. Those at greatest risk of hyperlactataemia or lipodystrophy were women on ART for six months or longer, and patients weighing 75kg or more at baseline. During this follow up period, patients who initiated a regimen containing d4T, initiated a d4T 40mg dose if their weight was greater than or equal to 60kg whereas patients with weight less than 60 kg initiated on a d4T 30mg dose. They concluded that a high proportion of adult patients are able to tolerate their initial ART regimen for up to three years and that the risk of known toxicities could be minimized through early identification of patients at higher risk regarding such clinical events. A recent study in Cote d'Ivoire highlighted the role of incident pregnancy and tuberculosis in increasing first line ART modification rates during treatment. In this cohort, a third of all treatment changes occurred for reasons other than intolerance to the drug or treatment failure. Twenty percent of EFV substitutions resulted from pregnancy and 18% of NVP substitutions were related to tuberculosis treatment ²⁹.

2.4 OTHER RELATED STUDIES

Data analysed from a Swiss HIV cohort study and two ART programmes in townships (Khayelitsha and Gugulethu) in Cape Town, South Africa, has provided valuable information in comparing outcomes in patients from the two vastly different populations ²⁰. In this study, 99% of the South African cohort received two NRTIs and an NNRTI, whereas almost half of the Swiss cohort received two NNRTIs and a PI.

More frequent toxicity-driven modifications were reported in the Swiss cohort compared to the South African cohort, despite the fact that in Switzerland more drugs with favourable adverse effect profiles are available. The cumulative probability of change at two years due to toxicity was 23.8% (95% CI: 21.0%-26.7%) in Switzerland, compared to 11.7% (95% CI: 10.0%-13.5%) in Khayelitsha and Gugulethu. By contrast, the probability of changes due to failure was similar in Switzerland and South Africa: 5.1% (95% CI: 3.7%-6.8%) and 3.9% (95% CI: 2.5%-5.6%) respectively. The types of toxicity leading to treatment changes were fairly similar in both settings, with the exception of

symptomatic hyperlactataemia or lactic acidosis, which was recorded in 32 patients in South Africa, but was not observed in Switzerland. This difference was attributed to the widespread use of d4T in South Africa ²⁰. However, in the South African cohort, fewer patients modified their treatment because of lipodystrophy, despite the widespread use of d4T, which is known to be implicated in lipodystrophy, possibly because the follow-up period was relatively short. Most mitochondrial related toxicities occur later during treatment and a previous analysis of the Khayelitsha and Gugulethu cohorts showed that drug substitutions due to lipodystrophy occurred mainly after the first year of treatment ¹⁹.

Another important finding on the comparison of these two cohorts was that the initial virological response was similar, despite differences in patient characteristics and the approach to antiretroviral therapy, and different viral strains causing the epidemics in the two countries. Compared to South Africa, about twice as many modifications to treatment regimens were recorded in Switzerland during the first two years. An estimated 30.9% (95% CI: 27.7%-34.1%) of patients had modified their regimens for other reasons in Switzerland compared to 14.1% (12.1%-16.3%) in South Africa ²⁰.

In an Australian HIV observational database study, which analysed a total of 596 patients over a median follow-up of 2.3 years, the overall rate of ARV treatment change was 45% of the combinations per year. A low CD4 cell count at baseline was associated with an increased rate of treatment change. Combinations that included an NNRTI were also associated with lower rates of change than treatment combinations including a PI. However, the researchers did note the possibility that clinician or patient concerns about low immunological status may have led to earlier treatment changes in this group. Other interesting insights from this study were the use of the rate of treatment change as the endpoint and the further suggestion that it is feasible to adopt this endpoint for the analysis of HIV-infected cohorts rather than traditional endpoints such as AIDS-defining illnesses, which are now rare with HAART ²¹.

In the Development of Anti-retroviral Therapy in Africa (DART) trial in which patients were initiated onto either co-formulated AZT and 3TC plus TDF,NVP or plus ABC, 219 of 3 314 (6.6%) of the study participants developed severe anaemia by week 48 (haemoglobin level less than 6.5g/dl). Abacavir (ABC) hypersensitivity reactions were reported in about 2% of the study participants ¹³. A Ugandan study also showed that

during ART, nearly 50% of the patients experienced some form of toxicity by 18 months. These rates are similar to those in other cohorts¹³⁻¹⁴. Without the development of less toxic drugs, the durability of first-line treatment regimens is constantly under threat.

2.6 CONCLUSION

Treatment discontinuations or modifications described in the literature range from 24% to almost 50%. Toxicity is the major reason for modification in all studies, and accounted for 21% to 40% of all reasons for modification described¹³⁻²¹. Most studies revealed gastrointestinal toxicities as the most common, however, it should be noted that these studies were done on patient populations using PI-based therapy¹⁵⁻¹⁸. Gastrointestinal side-effects are a known major setback with PI use²². The pattern of antiretroviral drug modifications and the related reasons have previously been not described in Swaziland. We conducted a retrospective cohort study in Swaziland, a resource-limited setting, using NNRTI-based therapy in order to inform the Swaziland AIDS Programme and programmes in a similar setting on the risk factors and reasons for poor first line ART durability and subsequent drug modifications..

CHAPTER 3

METHODS

3.1 STUDY SETTING

The Mbabane Government Hospital Antiretroviral Therapy Unit is the biggest HIV outpatient clinic in Swaziland. It currently has 15 800 registered patients, of which 7 000 are presently on ART [by end of 2009]. The clinic is the flagship of the national roll-out programme administered by the Swaziland National AIDS Programme, which falls under the Ministry of Health and Social Welfare, and enjoys the assistance of various international partners. Standard WHO adapted treatment and care guidelines for resource-limited settings are followed ⁴.

Initiation is based on the WHO immunological and clinical criteria. During the study period, the 2006 WHO treatment guidelines were in use. All patients with a CD4 cell count lower than 200 cells/mm³ and WHO Stage IV diseases are eligible for HAART. The first-line treatment regimen consists of one NNRTI, namely NVP or EFV, plus two NRTIs, namely 3TC and d4T. Recently, AZT has come to be preferred over d4T as part of first-line regimen, unless contra-indicated. The testing of viral loads is not routinely done, because of the cost. Such testing is only indicated when treatment failure is suspected. After initiation, at two weeks, patients are reviewed specifically for the tolerability of drugs and any related side-effects, especially NNRTI-related adverse effects. The patient care is mainly doctor-driven in the first three months after initiation. After that, patients have to be screened by nurses to determine whether or not they require an appointment with a doctor. Screening usually involves taking the patient's medical history, a physical examination and vital sign measurements. If laboratory or other investigations are required, these are ordered by the doctors. Only physicians can prescribe medications; and these are dispensed at the unit pharmacy. At baseline or before initiation, a CD4 cell count, a full blood count (FBC), an Aspartate Transaminase (AST), an Alanine Transaminase (ALT) and renal function tests are done. The ALT and

AST are then repeated after two weeks. These tests are all repeated every six months

5.

The clinic records are kept both in a paper-based form and in an electronic database, which is being developed. The paper-based records consist of an individual patient file and an outpatient patient booklet (see Appendix B). An electronic database system has recently been introduced, and after each nurse's or doctor's appointment, vital patient clinical information that has been collected, as well as drug prescriptions and refills are entered in the database by data capturers. It is hoped that in the immediate future, this information will be entered into the database in 'real time' as patients are seen by the health care workers. Patients are currently expected to attend monthly visits for drug refills, consultations and also scheduled laboratory tests. A home-based follow-up system is currently undergoing finalization. Under this system, patients who miss clinic visits for three consecutive months will be identified and home visits will be arranged in order to trace if they are still alive (defaulted treatment or accessing care elsewhere) or not.

This study was done retrospectively to evaluate the reasons, risk factors and timing of ART modifications among patients on HAART at Swaziland's largest HIV clinic. The drug substitutions and switches investigated in this study were initiated by a doctor or health care worker. Patient self-treatment interruptions, including medication defaulting, were not evaluated.

3.2 STUDY DESIGN

This study was a retrospective cohort study.

3.3 SUBJECTS

3.3.1 Study population

The population under study was of HIV-positive male and female adult patients older than 16 years attending the Antiretroviral Therapy Clinic at the Mbabane Government

Hospital in Mbabane, Swaziland. They all started HAART between 1 March 2006 and 31 March 2008. The end-date for the follow-up was 31 December 2008. We chose 31 December 2008 to allow at least 9 months of follow-up time for the last accrued patient.

3.3.2 Target population

All HIV-infected patients on first-line ART in the public sector in Swaziland formed the target population.

3.3.3 Inclusion criteria

The following inclusion criteria were used:

- patients who were 16 years or older;
- patients who had started HAART between 1 March 2006 and 31 March 2008;
- patients who were ART naïve, with the exception of short-term Prevention of Mother to Child Transmission of HIV (PMTCT) prophylaxis; and
- patients with at least two recorded visits.

3.3.4 Exclusion criteria

The following exclusion criteria were used:

- patients who were younger than 16 years;
- patients who had initiated HAART outside the study dates given above;
- patients who had been exposed to ART before; and
- patients who had made only one or no recorded visit.
- patients who had missing gender, baseline CD4, outcome and censorship dates, or reason for modification

3.3.5 Sample size calculation

The sample size estimation in survival analysis where comparisons between groups are using the Log-rank test requires estimates of hazards of the two groups of primary comparisons. In this cohort study the primary comparative groups were males and females.. Females are more likely to modify treatment than males (60:40 female and male ratio respectively). We assumed a 5 % level of significance, the use of a two sided test in the analysis and 21% and 14% hazards of modifying treatment between females

and males respectively, Table 3 presents estimated minimum sample size for varying power.

Table 3: Sample size estimation for varying power

Parameter	Sample size (Assumed parameter values)		
	1.26	1.26	1.26
Hazard ratio	1.26	1.26	1.26
Power	80%	90%	95%
Number per group	360	482	596
Total number of events required	589	788	974

Table 3 shows that with 80% power we required a minimum sample size of 360 per group (720 total), to detect a minimum hazard ratio of 1.26 of modifying treatment.

A systematic sampling technique was used. From the electronic database, a total of 2820 patients had started HAART within the time period March 01 2006 and March 31 2008. We estimated that about 50% of the patients may not be eligible based on exclusion criteria and inadequate records. Every eligible patient from every second month of HAART initiation was selected to approximate our sample size as shown above.

3.4 MEASUREMENTS

At the clinic, sources for information were used:

- A database in the form of an Excel spreadsheet was available at the ART clinic in which patient information is captured for every visit. The spreadsheet in the database contains mainly the following variables; name and surname, ART number, date of birth, initiating regimen and date, baseline weight, CD4, liver function test and renal function test results, CD4 and weight for each visit date, regimen at each visit. Most patient observations had this information.

- The paper patient visit files, with the same information, plus other information, such as incidental treatment and doctors' case notes, were also used
- Another source for study information was the patients' hand-held booklet. This is a hand-held patient booklet which is used for refilling medications. It contains all the necessary patient demographic information, such as age and sex. The patient's weight is filled in at every patient visit. The booklet also contains some clinical notes, especially related to ART (treatment modifications), since the primary purpose of this document is collecting medication. All treatment substitutions or switches are recorded in this booklet.

A data collection tool was developed for the study, in the form of an Epi-data software screen. All the information was gathered from the database. Information that was missing on the database was supplemented from the patient file. It was found that the reasons for treatment modification were not recorded on the database. Therefore, in order to capture these reasons, patients who had modified their regimen were identified from the database and a list was created. Using this list, files were pulled from the filing room to gather the data. Where a file was missing or no reasons were recorded in a file, the patient's hand-held booklet was used. By using this approach, the data on reason for treatment modification could be completed

3.5 STUDY VARIABLES

3.5.1 Potential Predictor variables

The following variables were identified and are shown in Table 4 below.

Table 4: Variables screened

Variable	Units
Age	years
Sex	
Time on treatment	months
Baseline weight	kg
Baseline CD4 cell count	cells/mm ³
NNRTI in regimen	
NRTI in regimen	

The following quantitative variables were categorized:

- Baseline weight category:
wt_cat =0 corresponds to weight < 60kg and **wt_cat =1** corresponds to weight > 60kg;
- Baseline CD4 category:
cat_CD4 =0 corresponds to CD4 values < 200 cells/mm³ and **cat_CD4 =1** corresponds to values ≥ 200.
- WHO stage:
cat_stage_WHO =0 corresponds to WHO Stages 1, 2 and 3, whereas **cat_stage_WHO =1** corresponds to WHO Stage 4.

3.5.2 Outcome variables

Drug modification was defined as either a substitution or a switch. A substitution occurs when a single drug is replaced by another ARV for a specific reason. A switch occurs when a drug regimen (the triple combination) is completely changed for another triple ARV regimen. This is usually done with confirmed treatment failure.

3.6 QUALITY CONTROL AND PILOT STUDIES

Three data collection assistants assisted with the entry of the data into the Epi-data™ software. The training of the assistants involved teaching them how to use the Epi-data software for data entry. This was done before the pilot process and also during the piloting of the tool. Data collection did not depend on patients' giving the information, which precluded recall bias. The assistants recorded the measurements directly from the patient file. The inclusion and exclusion criteria were strictly adhered to, to limit bias. Results were adjusted for confounding through multivariate analysis.

A pilot study was conducted once ethics approval had been granted and was run over a single day. This was done at the ART Unit in order to identify any logistic and data-entry problems that might have arisen. The main problem that arose was the heterogeneity in the reasons for treatment change – they did not fit into our predetermined categories for possible reasons for treatment modification. These predetermined categories for

reasons for treatment modification were therefore adjusted to incorporate the reasons identified from the patient records.

3.6.1 Recording, storing and reducing data

Some of the data appeared on the clinic database as a spread-sheet. This data was then re-entered to a record review tool on an Epi-data screen (Epi-data™ software, see Appendix B). Data that was not available on the database spreadsheet was supplemented from the patient's paper records, as explained in Section 3.4 above. This information was then exported to STATA (Version 10, College Station, Texas, USA) for data analysis. This data in Epi-data and STATA format was only accessible to the principal investigator and the supervisors. All patient names were removed and study identities were assigned. The data set was password-locked to ensure confidentiality.

3.6.2 Assessing data quality

The dataset we created was assessed for missing data and inconsistencies. We used the sum command in STATA to identify any missing data. Scatter plots and box plots were used to identify any outlying data. The data set was also manually edited. The quality checks incorporated into the Epi-data screen for entering data took care of other possible errors in entering data, such as for date of birth: the Epi-data programme blocked the entry of any data for a patient with an age outside the inclusion criteria.

3.7 STATISTICAL ANALYSIS

Patient demographics and the clinical indices at the initiation of treatment and at the study endpoints were described, using percentages for categorical data and medians, inter-quartile ranges for non-normally distributed continuous data and means for normally distributed data. All tests were two-tailed with a p value < 0.05 as the cut-off level of significance. We identified reasons for modification and also calculated incidence rates for modification for individual drugs.

The study time was measured from the time the subject initiated ART to the time when the subject experienced an outcome or was censored. Patients were censored at the

date of their last recorded visit or date of death if they did not experience an outcome. The Log-rank (LR) test and Kaplan-Meier plots were used to compare the survival time between any two groups that were compared i.e. being on a d4T based regimen versus being on a non-d4T based regimen. Multivariate Cox proportional hazards regression models were used to estimate the adjusted hazards for drug modification for each significant risk factor.

3.7.1 Variable selection procedure for the multivariate analysis

The Akaike information criterion (AIC) is the appropriate model fit test for non-nested models as well as nested. It penalizes a model for lack of parsimony (for overparameterization). It calculates AIC value for each model with the same data set, and the “best” model is the one with minimum AIC value.

$$\text{AIC} = -2 * \text{Log likelihood} + 3q$$

We used a hierarchic approach to come to the final model. We first fitted a null model, followed by models that contained each variable. The important predictor variable – baseline CD4 was fitted first, and then the other variables fitted hierarchically in combination.

3.7.2 Testing the proportional hazards assumption

One of the main assumptions of the Cox proportional hazards model is proportionality. An objective statistical test, *Schoenfeld residuals PH test* was done after the rescaled schoenfeld residuals were generated. Cox regression with time-invariant covariates assumes that the ratio of hazards for any two observations is the same across time periods. *Partial residual plots*, a graphical method was also used to examine if covariates met this assumption. Partial residual methods are the most common and preferred methods for testing for non-proportionality in Cox models.

3.7.3 Dealing with the proportionality violation

A number of methods are available in modelling co-variables in which the proportional hazards assumption is violated ²³. In this study, the variable “d4T-based regimen” violated the assumption and we decided to use a piecewise Cox model to deal with this violation. This piecewise model is a non-proportional hazards Cox model with discrete time intervals. The piecewise modelling approach addresses the non-proportionality of this violating variable (d4T-based regimen). In this approach, we categorized the follow up time on HAART; and we report hazards on the two different time-periods. According to the log-log plots and the Kaplan-Meier curves, the hazards for the variable ‘d4T-based regimen’ are proportional before and after 11 months of treatment (see Appendix A).

3.8 ETHICAL CONSIDERATIONS

Ethics approval to conduct the study and disseminate the findings was granted by the Ministry of Health and Social Welfare Ethics Committee, Swaziland and also by the Ethics Committee of the University of Pretoria’s Faculty of Health Sciences (see Appendix B).

As mentioned earlier, the dataset was password locked and could only be assessed by the principal investigator and the supervisors. All patient names and addresses were removed and replaced by unique identifier numbers.

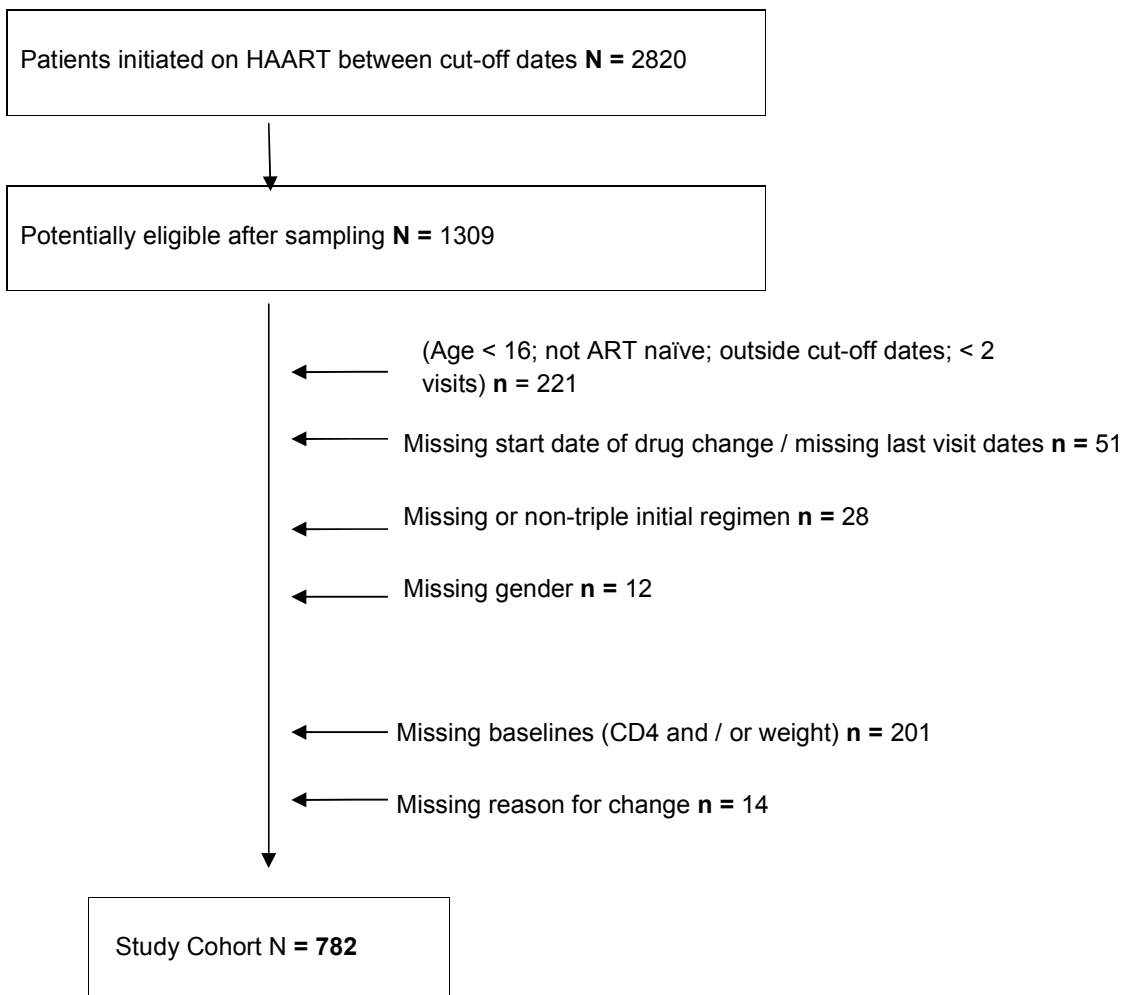
CHAPTER 4

RESULTS

4.1 STUDY SUBJECTS

The composition of the study cohort is depicted in Figure 3, below.

Figure 3: Study cohort



A total of 1309 out of 2 820 patients were potentially eligible for analysis after systematic sampling. Of the 527 patients who did not meet the inclusion and exclusion criteria, 306 patients had been excluded for missing data; 51 had missing important visit dates, 28 had missing regimens or ARV drugs, 12 had no gender recorded, 201 had missing important baseline measurements like weight and CD4 count and 14 had their regimen modified but the reasons were missing and could not be found from the records. A total of 782 patients were available for the analysis.

4.2 DESCRIPTIVE DATA

4.2.1 Baseline characteristics of study subjects

The baseline characteristics for the study cohort are summarized in Table 5 (next page). Out of the total 782 patients analysed, the majority (66.5%) were female, and the median age was 36 years. The median Cd4 cell count at initiation was 115 (IQR 64-183 cells/mm³), the median weight was 62 kg (55-70kg), and 52.8% of the patients were WHO Stage 3 and 4 (n=386). The most common regimens initiated were NVP/3TC/d4T (36.1%) and NVP/3TC/AZT (37.9%). Almost 20% of the patients started on EFV/3TC/AZT (19.6 %), whilst 5% started on EFV/3TC/d4T. Less than 1.6% of the patients started on a PI-based regimen.

Table 5: Baseline characteristics of the study participants

Characteristic at ART initiation	Summary
Total	782
Male, n (%)	262 (33.5%)
Female, n (%)	520 (66.5%)
Age (years), median (IQR)	36 (31 – 43)
CD4 count (cells/mm ³), median (IQR)	115 (64 – 183)
CD4 count < 200 cells/mm ³ , n (%)	629 (83%)
CD4 count ≥ 200 cells/mm ³ , n (%)	129 (17%)
Baseline weight (kg), median (IQR)	62 (55 – 70)
Baseline weight < 60kg, n (%)	305 (40.8%)
Baseline weight ≥ 60kg, n (%)	442 (59.2%)
W.H.O Stage IV, n (%)	186 (25.4%)
W.H.O Stage I/II/III, n (%)	545 (74.6%)
Initial first line ART regimen	
NVP-3TC-AZT, n (%)	296 (37.9%)
NVP-3TC-d4T, n (%)	282 (36.1%)
EFV-3TC-AZT, n (%)	153 (19.6%)
EFV-3TC-d4T, n (%)	38 (4.9%)
Other, n (%)	13 (0.7%)

All CD4 values are at baseline. IQR – interquartile range; NRTI – non-nucleoside reverse transcriptase inhibitors; HAART – highly active antiretroviral therapy; NVP – Nevirapine; EFV – Efavirenz; 3TC – Lamivudine; d4T – Stavudine; AZT – Zidovudine; Missing values: age (n=1); WHO stage (n=51); Some CD4 count (n=24) were set to missing as they were abnormally out of range (may not have been baseline values);.

4.2.2 Follow-up time

The subjects were followed up to a maximum of 33 months. The median follow-up time was 21 months (IQR 12.3-27.5 months). That is a total of 1 296.40 person-years of follow-up.

4.3 OUTCOME DATA

4.3.1 Reasons for drug modification

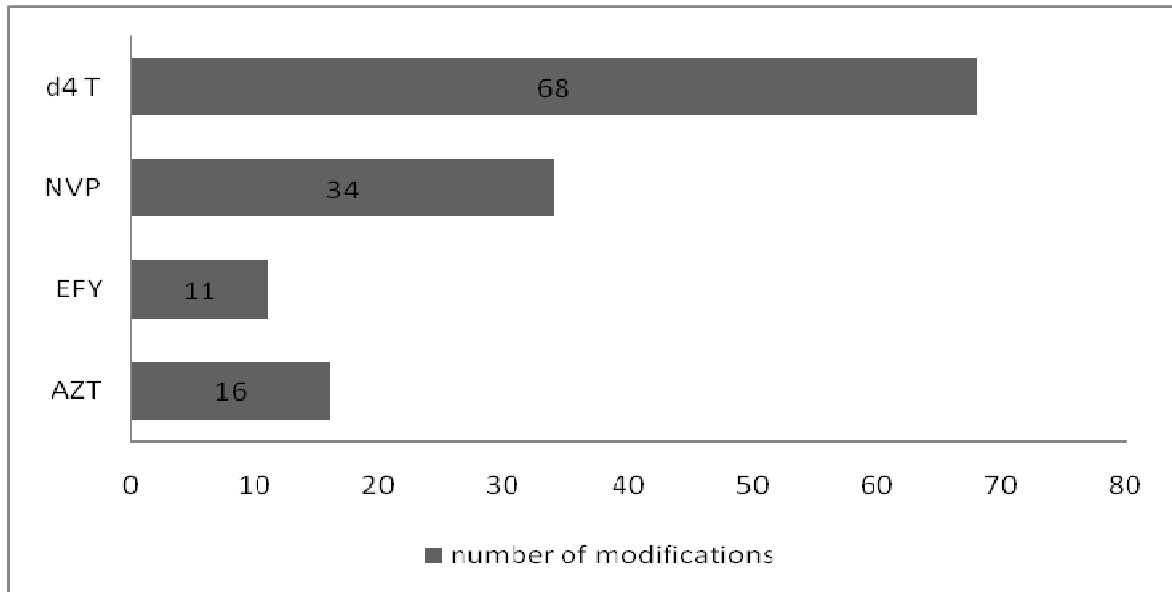
A total of 137 out of 782 patients (17.5%) had first line drug modifications during the study follow-up period. Drug toxicity was the commonest reason for drug change, 77%. Peripheral neuropathy and lipodystrophy (including lipoatrophy) were the most common toxicity-based reasons, 23.4% and 22.6% of the total number of drug changes respectively. This is illustrated in Table 6 (next page). Reasons related to drug contra-indication accounted for 19.7% of the treatment modifications, mainly TB treatment (3.1%, n=18) and pregnancy (1.5%, n=9). Of note, in Table 6, the reason known as “Drug shortage” refers to when patient’s regimens were modified due to unavailability of drugs, while “Pill load” refers to a patient who was on ritonavir boosted-saquinivir, lamuvidine and stavudine (6 tablets twice a day) and because of huge amount of drugs she was taking, this regimen was simplified to fixed dose Triomune (NVP/3TC/d4T).

Table 6: Reasons for Antiretroviral treatment modification

Reason	n (%)
Drug Contra-indication	
TB treatment	18 (13.1%)
Pregnancy	9 (6.6%)
Toxicity / Side-effect	
Peripheral neuropathy	32 (23.4%)
Lipodystrophy / Lipoatrophy	31 (22.6%)
Anaemia	10 (7.3%)
Hypersensitivity rash	9 (6.6%)
Hepatitis / raised transaminases	8 (6.0%)
CNS disturbances	5 (3.7%)
Lactic acidosis	3 (2.2%)
Vomiting	2 (1.5%)
Gynaecomastia	2 (1.5%)
Myalgia	2 (1.5%)
Darkening of nails	1 (0.7%)
Treatment Failure	2 (1.5%)
Other reasons	
Drug shortage	2 (1.46%)
Pill load	1 (0.73%)
Total	137 (100%)

TB – tuberculosis. Total (N=137): Drug contraindication (n=27, 19.7%); Toxicity (n=105, 77%); Treatment failure (n=2, 1.5%) and other reasons (n=3, 2.2%).

Figure 4: Drug modifications



AZT=16; EFV=11; NVP=34; d4T=68; NVP/3TC/AZT, n=1; NVP/3TC/d4T, n=6 and SQV/rt, n=1.

The majority of the modifications were single-drug substitutions; d4T (49.6%, n=68), followed by NVP (24.8%, n=34), then AZT (11.7%, n=16), EFV (8%, n=11) and 1 drug substitution was of ritonavir – boosted Saquinavir (SQV/rt) (due to an increased pill load). Figure 4 above illustrates this. Regimen switches accounted for 5% (n=7) of the modifications. Of these switches, six were of NVP/3TC/d4T (due to lactic acidosis, n=1; drug shortage=2; treatment failure, n=2; severe rash, n=1) and the other one was of NVP/3TC/AZT due to hepatitis.

The incidence rates for treatment change based on the different regimens are shown below in Table 7.

Table 7: Incidence rates for treatment change by regimen

Regimen	Incidence rate
d4T-based regimen	11.3 per 1 000 person-years of follow-up
AZT-based regimen	6.1 per 1 000 person-years of follow-up
NVP-based regimen	9.5 per 1 000 person-years of follow-up
EFV-based regimen	6.0 per 1 000 person-years of follow-up

4.4 KAPLAN-MEIER AND CUMULATIVE HAZARDS ESTIMATES FOR TREATMENT CHANGE

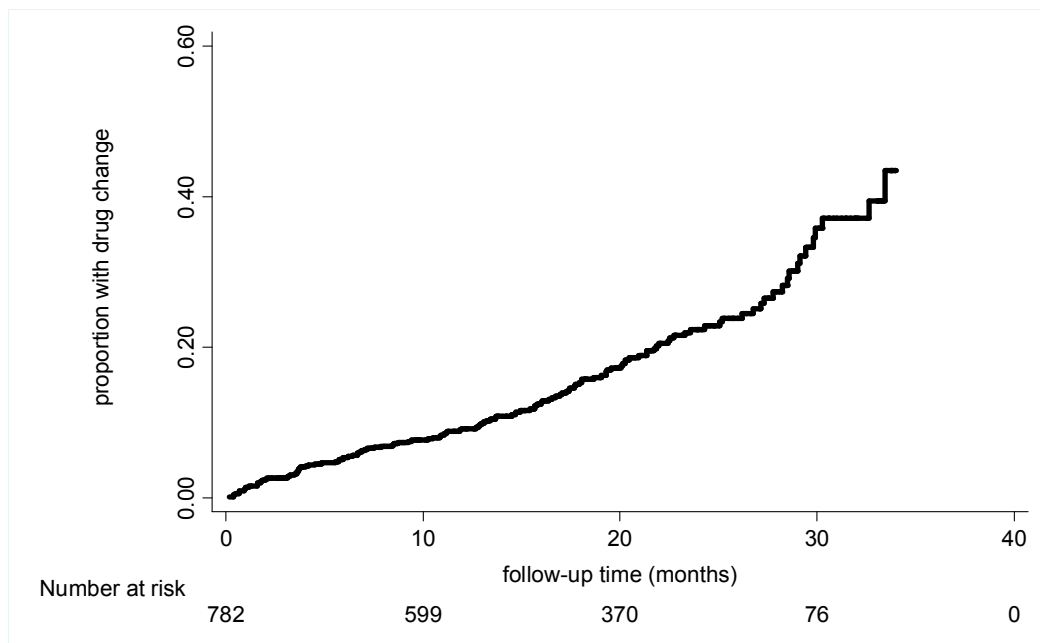
The table below (Table 8) shows the different probabilities of modifying treatment with time. The probability of treatment modification increased with the time spent on a treatment.

Table 8: Probability of modification according to time on treatment

Time on treatment	Probability modifying treatment (95% CI)
0 months	0
10 months	0.07 (0.06 – 0.10)
20 months	0.16 (0.13 – 0.19)
30 months	0.30 (0.25 – 0.36)

The overall survival plot showing the cumulative hazard estimates for treatment modification is shown below in figure 5.

Figure 5: Cumulative proportion modifying first-line ART regimen in the study cohort



The survival plots of time to treatment change stratified by the different categorical variables are shown below. These give insight into the shape of the survival function in each group. All the curves are approximately parallel, implying that the proportional hazards assumption has been met, except for the plot stratified by regimen. The following variables had significantly different survival curves; weight category < 60 kg versus weight category ≥ 60 kg at baseline (log-rank test: $p=0.002$) shown in figure 7; d4T versus TDF/AZT in regimen (log-rank test: $p=0.007$) shown in figure 8 and baseline CD4 category < 200 cells/mm³ versus baseline CD4 category ≥ 200 cells/mm³ (log-rank test: $p<0.001$) shown in figure 9. However, the survival curves were not significantly different for the following variables: male versus female gender (log-rank test: $p<0.12$) shown in figure 6; WHO stage 4 versus WHO stage 1, 2, 3 (log-rank test: $p<0.88$) shown in figure 10 and NVP versus EFV in regimen (log-rank test: $p<0.06$) shown in figure 11. These survival plots are shown below.

Figure 6: Cumulative proportion modifying regimen, stratified by gender

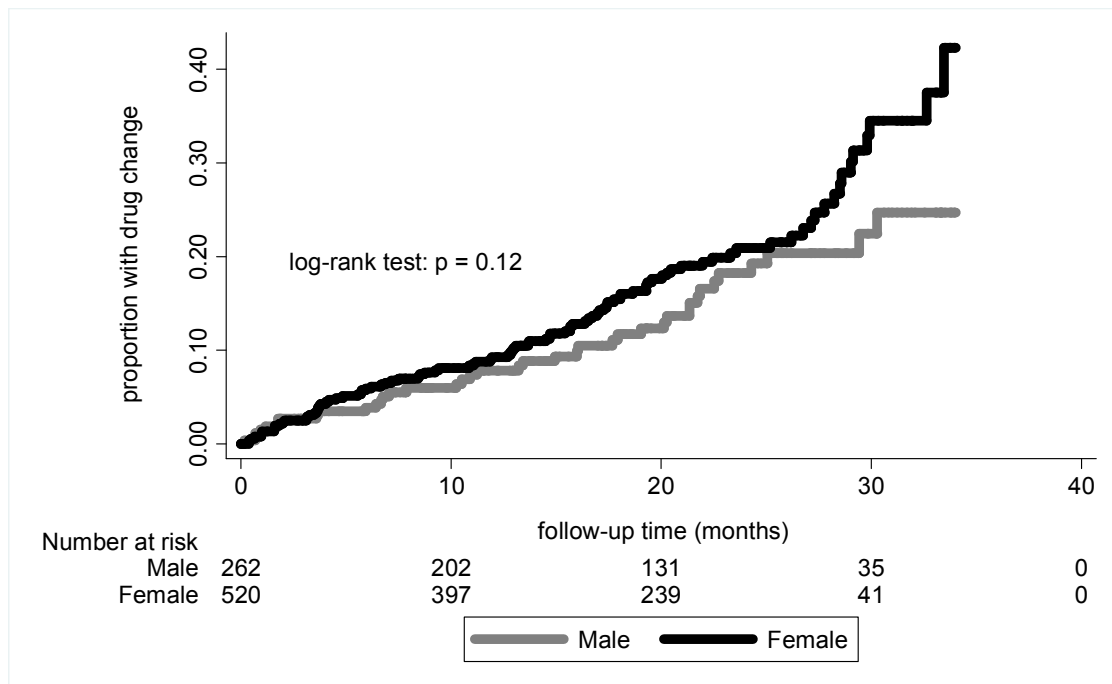


Figure 7: Cumulative proportion modifying regimen, stratified by weight

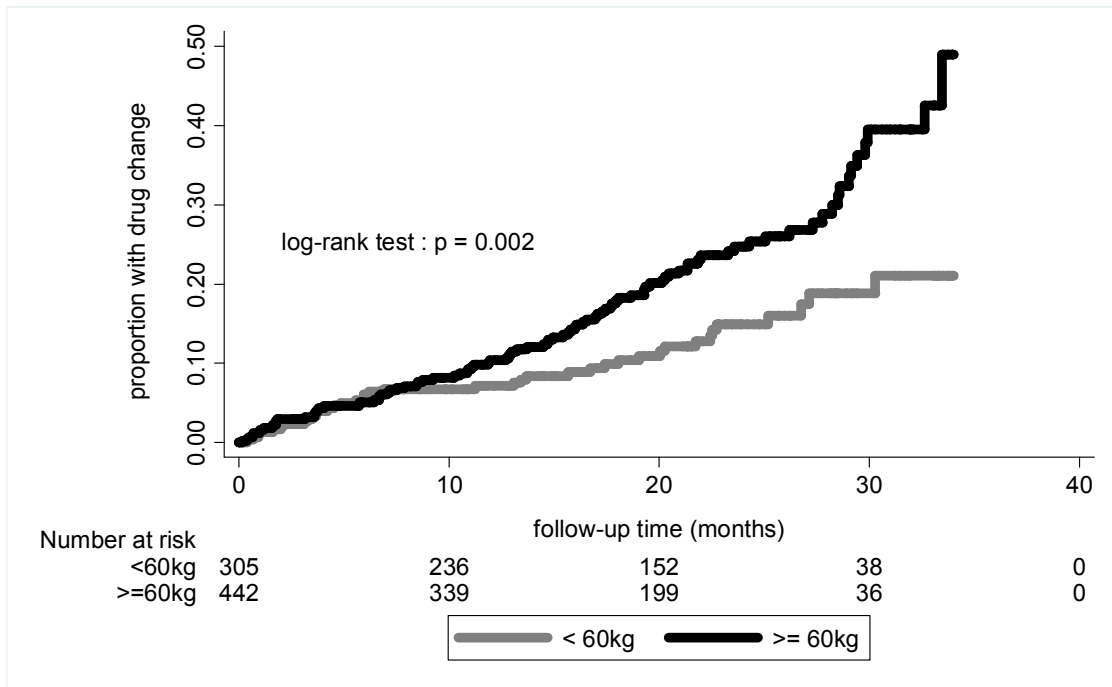


Figure 8: Cumulative proportion modifying regimen, stratified by NRTI regimen

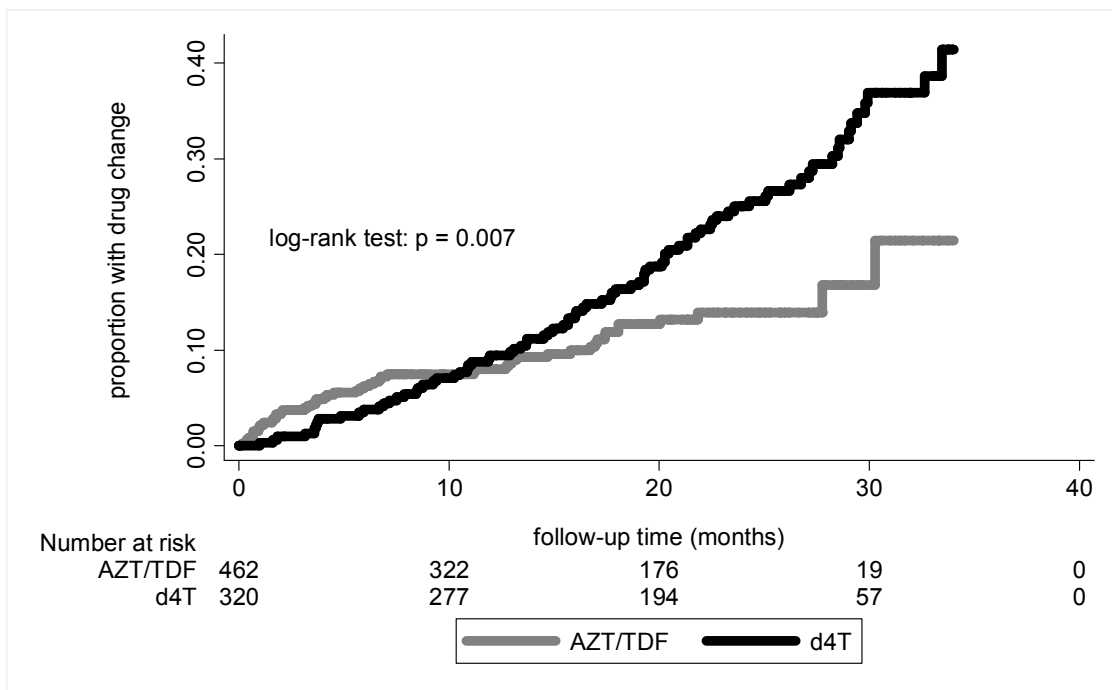


Figure 9: Cumulative proportion modifying regimen by baseline CD4 category status

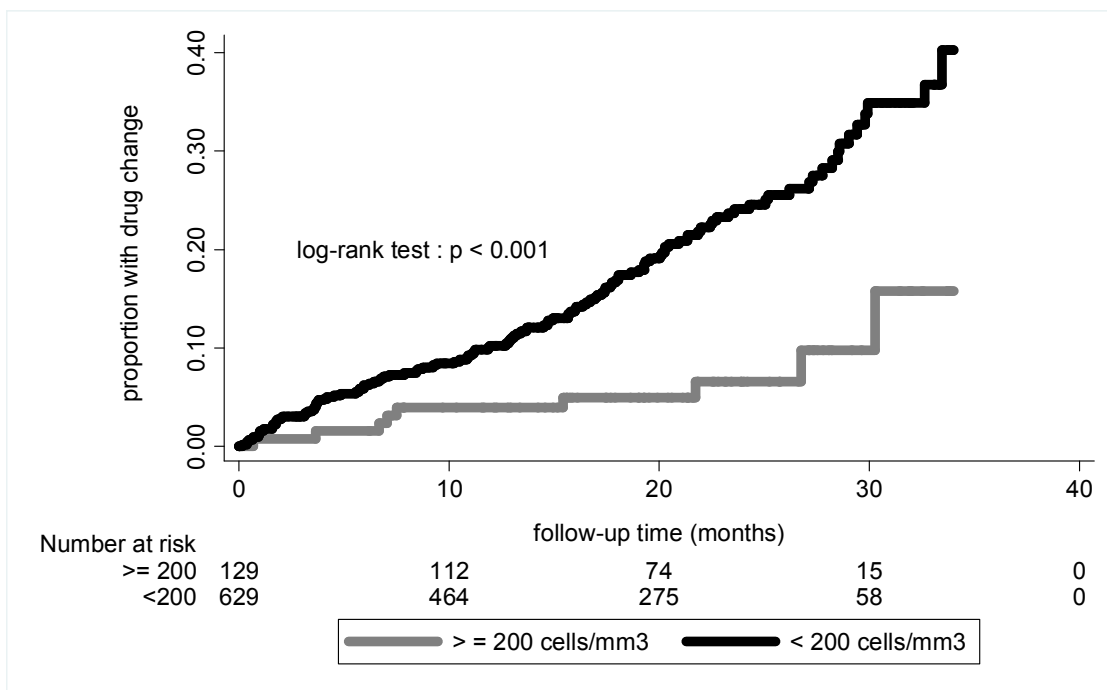


Figure 10: Cumulative proportion modifying regimen, stratified by baseline WHO stage

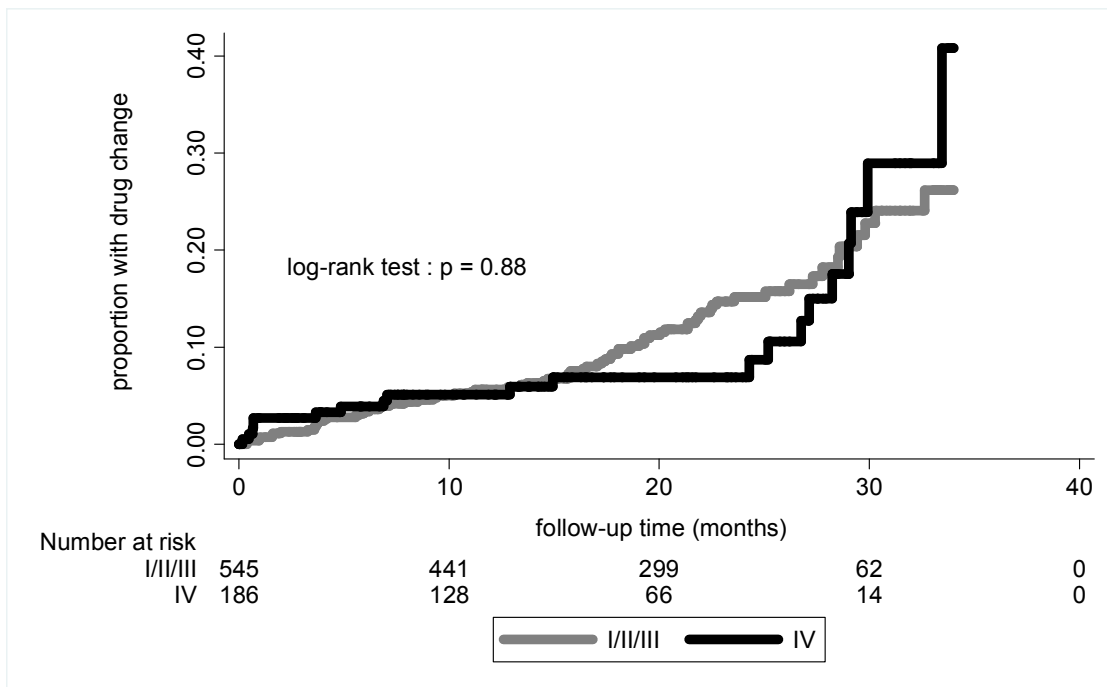
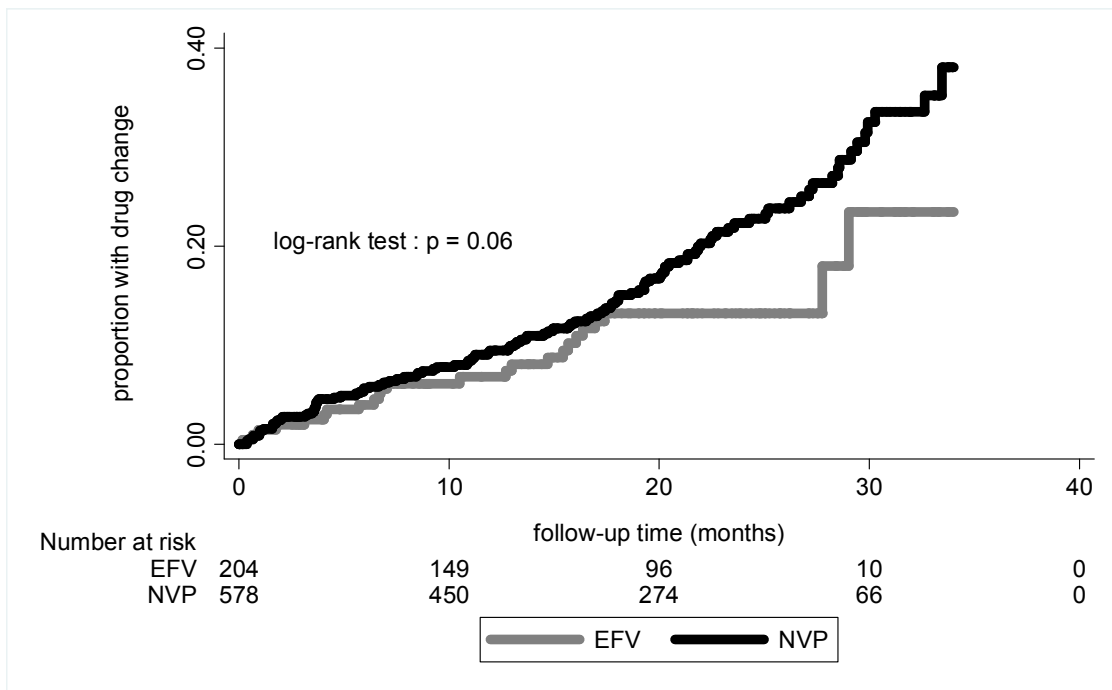


Figure 11: Cumulative proportion of modifying regimen, stratified by NNRTI regimen



4.5 UNIVARIATE COX PROPORTIONAL HAZARDS ANALYSIS

In the univariate analysis, patients with a CD4 < 200 cells/mm³ versus ≥ 200 cells/mm³ at the initiation of HAART had the strongest risk or hazard of treatment modification (HR =3.38, 95% CI: 1.72–6.65, p < 0.001). The initial regimen (d4T-based or NVP-based regimen), the WHO stage at initiation (stage 1, 2, 3 versus stage 4), and baseline weight (weight ≥ 60kg versus < 60kg) were also significantly associated with treatment modification in the univariate analyses (p < 0.05). However, gender and age were not statistically significant risk factors in this analysis.

The table (Table 9) below illustrates the results for the univariate analysis (crude hazard ratios).

Table 9: Crude hazard ratios for treatment modification

Risk factor	crude HR (95% CI)	p-value
Female vs male	1.34 (0.93-1.95)	0.12
Weight > 60kg vs weight < 60kg	1.82 (1.26-2.65)	0.002
Age (years)	1.01 (0.99-1.03)	0.31
CD4< 200 cells/mm ³ vs > 200 cells/mm ³	3.38 (1.72–6.65)	< 0.001
WHO stage I/II/III vs WHO stage IV	0.96 (0.56-1.58)	0.88
NVP in regimen vs EFV in regimen	1.53 (0.98-2.38)	0.06
d4T in regimen vs AZT / TDF in regimen	1.62 (1.14-2.30)	0.007

HR – hazards ratio; CI – confidence interval; NVP – Nevirapine; EFV – Efavirenz; AZT – Zidovudine; d4T – Stavudine

4.6 TESTING THE PROPORTIONALITY ASSUMPTION

The proportionality assumption did not hold for variable ‘d4T-based regimen’. This is shown below in Table 10 in the results of the Schoenfeld residuals Proportional Hazards test (stphtest). The annotated STATA log in Appendix A illustrates this. In this test, the null hypothesis is that the hazards are proportional for the covariate. A significant p value ($p < 0.05$) rejects this null hypothesis. Overall, the model did not violate the proportionality assumption (global test, $p > 0.05$), however the covariate d4T-in-regimen violated this assumption ($p < 0.05$).

Table 10: Results for the Schoenfeld residuals Proportional Hazards test

	rho	chi2	df	p-value
d4T in regimen	0.25	5.48	1	0.02
Weight > 60kg	0.12	1.28	1	0.26
CD4 > 200cells/ mm ³	-0.10	0.71	1	0.40
Global test		7.21	4	0.13

Since the proportional hazards assumption was violated we had to model using a different method. Options include stratifying the model by the offending variable, including time varying covariates, using a piecewise Cox model and using accelerated failure time models. We proceeded to model the data using a piecewise Cox regression model.

4.7 PIECEWISE COX PROPORTIONAL HAZARDS MODEL

This is a non-proportional hazards Cox model with discrete time intervals. The piecewise modelling approach addresses the non-proportionality of this violating variable (‘d4T-based regimen’). In this approach, we categorized the study observations to two different time periods: before 11 months and after 11 months of treatment; and we report hazards on the two different time-periods. According to the log-log plots and the Kaplan-Meier curves, the hazards for the variable d4T regimen are proportional before and after 11 months of treatment, in other words, the curves cross at this time

(see annotated STATA log – Appendix A). Table 11 shows the results of this analysis (see next page).

As the proportional hazards assumption did not hold, a piecewise Cox's regression model was fitted with two time periods, up to and including 11 months of time on ART and beyond 11 months on ART. This multivariate model was computed to estimate separate hazard ratios before and after 11 months on ART.

The model with the best fit / lowest AIC contained the following variables: baseline CD4 category, baseline weight category, WHO stage at initiation, age, gender and d4T in regimen. The model was significant at $p < 0.001$. See selected annotated STATA log section in the Appendix.

In the first 11 months of therapy, baseline CD4 < 200 versus CD4 ≥ 200 cells/mm³ (HR = 1.14; 95% CI: 0.45 – 2.90), d4T vs AZT/TDF in the regimen (HR = 1.41; 95% CI: 0.82 – 2.44) and baseline weight ≥ 60 kg vs < 60 kg (HR = 1.22; 95% CI: 0.71 – 2.11) and female gender (HR = 1.26; 95% CI: 0.59 – 2.70) increased the hazards for treatment modification, however these estimates did not reach statistical significance. A yearly increase in age seemed not to be associated with the risk of treatment modification (HR = 0.98; 95% CI: 1.00 – 1.05).

However, after 11 months of ART, the hazard estimates for these risk factors for treatment modification were higher and they attained statistical significance. These estimates were as follows: baseline CD4 < 200 versus CD4 ≥ 200 cells/mm³ (HR = 4.42; 95% CI: 1.62 – 12.1), d4T vs AZT/TDF in the regimen (HR = 2.64; 95% CI: 1.56 – 4.46) and baseline weight ≥ 60 kg vs < 60 kg (HR = 2.40; 95% CI: 1.43 – 4.04). Female gender (HR = 1.56; 95% CI: 0.86 – 2.85) was also a risk factor for modification but the estimates were not statistically significant. A yearly increase in age still was not strongly associated with the risk of treatment modification.

We evaluated the following interaction terms: baseline CD4 value and WHO stage; WHO stage and weight; and d4T and NVP in regimen. All three interaction terms were non-significant. The variables NVP and EFV in regimen showed strong collinearity. The

Spearman's rank correlation coefficient was -1. We dropped EFV from the analysis since most patients were on NVP based regimens.

Table 11: Risk factors for ART modification

Risk factor	Crude HR (95% CI)	Adjusted HR (95% CI)	
		duration on ART < 11 months	duration on ART > 11 months
d4T in regimen vs AZT/TDF in regimen	1.62 (1.14 – 2.30)	1.41 (0.82 – 2.44)	2.64 (1.56 – 4.46)
Weight ≥ 60kg vs weight < 60kg	1.82 (1.26 – 2.65)	1.22 (0.71 – 2.11)	2.40 (1.43 – 4.04)
CD4 < 200c/mm ³ vs CD4 ≥ 200c/mm ³	3.38 (1.72 – 6.65)	1.14 (0.45 – 2.90)	4.42 (1.62 – 12.1)
Female vs male	1.34 (0.93 – 1.95)	1.26 (0.59 – 2.70)	1.56 (0.86 – 2.85)
Age	1.01 (1.26 – 2.65)	0.98 (0.95 – 1.02)	1.03 (1.00 – 1.05)
WHO stage I/II/III vs stage IV	0.96 (0.56 – 1.58)	0.74 (0.34 – 1.62)	0.89 (0.44 – 1.78)
NVP in regimen vs EFV in regimen	1.53 (0.98 - 2.38)	-	-

HR–hazards ratio; 95% CI–95% confidence interval; NVP–Nevirapine; EFV–Efavirenz; AZT–Zidovudine; d4T–Stavudine and TDF-Tenofovir.

CHAPTER 5

DISCUSSION

Our study provides unique and important data on reasons for and risk factors involved in antiretroviral treatment modifications in routine clinical set-ups in resource-limited settings. These results are highly relevant to resource-limited settings since preferred treatment regimens and patient characteristics differ from widely reported observational cohorts in Europe, North America and clinical trial settings.

Over the median follow-up time of almost two years, fewer than 20% of the patients modified their initial antiretroviral regimen. Toxicity, namely lipodystrophy and peripheral neuropathy mainly due to stavudine (d4T) was the most common reason for treatment modification. Beyond 11 months of being on ART, having d4T in the initial regimen and a baseline weight over 60kg increased the hazards for modification almost three times, whereas initiating HAART with a CD4 cell count lower than 200 cells/mm³ increased the hazards for modification almost four times. Increase in age and female gender also increased risk for modification, though these estimates did not reach statistically significant.

This study clearly shows that, in this setting, overall a high proportion of patients were able to tolerate their initial antiretroviral regimen. Only 18% of the patients over a median follow-up period of 21 months modified their treatment. This percentage is far lower than reported in other observational cohorts, mainly in Europe and North America, where treatment modification rates were higher, 36 % to 53 %^{15-18, 21}. The lack of alternative treatment options in resource-limited settings may influence clinicians to be more reluctant in modifying regimens, regardless of the indication. Also current guidelines for treatment in limited resource settings encourage the use of rigid predetermined cost-effective regimens^{4, 5}. Another issue to consider is that patients in limited resource cohorts may be less informed about their treatment and treatment options whereas patients elsewhere are more informed about their care and would therefore anticipate any unusual effects that could be attributed to their treatment. Such informed patients would be ready to report any intolerance and have their drugs

modified. Also, cohorts in developed countries are treatment experienced and some of their patients have been on mono- or dual-therapy which may also be related to increased treatment modification rates.

Toxicity-related factors have been identified as the most common reason for treatment modification in other studies¹³⁻²¹. This finding is supported by the results of our study. Gastrointestinal toxicities – nausea, vomiting and diarrhoea – are the most commonly reported toxicities resulting in treatment modification, especially in European and North American cohorts^{15,16,18,22}. These kinds of toxicity may be due to the frequent use of protease inhibitors (PIs) as part of first-line regimens in developed countries, as PIs are known to cause serious gastro-intestinal toxic effects^{4,10,22}.

In contrast, mitochondrial-related toxicities such as lipodystrophy and peripheral neuropathy were the majority of the toxicities which resulted in treatment modification in this study. This is due to the widespread use of d4T in this clinical set-up, as well as the use of AZT. This is supported by a similar study in Cape Town, South Africa, where regimens used were very similar¹⁹. In this Cape Town cohort, the largest number of drug substitutions due to toxicity was in patients on d4T. Approximately 21% of those who originally started a d4T based regimen had substituted it because of toxicity. Of these d4T substitutions, 9% were due to lipodystrophy, 6.2% due to peripheral neuropathy and 4.7% were due to symptomatic Hyperlactaemia. Our findings also clearly demonstrate how poorly tolerated d4T-based regimens are and raises questions about the continued role of d4T in first-line treatment guidelines. It supports recent recommendations to move away from such regimens²⁴.

Treatment modification due to anaemia related to AZT toxicity were significant (7.3 % of the modifications). This highlights the need to screen patients for anaemia before the initiation of therapy. Similar results were shown in the DART trial¹³.

NVP in a treatment regimen was well tolerated, accounting for less than 10% of the reasons for modification. This finding is in contrast to those in well-resourced settings, where NVP use is discouraged, especially in patients with higher CD4 cell counts^{25,26}. However patients in our setting usually start on ART with lower CD4 counts. NVP is widely used in this resource-limited setting and is predominantly tolerable, which is consistent with other studies done in sub-Saharan Africa^{27, 28}. More studies are still

required in resource-limited populations to determine the safety and tolerability of NVP-containing regimens. However, were d4T is not used, NVP seems to contribute to a significant burden of toxicity as shown by results from a study looking at clinical outcomes after providing ART for 2 years in Kayelitsha, Cape Town²⁹. In this cohort of 287 patients beginning mainly AZT based regimens (only 2 out of 287 had d4T in their regimen), the highest proportion of drug modifications attributed to adverse events was for NVP (8.8% of patients had changed to EFV at 24 months). Only 4.7% had to change AZT to d4T due to anaemia. For all regimens combined, 8.4% of patients had an intolerance-driven modification to their first regimen cumulatively by 24 months. Most changes occurred soon after treatment was started (median 42 days; IQR, 28-56 days). A further 10 patients substituted from nevirapine to efavirenz due to a diagnosis of tuberculosis and 3 patients from efavirenz to nevirapine due to pregnancy or a wish to become pregnant. Drug contra-indications mainly due to drug-drug interactions with TB treatment and the diagnosis of pregnancy during HAART also contributed to modification in our study. About 13% of the reasons given for modification were due to a patient's initiating TB therapy; and 6.6% were due to a diagnosis of pregnancy during therapy. This clearly emphasizes the burden of TB in this setting and brings out the need for more aggressive TB screening in patients initiating HAART. Family planning programmes should also be routinely integrated into routine HIV care, to prevent unplanned and unwanted pregnancies. Patients most likely to become pregnant need to be identified early on during their treatment. These findings confirm recent findings by a recent study in Côte d'Ivoire³⁰. In this Côte d'Ivoire study, the rate of treatment modifications was 20.7/100 patient-years. Overall 24% of patients modified therapy (483 out of 2012 patients). The most frequent drug substitutions were due to intolerance (12.4/100 patient-years), pregnancy (4.5/100 patient-years) and tuberculosis (2.5/100 patient-years). Twenty percent of efavirenz substitutions resulted from pregnancy and 18% of nevirapine substitutions were related to tuberculosis treatment.

In contrast with the findings of other reported studies, gender was not a significant risk factor for treatment modification in this population^{9,15,18}. Age in this cohort was also not a significant risk factor for treatment modification, a finding which is consistent with what has been observed in other studies^{13,14,19}. However, the burden of toxicity requiring treatment modification from d4T-containing regimens threatens the tolerability of first-line regimens in resource-limited settings which rely heavily on stavudine. In July 2007,

amid some donor controversy, the Zambian Ministry of Health introduced TDF as part of first-line therapy, making it the first African country to use the drug on a wide scale. Despite the higher cost associated with these drugs, the Ministry of Health based their decision on the TDF's favorable toxicity profile, its high genetic barrier to resistance, and its once-daily dosing schedule. Preliminary safety and tolerability results are encouraging³¹.

Weight at initiating HAART was also a very strong risk factor for modification. However it is important to note that over the patient accrual period for this retrospective study, patients with a baseline weight over 60 kg were then recommended to initiate a higher dose of d4T (40mg if their weight was over 60 kg versus 30mg if their weight was less than 60kg) [5]. Doses of d4T above 30mg are no longer recommended, as they have been shown to have a worse toxicity profile, besides achieving a similar efficacy to the 30mg dose^{32,33}. Heavier patients have also been shown by some studies to be more susceptible to mitochondrial-related toxicities^{32,33}. Where other treatment options are not available, a risk score for toxicity and tolerability could be useful in pre-determining treatment regimens.

Patients initiating HAART with lower CD4 cell counts had poor regimen durability, compared to those with higher CD4 counts at initiation. A baseline CD4 cell count less than 200 cells/mm³ increased the hazards for treatment modification by over four times, compared to a baseline less than 200 cells/mm³. These results are consistent with other findings showing that sicker patients are more likely to have more side-effects and more regimen changes as they are on other medications for opportunistic infections, than those with higher CD4 at initiation^{34,35}. However, the very high hazards estimates need to be interpreted with caution, since the 95% confidence interval is wide for this hazard ratio. Currently, Swaziland treatment guidelines adapted from WHO guidelines for resource-limited settings recommend initiating HAART at a CD4 less than 200 cells/mm³, or if the WHO stage is advanced. Poor regimen durability shown in this subgroup of patients initiating HAART also provides evidence that initiating HAART earlier, at CD4 cell counts well above 200 cells/mm³ should be the current standard of care. Besides improving patients' clinical prognosis, this approach will also improve the ART regimen durability²⁴. This is of paramount importance, especially in resource-limited

settings where ART options are restricted. Current guidelines are being revised to reflect this.

The major strength of this study is that the data comes out of a typical under-resourced setting which mirrors routine clinical practice in undeveloped places, especially Africa. This is in contrast to other studies either from Europe, North America, clinical trial settings or academic institution-affiliated treatment sites in which the practice may be different^{15,16,18,22}.

However, this study has some limitations. A retrospective review of medical records has a risk of misclassification bias since information that was not recorded appropriately during patient follow-up may be misinterpreted or coded wrongly. A lot of records were excluded because of missing values and these may have been informative on our outcome. The analysis of a single treatment site, even though it is the largest in the country, may only reflect treatment practices at that centre, which cannot be generalized to other sites. Another very important limitation is the strong possibility of informative censoring bias. Events resulting in censorship could have been related to the outcome of the study i.e. patients lost to follow up might have done so due to poor drug tolerability. This potentially underestimates our modification rate.

In conclusion, we report lower rates of ART modifications in this population than in cohorts in resourceful settings. However, the burden of peripheral neuropathy and lipodystrophy related to d4T use is of major concern, as it accounts for the majority of modifications. Another concern is that a significant number of patient's treatment is modified due to TB therapy and pregnancy. Safer and more tolerable drugs such as TDF should be made more accessible to treatment programmes in resource-limited settings. Screening for TB should be intensified and routine before patients start HAART. Family planning programmes should also be integrated into routine HIV care. Addressing these issues will further reduce modifications and improve initial ART regimen tolerability, thereby increasing the probability of achieving sustained viral response, and at the same time preserving future treatment options.

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APPENDICES

APPENDIX A: SELECTED ANNOTATED STATA LOG – TESTING
MODEL ADEQUACY

APPENDIX B: ETHICS DOCUMENTATION

APPENDIX C: QUESTIONNAIRE AND COPY OF PATIENT RECORDS

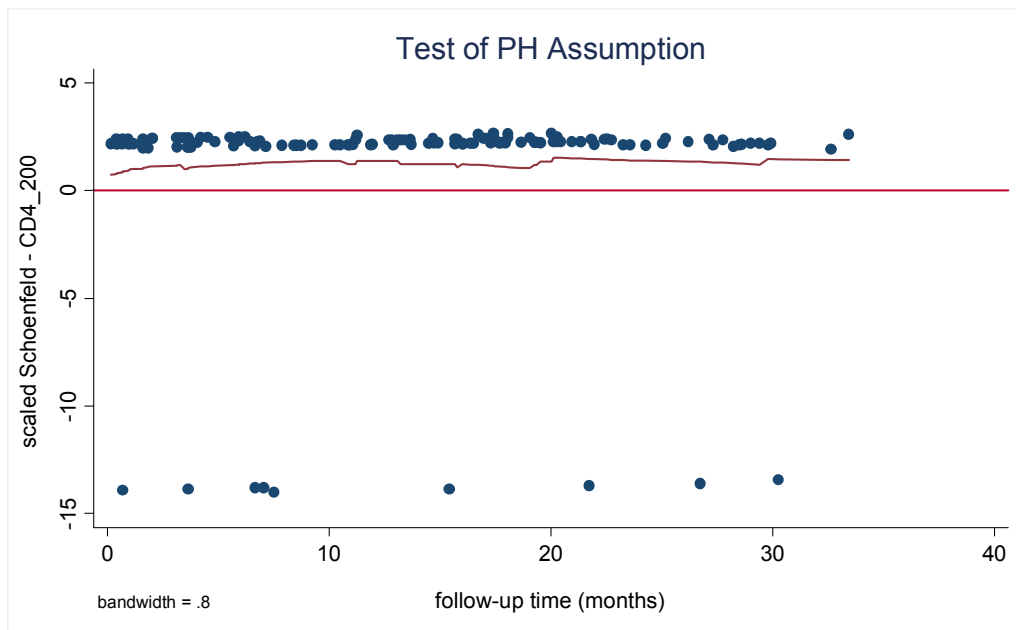
APPENDIX A: SELECTED ANNOTATED STATA LOG – TESTING MODEL ADEQUACY

1. Testing the proportionality assumption – Graphical method

Cox regression with time-invariant covariates assumes that the ratio of hazards for any two observations is the same across time periods. *Partial residual plots (Schoenfeld residuals PH test)*, graphical methods were also used to examine if covariates met this assumption. In STATA one creates a plot of scaled Schoenfeld residuals on the y axis against time on the x axis, with one such plot per covariate. A smoothing line summarizing the residuals should be close to the horizontal 0 reference line for the y axis, since the average value of residuals at an time should be zero if the effects of the covariate being plotted are proportional [34]. Partial residual methods are the most common and preferred methods for testing for non-proportionality in Cox models. Two examples are used below.

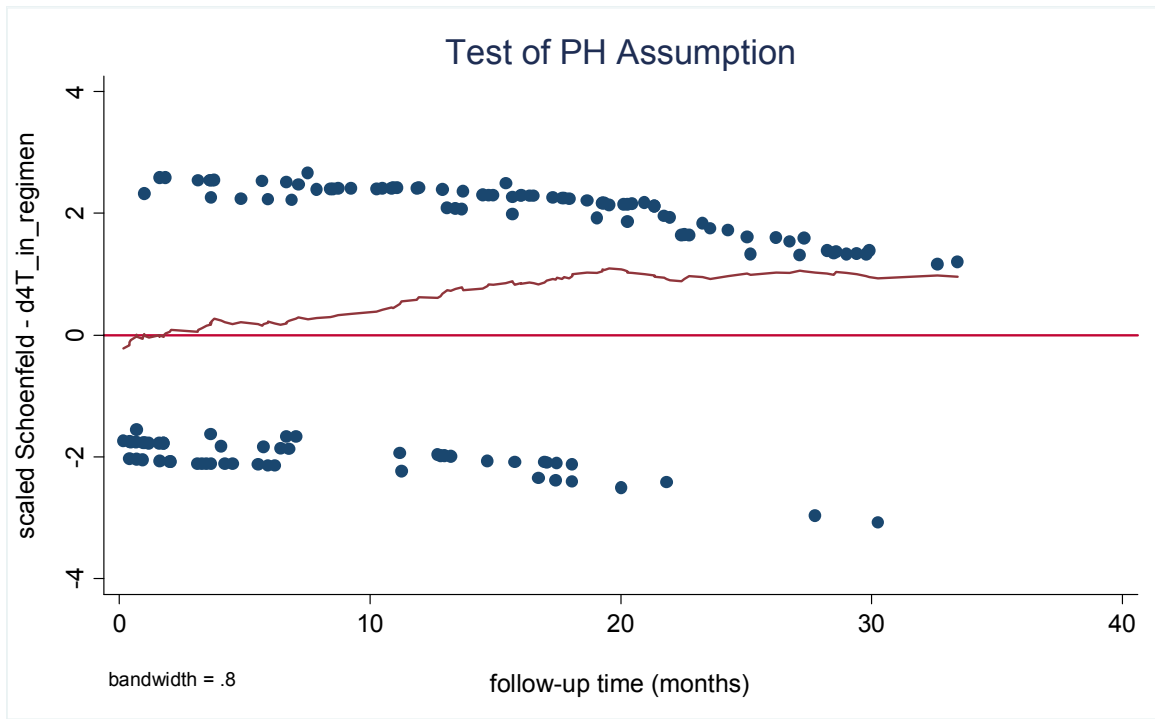
- CD4 category – ASSUMPTION MET

stphtest, plot (cd4_200) yline(0)



- d4T in regimen – ASSUMPTION VIOLATED

stphtest, plot (d4T_in_regimen) yline(0)



2. Testing overall model fit

Model fit should be assessed to assure that the most appropriate model has been selected. Model fit can be assessed through likelihood ratio tests, Wald test and the Akaike information criterion. The AIC test and to some extent the LR test are preferred to the Wald test.

The Akaike Information Criterion (AIC) is a way of selecting a model from a set of models. The chosen model is the one that minimizes the Kullback-Leibler distance between the model and the truth. $AIC = -2 * \log(\text{likelihood}) + 3 K$. The step by step variable selection procedure is shown in the table below:

Table A: Variable selection procedure (Best model)

VARIABLES IN MODEL	- 2 * Log L	P -value
null	1667.40	0.31
CD4	1629.24	<0.001
d4T	1660.55	0.006
Wt	1632.30	0.001
WHO	1088.56	0.130
age	1666.40	0.31
gender	1665.48	0.12
CD4 + d4T + Wt + WHO + age + gender	1020.21	<0.001
CD4 + d4T + Wt + WHO + age	1022.32	<0.001
CD4 + d4T + Wt + WHO	1023.77	<0.001
CD4 + d4T	1622.90	<0.001
CD4 + Wt + WHO	1053.77	<0.001
CD4 + d4T + Wt	1586.60	<0.001

APPENDIX B: ETHICS DOCUMENTATION

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**MINISTRY OF HEALTH
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THE KINGDOM OF SWAZILAND

FROM: The Chairman
Scientific and Ethics Committee
Ministry of Health & Social Welfare
P. O. Box 5
Mbabane

TO: Dr Simbarashe G. Takuva

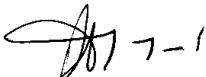
DATE: 25th September, 2009

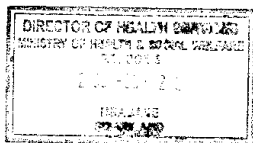
REF: MH/599B

RE: RETROSPECTIVE COHORT ANALYSIS OF ANTIRETROVIRAL TREATMENT MODIFICATIONS AT THE REFERRAL HIV CLINIC IN MBABANE, SWAZILAND

The committee has received your response on the comments that were raised in our meeting. In view of the fact that you have addressed all the issues that were of concern to the committee, you are therefore granted authority to conduct the study in Mbabane government hospital at the ART clinic. You are kindly requested to adhere to the processes outlined in the protocol and if there are any changes, you are advised to notify the chairman of the committee before you effect any changes.

The committee is looking forward to the findings of the study to inform decision making in this area.


DR. S. V. MAGAGULA
CHAIRMAN OF SEC



APPENDIX C: QUESTIONNEER AND COPY OF PATIENT RECORDS

