The role of side effects in shifting patients from first line to second line ART at Nthabiseng Clinic in Soweto, Johannesburg.

A Research Report Presented

By

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A research report submitted to the School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Science in Epidemiology in the field of Epidemiology and Biostatistics.

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DECLARATION

I, Munyaradzi Pasipamire, hereby declare that this research report is my own work except as indicated in the references and acknowledgements and I am submitting it in partial fulfilment of the Master of Science degree in Epidemiology in the field of Epidemiology and Biostatistics in the School of Public Health at the University of the Witwatersrand, Johannesburg. I can further confirm that this work has not been submitted for any other degree at this or any other University.

Full Name             Munyaradzi Pasipamire

Signature

Signed at  Wits School of Public Health

On the  25th day of September 2013
DEDICATION

This research report is dedicated to my wife, Lorraine, and our son Blessing. I applaud their support and resilience when I was away from home for the greater part of the year 2012.
ABSTRACT

Background
The Human Immunodeficiency Virus (HIV) which causes Acquired Immunodeficiency Syndrome (AIDS) has caused a global scare with mainly poor African countries suffering the greatest burden. Treatment of HIV is more of palliation rather than cure such that there is no room for treatment interruption if treatment goals are to be met. Antiretroviral treatment is associated with short term and long term side effects which have the potential to negatively impact on the high levels of adherence to treatment that is required to maintain virological suppression and may eventually lead to development of drug resistance and treatment failure. This research aims to identify the extent to which these side effects, through possible poor adherence, impact on treatment successes by measuring the risk that side effects contribute towards treatment failure.

Methods
Secondary data analysis was conducted on a cohort of patients who initiated ART between 2004 and 2010 at a large tertiary facility in Johannesburg. Patients who were switched to second line ART due to treatment failure were identified. Assessment of side effects on adherence was done. The hazards of side effects among patients switching and not switching to second line were calculated using Cox proportional hazards regression adjusting for other socio-demographic and clinical predictors for treatment failure. Interaction between side effects, gender, age and that of side effects and adherence was investigated. Time dependent covariates were also investigated. Confounding was controlled using multivariate Cox regression analysis.
Results

There were 5285 patients in the baseline cohort with multiple entry points who contributed 16035 person-years of follow up. The cohort consisted of 63.2% females and 36.8% males. Of these 85.9% were initiated on stavudine (d4T)-based regimen, 7.1% on tenofovir (TDF), 6.3% on zidovudine (AZT)-based regimen and 0.7% on other regimens. The median and mean time at risk per subject was 2.2 and 2.3 years respectively. A total of 770 episodes of side effects due to first line ART were experienced with some patients recording multiple side effects at different time points. Adherence data were found to be missing and incoherent in some of the regimen dosages and could not be used to objectively compare patients. There were 430 patients who were switched to second line ART due to treatment failure. Relative to the group of no side effects, the adjusted hazard ratios for mild, moderate and severe side effects were 1.40 (95% CI=0.94-2.09) p=0.10; 1.72 (95% CI=1.35-2.20) p<0.01 and 1.24 (95% CI=0.65-2.35) p=0.52 respectively. Therefore, overall side effects did not seem to play a role in the time to switch to second line ART. Sex, baseline CD4 cell count, the period during which ART was initiated and the time between date of testing HIV positive and date of initiating were significantly associated with the time to switching to second line ART.
Conclusion

The study informs that side effects overall may not play a significant role in switching patients from first line to second line ART with the exception of moderate side effects. However, patients who experience side effects should be closely monitored and adequately counselled to help them cope with the side effects so that optimal adherence levels are maintained. Availability of adherence scores or additional information on pills that should have been taken on periods during which pills were reported to have been missed would have made the research more valuable by allowing objective comparison of adherence among patients.
ACKNOWLEDGEMENTS

I would like to thank Anova Health Institute for providing me with the dataset for use for this project. I extend my gratitude to Nthabiseng Clinic management for allowing their data to be used for the research.

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<td>Lamivudine</td>
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<td>ART</td>
<td>Antiretroviral therapy</td>
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<td>NNRTI</td>
<td>Non-nucleoside reverse transcriptase inhibitor</td>
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<td>Nevirapine</td>
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<td>TDF</td>
<td>Tenofovir</td>
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CHAPTER 1: INTRODUCTION

1.1 Background

Human Immunodeficiency Virus (HIV) infection is a global health issue with approximately 34.0 million people living with the virus [1]. There were 8 million people receiving HIV treatment at the end of 2011 which was 20 times more compared to 2003[1] when rolling out of ART was initiated in many countries. In 2011 alone, 2.5 million (2.2 million–2.8 million) new HIV infections and 1.7 million (1.5 million–1.9 million) AIDS deaths were recorded worldwide [1]. Sub-Saharan Africa (SSA) is the worst affected region accounting for 23.5 million of the total HIV-infected population[1]. Prior to the mid-1990’s breakthrough in highly active antiretroviral therapy (HAART), HIV infections caused severe immune deficiency which carried a grave prognosis [2, 3]. South Africa had a population of 51 770 560 according to the 2011 census [4]. In 2011, 5.38 million people of South Africa’s total population were living with HIV [5]. It was estimated that 16.6% of South Africans in the age group 15-49 years were HIV positive [5]. By the middle of 2011, 1.79 million people were receiving ART in South Africa [6].

Widespread use of antiretroviral agents (ARVs) in SSA due to easier accessibility has characterised the new millennium [7]. The 2011 political declaration on HIV/AIDS at the United Nations General Assembly aim to further expand the provision of ART by treating 15 million people living with HIV by 2015 [1, 8]. However, the expansion and prolonged use of combination ART has been associated with the appearance of side effects which negatively impact on the quality of life (QOL) [9]. Side effects have been shown to decrease adherence to treatment and may result in the development of drug
resistance [9, 10]. Sub-optimal adherence resulting from HIV treatment-related side effects result in sub-therapeutic drug levels which potentiates the emergence of drug resistance and treatment failure [10-12]. Optimal adherence is defined as taking at least 95% (not more than three missed doses per month for a patient on a twice daily dosing schedule of ART) of the lifelong treatment in order to sustain suppression of viral replication [2]. Attaining these high levels of adherence may be hampered by several factors such as convenience, pill burden, side effects [2, 12] and the costs of frequent clinic visits for refill as well as the threat of losing employment due to absenteeism associated with frequent clinic visits [13]. Therefore, widespread ART expansion is significantly threatened by the emergence of treatment failure [2, 14].

1.2 Statement of the problem

ART use is associated with the pervasive challenge of side effects [15]. Side effects can negatively impact on adherence which may ultimately lead to treatment failure [2, 16-19] and the need for second line therapy. There is little information on whether side effects through impairing optimal adherence will ultimately result in treatment failure and patients being switched to second line therapy. This study assesses the impact of side effects from first line ART, as one of the potential causes of poor adherence, on the likelihood of patients being switched to second line therapy due to treatment failure over time.

A number of studies have shown that the majority of drug resistant HIV species emerge as a result of poor adherence to ART [2, 12, 13, 16-18, 20-22]. As side effects to ART
prevail, the recipe for poor adherence is potentiated [2, 16-19] and thus higher likelihood for drug resistance and eventual treatment failure. In these situations, the decision to start second line therapy may not yield desired results unless a more patient-centred intensified treatment of side effects is in place bearing in mind the greater toxicities associated with second line therapy [23]. A prospective study in Johannesburg (from 2004 to 2008) indicated that 11% of patients switched to second line therapy within the first four years after initiating ART [24]. The same study demonstrated shorter duration of the first line regimens’ use due to toxicities [24]. Side effects may be sufficiently disturbing to cause prolonged poor adherence resulting in drug resistance and ultimately switch to second line therapy. Such situations tend to limit the success of second line treatment which comes with a heavier burden of side effects [23] unless mechanisms are put in place to reduce and also to help patients cope with the side effects. This study builds upon the established close association between the occurrence of side effects and the possibility of poor adherence [16-19] and attempts to quantify whether side effects, as a background factor, significantly affects the time to switching to second line ART.

1.3 Justification of the study

The study provides more evidence on the contribution of side effects to poor adherence and treatment failure. The ultimate role of side effects to the latter has not been studied much. In addition, significant findings from this study will be useful tools in advocating for the development of less toxic second line drugs compared to those currently available and registered for use. In line with safe and sustainable ART provision the WHO and UNAIDS Secretariat launched the Treatment 2.0 strategy in July 2010 [25].
The Treatment 2.0 strategy has multiple components one of which is centred around drugs and advocates that well tolerated simple drug regimens be developed [25-27] as the world prepares for a new era in HIV care where greater emphasis is now on treatment-as-prevention (TasP) programmes [25, 28] which aim to continue ART scale up despite fiscal constraints. This study, through improving awareness of side effects, will add value to the advocacy considering the toxicity profiles with current regimens hence the emerging concerns regarding early ART which is the hallmark of TasP programmes [28].

1.4 Literature review

1.4.1 Recommended (standard) first-line ART regimens

Treatment naïve HIV infected patients are initiated on first line ART consisting of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) [29-32]. The commonly used NRTIs are stavudine (D4T), zidovudine (AZT), didanosine (DDI), abacavir (ABC) and tenofovir (TDF). The available NNRTIs are nevirapine (NVP) and efavirenz (EFV) [33]. D4T, 3TC and EFV or NVP has been the recommended and commonly used first line regimen during the initial scale up of ART in South Africa [33, 34]. D4T is being phased out gradually and replaced by TDF in South Africa because of its mitochondrial toxicity-related side effects [35]. These regimens are preferred in resource poor countries and are recommended by WHO because they are affordable and available in fixed-dose combinations [36]. Toxicities from the ARV agents have also been considered by WHO
in making their recommendations for first line ART regimens [36]. Combination ART of at least three drugs (triple therapy) as indicated above is prescribed instead of mono-therapy or dual therapy in order to minimise the emergence drug resistant HIV strains. The later prescribing practices have been listed as one of the seven HIV-drug resistance (HIV-DR) early warning indicators which usually precede treatment failure [37].

1.4.2 Influence of side effects on successful first-line ART

Side effects to first line ART follows a wide spectrum ranging from reported symptoms (such as diarrhoea) to observable signs (rashes and jaundice) and measurable effects (raised liver or pancreatic enzymes) [15]. All side effects differ in severity and can be classified as mild (grade 1), moderate (grade 2), severe (grade 3) or life-threatening (grade 4) [33]. Side effects, being undesirable, are almost always reported by those affected or at least objectively identified by clinicians. Proper identification and timely management of side effects is of paramount importance because side effects have been consistently found to predict poor drug adherence which may ultimately result in treatment failure [38, 39]. In addition side effects are viewed as ultimately controllable, such that one has the power to either stop taking the medication or reduce the frequency of dosing in order to eliminate side effects [10, 40]. This may result in suboptimal drug levels in the body and potential drug resistance which decreases the hopes of prolonged and successful first line ART. Ultimately the proportion of patients switched to the more expensive [41] and even less tolerable second line therapy increases. An investigation of side effects as one of the possible reasons for poor adherence is useful given that adherence per se is difficult to measure accurately [42].
Due to the limited ARV drug options and the associated class-specific side effects [15], patients may continue to experience similar side effects despite substitution to less toxic drugs. Perhaps one of the most overt and striking class-specific side effects associated with NRTIs is lipodystrophy due to its disfiguring effects. Lipodystrophy is the maldistribution of body fat which include peripheral fat loss on the face and extremities (called lipoatrophy) and/or central fat accumulation [9]. Lipodystrophy has been closely associated with the use of stavudine (d4T) [9, 18, 43, 44]. Stavudine (d4T)-based regimens have been widely used during the scale up of ART in Southern Africa. The incidence of lipodystrophy in South Africa was 4.6/100 person-years (PY) with d4T regimens compared to 3.0/100 PY with non-d4T based regimens (zidovudine (AZT) or tenofovir (TDF)) [45]. Some of the patients who had substitutions from d4T to AZT have continued to experience progressive lipodystrophy. The cosmetic effects of lipodystrophy may leave patients contemplating to stop ART thereby compromising adherence leading to virological failure and even clinical failure [27]. It remains to be seen how far patients can tolerate the undesirable physical changes to their body shapes before they are tempted not to adhere to the treatment or completely stop altogether.

Treatment failure leading to switch to second line ART has been linked to limited access of well tolerated ARV regimens [19]. A review of the outcomes of viral suppression in the United States found that sustained virological suppression increased from 45% in 2001 to 72% in 2010 and this was partly attributed to the increasing availability of simplified and well tolerated regimens [46, 47]. Even the benign symptoms may become persistent and potentially cause psychosocial distress among the affected patients.
Such symptoms are associated with increased risk of poor adherence and intentional interruption of the treatment by affected patients [16, 17, 48]. A cross-sectional survey was conducted on Swiss HIV care physicians to determine reasons for not prescribing ART to eligible patients. The physicians indicated that 18% of those eligible for ART refused treatment due to fear of side effects. Among those who had actually stopped ART in the same study, 25% stopped due to fear of side effects and 61% stopped ART due to actual side effects [49]. This evidence was supported by a systematic review investigating the causes and effects of treatment interruptions [50]. Stopping ART by patients themselves constitute unstructured treatment interruption which is associated with selection and replication of resistant strains of HIV thus increasing the risk of early treatment failure even if substitute ART is restarted at a later stage [50].

1.4.3 Factors associated with side effects among ART patients and the role of the management of side effects.

The types of ARVs used were found to be associated with the development of side effects in a Nigerian cohort [51]. AZT regimens were found to be associated with anaemia, d4T regimens with peripheral neuritis and lipodystrophy, NVP/EFV with rash and hepatotoxicity, TDF regimens with renal failure and PI containing regimens were linked to the development of diabetes mellitus and gastrointestinal disturbances [15]. The duration of treatment was found to positively predict the development of side effects but not sex or CD4 cell count [51]. However, female sex and older age were found to be associated with side effects and required ART treatment modifications in other studies [52, 53]. Female sex and higher baseline CD4 cell count were shown to be independent risk factors for severe rash from use of NVP [54].
Adequate and timely management of side effects optimises adherence and improves the efficacy of treatment [15]. Adequate management involves educating patients, from the time of ART initiation, about possibility of developing ART-related side effects which may require regimen changes and treatment-switch during therapy [55]. The individual factors that may predispose to side effects need to be taken into consideration when choosing a regimen for individual patients.

1.4.4 Measurement of adherence
Adherence can be measured using pill counts, patient’s self-report of missed doses or electronically using Medication Event Monitoring System (MEMS) cap data [56, 57]. The MEMS uses an electronic chip placed on the cap of an ARV bottle and the chip records information each time the bottle cap is opened [56]. Missed clinic appointments have also been used as markers for poor adherence [53].

1.4.5 Rates of switching to second-line ART in South Africa
In developing countries like South Africa, first line treatment consists of a population-based standardised regimen due to limited financial resources to obtain baseline HIV resistance patterns for individual patients which in reality is not time feasible [58]. The primary goal of HAART is to maintain viral suppression for as long as possible [59]. Adult patients who fail first line treatment are switched to second line treatment which consist of at least one new NRTI (never used in first line) and a boosted protease inhibitor [36, 60, 61]. It was estimated that 3% of patients in SSA are receiving second line therapy [62]. In the South African public ART program, it was demonstrated that 20.6% of HIV infected patients experience viral rebound within the first 3 years of
initiating first line ART [24] and 9.8% of adult patients are switched to second line ART by the end of the third year after initiating treatment [63].

1.4.6 Factors associated with treatment failure and switching to second-line ART

Besides side effects compromising adherence, there are various factors that have been identified to positively predict switching to second line ART. Younger age, low baseline CD4 cell count and high baseline viral load were associated with increased likelihood of treatment failure and switching to second line therapy in three different studies [20-22]. The transmission of HIV-drug resistant strains (HIV-DR) results in primary resistance causing early virological failure that is independent of the level of adherence and its associated proxy-factors [64]. These factors need to be taken into consideration if efforts to maintain patients successfully on first line therapy for longer periods are to be fruitful. The success of first line ART is also critical to limit the need to switch to the more expensive second line ART regimens [37, 41]. especially in light of generalised global recession that has seen donor funds for HIV/AIDS shrinking [65]. This requires sustained collaborated and integrated inter-disciplinary efforts from areas such as public health, psychology and medicine [13]. Timely active management of side effects is an essential component of the process.

WHO indicated that assessment, understanding and prevention of adverse events and side effects should be a key component of comprehensive patient care and safe use of medicines [36]. It further highlighted that not monitoring and managing these events can result in poor adherence, treatment failure and lowers the confidence in ART by PLHIV and even healthcare workers [36]. A systematic review into the risk factors of ART
interruptions found that drug toxicity, adverse events and side effects\textsuperscript{1} were the most frequent reasons for interrupting ART and that these interruptions increased the risk of virological failure, development of drug resistance and poor immunological recovery [50]. Another worrying observation was that the likelihood of remaining free from side effects diminishes as the time on ART increases [48]. This suggests that an association between side effects and the time to switching to second line ART is worthy being investigated.

1.5 Definition of terms

Adverse drug reaction: a harmful or unpleasant response, resulting from the use of medicinal products, which predicts hazard from future administration and warrants specific treatment, dosage alteration or withdrawal of the product [66].

Adverse event: An unexpected occurrence that may present during treatment with pharmaceutical product but does not necessarily have a causal relation to the treatment [66].

Pre-ART duration: a period in which a patient is known to be HIV positive but has never taken combination ART for the treatment of HIV. It is estimated by subtracting the date of HIV-testing from the date of initiation. However, the exact period is unknown because the time of HIV infection is unknown.

\textsuperscript{1}Wording may differ due to different studies reviewed even if these are shared undesirable effects
**Side effects**: are predictable, undesirable, and dose-related pharmacologic and clinical effects that occur within therapeutic dose ranges [10].

**Substitution**: changing part of the ART regimen due to indications other than treatment failure such as pregnancy or toxicity.

**Switch**: the change from first line to a completely new second line ART regimen due to failure to achieve virological control.

**Toxicity**: refers to unwanted and undesirable effects, occurring early or late in the course of drug therapy and are related to drug dosage and duration of treatment [67].

**Treatment failure**: failure to achieve virological control (decrease in viral) and/or immune reconstitution (increase in CD4 cell count). It is also defined as clinical failure characterised appearance of new WHO stage 3 and 4 opportunistic infections in a patient on ART.

**Viral rebound**: appearance of detectable HIV-RNA levels >50 copies/ml in a patient who previously had two consecutive measurements of undetectable viral load [68].

**Virological failure**: failure to attain undetectable viral loads (<400 or <50 copies per ml depending on the testing kit used) after at least 3 months of ART.
1.6 Aim and objectives

Study aim: To investigate the association between ART side effects and switching from first line to second line ART.

Research question: Are side effects due to first line ART, as a proxy to poor adherence, associated with earlier time to switching to second line therapy among adult ART patients at Nthabiseng Clinic.

Null Hypothesis: Side effects to first line ART are not associated with the time to switching ART patients to second line therapy at Nthabiseng Clinic.

Study objectives

1. To compare the socio-demographic characteristics of patients who are switched to second line ART and those who remain on first line ART during the period 2004 to 2011.

2. To assess the effect of side effects, as a driver of poor adherence, on the time to switching to second line ART amongst patients from 2004 to 2011.

3. To determine risk factors for poor outcome, defined as switch to second line therapy due to treatment failure. Some of the factors to be considered include age, sex, marital status, alcohol use and the baseline CD4 cell count (as a proxy for delayed initiation of ART).
CHAPTER 2: METHODS

2.1 Study design

This is a secondary data analysis of an open cohort of patients on whom data had been collected routinely at Nthabiseng Adult HIV Clinic. Patients’ data were prospectively collected from January 2004 to October 2011. A prospective cohort analytic design will be used in this study because the original data collection was done prospectively and a prospective review of this data was carried out [69].

The 2004 starting period marked with the beginning of a public and free ARV roll-out programme in South Africa and at Nthabiseng Clinic [70]. The end-point (October 2011) was determined by availability of the data for analysis.

2.2 Study population

A total of 8341 patients were registered at Nthabiseng Adult HIV Clinic at Chris Hani Baragwanath Hospital (CHBH) and 5541 patients were eligible to participate in this study. Of the above, 5285 were available for analysis. The 5285 individuals were patients aged 18 years or older, who had started ART and had a treatment commencement date, and had at least one follow up visit after starting ART.

2.2.1 Inclusion criteria:  
Only those patients who were initiated from 21 January 2004 to 1 November 2010 were eligible for inclusion into the study. All the patients were given the opportunity to be followed up for at least 12 months from the date of initiating ART. Therefore, the study period ended on 31 October 2011 to accommodate those initiated on 1 November 2010.
2.2.2 Exclusion Criteria
Patients who were transferred-in whilst already on second line therapy were excluded because their side effects profile during their initial period on first line therapy could not be satisfactorily established.

2.3 Study setting
CHBH is the largest hospital in South Africa occupying 173 acres [71] and houses Nthabiseng Adult HIV Clinic. It has 3 200 beds and houses about 6 760 employees [71]. CHBH is a tertiary institution, within the Gauteng Provincial Health Department [72], with various clinical departments. The Head of Department for Infectious Diseases which is a subspecialty of CHBH’s Department of Internal Medicine is in charge of the operations at Nthabiseng Clinic [73]. Nthabiseng Clinic is located in the Diepkloof area of Soweto south of Johannesburg. Soweto is populous community in which overcrowding and high unemployment are perennial problems [74]. Contrasting lifestyles characteristic of South Africa is evident in Soweto ranging from the old squatter misery of poverty to the new affluent lifestyles [74]. Nthabiseng clinic was one of the first health facilities to offer ARVs in 2004 on a public scale. It continues to serve an extensive treatment cohort.

2.4 Measurement and data sources

2.4.1 Description of the primary data
The primary data were routinely collected using a clinician administered hospital case report form. Data were collected during the clinical process of history taking and physical examination of patients each time they visited the clinic. The data were entered
and stored in Microsoft Access database. The primary data are used for patient care
and record keeping, follow up and generating reports.

2.4.2 Data extraction

The dataset was received in the Microsoft Excel, and imported into STATA/IC version
12.1 (© 1985-2011 StataCorp LP, Texas USA).

2.4.3 Description of data variables

The main exposure variable is ‘side effects’ and the outcome variable is time to switch
to second line therapy. The main exposure variable was defined using the guidelines
of 46 listed side effects that can arise from use of ART which were used at Nthabiseng
Clinic as shown in Appendix A. The 46 side effects were combined into 8 groups to
allow easier data handling. Table 1 shows how the 46 side effects were merged into 8
groups. The eighth group comprised of a pooled set of the less common side effects.
Most of the side effects in the eighth group were not experienced by the cohort.

The side effects were classified into three ordered levels representing the severity of the
side effects ranging from mild (I) and moderate (II) to severe (III). Therefore, four
different groups were created consisting of those who did not experience side effects
and the three groups for those who experienced side effects as described above.
Comparison of these groups was done. The side effects’ levels were defined by the
attending clinician based on set standards or guidelines of defining severity for some
side effects [33]. These classifications used both clinical (such as rash and
paraesthesia) and measurable laboratory-based side effects such as anaemia or
leucopaenia among other criteria. The severity of clinical side effects like diarrhoea and
dermatitis may be subject to the attending clinician’s interpretation of the side effects’ severity at presentation.

**Table 1: Merging of side effects into 8 groups**

<table>
<thead>
<tr>
<th>Original side effects listed</th>
<th>Merged group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Lipodystrophy</td>
<td>Lipodystrophy</td>
</tr>
<tr>
<td>2 Neuro-cerebellar; Neuro-psychiatric; Paraesthesia; Neuro-motor; Myalgia; Arthralgia; Neuro-sensory</td>
<td>Neurological</td>
</tr>
<tr>
<td>3 Elevated triglycerides; Elevated cholesterol</td>
<td>Hyperlipidaemia</td>
</tr>
<tr>
<td>4 Elevated AST; Elevated ALT; Elevated ALP; Hyperbilirubinaemia; Clinical hepatitis</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>5 Rash/dermatitis; Local reaction; Fever; Headache; Allergic reaction; Fatigue; Eye (conjunctivitis)</td>
<td>Hypersensitivity reactions</td>
</tr>
<tr>
<td>6 Dysphagia; Nausea; Vomiting; Diarrhoea; Constipation; Abdominal pain</td>
<td>Gastrointestinal symptoms</td>
</tr>
<tr>
<td>7 Elevated lactate; Symptomatic hyperlactaemia</td>
<td>Hyperlactaemia</td>
</tr>
<tr>
<td>8 Anaemia; Neutropaena; Leucopaenia; Thrombocytopenia; Hyponatraemia; Hypernatraemia; Hypokalaemia; Hyperkalaemia; Elevated urea; Elevated creatinine; Hypoglycaemia; Hyperglycaemia; Elevated amylase; Elevated lipase; Elevated CPK; Cardiovascular disease</td>
<td>“Other” (Haematological and other metabolic disturbances)</td>
</tr>
</tbody>
</table>
The national ART guidelines provided the categorisation of both clinical and laboratory abnormalities using a grade scoring system from grade 1 (mild) through to grade 4 (serious/life threatening) based on the AIDS Clinical Trials Group (ACTG) grading system [33]. The guidelines used by clinicians in classifying these side effects were elaborated as follows and are included in Appendix A:

- **Mild (I)** - were transient symptoms and signs for which no medical intervention was required.
- **Moderate (II)** - were associated with mild to moderate limitation in activity and minimal to no intervention was required.
- **Severe (III)** - were characterised by marked limitation in activity, intervention was required.
- **Life threatening (IV)** - intervention was required, hospitalisation was probable for individuals falling in this category.

The category of life threatening side effects was merged with severe side effects because of very small numbers in this category.

The outcome variable is time to switch to second line ART. It was the calculated time in years from date of ART initiation to date of switch to second line ART. Apart from the time to switching to second line ART, participants were also censored at the time when one of the following occurred:

- Transfer out
- Lost to follow up
- Death
- Reaching 31 October 2011 and still active on ART

The time from initiation date to one of the above- whichever occurred first- constituted the observation time of an individual in the study and side effects were tracked during observation time. Patients who switched without ever experiencing side effects were classified as never experienced side effects and censored at the time of switching.

The intermediate variable “adherence” had no objective data of assessing it from the dataset. In addition the information was based on subjective answer by patients to the question “In the past 3 days how many pills do you think you missed?” There were instances where the data for adherence were not plausible. For example, there were instances where individuals reported missing between 15 and 46 pills during the previous 3 days before their consultations which were far greater than the possible maximum they would have taken considering their prescribed ART regimens.

Covariates such as socio-demographic variables and baseline CD4 cell count will also be considered. New variables such as age and duration of untreated HIV (from HIV test date to ART start date) were also generated in STATA.

2.5 Data processing methods

All data analyses were done using STATA/IC version 12.1 (© 1985-2011 StataCorp LP, Texas USA). The datasets were provided in separate excel files which required importation into STATA, merging and reshaping to obtain a self-contained dataset ready for analysis. The datasets had a consistent unique identifier for each patient. The
process involved 1:1 merging for datasets for baseline information and 1:m merging to incorporate the follow up datasets. The 1:1 merge refers to joining two datasets one-to-one by observations on specified key merge variable(s) [75]. The 1:m refers joining two datasets one observation of the ‘master’ (first) dataset to many observations of the ‘using’ (second) dataset using specified key merge variable(s) [75]. The m:m merging of these datasets was avoided. The dataset was finally presented in long-format follow up data for survival analysis. Notable queries addressed included:

- Missing more than 15 pills during the previous 3 days prior to consultation was still considered poor adherence even though the number of pills missed were inconsistent and incoherent with the patients’ ART regimens. There were no adherence scores or percentages in the dataset which would have been used to objectively compare adherence among patients. The adherence variable was dichotomised into good (no missed pills) and poor (missing at least one tablet). Ordinal categorisation or adherence scores could not be done because it was impossible to determine whether those who missed greater number of pills were taking greater number of pills per dose or not, compared to those who missed fewer pills.

- Weight values above 150kg (i.e. 999.9 and 1000) were not plausible and were set to missing. Other large and very small-for-adult baseline weight values were extensively interrogated using weight values recorded separately on every visit. Baseline weights which were not plausible were replaced by weight on the first visit from follow up dataset.
missing sex were set to female if last menstrual period date (LMP) appeared in at least two occasions over a month apart and to male if LMP dates were missing for the entire follow up duration which was at least 4 visits long.

Changes to all three first line drug regimens at the same time to a completely new drug combination which included a protease inhibitor was set to treatment switch e.g. D4T/3TC/EFV to AZT/DDI/Kaletra. AZT/DDI/Lopinavir-ritonavir drug combination has been the recommended second line regimen used in South Africa [32, 34]. In addition single substitutions of NRTIs (e.g. to adverse effects) were reset from treatment switch to other e.g. D4T/3TC/EFV to AZT/3TC/EFV.

Some ART initiation regimens were classified into the category ‘other’ because they are not commonly used. These regimens included triple NRTIs for example ABC/3TC/DDI, D4T/3TC/TDF and others that may have been recorded in error because they are not recommended such as D4T/3TC/AZT due to proven antagonism [76].

CD4 cell count and weight measurements were analysed in continuous form but were divided by 100 and 5 respectively in order to get more informative estimates of the effect sizes and their confidence intervals.

2.6 Statistical analysis

Data was set up for survival analysis with a yearly time scale and risk origin set-up at the time ART was initiated. Exit was the time of switching to second line or through censoring.
2.6.1 Descriptive statistics

Tables containing descriptive statistics for study participants and also a comparison table of those switched and not switched were used for baseline socio-demographics. Frequencies and proportions were used for categorical data such as sex and marital status and means or medians (interquartile range) were used for continuous data such as weight and CD4 cell count. Student t-test, Kruskal-Wallis, Chi-square and/or Fishers Exact tests were used, as appropriate; to test differences between baseline continuous variables and for testing associations between baseline categorical variables with switching to second line ART. Kaplan Meier curves were used to describe and estimate the time to switching to second line ART among those with and those without side effects as well as other categorical variables.

2.6.2 Inferential statistics

Kaplan Meier curves were used to graphically compare the time to switching therapy between those experiencing side effects and those without side effects. Log rank test was used to statistically compare the differences in the time to switch between the different groups of the levels of side effects and those not experiencing side effects as well as groups of other categorical covariates. All estimates were reported with 95% confidence interval and all p-values were two sided. Cox proportional hazards regression analysis was used to determine the relationships between time to switch and side effects controlling for the other covariates. In univariate analysis using Cox regression, a significance level of 0.15 was used to determine entry into the final multivariable model and only those variables significant at 0.05 in the final model were retained for the final multivariable model. Important variables that did not meet the
above criteria (for example age) were investigated for their influence on the model to predict the outcome [77]- switching to second line ART in light of side effects. This was done by allowing the age variable into the final model and comparing, by likelihood ratio test, the extended model with the original one of significant predictors only.

In the final model, Cox proportional hazards regression was used to provide the estimates of the effect sizes and confidence intervals of the covariates. The hazard function of an individual switching to second line ART \((h)\) was modelled as a function of the baseline hazard \(((h_0)t)\) and the covariates \(X_1, X_2, \ldots, X_i\). Graphical assessments and testing for interaction between the covariates and time \((t)\) was done. The significance of variables interacting with time were tested by including the time-varying-covariate \(tvc\) option in the multivariable model [78]. Significant interactions with time were retained in the multivariable model. The hazard function for switching to second line ART was modelled as shown by the following equation:

\[
h(t; X_1, X_2, \ldots, X_i) = h_0(t) \exp(\lambda_1(t)X_1 + \lambda_2(t)X_2 + \ldots + \lambda_i(t)X_i) \quad \text{................. (1)}
\]

where:

- \(X_1\) represents the main exposure side effects
- \(X_2, \ldots, X_i\) represents the other covariates such as age and CD4 cell count
- \(\lambda_1, \lambda_2, \ldots, \lambda_i\) are a vector of regression coefficients which are exponentiated \((exp)\) to give the hazard ratios
- \(h_0(t)\) is the baseline hazard at time \(t\)
- \( h(t; X_1, X_2, ..., X_i) \) represents the hazard function at time \( t \) given the values of the covariates \( X_s \) at \( t \)

Interactions of covariates with either age or sex were investigated by including interaction terms in the model and checking the significance of the interactions as well as assessing any improvements in the model in predicting the outcome using likelihood ratio tests when compared with the simpler models. An attempt to investigate for interaction between side effects and adherence was made. Confounding was adjusted for using multiple Cox regression analysis. Proportional hazards were graphically assessed using Kaplan-Meier curves and then later tested by the global test. Variables that interacted with time and hence proportional hazards did not hold in such cases, were modelled as time dependent covariate. The models were compared by the likelihood ratio test. Models with variables which had significant interactions with time were handled by first expanding the data using st-splitting (at failure times) and then a dynamic Cox regression model using factor variables specifying the interactions was employed. In the dynamic Cox model the variables whose effects changed with the values of the covariates were interacted with the function of time \(_t\) and the interaction terms were included with other covariates [79]. This allowed for the assessment of model adequacy and prediction of residuals for such models where the hazards will be assumed proportional at specific times in relation to the time varying covariates. The final model was reported after residual diagnostics had been carried out. Scaled Schoenfeld residuals were plotted and the Cox-Snell residuals were used to assess the overall goodness of fit [77].
2.7 Ethical issues and dissemination

This research was granted ethical approval by the University of the Witwatersrand Human Research Ethics Committee (Medical) with clearance certificate number M120855. The ethics clearance certificate is attached as Appendix B. Permission to use the data from Anova Health Institute was granted and the memorandum of understanding (MOU) signed between the parties is shown in Appendix C. The primary data were collected routinely as part of patient management and not for study purposes hence no ethical approval was required for collection of the primary data. Publication of results will only be done if and only if all parties agree including the HIV clinic (herein referred to as the Clinic) where the primary data was collected as stipulated by the MOU. However, a two page summary of findings will be written and submitted to the Clinic and Anova, and School of Public Health (Faculty of Health Sciences) for the benefit of clinicians should the findings be significant.
CHAPTER 3: RESULTS

3.1 Description of study participants

There were 8,341 eligible patients enrolled on ART from 21 January 2004 to 1 November 2011. However, 5,285 were included for analysis. The majority of exclusions (83.5%) were patients who did not have an ART start date and/or initiation regimens were not recorded as illustrated in Figure 1. These two variables were necessary to track the side effects and the outcome.

Figure 1: Enrolment process
3.2 Characteristics of study participants

There were 3 341 (63.2%) females and 1 942 (38.8%) males. The majority (4 554 (86.2%)) were aged 25-49 inclusive. The median CD4 cell count at initiation was 89 cells/μL [IQR= 33-155]. Most patients started ART with advanced disease with 4 061 (76.9%) patients having WHO clinical stage 3 or 4 and 1 222 (23.1%) staged 1 or 2 at initiation. Table 2 details the characteristics of the study participants at the time of initiation.

Table 2: Baseline characteristics of the study participants

<table>
<thead>
<tr>
<th>Characteristics of the population</th>
<th>Frequency^** n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population:</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1942 (36.8)</td>
</tr>
<tr>
<td>Females</td>
<td>3341 (63.2)</td>
</tr>
<tr>
<td>Age (at initiation) category (years):</td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>259 (4.9)</td>
</tr>
<tr>
<td>25-49</td>
<td>4554 (86.2)</td>
</tr>
<tr>
<td>≥50</td>
<td>472 (8.9)</td>
</tr>
<tr>
<td>Employment status:</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>2217 (78.2)</td>
</tr>
<tr>
<td>Employed</td>
<td>617 (21.8)</td>
</tr>
<tr>
<td>Social assistance type:</td>
<td></td>
</tr>
<tr>
<td>Ineligible</td>
<td>1639 (57.8)</td>
</tr>
<tr>
<td>Pension</td>
<td>63 (2.2)</td>
</tr>
<tr>
<td>Child support</td>
<td>602 (21.3)</td>
</tr>
<tr>
<td>Disability</td>
<td>290 (10.2)</td>
</tr>
<tr>
<td>Other</td>
<td>241 (8.5)</td>
</tr>
<tr>
<td>Marital status:</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>2215 (78.1)</td>
</tr>
<tr>
<td>Married</td>
<td>421 (14.9)</td>
</tr>
<tr>
<td>Separated/divorced</td>
<td>106 (3.7)</td>
</tr>
<tr>
<td>Widowed</td>
<td>93 (3.3)</td>
</tr>
</tbody>
</table>

(Continued on next page)
<table>
<thead>
<tr>
<th>Characteristics of the population</th>
<th>Frequency(^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker at baseline:</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2495 (88.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>340 (12.0)</td>
</tr>
<tr>
<td>Alcohol consumption at baseline:</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2698 (95.2)</td>
</tr>
<tr>
<td>Yes</td>
<td>137 (4.8)</td>
</tr>
<tr>
<td>Baseline WHO clinical stage:</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>65 (1.2)</td>
</tr>
<tr>
<td>II</td>
<td>1157 (21.9)</td>
</tr>
<tr>
<td>III</td>
<td>1989 (37.7)</td>
</tr>
<tr>
<td>IV</td>
<td>2072 (39.2)</td>
</tr>
<tr>
<td>Duration of untreated HIV (years)‡:</td>
<td></td>
</tr>
<tr>
<td>(\leq 1)</td>
<td>2153 (49.6)</td>
</tr>
<tr>
<td>1 - 3</td>
<td>1123 (25.9)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>1065 (24.5)</td>
</tr>
<tr>
<td>Baseline ART regimen:</td>
<td></td>
</tr>
<tr>
<td>D4T-based</td>
<td>4539 (85.9)</td>
</tr>
<tr>
<td>AZT-based</td>
<td>333 (6.3)</td>
</tr>
<tr>
<td>TDF-based</td>
<td>378 (7.1)</td>
</tr>
<tr>
<td>Other combinations</td>
<td>35 (0.7)</td>
</tr>
<tr>
<td>Previous ART experience:</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4812 (91.1)</td>
</tr>
<tr>
<td>Yes</td>
<td>471 (8.9)</td>
</tr>
<tr>
<td>Period initiated ART:</td>
<td></td>
</tr>
<tr>
<td>2004-2006</td>
<td>2685 (50.8)</td>
</tr>
<tr>
<td>2007-2010</td>
<td>2600 (49.2)</td>
</tr>
<tr>
<td>Median baseline CD4 cell count (cells/μL) [IQR(^ξ)]</td>
<td>89 [33-155]</td>
</tr>
<tr>
<td>Median baseline weight [IQR(^ξ)]</td>
<td>57 [50-66]</td>
</tr>
<tr>
<td>Median age at initiation (years) [IQR(^ξ)]</td>
<td>36.7 [31.3-43.2]</td>
</tr>
</tbody>
</table>

\(^*\)Frequencies reported as: number (percentage), unless stated otherwise
\(^\dagger\)Duration given as number of years from date of HIV test to date ART started
\(^ξ\)Interquartile range for continuous variables
3.3  The follow up period

The total follow up time was 16 035 person-years (PY). Participants were followed up from the date they were initiated on first-line ART to the time they were switched to second-line ART due to treatment failure or they were censored at transfer out to other care facility, if they died, if they stopped ART or at the end of the study on the 31st October 2011. The crude incidence rate of switching to second line ART was 2.68 [95% CI: 2.44-2.95] per 100 PY. The absolute number of events that were observed was 430.

3.4  Characteristics of exposure experience

During the whole follow up period 770 episodes of side effects were observed among participants with some patients experiencing multiple and recurrent side effects over time. Of these 271 were experienced during the first year of starting ART, 157 during the second year and the remaining 342 occurred after the second year of starting ART. The severity of side effects experienced in relation to the duration since starting ART is shown in Table 3.

<table>
<thead>
<tr>
<th>Side effects severity</th>
<th>No. of episodes in specific durations of ART</th>
<th>Total episodes experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Up to 1 year</td>
<td>1-2 years</td>
</tr>
<tr>
<td>Mild</td>
<td>128</td>
<td>63</td>
</tr>
<tr>
<td>Moderate</td>
<td>96</td>
<td>69</td>
</tr>
<tr>
<td>Severe</td>
<td>47</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>271</td>
<td>157</td>
</tr>
</tbody>
</table>
Of the 770 side effects experienced during follow up, 79.0% were neurological and lipodystrophy related adverse events (42.2% and 36.8% respectively). The other less common side effects reported were gastrointestinal symptoms, hyperlactaemia, hypersensitivity reactions, hepatitis and hyperlipidaemia which accounted for the remaining 21.0%. Stavudine alone was associated with 74.4% of the side effects due to first-line ART followed by efavirenz with 16.6%. Zidovudine related side effects occurred in 5.8% of the time whilst the other first line ART drugs were associated with the remaining 3.2% of the occurrence of side effects.

After dichotomising adherence, there were 177 unique visits where 160 patients reported to have missed at least one pill 3 days prior to their clinic visits throughout the entire follow up period. Two patients reported missing pills on 3 different visits, 13 patients reported on 2 different occasions and the remaining 145 patients had missed pills only once. Only 1 patient who had side effects and poor adherence was switched.

There were 297 patients who had incomplete follow up. These patients neither switched to second line ART nor reached the end of the study but contributed some follow up time up to the time of censoring. The nature and timing of those with incomplete follow up are illustrated in Table 4.
Table 4: Participants with incomplete follow up per follow up period

<table>
<thead>
<tr>
<th>Nature of censoring†</th>
<th>Time to censoring</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Up to 1 year</td>
<td>1-2 years</td>
</tr>
<tr>
<td>Transfer out</td>
<td>43</td>
<td>29</td>
</tr>
<tr>
<td>Death</td>
<td>54</td>
<td>12</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Stopped for other reasons</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>114</td>
<td>47</td>
</tr>
</tbody>
</table>

†For those who neither switched ART nor reached the end of the study (31/10/2011).

3.5 Description of the outcome: - switch to second line ART

There were 430 patients who were switched to second-line ART as a result of treatment failure. Of these 100 were switched during the first year of initiating ART, 159 during the period after 1 year until 2 years and 171 after 2 years of initiating ART. Stavudine was the widely used first line ART component and 91.2% of those switched to second line ART had used stavudine as a component of their initiation regimen. About 5.6% of those on AZT-based first regimen were switched to second line ART whilst TDF-based and other regimens contributed 1.6% each of all the observed switches to second line ART.

3.6 Incidence of switching to second line ART

By 31 October 2011, the overall crude incidence rate of switching to second-line ART was 2.68 per 100 PY (95% CI = 2.44-2.95). Those who experienced moderate side effects had the highest incidence rate of 9.04 per 100 PY (95% CI = 4.70-17.38) and were the only group with a median survival time of 5.86 years. Patients who never
experienced side effects had the lowest incidence rate of switching (2.62 per 100 PY). The rates in groups of mild and severe side effects were 4.30 (95% CI = 1.61-11.46) and 7.93 (95% CI = 2.56-24.58) per 100 PY respectively.

### 3.7 Description of the time to switching by predictor variables

The probabilities (y-axis) plotted in the Kaplan-Meier curves were all cumulative probabilities that a patient (who had remained at first line ART at time $t$) will still remain on first line ART in the next period of observation at time $(t + \delta t)$. The curves illustrate the unadjusted effect of the variables on the time to switch. The p-values from log-rank test are also displayed showing whether or not differences existed between the plotted curves. The median survival line is also plotted in cases where the curves cross the line in relevant situations.

The smoothed hazard estimates were also compared with Kaplan-Meier curves for some of the variables and the hazards are described together with information from the Kaplan-Meir curves.

**Side effects:** The Kaplan-Meier curve for side effects showed that those who never experienced side effects were less likely to be switched from first line ART compared to those who experienced side effects (Figure 2). The hazards of switching with respect to side effects are shown in Figure 2. During the first 3 years of starting ART those experiencing severe side effects were more likely to be switched compared to those with mild or moderate side effects. Statistical comparison of the survival distributions between these groups of side effects by log-rank test indicated that the curves were
different. With a log-rank p-value<0.01, there was strong evidence against the null hypothesis that the survival curves (by side effects) were statistically the same.

The smoothed hazards estimates graph shows that the side effects are associated with higher switching hazards compared to the baseline (no side effects). The baseline hazard is fairly constant and consistently lower than that of side effects. The hazards of switching shows an increasing trend with time for the mild side effects category thought this can only be said for the period of between 2 and 4 years on ART. The hazard of moderate side effects slowly rises for the period 2 to 4 years and then sharply increases thereafter. Very little information can be deduced from the hazards of severe side effects.

Figure 2: (a) Cumulative probabilities of remaining on 1st line ART and (b) hazards of switching ART by side effects grouping
Pre-ART duration: Individuals who started ART early after testing HIV-positive were more likely to be retained on first line ART for longer periods than those who started ART later. Patients who were initiated 1-3 years after testing HIV positive were more likely to be switched to second line ART than those who were initiated within 1 year of testing positive. However, during the first 5 years on ART, those who were initiated 1 to 3 years after testing HIV positive were more likely to be switched early compared to those who were initiated more than 3 years after testing as shown in Figure 3.

The hazards of switching were higher during the first 2 years in all groups compared to after 2 years. Except for the group with pre-ART duration of more than 3 years, the hazards of switching continued to decline until after 5 years when the hazards started to go up again Figure 3. The hazards of switching with respect to group with more than 3 years were always higher than the other groups from the fourth year of therapy.

![Figure 3](image_url)

Figure 3: (a) Cumulative probability of remaining on 1st line and (b) hazards of switching to second line ART by pre-ART duration
**Period of initiation:** Patients who were started ART during the years 2004-2006 were more likely to be switched to second line ART compared to those who started from 2007 to 2010 throughout the whole period of observation (Figure 4). The log-rank test for the two Kaplan Meier curves had a p-value of <0.01 indicating statistically significant differences in the curves. The maximum follow up time for the sub-cohort initiated in the second period (2007-2010) was 4.7 years compared to 7.5 in the first sub-cohort.

The hazards of switching to second line ART for the period 2007-2010 were consistently lower than those of 2004-2006 (Figure 4). Both hazards showed an initial sharp rise for the first period from 6 to 18 months followed by a sharp decrease until 2 years. Hazards for 2004-2006 continued the trend until close to 4 years when it stabilised before rising again after 6 years of follow up. The period 2007-2010 had a bimodal peak, starting to decline again after 3 years and had shorter observation period of less than 4 years.

**Figure 4:** (a) Cumulative probability of remaining on 1st line ART and (b) hazards of switching to second line ART by period ART initiated
**Sex:** During the first half year of starting ART males and females had almost similar hazards of switching to second line ART. However, females were more likely to be switched compared to their male counterparts after this initial 6 months (Figure 5). The curves between males and females were statistically different (p-value= 0.04).

![Kaplan-Meier survival estimates by sex](image)

**Figure 5:** Cumulative probability of remaining on 1\textsuperscript{st} line ART by sex

**Initiation regimen:** Patients who were initiated on TDF-based regimens were less likely to be switched to second line compared to those who were initiated on AZT and d4T-based regimen respectively. However, these differences were clearer after the first year of starting ART. Except for the first year on ART, patients on AZT were less likely to be
switched than those on D4T throughout the study period. Those who were on regimens that were not commonly used, which include triple NRTIs, had the highest risk of switching to second line ART throughout the period of observation (p<0.01) as illustrated by the Kaplan-Meier curve in Figure 6.

**Figure 6**: Cumulative probability of remaining on 1st line ART by the initiation regimen

**Age group**: Patients who were younger than 25 years were more likely to switch to second line ART early than the older age groups (Figure 7). The curves for those aged 25-49 and those aged 50 and above crossed one another at multiple points. The
Kaplan-Meier survival curves by age group were statistically similar and the p-value was 0.24 (Figure 7).

Figure 7: Cumulating probability of remaining on 1st line ART by age group

### 3.8 Kernel-smoothed and Nelson cumulative hazards of switching

The Kernel-smoothed hazards and the Nelson cumulative hazards of switching to second-line ART are shown by the combined graphs in Figure 8. The Kernel smoothed hazards of switching to second line ART rises sharply from the first 6 months and peaked at 0.038 of the log hazards at about 1.5 years and then gradually decreased...
until about after 5.5 years of follow up when it started to rise again. The last person was switched to second line ART after 6.8 years of observation.

![Smoothed hazard estimate and Nelson-Aalen cumulative hazard estimate](image)

**Figure 8:** The smoothed and cumulative hazard estimates of switching

### 3.9 Comparison of baseline covariates with the outcome

Crude associations between baseline predictor variables and switching to second line ART were tested using Chi-square (or Fisher's exact) and Kruskal-Wallis tests and the results are showed in Table 5. Baseline CD4 cell count, WHO clinical stage, time between testing HIV-positive and initiating ART, the initiation ART regimen and the period a patient enrolled were strongly associated with switching to second line.
Table 5: Associations between switching to second line ART and baseline covariates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Outcome</th>
<th>P-value: Chi square/Fisher’s exact test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not switched n (%)</td>
<td>Switched n (%)</td>
</tr>
<tr>
<td>Sex:</td>
<td>Males</td>
<td>1803 (92.8)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>3050 (91.3)</td>
</tr>
<tr>
<td>Median baseline CD4 cell count (cells/μL)‡</td>
<td>92 [35-156]</td>
<td>63 [25-140]</td>
</tr>
<tr>
<td>Median baseline weight‡</td>
<td>57 [50-66]</td>
<td>59 [51-66]</td>
</tr>
<tr>
<td>Age group at initiation (years):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>233 (90.0)</td>
<td>26 (10.0)</td>
</tr>
<tr>
<td>25-49</td>
<td>4183 (91.9)</td>
<td>371 (8.1)</td>
</tr>
<tr>
<td>≥50</td>
<td>439 (93.0)</td>
<td>33 (7.0)</td>
</tr>
<tr>
<td>Baseline WHO stage:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>58 (89.2)</td>
<td>7 (10.8)</td>
</tr>
<tr>
<td>II</td>
<td>1013 (87.6)</td>
<td>144 (12.5)</td>
</tr>
<tr>
<td>III</td>
<td>1841 (92.6)</td>
<td>148 (7.4)</td>
</tr>
<tr>
<td>IV</td>
<td>1941 (93.7)</td>
<td>131 (6.3)</td>
</tr>
<tr>
<td>Previous ART:</td>
<td>No</td>
<td>4419 (91.8)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>434 (92.1)</td>
</tr>
<tr>
<td>Duration of untreated HIV (years):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>2014 (93.5)</td>
<td>139 (6.5)</td>
</tr>
<tr>
<td>1-3</td>
<td>1002 (89.2)</td>
<td>121 (10.8)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>963 (90.4)</td>
<td>102 (9.6)</td>
</tr>
<tr>
<td>Marital status:</td>
<td>Single</td>
<td>2118 (95.6)</td>
</tr>
<tr>
<td></td>
<td>Married</td>
<td>403 (95.7)</td>
</tr>
<tr>
<td></td>
<td>Separated/Divorced</td>
<td>103 (97.2)</td>
</tr>
<tr>
<td></td>
<td>Widowed</td>
<td>91 (97.9)</td>
</tr>
<tr>
<td>Smoking at baseline:</td>
<td>No</td>
<td>2382 (95.5)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>333 (97.9)</td>
</tr>
<tr>
<td>Alcohol consumption at baseline:</td>
<td>No</td>
<td>2584 (95.8)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>131 (95.6)</td>
</tr>
</tbody>
</table>

(Table continued on next page)
### 3.10 Inferential analyses

#### 3.10.1 Univariate analyses

**3.10.1.1 Side effects**

In the unadjusted Cox proportional hazards regression models, mild side effects were not significantly associated with time to switching (HR=1.52; 95% CI=0.57-4.06; p-value=0.41) when compared to those with no side effects. Experiencing moderate or severe side effects was significantly associated with increased risk of switching to second line ART early (HR=3.40; 95% CI=1.75-6.58; p-value<0.01 and HR=3.01; 95% CI=0.97-9.37; p-value=0.06, respectively). Thus those with moderate side effects to first line ART were 3.40 times more likely to be switched to second line ART earlier compared to those with no side effects. Similarly, those with severe side effects were 3.01 times more likely to be switched treatment early.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Outcome</th>
<th>Not switched n (%)</th>
<th>Switched n (%)</th>
<th>P-value: Chi square/Fisher’s&lt;sup&gt;a&lt;/sup&gt; exact test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ART initiation regimen:</strong></td>
<td>D4T-based</td>
<td>4147 (91.4)</td>
<td>392 (8.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>AZT-based</td>
<td>309 (92.8)</td>
<td>24 (7.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TDF-based</td>
<td>371 (98.2)</td>
<td>7 (1.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other combinations</td>
<td>28 (80)</td>
<td>7 (20)</td>
<td></td>
</tr>
<tr>
<td><strong>Period enrolled:</strong></td>
<td>2004- 2006</td>
<td>2338 (87.1)</td>
<td>347 (12.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>2007- 2010</td>
<td>2517 (96.8)</td>
<td>83 (3.2)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Estimates by Fisher’s exact tests variables with cell values of less than 5

<sup>b</sup>Continuous variables estimated using Kruskal-Wallis test for medians
3.10.1.2  **Sex and age**

Female sex was significantly associated with increased chances of earlier switching to second line ART compared to the males (HR=1.24; 95% CI=1.01-1.52; p-value=0.04). Therefore, female patients were 1.24 times more likely to be switched compared to their male counterparts. With reference to those aged less than 25 at baseline, those aged 25-49 inclusive had an insignificant 28% reduction in the hazards of switching to second line ART (HR=0.72; 95% CI=0.48-1.07; p-value=0.10). Those aged 50 and above at baseline were also not associated with significant reduction in the likelihood of switching (HR=0.69; 95% CI=0.41-1.15; p-value=0.15).

3.10.1.3  **Other clinical parameters**

Baseline CD4 cell count, rescaled to a factor of 100 cells/μL, was significantly associated with switching (HR=0.84; 95% CI=0.74-0.95; p-value<0.01). Thus an increase in the baseline CD4 cell count by 100 cells/μL was significantly associated with a 16% reduction in the risk of switching to second line ART early. The duration of the pre-ART period was significantly associated with the time to switching. Relative to those initiated during the first year of their HIV test date, those who were initiated after 1-3 years were 1.45 times more likely to switch to second line ART (HR=1.45; 95% CI=1.14-1.85; p-value<0.01) whilst those initiated after 3 years from HIV testing date were 1.34 times more likely to be switched to second line ART (HR=1.34; 95% CI=1.04-1.74; p-value=0.02).
Patients who were initiated from 2007 to 2010 had significantly lower risk (43% risk reduction) of switching to second line ART compared to those who started ART from 2004 to 2006 (HR=0.57; 95% CI=0.45-0.73; p-value<0.01). Patients who were initiated on AZT and TDF-based regimens had an insignificant lower risk of switching compared to those initiated on D4T-based regimens (AZT-based: HR=0.74; 95% CI=0.49-1.11; p-value=0.15, TDF-based: HR=0.64; 95% CI=0.30-1.36; p-value=0.25). However, those who were initiated on other regimens which included triple NRTIs were 3.16 times more likely to be switched to second line ART than those on D4T (HR=3.16; 95% CI=1.50-6.67; p-value<0.01).

The unadjusted effects of exposure variables are summarised in Table 6. Side effects, sex, baseline CD4 cell count, pre-ART duration, period of starting ART, baseline WHO stage, serial weight recordings and the ART initiation regimen were included in the final multivariable model. The influence of age group in the multivariable model was also examined because the age group has been significantly associated with switching to second line ART in other studies [80, 81].
Table 6: Factors associated with the time to switching to second line

<table>
<thead>
<tr>
<th>Variable (Reference (Ref) group)</th>
<th>Univariate (Unadjusted)</th>
<th>Multivariable (Adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (HR) [95% CI]</td>
<td>P-value</td>
</tr>
<tr>
<td>Side effects: (None) Mild Moderate Severe</td>
<td>1.00 (Ref) 1.52 [0.57-4.06] 3.40 [1.75-6.58] 3.01 [0.97-9.37]</td>
<td>0.41 &lt;0.01 0.06</td>
</tr>
<tr>
<td>Sex: (Male) Female</td>
<td>1.00 (Ref) 1.24 [1.01-1.52]</td>
<td>0.04</td>
</tr>
<tr>
<td>Baseline WHO clinical stage: 1 2 3 4</td>
<td>1.00 (Ref) 0.76 [0.36-1.63] 0.49 [0.23-1.01] 0.53 [0.25-1.13]</td>
<td>0.49 0.07 0.10</td>
</tr>
<tr>
<td>*Duration of Pre-ART (years): ≤1 1-3 &gt;3</td>
<td>1.00 (Ref) 1.45 [1.14-1.85] 1.34 [1.04-1.74]</td>
<td>&lt;0.01 0.02</td>
</tr>
<tr>
<td>Period initiated: 2004-2006 2007-2010</td>
<td>1.00 (Ref) 0.57 [0.45-0.73]</td>
<td>&lt;0.01 0.02</td>
</tr>
<tr>
<td>ART initiation regimen: D4T-based AZT-based TDF-based Other combinations</td>
<td>1.00 (Ref) 0.74 [0.49-1.11] 0.64 [0.30-1.36] 3.16 [1.50-6.67]</td>
<td>0.15 0.25 &lt;0.01</td>
</tr>
<tr>
<td>Baseline CD4 cell count (per 100cellsμL⁻¹ increase)</td>
<td>0.84 [0.74-0.95]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Weight at each visit (per 5kg gain)</td>
<td>0.97 [0.93-1.01]</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*All HRs and p-values corrected to 2 decimal places
†Status measured at baseline
‡Number of years from HIV testing date to date of starting ART
*CTX refers to the antibiotic Cotrimoxazole used for preventing opportunistic infections
3.10.2 Multivariable Cox regression model

The final model showed that moderate side effects, female sex, low baseline CD4 cell count and initiating ART between 2004 and 2006 were significantly associated with higher risk of early switching to second line ART. The time from testing HIV-positive to initiating ART and the ART initiation regimen used were also significantly associated with time to switching to second line ART. There was no evidence of multi-collinearity between the independent variables.

In the adjusted model and relative to the group with no side effects, the hazard ratios (95 % CI) for mild, moderate and severe side effects were respectively as follows: 1.40 (0.94-2.09), p-value=0.10; 1.72 (1.35-2.20), p-value<0.01 and 1.24 (0.65-2.35), p-value=0.52. Therefore, mild and severe side effects were not statistically significant but moderate side effects were statistically significant in predicting switching to second line ART after adjusting for sex, weight, pre-ART duration, period of ART initiation, baseline WHO stage and CD4 cell count (Table 6). Thus those with moderate side effects were 1.72 times more likely to be switched than those without side effects. The 1.40 and 1.24 times higher risks to switching that were associated with mild and severe side effects, respectively, relative to the group of no side effects did not play a significant role in predicting switching to second line ART. There were significant interactions effects between side effects and time. There were no significant interactions between side effects and sex or side effects and the regimen used.

Sex was significantly associated with time to switching after adjusting for other variables (HR=1.28; 95% CI=1.02-1.60; p-value=0.03). Females were 1.28 times more likely to switch early to second line ART than their male counterparts after controlling for other
variables. Baseline CD4 cell count (on a scale of every 100 cell/μL increase) was statistically significant in predicting switching to second line (HR=0.76; 95% CI = 0.66-0.89; p-value<0.01). Thus every 100 cell/μL increase in baseline CD4 cell count was associated with a 24% reduction in the risk of switching to second line ART with all other factors included in the model held constant.

The period of starting ART (2007-2010 versus 2004-2006) was also statistically significant in predicting time to switch to second line ART (HR=0.57; 95% CI=0.43-0.77; p-value<0.01), after adjusting for other covariates. Therefore, those who were initiated ART from 2007 to 2010 had a 43% lower risk of switching to second line ART compared to those initiating before the year 2007 when other covariates are kept constant. The hazards of switching to second line ART were also significantly higher for longer pre-ART durations. Compared to those who were initiated ART within the first year of being diagnosed HIV, the hazards ratios (95% CI) for those who were initiated ART 1 to 3 and over 3 years after testing HIV-positive were 1.39 (1.09-1.78), p-value=0.01 and 1.33 (1.03-1.73), p-value=0.03, respectively. Thus there was a 39% and 33% increased risk to switching to second line ART among the respective groups relative to those initiating within the first year of testing positive when all the other factors are held constant.

Use of ‘other’ initiating regimens was significantly associated with switching compared to D4T-based regimens. Relative to D4T, the hazard ratios (95% CI) of switching when AZT, TDF or ‘other’ regimens are used were respectively: 0.81(0.52-1.25), p=0.34; 1.51 (0.69-3.32), p-value=0.31 and 4.62 (2.17-9.82), p-value<0.01. There was a 4.62 times higher risk of early switching among patients who started other regimens compared to D4T-based regimens (HR=4.62; 95% CI = 2.17-9.82; p-value<0.01), other factors held
constant. Except for baseline WHO clinical stage 3, there were no significant associations between baseline WHO clinical stage and switching to second line ART. Compared with baseline WHO clinical stage 1, stage 3 had a hazard ratio of 0.44 (95% CI = 0.19-0.99; p-value=0.05). In this study baseline WHO clinical stage 3 was associated with a 56% reduction in the risk of switching to second line ART, other factors held constant. A gain in weight of 5kg at any point during the study did not significantly reduce the risk of switching to second line ART (HR=0.99; 95% CI=0.98-1.01; p-value=0.46).

Including age group into the model did not improve the significance of the model (likelihood ratio test: $LR \chi^2=2.54$; p-value=0.28). Interactions between age and the variables: baseline WHO clinical stage, sex, baseline CD4 cell count and the duration of pre-ART were tested and these did not play a significant role in predicting switching to second line. Introducing, adherence into the model did not change the results and adherence was not included in the final model. Interaction between side effects and adherence were not significant. The full results of the multivariable model are presented in Table 6.

### 3.10.3 Model fit assessment

After expanding by st-splitting, and remodelling the significant interactions with time, the proportionality assumption was just met with global test $\chi^2=24.95$; df=15 and p-value=0.0503 and the detailed results of the global test are shown in Appendix D. Scaled Schoenfeld and Cox-Snell residuals were used to examine how well the model
fitted the data. The scaled Schoenfeld and logarithm plots of some of the variables in
the multivariable model are also attached as Appendix D and Appendix E respectively.
The Cox-Snell residual plot indicated that the fitted line was close to the 45° reference
line but deviated for longer time values (Figure 9) predicting poor fit for those observed
for longer durations. Overall the model fit is reasonable.

Figure 9: Cox-Snell residuals plot
CHAPTER 4: DISCUSSION

4.1 Overview of study findings

The introduction of ART in the South African public health sector in 2004 has seen an increase in the life expectancy from 49.2 in 2003 to 60.5 years in 2011 [82]. The long-term benefit of ART is sustained through optimal patient adherence to treatment [40] which has been investigated and shown to be achievable among ART patients in Soweto in 2004 [83]. However, long-term ART use is associated with the development of side effects [9] which had been shown to be associated with non-adherence to ART [51, 84] and unstructured ART interruption [50, 55]. Side effects, non-adherence and treatment interruptions had been shown to be associated with treatment switching [12, 50, 85, 86].

In this study, neurological symptoms (mainly numbness or tingling sensation) were the most common side effects experienced by patients in this study. Similar findings were reported from a cohort of four sentinel sites in three South African provinces [87]. A study on the prevalence of pain and other symptoms among patients at South African HAART clinics also showed that numbness and tingling of hands and feet were the most common physical symptoms and overally only surpassed by feeling sad and irritable [88]. More than half of the episodes of the side effects were experienced during the first 2 years of follow up. The rate of switch to second line ART was 2.68 per 100 PY which was lower than 5.2 per 100 PY found in community based ART programmes in Cape Town [89]. A West African study indicated that experiencing side effects was
significantly associated with shorter times from ART initiation to switch to second line compared to situations where switch was only motivated by virological failure [90].

The expected sequence of events were starting ART and having side effects to ART with the possibility of poor adherence resulting in poor treatment outcomes requiring switch to second line ART [27]. However, this causal model could not be adequately investigated due to missing and incoherent data on adherence from the dataset.

4.2 The role of side effects in switching patients to second line ART

The study showed that stavudine was the commonly used NRTI drug (excluding lamivudine) during this period which was in line with the South African ART guidelines during the period 2004-2010 [33, 41]. The commonest side effects associated with its use were neurological (mainly peripheral neuropathy) and lipodystrophy. This is similar to the observation made in the Themba Lethu cohort study between 2004 and 2007 [45]. The findings are also supported in a different setting in Cambodia [91]. In the unadjusted models, moderate side effects (HR=3.4 (1.75-9.37), p value<0.01) were significantly associated with switching whilst the borderline association between severe side effects and switching (95% CI=0.97-9.37; p-value=0.06) still remained of interest in the analysis. However, after adjusting for other variables moderate side effects remained significantly associated with switching whilst the other two levels, mild and severe were no longer associated with switching to second line ART. The dose response effect was not evident since the HR declined from moderate to severe side effects. Therefore, side effects may not be significantly contributing towards switching patients to second line ART in this study.
Additionally, in as much as one would expect the severity of side effects to correspond to the increased likelihood of switching therapy, it may not be necessarily the case because clinicians may be more likely to substitute the offending drug to another less toxic first line drug early in cases of severe side effects thereby limiting detrimental effects of the drug. This is partially because clinicians are compelled through guidelines to stop the offending drugs at once in cases of severe and life threatening side effects whilst they are allowed to symptomatically manage and continue the offending drugs in cases of mild and moderate side effects [33]. The practice is good because it ensures future options of ARVs are available should more serious adverse events or drug failure occur. However, it may lead the patients to silently miss or reduce doses or even stop the treatment altogether without the physicians knowing as they make their own efforts to minimise the various forms of trauma resulting from these side effects [10, 40]. This may lead to drug resistance and switching to second line at early stages of treatment.

Data on adherence levels to ART treatment among the cohort were inconsistent and missing such that no in-depth explorations were done to determine whether there may be a connection between side effects experience and poor adherence as has been found in other studies [92, 93] and ultimately leading to treatment failure. A subgroup analysis between side effects and adherence would be worthy an effort to dissect and explain the causal pathways between side effects and switching to second line ART.
4.3 Risk factors for switching to second line ART

4.3.1 Low CD4 cell count: a consistent factor
Baseline CD4 cell count was consistently associated with risk of switching in both univariate and multivariable model. The findings are similar to studies done in different settings [81, 94, 95]. Lower CD4 cell counts are indicative of profound immunosuppression and advanced HIV disease. The clinical and immunological responses to ART were noted to be better when treatment is started early rather than late in a randomised trial in Haiti [96]. In this trial, the median CD4 cell count increased from 280 (at baseline) to 520 cells per millilitre in the early-treatment group compared to the drop from 282 to 270 in the late-treatment group at 36 months after initiating ART [96]. This was partly the reason for WHO to recommend to countries to adopt an early treatment initiative by starting ART in HIV-infected people with a CD4 cell count of 350 rather than the 200 cells/μL which have been used during the roll-out in the early to mid-2000s [61, 96, 97].

4.3.2 Period 2004-2006 and the associated factors
The period 2007-2010 was associated with a 43% risk reduction in switching patients compared to the first period 2004-2006. In the ART-LINC multicentre study in less developed countries including South Africa, stratification by period of ART initiation showed significant risk reductions in switching to second line ART for the periods 2002-2004 and 2005-2005 compared to the period before 2002 [94]. The period 2007-2010 had favourable outcomes partly because it was characterised by significantly shorter times on pre-ART (median 0.63 years, IQR=0.22-2.75) compared to 2004-2006 (median 1.3 years, IQR 0.43-3.09). The CD4 cell counts may also partly explain why patients
who were initiated before 2007 showed higher failure rates than those initiated from 2007 to 2010. An analysis into the temporal changes (2002-2007) in patient characteristics in South African public sector ART programme demonstrated an increase in baseline median CD4 cell count from 68 to 113 cells/mm³ and a decrease in the proportion of those with baseline WHO Stage IV disease from 50% to 28% indicating earlier enrolment into ART as the South African ART programme matures [98].

At roll-out of ART in 2004 South African guidelines recommended starting ART when CD4 cell count was 200 cells/μL or less [33]. Due to poor outcomes associated with late ART intervention, WHO recommended that countries should adopt initiating ART in all patients with a CD4 cell count of 350 cells/μL or less in 2009 [61]. Even though South Africa adopted the strategy only for TB patients and pregnant women during this period (2007-2010) [99], some benefits would be expected considering the high TB and HIV co-infection rates which stood at 60% in 2009 [100] rising to 65% in 2011 [101] and the prevalence of HIV among pregnant mothers peaking in 2010 to 30.2% [102]. This may have resulted in patients initiating earlier before they need to take wider drug cocktails owing increased co-infections associated with late HIV disease or become too sick to even tolerate the first line ARVs thus resulting in improved adherence and better outcomes.

The period 2007-2011 was characterised by greater political will and participation [103]. The government aimed to increase coverage of HIV testing and counselling services and ART provision to 80% of those eligible as revealed in the Department of Health’s (South Africa) 2007-2011 National Strategic Plan [103, 104]. With the above target met
[70], patients initiated during the period 2007-2010 were started ART earlier at least for the later part of the period as supported by higher values of baseline CD4 cell counts (median 99cells/μL; IQR 37-171) compared to 2004-2006 which had significantly lower (median 81; IQR 30-141) baseline CD4 cell counts (p<0.01). Another argument that can explain the favourable outcomes for the period 2007-2010 may be the reduction in the dose of stavudine from 40mg twice daily, which was linked to more severe side effects[35, 87, 105], to 30mg twice daily and also the availability of better tolerated tenofovir as an alternative [35, 106]. These factors not only improve adherence but may also improve the success and retention of first line ART. Improvement and maturity of the ART programme over time may also be considered as a possible explanation to these findings.

4.3.3 Longer time spans between testing HIV-positive and ART initiation
In the adjusted model, longer times from date of testing HIV-positive to date of ART initiation increased the risk of switching to second line ART. The date tested positive does not indicate or imply in any way the date of HIV infection and therefore does not estimate the period between infection and starting treatment. However, it serves as a way of providing known estimates of the period between the start of symptomatic HIV or voluntary counselling and testing and treatment initiation. Coming from an environment where individuals perceive that testing is necessary for people with symptoms of AIDS [107] and where patients are motivated to get an HIV test by sickness [100], one would expect that most should be eligible by the end of one year after testing positive for HIV.

In chronic HIV infection, HIV continues to multiply in the body reaching millions (10^6) of copies/ml [108] unless the patient is put on ART [108-111]. Therefore, the longer pre-
ART durations are more likely to be indicative of more advanced HIV/AIDS disease in which the regenerative ability of key cellular components of the immune system is poor [108]. Damage to the T-cell receptor (TCR) repertoire diversity is also associated with progressive loss of CD4 cells and poor immune reconstitution after starting ART [112].

It has been shown that it may be too late to obtain consistent immune reconstitution if immunity is severely compromised [113]. The marked loss in CD4 cells has been associated with increased risk of opportunistic infections [96, 106, 111] and poorer outcomes [20, 21]. A systematic review of retention into HIV care highlighted that the odds of successful ART were lower for those initiating late with lower CD4 cell counts compared to those initiating early with higher CD4 cell counts [114]. It should be noted, however, that the progression of the disease and decline in CD4 cell counts differs between individuals with some being slow progressors, who are elite controllers or long term non-progressors, who are able to control the viral replication [115] for long periods without ART and others being fast progressors who quickly succumb to AIDS within the first 5 years without ART [116]. These differences may partly shed more light to the lack of consistency in the hazard ratios observed for those initiating ART after 3 years (HR=1.33) compared to those initiating earlier from 1 to 3 years after HIV testing (HR=1.39) although this study cannot be used to deduce such an explanation.

4.3.4 Effect of sex

In this study female sex was associated with early switching to second line ART. Females had 28% higher risk of being switched to second line ART than males, other factors being held constant. A multicentre study in African, Asian and South American settings (ART-LINC) [94] and two other studies in Brazil [20] and France [21] showed no
sex differences in predicting switching. Uptake of ART was higher in women (63.2%) than in men (36.8%) in this study. Further research should involve a qualitative study to ascertain the reasons why females are at greater risk of failing when they are capable of accepting their status and getting on ARV treatment earlier than men in this setting [117]. The socio-cultural dynamics of the society may also be contributing to such observations. Issues surrounding disclosure, gender inequalities on the cultural strata and discordant couples may all play a role and make women more vulnerable in such situations [13]. For example, if one considers a less empowered woman who has accepted ART but whose husband is in denial and ignorant of ARVs; she may be forced to stop ART by the husband whose traditional gender roles may be affording him the power to deny the woman access to healthcare [118]. The associated negative effects in this situation coupled with the demanding family and child care roles may ultimately result in treatment failure due to failure to maintain optimal adherence [13]. The situations require a more family or couple centred approach, starting with couple HIV counselling and testing [119], when offering ART care to ensure that possible impediments are handled well prior to ART initiation and at the same time ensuring that such activities do not become bottlenecks to ART initiation. However, this may not explain the same findings in more women-empowered communities in the USA [120]; instead, genetic barriers to drug resistance between men and women may need further exploration.

4.3.5 Nature of the initiation regimen
The ART initiation regimens were grouped by the NRTIs used. A better approach would have been to group by NNRTIs due to fewer groups but this was not possible because
the NNRTIs were missing in some patients. However, those regimens that had 3 NRTIs, ABC combinations and single NNRTIs with no NRTIs recorded were pooled into 1 group called ‘other’. Use of these ‘other regimens’ were associated with 4.62 times higher risk of switching to second line ART compared to those initiated on D4T-based regimens. Triple NRTIs are known to be associated with greater risk of virological failure compared to a combination of NRTIs and an NNRTI/PI [121]. WHO does not currently recommend the use of the following triple NRTIS: ABC/3TC/TDF and TDF/DDI/3TC [76]. There were errors in the documentation of the initiation regimens where combinations such as D4T/3TC/AZT which are never used in clinical practice due to their pharmacological antagonism were reported in four patients. Therefore, there are limitations with the findings on the effect of the initiation ART regimen and these findings may not reflect the exact situation at the clinic. The lower risk of switching to second line ART associated with use of TDF and AZT compared to D4T in univariate model was not seen in the multivariable model showing that D4T, TDF and AZT are statistically similar.

4.3.6 Other clinical parameters
Baseline WHO clinical stage was not associated with switching to second line ART except for stage 3 which surprising indicated that those staged 3 were 0.44 times less likely to be switched to second line compared to stage 1. Dichotomised baseline stage did not significantly predict switching to second line in the ART-LINC study (HR=1.02; 95% CI=0.67–1.57) in which they compared advanced stages to the less advanced [94]. A Kenyan case-control study also found that dichotomised baseline stage (high and low) did not predict first line ART failure but there may be biased due to the study design if those with high baseline stages died early before they could fail first line ART
[95], typically leading to incidence-prevalence bias between those switched and high baseline stage. Generally higher baseline stages are signs of profound immunodeficiency and therefore starting ART is usually late and poorer outcomes may be expected. However, some of the reported lower baseline WHO clinical stages in this study did not correspond to the higher order AIDS defining conditions that were reported at the time of enrolment thus introducing some bias in the findings. The reduction in the risk of switching ART with increase in weight was not significant. There were no significant differences in the time to switching between different age groups. There is contrasting evidence on the effect of age on the time to switching with one study finding no differences [122] and another predicting higher risk of early switching among younger age groups [81].

4.4 Causality
This study is based on patient records entered prior to the beginning of the study and the findings reported do not imply any causal relationships. The postulated causal model in which side effects may cause poor adherence leading to treatment failure and the necessity to switch to second line ARV regimens [9, 10, 27] could not be adequately investigated due to the limitation on data for adherence which were missing and incoherent in the dataset.

4.5 Strengths and limitations
The study involved the whole cohort that was reported to have initiated ART from 2004 to 2010 thus has a large sample size. The follow up period was long enough (7.47 years maximum) to be able to detect more outcomes. The design was also able to estimate
directly the risk, associated with several covariates, of switching from first line ART to second line ART.

The limited data on adherence negatively affected the study. The available data on adherence was based on patient’s ability to recall the number of pills missed during the last 3 days prior to consultation. This method was not objective and was prone to recall bias [123]. The method also assumed that patients always gave honest answers [57]. In addition reporting number of pills missed alone does not give any indication of the level adherence. The number of pills dispensed and the number of pills that were supposed to be been taken were needed to calculate objective adherence levels. Honouring appointment dates could not be used as one of the markers of good adherence [53] because next-visit dates were not consistently provided for each clinic visit in the dataset.

Typical to other secondary data analyses, data were missing in some fields as was highlighted in the preceding paragraphs. This may lead to possible biases if those missing data were associated with the exposure and/or outcome leading to under-estimation or over-estimation of the effects of the variable. There were inconsistencies between age and date of birth with some dates of birth similar to date of HIV diagnoses in adult patients. The documented age was used in these cases after thorough data interrogation of the socio-demographic information provided. Some available dates of birth did not match the ages at enrolment and therefore misclassification of the ages was possible.
Very few height measurements were recorded (n=194) such that estimations of body mass index (BMI) could not be representative of the study population resulting in weight only being used in analysis. BMI is widely used and gives more valid nutritional assessment than weight alone [124]. BMI is also more informative because it takes into account the height of the patient.

4.6 Generalizability

The study was conducted at a busy urban clinic where the operational systems may differ from rural settings. South Africa has a well-established and technically functioning health system [125]. The Johannesburg metropolitan area is economically privileged compared to the rest of the country and enjoys better infrastructure and human resource capital. Therefore, extrapolation to rural settings in South Africa or different regions where there socioeconomic landscapes are different may be difficulty and may not reflect the reality in those communities.

4.7 Conclusion

The study informs that side effects may not play a role in patients failing first line ART. However, side effects remain a challenging burden to clinicians and patients due to its overall effects of reducing quality of life and negative effects on follow-up outcomes. Therefore patients who experience side effects should be closely monitored and a holistic approach should be advocated when treating and supporting such patients to ensure that their adherence levels remain optimal. Clinicians should actively seek symptoms from patients rather than waiting for them to report as has been suggested by Farrant et al [88]. Only time will tell whether ARVs will be safer and easier than they
are today in comparison with other easily manageable chronic diseases like hypertension; and better still if HIV would become vaccine preventable. The study also shows the need for a standardised reporting on adherence that should control for different pills, different tablet strengths and different daily dosing schedules between patients. This information would provide an accurate denominator for calculating adherence percentage. Adherence scores using pill counts or combination of pill count and self-report of missed doses may be more informative. Meanwhile public awareness of ART side effects, reporting of side effects by health institutions and the quest for the development of safer third generation ARVs should continue.
REFERENCES


71. Chris Hani Baragwanath Hospital. [Internet] [cited 18 September 2013]; Available from: http://www.chrishanibaragwanathhospital.co.za/.


73. Chris Hani Baragwanath Hospital. [Internet] [cited 19 September 2013]; Available from: http://www.wits.ac.za/academic/health/clinicalmed/internalmedicine/hospitals/9544/chris_hani_baragwanath.html.


Appendix A: List of side effects included in the study

| Field Name: fk_core_PatientID | Description: An integer value which uniquely identifies the patient. | Options: Not applicable |
| Field Name: Aeve_VisitDate | Visit date | Options: Not applicable |
| Field Name: fk_aevd_AdverseEventID | Event code | Options: |

<p>| | | 1 | 11 Anaemia / Haemoglobinaemia |
| | | 2 | 12 Neutropenia |
| | | 3 | 13 Leukopenia (decreased WBC) |
| | | 4 | 14 Thrombocytopenia |
| | | 5 | 21 Hyponatraemia |
| | | 6 | 22 Hypernatraemia |
| | | 7 | 23 Hypokalaemia |
| | | 8 | 24 Hypokalaemia |
| | | 9 | 25 Elevated Blood Urea (BUN) |
| | | 10 | 26 Elevated Creatinine |
| | | 11 | 27 Hypoglycaemia |
| | | 12 | 28 Hyperglycaemia |
| | | 13 | 31 Elevated Triglycerides |
| | | 14 | 32 Elevated Cholesterol |
| | | 15 | 41 Elevated AST (SGOT) |
| | | 16 | 42 Elevated ALT (SGPT) |
| | | 17 | 43 Elevated ALP |
| | | 18 | 44 Hyperbilirubinaemia |
| | | 19 | 45 Elevated Amylase |
| | | 20 | 46 Elevated Lipase |
| | | 21 | 47 Elevated CPK |
| | | 22 | 48 Elevated Lactate |
| | | 23 | 51 Oral discomfort / dysphagia |
| | | 24 | 52 Nausea |
| | | 25 | 53 Vomiting |
| | | 26 | 54 Diarrhoea |
| | | 27 | 55 Constipation |
| | | 28 | 56 Abdominal Pain |
| | | 29 | 57 Clinical Hepatitis |
| | | 30 | 58 Symptomatic Hyperlactaemia |
| | | 31 | 61 Rash / Dermatitis |
| | | 32 | 62 Local Reaction |</p>
<table>
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<th>EventSeverityID</th>
<th>Severity</th>
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<tbody>
<tr>
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<tr>
<td>34</td>
<td>64 Headache</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>65 Allergic Reaction</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>66 Fatigue</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>67 Eye</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>68 Lipodystrophy</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>69 Cardiovascular Disease</td>
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</tr>
<tr>
<td>40</td>
<td>71 Neuro-Cerebellar</td>
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</tr>
<tr>
<td>41</td>
<td>72 Neuro-Psychiatric (Mood, sleep changes)</td>
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</tr>
<tr>
<td>42</td>
<td>73 Paraesthesia (Burning, tingling)</td>
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</tr>
<tr>
<td>43</td>
<td>74 Neuro-Motor (Proximal Myopathy)</td>
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<tr>
<td>44</td>
<td>75 Neuro-Sensory (Peripheral Neuropathy)</td>
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<td>45</td>
<td>76 Arthralgia / Arthritis</td>
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<tr>
<td>46</td>
<td>77 Myalgia</td>
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</table>

**Severity Definitions:**

1. Mild (Transient, no medical intervention required)
2. Moderate (Mild-moderate limitation in activity, minimal/no intervention required)
3. Severe (Marked limitation in activity, intervention required)
4. Life Threatening (Intervention required, hospitalisation probable)
Appendix B: Ethics clearance certificate- No. M120855

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

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49  Dr Munyaradzi Pasipamire

CLEARANCE CERTIFICATE
PROJECT
M120855
The Role of Side Effects in Shifting Patients from First Line to Second Line ART at Nthabiseng Clinic in
Soweto, Johannesburg

INVESTIGATORS
Dr Munyaradzi Pasipamire
DEPARTMENT
School of Public Health
DATE CONSIDERED
31/08/2012
DECISION OF THE COMMITTEE*
Approved unconditionally

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

DATE

CHAIRPERSON
(Professor P E Cleaton Jones)

*Guidelines for written ‘informed consent’ attached where applicable
cc: Supervisor: Dr Edmore Marinda

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
Appendix C: MOU for the use of Anova Health Institute data

10 May 2012
Munyaradzi Pasipamire

Memorandum of Understanding between Anova Health Institute and Munyaradzi Pasipamire for access to Anova-support clinic data for research purposes

Preamble:
Anova supports and maintains a number of database across South Africa. These contain personal information about the clients who make use of the health care services Anova support. These data contain a range of information that may be useful to researchers and students who aim to gain insight into HIV in South Africa. This data is made available on request to individual researchers, or research organisations, wishing to examine specific issues. This document outlines the terms and conditions of the use of facility’s/ies’ data that Anova supports for research purposes.

1. Partners
The partners of this memorandum of understanding are Anova, represented by

Joshua Murphy
Unit 3 Medical School
represented by
Munyaradzi Pasipamire

2. Research projects
Objectives and details of research projects for which Anova data are required:

For fulfillment of MSc Research Project

3. Details of understanding
The partners, after due consideration of the data requirements of the proposed research, have agreed to the following understanding with regard to this research.
Anova will provide, free of charge, the dataset from the clinic database in a machine readable format, with relevant documentation required to assist in the meaningful analysis of this data. Data will be stripped of any identifying terms that could be used to link them to patients’ personal identifiers.

The data provided by Anova will only be used for the research projects listed in section 2.

The intention to use the data provided by Anova for any other research project will require advance notification of Anova, and the provision of written provision by Anova.
Munyaradzi Pasipamire will strictly maintain the confidentiality of any data that could lead to disclosure of the identity of any of Anova’s patients, and will take
adequate precautions to ensure that it will be impossible to identify individual patients based on the outputs of research.

The data provided by Anova will not be used for any commercial purpose.

The data provided by Anova will not be passed on, either in part, or in full, to any other data user or disseminator.

The research outputs will be made available to Anova in full, free of cost.

Publication of any data provided by Anova must be confirmed and approved by all relevant stakeholder before proceeding.

All research outputs based on Anova data will acknowledge Anova as the source of data. All costs involved in the completion of the research project/s will be borne by [ANOVACAPTIONS]

4. Date of effect

The Memorandum of Understanding will come into effect on the date of signature, and will remain in effect until either partner delivers written notification to the other of its intention to terminate the Memorandum.

5. Modification

The MOU may be amended by mutual consent of both partners.

6. Signatures

Signed, on the 10th day of May (month),

2012 (year) at ANOVA OFFICES JOHANNESBURG

For Anova: Joshua Murphy (name) (signature)

For MNTU MEDICAL SCHOOL: [signature] (signature)
Appendix D: Tables and plots from assessing the model fit

Object D1: Detailed global test of all variables in the multivariable model

Test of proportional-hazards assumption

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<th>df</th>
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global test: 24.97, df = 15, Prob > chi2 = 0.0503

Object D2: Plot of scaled Schoenfeld residuals for CD4 cell count - baselineCD4_100

Running mean smoother with bandwidth = .8
Object D3: Plot of scaled Schoenfeld residuals for interaction term - c.weight_5#c._t

Object D4: Plot of scaled Schoenfeld residuals for interaction term - 2.PreART_duration
Appendix E: Stpht plots for selected variables

Object E1: Plot by side effects

Object E2: Plot by sex
Object E3: Plot by period of initiation

Object E4: Plot by duration of Pre-ART