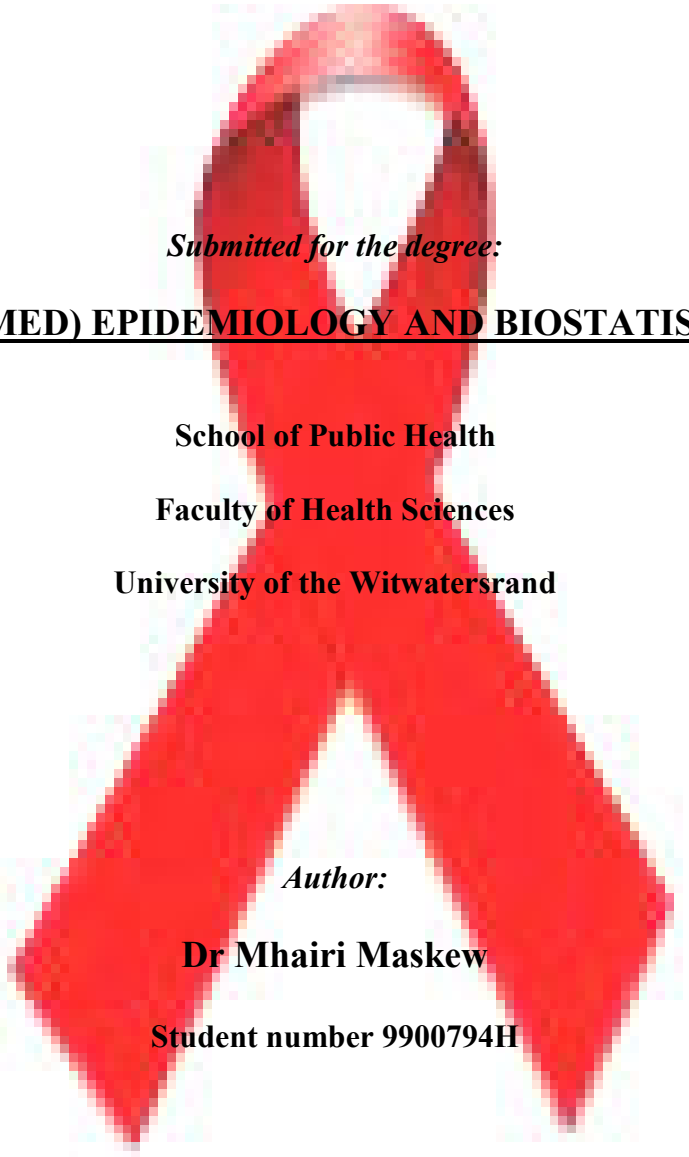
RESEARCH REPORT

TITLE

Gender Differences in clinical and immunological outcomes in South African HIV-infected patients on HAART



Submitted for the degree:

MSc (MED) EPIDEMIOLOGY AND BIOSTATISTICS

School of Public Health

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CANDIDATES DECLARATION

I, Mhairi Maskew (student number 9900794H) am a post-graduate student registered for the degree MSc (Med) Epidemiology and Biostatistics in the Wits School of Public Health.

I am submitting written work for the research report component of the afore-mentioned degree.

I hereby declare the following:

- I confirm that the work submitted for the above course is my own work, except where I have stated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.

Signed: _____

Date: _____

DEDICATION

I dedicate this work to all the healthcare workers, counselors, campaigners and volunteers who, despite personal and political hardship, tirelessly continue the fight against HIV and AIDS everyday.

Mhairi Maskew

January 2008

ABSTRACT

Introduction

South Africa is estimated to have the largest number of HIV infected adults in Southern Africa with a higher HIV prevalence in females compared to males. While significant reductions in morbidity and mortality due to HIV and AIDS have been realized for over a decade internationally, HIV treatment involving highly active antiretroviral therapy (HAART) is still a relatively new phenomenon in this country and gender differences in HIV outcomes between males and females in South Africa have not been previously well described. This study aimed to determine and describe gender differences in clinical and immunological outcomes in a population of HIV infected South African adults initiated on HAART.

Materials and Methods

This retrospective data analysis reviewed 6,617 HIV-infected adults initiated on HAART at the Themba Lethu Clinic, an urban public-sector antiretroviral rollout facility in Johannesburg, South Africa between 1st April 2004 and 31st March 2007. Clinical data from these antiretroviral naïve patients was analysed for gender differences in mortality, rates of loss to follow up, CD4 cell count response, virologic suppression and weight gain. Cox regression models and logistic regression models were used to estimate hazard ratios (HR) and odds ratios (OR), respectively, for associations between gender and outcomes. Models were adjusted for age and baseline CD4 count.

Results

At baseline, 4,388 (66.3%) women were significantly younger ($p<0.0001$) and

less likely to be employed than the 2,229 (33.7%) men ($p<0.001$). Furthermore, women had significantly higher baseline CD4 counts ($p<0.0001$) and higher body mass index (BMI) ($p<0.0001$). Males experienced significantly reduced survival compared to females ($p=0.0053$) by Kaplan-Meier analysis. In adjusted multivariate analysis, men were 22% more likely to die or become lost to follow up than women [HR = 1.22 (95% CI 1.06 - 1.39]. The period with the highest risk of mortality or loss to follow up was within six months of starting HAART.

Female gender was associated with better CD4 count response. In multivariate analysis adjusted for age and baseline CD4 count, women were 35% more likely to achieve a 100 cell increase in CD4 count at four months after initiation of HAART [OR =1.35 (95% CI = 1.19 -1.54)] and 45% more likely to increase their CD4 counts by 100 cells/mm^3 after ten months on HAART [OR =1.42 (95% CI = 1.20 -1.68)] when compared to men. Women were also more likely to achieve virologic suppression at ten months post HAART initiation [OR =1.54 (95% CI =1.21-1.97)] and were more likely to have gained weight after four months on treatment than males [OR = 1.26 (95% CI = 1.07–1.49)] after adjusting for age, baseline CD4 count and baseline BMI.

Conclusions

Women had significant advantages over men in terms of short-term clinical and immunological outcomes. Earlier access treatment for men should be facilitated and adherence should be promoted once on treatment. Further research is required to determine if these gender differences persist during long-term HAART.

ACKNOWLEDGEMENTS

Firstly, I would like to sincerely thank the Clinical HIV Research Unit of the Department of Medicine, University of the Witwatersrand and the non-profit organization Right to Care, for without their generous financial assistance and support, the conduct of this research would not have been possible.

I am eternally indebted to my inspirational supervisor, Professor Patrick MacPhail. His advice, encouragement and seemingly endless patience were invaluable to me during the process of writing this research report. His compassion for those living with HIV and dedication to promoting the treatment of all AIDS sufferers will be with me all my days.

Babatyi Malope-Kgokong, epidemiologist at the Clinical HIV Research Unit, my wonderful colleague and friend, assisted me with the acquisition of the de-identified data on which this project is based. Her advice on data management has also provided valuable lessons which I will take forward to future projects.

Several draft sections of this report were read by Mr. Matthew Fox, Assistant Professor for the Centre for International Health and Development, Boston University School of Public Health. I am very grateful for his insightful comments.

Finally, I thank my family, in particular my husband, Darryl, for enduring this journey with me.

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NOMENCLATURE

ARV	antiretroviral therapy
HAART	highly active antiretroviral therapy
BMI	body mass index
HIV	human immunodeficiency virus
NRTI	nucleoside reverse transcriptase inhibitor
AIDS	Acquired Immunodeficiency Syndrome
WHO	World Health Organisation

CHAPTER ONE: INTRODUCTION

In this chapter the significance of the HIV epidemic in South Africa is reviewed. Sources and implications of gender inequalities amongst HIV infected persons are explored. The published literature on gender differences in clinical and immunological outcomes of HIV infection is reviewed and the chapter ends with the aims and objectives of the study described in this Research Report.

Background

The use of highly active antiretroviral therapy (HAART), since its advent in 1996, has resulted in significant reductions in mortality from HIV-related illness worldwide [1, 2]. Developing countries including those in sub-Saharan Africa have shown similar improvements in survival and clinical outcomes in HIV-infected individuals receiving HAART compared to developed countries despite resource poor settings [3].

However, there are significant differences in access to antiretroviral therapy between the developed and the developing world, leaving many patients in resource-limited countries with no access to antiretroviral therapy despite a decade of availability of these potentially life-saving drugs [4]. Moreover, the poorest and most vulnerable sections of society in these resource-limited countries are the least likely to access HAART; sections in which women are often over-represented. In such settings one may expect to see significant differences in survival and clinical outcomes between HIV infected women and men.

South Africa is one such country. South Africa is estimated to have the largest number of HIV infected adults in Southern Africa [5] with a higher HIV prevalence in females compared to males (female: male ratio estimated between 1.2 and 2.3) [6]. The government antiretroviral rollout was officially launched in South Africa in 2004; therefore, comprehensive HIV treatment involving HAART is still relatively new in this country. It is for this reason that gender differences in HIV outcomes in South Africa have not been well described.

Additionally, if such gender differences in HIV outcomes based on access to treatment exist, it is important to determine if such differences persist when access to treatment is equal. If this is the case, it may warrant a re-evaluation of the current single guideline for both genders regarding treatment of HIV involving HAART to address these differences.

Statement of the problem

Gender differences in HIV outcomes may persist despite equal access to HAART. This has not been well described in South African patients receiving HAART and may have an impact on the treatment guidelines recommended for men and women receiving HAART.

Justification for the study

HIV care, including the provision of antiretroviral therapy, places an enormous financial burden on health care especially in resource-limited settings. It is, therefore, essential to know if there is a difference in HIV outcomes between men and women receiving HAART so that resources may be used optimally to maximize positive health outcomes.

The researcher is unaware of any published study examining such gender differences in HIV outcomes for patients receiving HAART in South Africa. There have been conflicting results from studies done in other countries with some showing significant gender differences in HIV outcomes [10-13] and others which found no differences between males and females [8-9,] once HAART is initiated.

The published literature reviewed has studied mostly white men who have sex with men (MSM) or IV drug users in North America and Europe and the results of these studies may differ to studies of South African HIV infected individuals where transmission occurs largely through heterosexual intercourse and women have a higher prevalence of HIV infection than men.

Literature review

Introduction

The prognosis for HIV-infected patients has considerably improved since the introduction of HAART into the management of HIV infection. Disease progression and mortality rates have dropped significantly with use of HAART worldwide [1, 2] and individuals infected with HIV can expect a quality and prolongation of life that would not have been possible in the pre-HAART era. HIV incidence rates remain high, particularly in sub-Saharan Africa despite mass education and prevention campaigns [7], resulting in ever-increasing numbers of individuals requiring treatment with HAART.

Access to Antiretrovirals

Yet there appears to be inequality in the distribution of HAART, not only between developing and developed countries, but also between men and women even when access to these potentially life saving drug is secured [8, 14]. Mocroft et al [8] showed that despite free access to antiretrovirals, women were significantly less likely than men to start antiretroviral therapy and particularly less likely to receive a protease-inhibitor containing regimen than their male counterparts. Proposed reasons for this disparity included the poorer socio-economic circumstances that women may experience as well as family commitments and lack of child care that may be obstacles that women experience in keeping HIV clinic appointments.

Clinical Presentation

However, when women do present to clinics for initiation of HAART, they do so with significantly higher baseline CD4 counts and with a lower proportion of AIDS defining illnesses than men [8]. Women have also been reported in other studies to have lower baseline viral loads, higher baseline CD4 counts and are less likely to have an AIDS diagnosis at the time of starting HAART [11]. This suggests that women may display earlier help-seeking behaviour compared to men. It must also be considered that there is evidence of biological differences in the normal range of CD4 counts between men and women (analogous to the differing normal ranges of haemoglobin levels according to gender) with women having higher CD4 counts than their males counterparts in HIV negative individuals and in HIV positive individuals even up to 5 years after infection [11].

Clinical Outcomes after Initiation of HAART

The debate over potential gender differences in the effect of clinical outcome after starting HAART is ongoing and the results are conflicting. Some studies have shown a possible benefit for women compared with men in the rate of outcomes after HAART use [10]. This includes decreased rates of hospital admissions, lower rates of progression to new AIDS defining illness, faster rates of achieving virologic suppression. These results may have been limited by the inability to adjust for adherence rates which were suspected to be better in women but not available for analysis in the data. HIV infected males have also been shown to experience higher mortality rates [16] and have a greater risk of premature atherosclerosis and cardiovascular events than their female HIV counterparts in adjusted analyses [18].

Other studies have shown the converse to be true - suggesting that women receiving HAART may fare less well than their male counterparts. The women in these studies had a higher risk of virological rebound [11], increased hospitalization rates [11, 12] and higher likelihood of adverse effects and toxicities of antiretroviral drugs [13]. These studies did consider the possibility that the gender differences were more likely to be as a result of inequality in access to care rather than in a fundamental biological difference in response to treatment. Other theories postulate that women have poorer outcomes as they are more likely than men to encounter social challenges such as having difficulty taking HAART openly at home due to the stigma associated with HIV infection [15].

Still other studies have shown no difference at all between the genders in terms of disease progression and immunological or virological response to a HAART treatment regimen [8-9, 17, 19]. However most of these studies had very small numbers of women included in the analyses which may have decreased these studies' power to detect differences between men and women.

Studies evaluating weight gain after initiation of HAART have shown moderate increases in weight for those receiving HAART compared to treatment naïve patients [21, 22]. Study participants with lower baseline CD4 counts in these studies tended to present with lower baseline weight and BMI (body mass index) but also showed greater weight gain within the first four months on treatment. However, no significant gender differences in weight gain were reported.

Conclusion

While previous research provides a useful background to the possible gender differences that may exist in South African patients receiving HAART, the results of these studies may not be consistently reproduced in the South African HIV-infected population for a number of reasons. Firstly, while most of the published literature studied mostly white MSMs and IV drug users with only a small proportion of infected females, South African HIV transmission occurs mainly through heterosexual contact and a larger proportion of women are infected than men. Additionally, the nadir CD4 count for starting HAART in some of the studies was 500 cells/mm3, much higher than the 200 cells/mm3 cutoff currently used in South Africa.

In conclusion, gender differences in HIV outcomes may be present amongst South African HIV-infected adults receiving HAART, but has not been well described as yet. Hence this research project to investigate and describe potential gender differences in the clinical and immunological outcomes amongst HIV-infected adults receiving HAART from a public-sector antiretroviral rollout clinic based in Johannesburg, South Africa.

Definition of terms

HAART

Highly active antiretroviral therapy is defined as combination of three or more nucleoside reverse transcriptase inhibitors (NRTI) or a combination of two NRTIs plus a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor (NNRTI).

HIV outcomes

This term encompasses clinical outcomes (death and weight gain), immunologic responses to HAART (as measured by an increase in CD4 count) and virologic response (defined as a decrease in HIV viral load to undetectable limits).

BMI

Body mass index is an anthropometric measure which is calculated as follows: weight in kilograms divided by the square of height in metres.

Study Objectives

General objective

To determine and describe gender differences in HIV outcomes in a population of HIV infected South African adults.

Specific objectives

- To describe the gender distribution of South African adult HIV infected patients receiving HAART
- To measure differences in weight gain, mortality rates and rates of loss to follow-up between male and female HIV infected South African adults taking HAART
- To determine if men are more likely to show short term immune reconstitution to HIV once HAART is initiated than women as measured by response in CD4 count and viral load suppression

CHAPTER TWO: METHODOLOGY

Introduction

In this chapter, the study design and methodology are presented. The study population is described and selection of the study sample is explained. The data collection system at the study site is described and details of the variables to be analysed are presented. Definition of each clinical and immunological outcome of interest is given and the chapter ends with a review of the data analysis plan and ethical considerations of this project.

Study Design

This study is a retrospective analytic cohort study conducted as a secondary data analysis of data collected from HIV positive adults at the Themba Lethu Clinic.

Study site

The Themba Lethu Clinic is an urban antiretroviral rollout site based at Helen Joseph Hospital, a provincial public hospital in Gauteng, South Africa. Since its inception in 2004, the clinic has enrolled over 8000 HIV infected adults from Johannesburg and environs. Currently, the clinic provides free antiretroviral therapy to more than 7000 of these patients according to the South African National Department of Health's guidelines on rollout of antiretroviral therapy [20]. This site was chosen as the Themba Lethu Clinic is one of the largest public antiretroviral rollout sites and its population can be considered representative of urban populations accessing antiretroviral therapy in the public sector.

Additionally the clinical data from the patients' records at this site is captured electronically and, as such, was one of the few sites with data available and accessible for secondary analysis.

Study population

The study population consists of the 9,834 HIV positive adults enrolled at the Themba Lethu Clinic since its inception on 1st April 2004.

Study sample

The study sample consists of 6,617 male and female adults initiated on HAART at the Themba Lethu Clinic between 1st April 2004 and 31st March 2007 who met the following inclusion criteria:

- Patients older than 18 years of age at the time of enrollment in the clinic
- HAART naïve prior to the initiation visit at the clinic
- Blood results were available for CD4 count tested at the initiation (baseline) visit

Exclusion criteria:

- Patients transferred in from other clinics or rollout sites already initiated on HAART

Details of the exclusion process are outlined in Chapter three.

Measurement

The Themba Lethu clinic records both demographic and clinical patient information on an electronic database, Therapy Edge. Data are captured from the patient files by trained data capturers after each clinic visit. The patients' demographic and contact details are recorded at the initiation visit on the "ARV Initiation Form" (Appendix A). At every visit the patient's vitals and weight are recorded as well as any symptoms and new diagnoses made on the "Follow-up Visit Form" (Appendix B). Additionally, blood tests results for CD4 count, HIV viral load, full blood counts as well as liver function tests which are tested at each scheduled visit (four months after initiation and six monthly thereafter) are collected and entered onto the database. Any clinically indicated additional investigations and results are also recorded on the database. All data used in the study was obtained from variables already captured on this electronic database. All data was de-identified and unique study numbers were allocated to each individual before the data was provided for analysis.

Study variables

The exposure to be measured is gender and the outcomes of interest include clinical outcomes (weight gain, death or loss to follow up) and immunological outcomes after initiation of HAART. Immunological outcomes were measured using CD4 count response and HIV viral load suppression. The outcomes are defined as follows:

- Death or loss to follow up using confirmed date of death recorded on the database or, in the case of loss to follow up, the date of last clinic visit

- Weight gain defined as an increase in body weight of five percent or more from baseline weight at initiation on HAART or a five kilogram increase in weight after initiating HAART
- CD4 count response defined as an increase in CD4 count from the baseline CD4 count, or a 50% increase in CD4 count or achieving a 100 cell rise in CD4 count after initiation of HAART.
- HIV viral load suppression defined as decrease in HIV viral RNA to less than 400 viral copies after initiating HAART

The outcomes data was provided from the clinic's electronic database after any identifying information is removed. Data was also obtained on the following baseline characteristics: age, race, HAART regimen, and socio-economic status (using employment status as a proxy).

Data Quality Control

The data at the Themba Lethu Clinic is captured from the medical records to an electronic database via a medical management software system, TherapyEdge-HIV^{TM}. The database is managed and maintained by a non-profit organization, Right to Care who through a team of trained data capturers, capture the data electronically and do quality assurance checks. Right to Care and the Clinical HIV Research Unit of the Department of Medicine (WITS University) agreed to work with the researcher to create a de-identified dataset containing the required fields of interest. Furthermore observations with values which seemed implausible were set to missing by the researcher as verification of data was not

possible due to the de-identified nature of the data. Variables which were cleaned in this way included:

Height – plausible values were deemed to be between 135 and 200 centimetres

Weight - plausible values were deemed to be between 30 and 200 kilograms

CD4 counts – these are reported as integers by the laboratory and so values with decimal places were considered typing or capturing errors and set to missing

Data processing Methods and Data Analysis

Data analysis was done using the STATA 9.0 statistical software package. All statistical significance was calculated at the 5% confidence level. The baseline characteristics of the two exposure groups (males and females) were summarized with descriptive statistics and presented in Table 1. Odds ratios or hazard ratios of each outcome were calculated for both genders. Univariate analysis of the associations between gender and each outcome was done using the Chi squared test for proportions (proportion showing CD4 count response or HIV viral load suppression and proportion dead or lost to follow up etc).

Time-to-event analysis was performed using survival techniques including Kaplan-Meier estimates, a log rank test and proportional hazards model. Multivariate model building was conducted in the following manner:

- Variables which modified the hazard ratio for the effect of gender on each outcome by more than ten percent were included in the multivariate analysis.
- If no variable modified the effect by more than ten percent then variables from the univariate analysis were retained in the model at an alpha of 0.20.

Assumptions testing for the models are presented in Appendix E.

Ethical considerations

The individuals in the study sample were identified by a unique identifier that does not relate to the participant's date of birth. Any personal identifiers were removed prior to the data being given to the researcher for secondary analysis and as such, the researcher was unable to identify individuals in the sample or to collect informed consent from the sample population. The study was conducted according to the Standard Operation Procedure (SOP) of the Clinical HIV Research Unit governing the analysis of data from the Themba Lethu Clinical Cohort (see Appendix C) which includes *inter alia* the approval of the research protocol by the University of the Witwatersrand Committee for Research on Human Subjects (Medical) (see Appendix D) and permission to conduct the study from the CEO of Helen Joseph Hospital where the Themba Lethu Clinic is based.

CHAPTER THREE: RESULTS

Introduction

In order to meet the aims and research objectives of this report, the clinical and immunological outcomes data was analysed systematically by gender and the results are presented in this chapter. The baseline characteristics of the cohort are described and any differences in baseline characteristics between the genders measured. The clinical outcomes, death and loss-to-follow up are considered next, followed by the immunological outcomes (CD4 count and viral load). The chapter ends with the analysis of final clinical outcome, weight gain, and a comparison between the genders.

Cohort demographics

The study population consisted of the 9,834 adults enrolled on the antiretroviral rollout programme at the Themba Lethu Clinic between 1 April 2004 and 31 March 2007. Of these, 1,146 were excluded from the study because they were transferred into the clinic from other antiretroviral treatment programmes, and a further 2,071 subjects were already on treatment at the time of enrolling at the Themba Lethu clinic, or they had received antiretroviral treatment at some point previously and thus could not be considered treatment naïve. The study sample that remained consisted of 6,617 individuals. The baseline characteristics of this overall cohort, as well as the baseline characteristics compared by gender, are presented in Table 1. Assumptions testing for normally distributed data and t-tests are presented in Appendix E.

Table 1: Baseline Characteristics of the Themba Lethu Clinical Cohort at Initiation of Antiretroviral therapy

	Overall *N (%)/* $\bar{x}$, std	**Males** *N (%)/* $\bar{x}$, std	**Females** *N (%)/* $\bar{x}$, std	**χ2 (p value)**
Frequency (n, %)	6617 (100)	2229 (33.7)	4388 (66.3)	
Age (years)	n = 6617	n = 2229	n = 4388	
($\bar{x}$, std)	37.7 (8.6) ‡	39.8 (8.4) ‡	36.6 (8.6) ‡	14.3 (<0.0001)†
Employment (n, %)				
- yes	2396 (38.5)	950 (45.1)	1446 (35.2)	
- no	3823 (61.5)	1156 (54.9)	2667 (64.8)	58.3 (<0.001)
Initiating ARV regimen (n, %)				
- 1a (3TC, efv, d4T/AZT)	4272 (64.6)	1484 (66.6)	2788 (63.6)	
- 1b (3TC, d4T, nvp)	452 (6.8)	122 (5.5)	330 (7.5)	
- any first line incl lopinavir	527 (7.6)	160 (7.1)	367(8.4)	
- 2nd line (ddI, AZT, LPV/r)	226 (3.4)	73 (3.3)	153 (3.5)	
- other	304 (4.6)	110 (4.4)	194 (4.9)	14.366 (0.006)
Baseline weight (kg)	n = 5001	n= 1696	n = 3305	
($\bar{x}$, std)	60.1 (13.3) ‡	60.3 (11.0) ‡	59.9 (13.3) ‡	0.92 (0.3571) †
Baseline BMI (kg/m^2)	n = 4990	n = 1694	n = 3296	
($\bar{x}$, std)	22.5 (5.0) ‡	20.5 (3.6) ‡	23.4 (5.4) ‡	-20.0(<0.0001)†
Baseline BMI (kg/m^2) (n, %)				
- Underweight (<18.5)	2812 (56.4)	1070 (63.2)	1742 (52.9)	
- Normal (18.5 – 25)	978 (19.6)	466 (27.5)	512 (15.5)	
- Overweight (>25)	1200 (24.0)	158 (9.3)	1042 (31.6)	334.1 (<0.0001)
Baseline CD4 count ($cells/mm^3$)	n = 6124	n = 2096	n = 4028	
($\bar{x}$, std)	90 (67) ‡	80.1 (65.5) ‡	95.1 (67.2) ‡	74.4 (0.0001)†
Baseline CD4 count (cells/mm3) (n, %) - > 100 cells/mm3	2588 (42.3)	763 (36.4)	1825 (45.3)	
- 50 – 100 cells/mm3	1324 (21.6)	425 (20.3)	899 (22.3)	
- <50 cells/mm3	2212 (36.1)	908 (43.3)	1304 (32.4)	74.27 (<0.001)
Year of initiation (n, %)				
- 2004/2005	1642 (24.8)	501 (22.5)	1141 (26.0)	
- 2005/2006	2230 (33.7)	728 (32.7)	1502 (34.2)	
- 2006/2007	2745 (41.5)	1000 (44.8)	1745 (39.8)	8.89 (0.0001)

† z score and associated p values used for continuous variables compared using the student's t test or Kruskal Wallis test as appropriate, assumption testing at the end of the chapter

‡ Assumption testing for normally distributed data presented in Appendix E.

Two thirds of the cohort was female with a female to male ratio of 2:1. The men were significantly older than the women and the odds for being employed were 34% less for males compared to females (OR = 0.66 95% CI = 0.59; 0.73). The majority of the cohort was initiated on Regimen 1a (lamivudine, stavudine and efavirenz) which is the regimen recommended by the DOH guidelines for initiating antiretroviral therapy. Women were more likely to be on Regimen 1b (lamivudine, stavudine and nevirapine) or lopinavir/ritonavir containing first line regimens than their male counterparts. Very few participants were initiated on second line therapy (two NRTI's and a PI or three NRTI's).

There was no difference in baseline weight between men and women; however women had significantly higher BMI at initiation of treatment than men. Women also had significantly higher mean baseline CD4 counts than men (95.1 cells/mm^3 versus 80.1 cells/mm^3 respectively). The overall CD4 count at initiation of HAART for this cohort was 90 cells/mm^3 which is significantly lower than the cutoff CD4 count of 200 cells/mm^3.

The enrollment rates at the Themba Lethu Clinic have been increasing steadily over the three years since the antiretroviral rollout programme began on the 1st April 2004 with over 40% of the overall cohort enrolled between 1st April 2006 and 31st March 2007. There have always been a greater proportion of women enrolling on the programme but over time, the rates of male enrollments have been increasing and 45% of the male cohort was enrolled between 1st April 2006 and 31st March 2007. This has resulted in a change in the female to male ratio amongst newly initiated patients over the three years. In the

2004/2005 enrollment year the ratio was 2.3: 1; in 2005/2006 the ratio had dropped to 2.1: 1 and in the last year 2006/2007 the ratio was at its lowest to date at 1.7: 1. This increase is depicted in Figure 1.

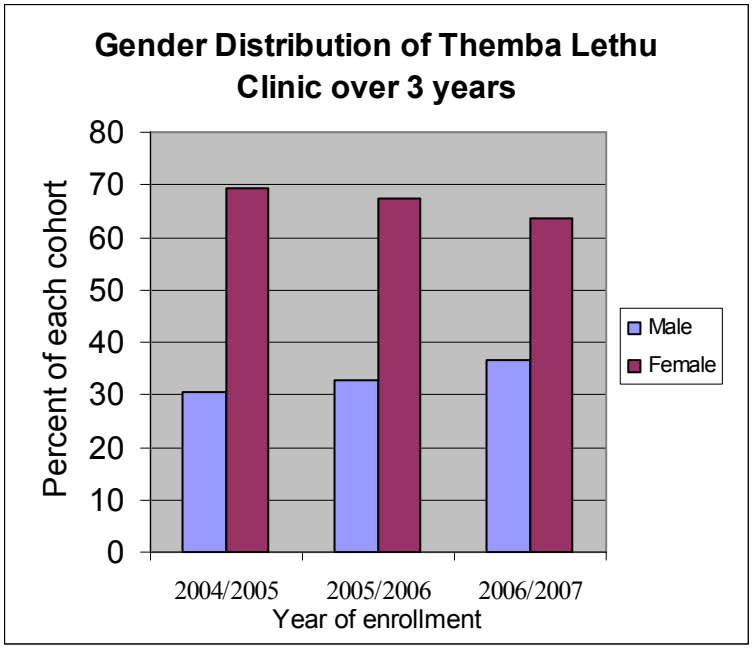


Figure 1: Gender distribution of the Themba Lethu Clinical cohort from 2004 to 2007

Death and Loss-to-follow-up

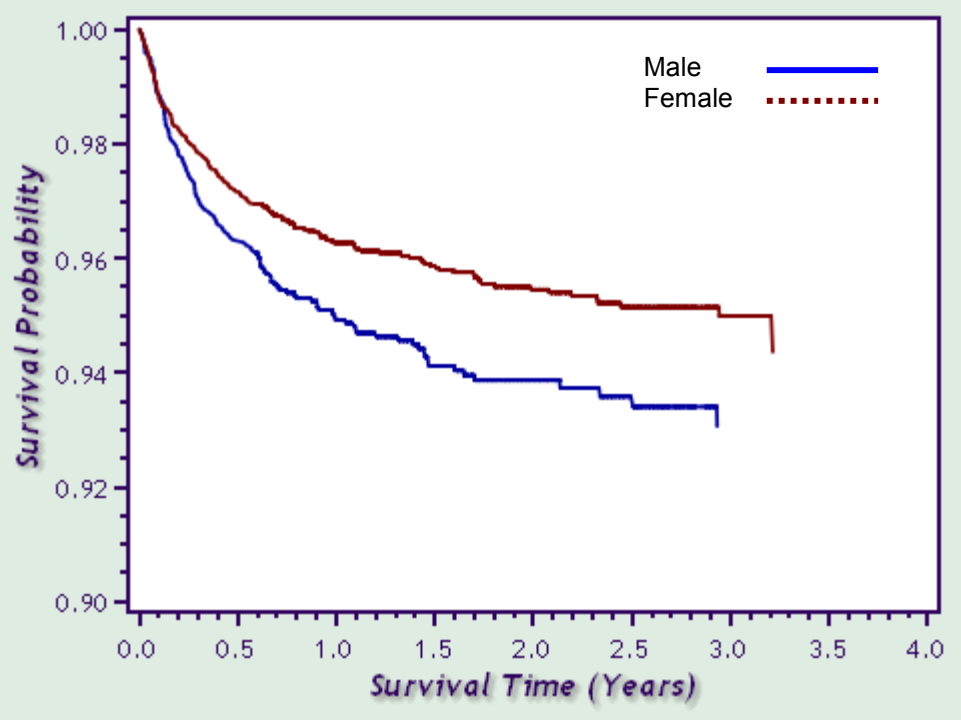
Of the 6,617 participants in this cohort, 321 individuals (4.9%) were confirmed dead by the end of the study period (31st October 2007). A further 708 (10.8%) were confirmed lost to follow up by this time. Patients were considered lost to follow up if they missed their next scheduled appointment by more than 90 days or at least 180 days had lapsed since their last visit. However, it is certain that some of the patients who are lost to follow up are deceased and so it may be more logical to consider patients who are either dead or lost to follow up together. Together there were 1,021 (15.4%) patients in this cohort who

were lost to follow up or dead by the end of the study period (31st October 2007). All three analyses are presented.

1. Death

There were 6,617 subjects for survival analysis and 321 deaths (4.9% of the total cohort) were recorded before the censor date 31st October 2007. Of those who died, 191 (59.5%) were female and 130 (40.5%) were male. The Chi-square test showed that the proportion of men who died was significantly greater than the proportion of women who died (χ^2 = 7.0080 p = 0.008).

These subjects contributed 12,008.4 person years of observation for analysis during which 321 failure events (deaths) occurred. If the hazard function could be assumed to be constant, it would be estimated at 0.027 deaths per person-year. Mortality was estimated using Kaplan-Meier (KM) survival curves and incidence rates expressed per person-years. The survival of this cohort by gender, including a risk table demonstrating the numbers at risk for selected follow-up durations, is depicted in Figure 2.



time	0	6mo	1 yr	18mo	2 yr	2.5 yr	3 yr
n at risk							
Male	2229	2147	1706	1233	826	523	227
Female	4388	4366	3503	2704	1919	1222	502

Figure 2: Kaplan-Meier survival plots for the Themba Lethu Clinical Cohort by gender

The log-rank test for equality of survivor functions showed that the survival of females was significantly greater than that of males (χ^2 =7.76 p = 0.0053).

The timing of these deaths was investigated and is presented in Table 2. The highest mortality occurred in the first three months after initiating treatment (24.1 deaths per 100,000 person days) and then decreased steadily over time until, after three years on treatment, the death rate was 2.1 per 100,000 person days. This trend was consistent for

both genders. The greatest difference in mortality between men and women occurred between three and six months after treatment initiation.

Table 2: Period Incidence rates for mortality at specified time periods after initiation of HAART

Time post HAART initiation	Overall Period Incidence (per 100,000) (CI)	All Deaths (n)	Male Period Incidence (per 100,000) (CI)	Male Deaths (n)	Female Period Incidence (per 100,000) (CI)	Female Deaths (n)
0–3mnths	24.1 (20.5 – 28.5)	142	28.3 (21.8 – 36.8)	56	22.0 (17.8 – 27.2)	86
3-6 mnths	11.0 (8.6 – 14.1)	64	22.0 (17.8 – 27.2)	26	9.9 (7.2 – 13.5)	38
6– 9 mnths	7.3 (5.4 – 9.9)	41	10.1 (6.5 – 15.9)	19	5.9 (3.9 – 8.9)	22
9–12mnths	4.4 (2.9 – 6.7)	22	4.8 (2.4 – 9.6)	8	4.2 (2.4 – 7.0)	14
1 – 2 years	2.6 (1.9 – 3.6)	38	3.3 (2.0 – 5.5)	15	2.3 (1.5 – 3.5)	23
2 – 3 years	1.6 (0.8 – 2.9)	10	2.1 (0.8 – 5.6)	4	1.3 (0.6 – 3.0)	6
>3 years	2.1 (0.3 – 15.3)	1	0	0	3.2 (0.4 – 22.4)	1

Risk factors for mortality after initiation of HAART were estimated using Cox proportional hazards models. Hazard ratios for each variable were calculated and are presented in Table 3 for both univariate and multivariate analyses. In the univariate analysis, the hazard of death was 37% greater for men when compared to women. Other significant predictors of death in the univariate analysis included age, low baseline weight, baseline CD4 count <100 cells/mm^3 and unsuppressed HIV viral load at four months after initiation of HAART.

Those variables in the univariate analysis which changed the hazard ratio for gender by 10% or more were entered into the multivariate analysis and retained at α=0.05. The

variables included in the final model were sex, age and baseline CD4 count. Interaction terms were tested for but no significant interactions were found. Assumption testing for these models is presented in Appendix E.

Table 3 : Factors associated with mortality after initiation of HAART

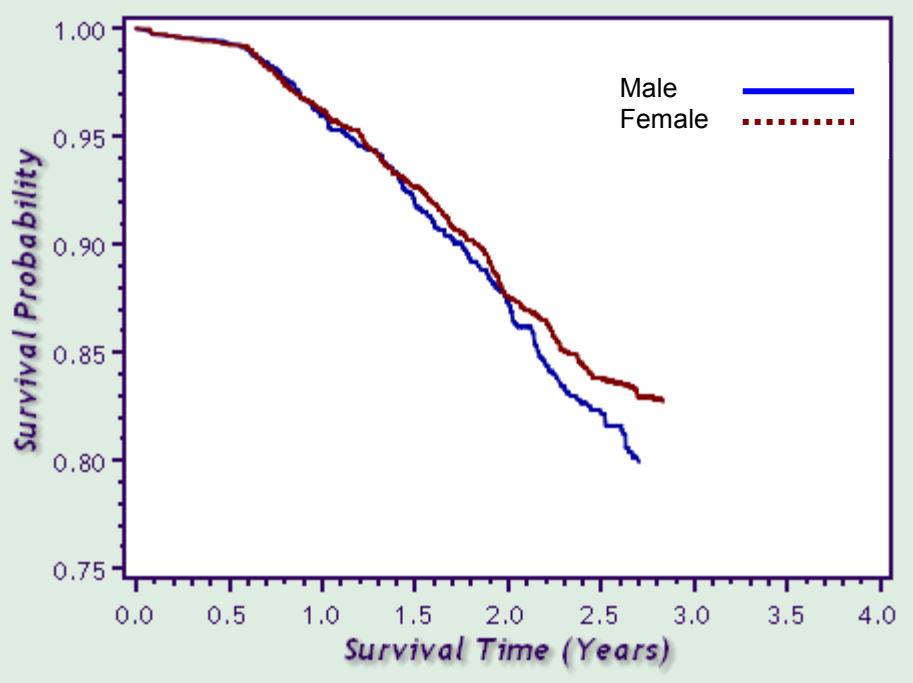
Factor	Univariate Model Hazard Ratio (CI) p - value	Multivariate Model Hazard Ratio (CI) p - value
Sex		
Females	1	1
Males	1.37 (1.10 – 1.71) 0.006	1.18 (0.93-1.49) 0.172
Age (in 5 year increments)	1.08 (1.02 - 1.15) 0.008	1.09 (1.02 - 1.17) 0.007
Baseline weight (in 5kg increments)	0.92 (0.87 – 0.97) 0.001	
Baseline CD4 count (in 10 cells/mm^3 increments)	0.90 (0.89 – 0.92) <0.001	0.91 (0.89 – 0.92) <0.001
Baseline CD4 count (cells/mm^3)		
- > 100 cells/mm3	1	
- 50 – 100 cells/mm3	1.53 (1.06 – 2.21) 0.022	
- <50 cells/mm3	3.40 (2.56 - 4.52) <0.001	
Baseline BMI (kg/m^2)		
- Normal (18.5 – 25)	1	
- Underweight (<18.5)	2.18 (1.61 – 2.94) <0.001	
- Overweight (>25)	0.88 (0.61 – 1.27) 0.493	
Virologic response (at 4 months)		
Yes	1	
No	2.81 (1.44 – 5.52) 0.003	
Employment status		
Employed	1	
Unemployed	1.10 (0.87 - 1.40) 0.422	
Initiating ARV regimen		
- 1a (3TC, efv, d4T/AZT)	1	
- 1b (3TC, d4T, nvp)	1.08 (0.72 - 1.64) 0.704	
- any first line incl lopinavir	0.97 (0.53 – 1.79) 0.946	
- 2nd line (ddI, AZT, LPV/r)	0.92 (0.63 – 1.08) 0.156	
- other		
Year of initiation		
2004/2005	1	
2005/2006	1.42 (1.06 – 1.91) 0.020	
2006/2007	1.41 (1.04 – 1.92) 0.025	

Despite an apparently strong association between gender and death in the univariate analysis, the effect of gender on hazard of death disappeared after adjusting for age and baseline CD4 count in the multivariate analysis. Age and baseline CD4 count remained statistically significant predictors of hazard of death in the adjusted model.

2. Loss to follow up

There were 6,617 subjects for analysis of loss-to-follow-up. Of these, 708 individuals were confirmed lost to follow up before the censor date 31st October 2007: 243 of these were male and 465 were female. The Chi-square test for difference between two proportion showed no difference in the proportion of females lost to follow up compared to males (χ^2 =0.1436 p = 0.705).These subjects contributed 11,849.9 person years of observation for analysis. Gender differences in rate of loss to follow up were estimated using Kaplan-Meier (KM) survival curves and incidence rates expressed per person-years. The rate of loss to follow up of this cohort by gender, including a risk table demonstrating the numbers at risk for selected follow-up durations, is depicted in Figure 3.

The log-rank test for equality of survivor functions showed no evidence of a difference in the time to lost to follow up between females and males (χ^2 =1.99 p = 0.1584).



time	0	6mo	1 yr	18mo	2 yr	2.5 yr	3 yr
n at risk							
Male	2229	2213	1723	1197	777	468	215
Female	4388	4355	3497	2616	1789	1105	474

Figure 3: Kaplan-Meier plots for Loss to Follow-up for the Themba Lethu Clinical Cohort by gender

Risk factors for loss to follow up were estimated using Cox proportional hazards models. Hazard ratios for each variable were calculated and are presented in Table 4 for both univariate and multivariate analyses. There was no difference in hazard of becoming lost to follow up between men and women in the univariate analysis. Age, baseline CD4 count, baseline BMI and year of initiation on HAART were significantly associated with hazard of becoming lost to follow up in the univariate analysis. Those variables in the univariate analysis which changed the hazard ratio for gender by 10% or more were

entered into the multivariate analysis and retained at $\alpha=0.05$. The variables included in the final model were sex, age and baseline BMI category. Assumption testing for these models is presented in Appendix E.

Table 4: Factors associated with loss-to-follow-up after initiation of HAART

Factor	Univariate Model Hazard Ratio (CI) p - value	Multivariate Model Hazard Ratio (CI) p - value
Sex		
Females	1	1
Males	1.12 (0.96 -1.31) 0.159	1.28 (1.05 - 1.55) 0.013
Age (years)	0.98 (0.97 - 0.99) <0.001	0.98 (0.97 - 0.99) 0.002
Baseline weight (kgs)	1.00 (0.99 - 1.00) 0.764	
Baseline CD4 count (cells/mm^3)	1.00 (1.00 - 1.00) 0.216	
Baseline CD4 count (cells/mm^3)		
- > 100 cells/mm3	1	
- 50 – 100 cells/mm3	1.53 (1.06 – 2.21) 0.022	
- <50 cells/mm3	3.40 (2.56 - 4.52) <0.001	
Baseline BMI (kg/m^2)	1.00 (0.98 -1.01) 0.841	
Baseline BMI (kg/m^2)		
- Normal (18.5 – 25)	1	1
- Underweight (<18.5)	1.51 (1.22 - 1.87) <0.001	1.44 (1.16 - 1.78) 0.001
- Overweight (>25)	1.38 (1.13 - 1.69) 0.002	1.48 (1.21 - 1.82) <0.001
Employment status		
Employed	1	
Unemployed	1.15 (0.98 - 1.36) 0.086	
Initiating ARV regimen		
- 1a (3TC, efv, d4T/AZT)	1	
- 1b (3TC, d4T, nvp)	0.86 (0.63 -1.17) 0.355	
- any first line incl lopinavir	1.47 (1.16 - 1.87) 0.002	
- 2^{nd} line (ddI, AZT, LPV/r)	0.57 (0.33 - 0.98) 0.043	
- other	1.20 (0.86 - 1.68) 0.283	
Year of initiation		
2004/2005	1	
2005/2006	1.61 (1.35 - 1.91) <0.001	
2006/2007	1.66 (1.30 - 2.11) <0.001	

The apparent lack of association between gender and loss to follow up in the univariate analysis was reversed after inclusion of the significant covariates age, baseline BMI and year of initiation on HAART. The hazard of becoming lost to follow up was 1.28 times greater for males when compared to females assuming age, baseline BMI and year of

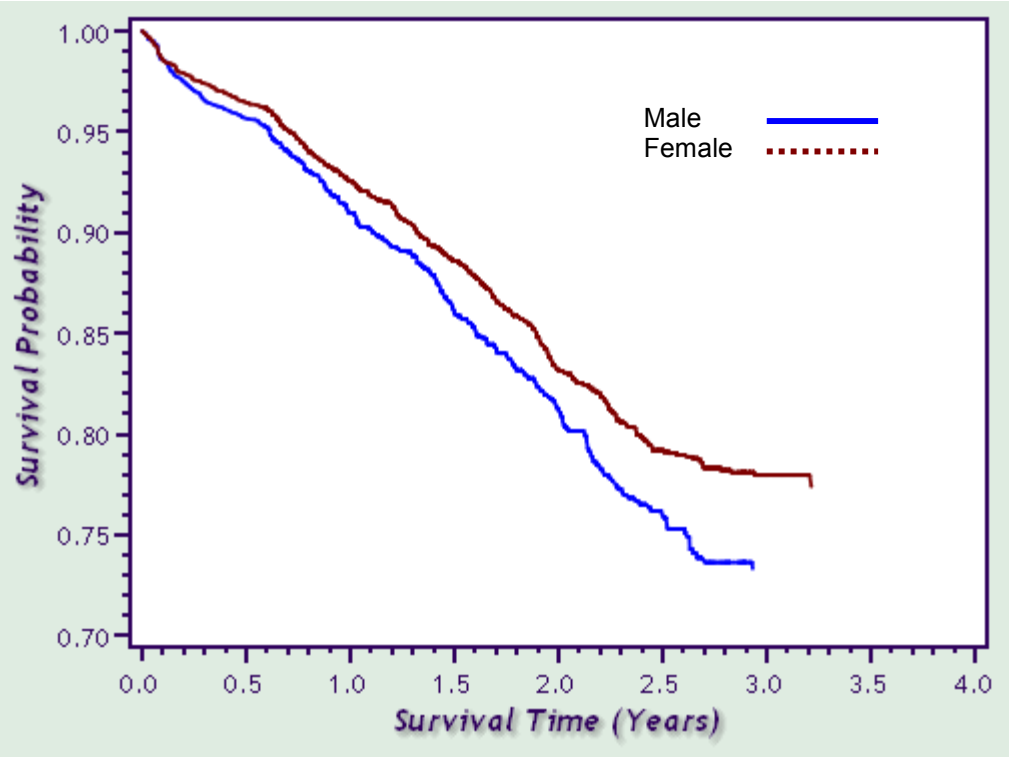
initiation onto HAART were equal. However, interaction terms were investigated and there was significant interaction between sex and baseline BMI. The model was then stratified by baseline BMI and for those with normal baseline BMI, the hazard of becoming lost to follow up was 1.55 times greater for males when compared to females assuming age and year of initiation onto HAART were equal [HR = 1.55 (95% CI = 1.20 - 2.00)]. There was no significant relationship between sex and hazard of becoming lost to follow up for those who were either underweight or overweight at baseline.

Model fit and assumption testing was performed, and only the model for those with normal baseline BMI did not violate the assumption of proportional hazards and the model appeared to fit the data well. The models for those who were under- or overweight at baseline violated assumption testing and did not fit the data well. This apparent association between gender and hazard of loss to follow up observed in the multivariate analysis is likely to be a significant association only for those with individuals who initiate HAART with a normal baseline BMI.

3. Death or Loss to follow up

There were 6,617 subjects for loss-to-follow-up analysis and 1,021 individuals were confirmed dead or lost to follow up before the censor date 31st October 2007. Of these, 370 were male and 651 were female. The Chi-square test for difference between two proportion showed no difference in the proportion of females dead or lost to follow up compared to males (χ^2 =3.52 p = 0.060).These subjects contributed 11,408.7 person years of observation for analysis. Gender differences in rate of death or loss to follow up

were estimated using Kaplan-Meier (KM) survival curves and incidence rates expressed per person-years. The rate of loss to follow up of this cohort by gender, including a risk table demonstrating the numbers at risk for selected follow-up durations, is depicted in Figure 4.



time	0	6mo	1 yr	18mo	2 yr	2.5 yr	3 yr
n at risk							
Male	2229	2133	1631	1123	727	435	198
Female	4388	4233	3364	2510	1714	1056	451

Figure 4: Kaplan-Meier plots for Death or Loss to Follow-up for the Themba Lethu Clinical Cohort by gender

The log-rank test for equality of survivor functions showed that the time to death or loss to follow up of females was significantly greater than that of males (χ^2 =8.61 p = 0.0033).

Risk factors for death or loss to follow up were estimated using Cox proportional hazards models. Hazard ratios for each variable were calculated and are presented in Table 7 for both univariate and multivariate analyses. Men were 1.21 times more likely than women to die or become lost to follow up in the univariate analysis. Low baseline CD4 count (<50 cells/mm^3) and abnormal baseline BMI were also significantly associated with hazard of death or loss to follow up. No variables in the univariate analysis changed the hazard ratio for gender by 10% or more. Variables in the univariate analysis with α=0.10 were entered into the multivariate analysis and retained at α=0.05.

Table 5: Factors associated with death or loss-to-follow-up after initiation of HAART

Factor	**Univariate Model** Hazard Ratio (CI) p - value	**Multivariate Model** Hazard Ratio (CI) p - value
Sex		
Males	1	1
Females	1.21 (1.07 - 1.38) 0.003	1.22 (1.06 - 1.39) 0.004
Age (in 5 year increments)	0.97 (0.93 - 1.01) 0.121	0.99 (0.95 - 1.03) 0.529
Baseline weight (kgs)	1.00 (0.99 -1.00) 0.153	
Baseline CD4 count (in 10 cells/mm^3 increments)	0.98 (0.97 - 0.98) <0.001	0.98 (0.97 - 0.99) <0.001
Baseline CD4 count (cells/mm^3)	1	
- > 100 cells/mm3	0.97 (0.81 - 1.16) 0.755	
- 50 – 100 cells/mm3	1.45 (1.26 - 1.67) <0.001	
- <50 cells/mm3		
Baseline BMI (kg/m^2)	0.98 (0.97 - 0.99) 0.023	
Baseline BMI (kg/m^2)	1	
- Normal (18.5 – 25)	1.76 (1.48 - 2.10) <0.001	
- Underweight (<18.5)	1.23 (1.03 - 1.46) 0.023	
- Overweight (>25)		
Employment status	1	
Employed	1.13 (1.00 - 1.30) 0.059	

Unemployed		
Initiating ARV regimen	1	
- 1a (3TC, efv, d4T/AZT)	0.94 (0.74 - 1.22) 0.643	
- 1b (3TC, d4T, nvp)	1.26 (1.02 - 1.55) 0.035	
- any first line incl lopinavir	0.72 (0.48 - 1.07) 0.107	
- 2nd line (ddI, AZT, LPV/r)	1.05 (0.79 - 1.41) 0.723	
- other		
Year of initiation	1	1
2004/2005	1.56 (1.34 - 1.81) <0.001	1.53 (1.30 - 1.79) <0.001
2005/2006	1.61 (1.33 -1.94) <0.001	1.57 (1.28 - 1.90) <0.001
2006/2007		

In the multivariate analysis, the hazard of death or lost to follow up was 1.22 times greater for men when compared to women after adjusting for baseline CD4 count, age and year of initiation on HAART. Age and baseline CD4 count did not independently have an effect on the hazard of death or loss to follow up. Gender was the only covariate which did not violate the assumption of proportional hazards. Thus the most parsimonious model included only gender. Interaction terms were tested for but no significant interactions were found. Assumption testing for these models is presented in Appendix E.

CD4 cell count Response

6,326 participants had CD4 counts for analysis. 202 of these participants did not have baseline CD4 counts and were excluded form further analysis. This left 6,124 subjects for further analysis. The mean baseline CD4 count amongst these individuals was 90 cells/mm^3 (± 67 cells/mm^3). The question of interest was whether there was any difference in CD4 cell count responses between men and women. Two time periods were considered – CD4 cell count response four months after initiation of HAART and ten

months after initiation of HAART. The time to 100 cell increase in CD4 count was also estimated and all three analyses are presented below.

Women had higher baseline CD4 count than males and the gender difference between the mean CD4 count at four and ten months after HAART initiation increased even further. This is shown in Figure 5.

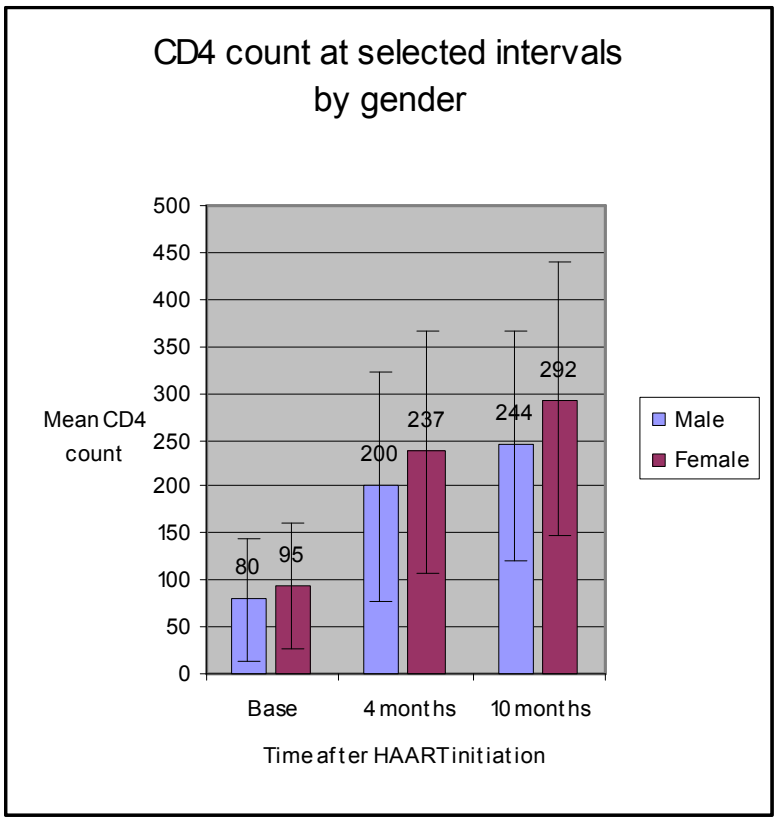


Figure 5: Mean CD4 count at selected intervals after initiation on HAART by gender

CD4 cell response at four months after HAART initiation

4,567 individuals (75% of the cohort included in this analysis) had CD4 cell counts recorded at four months after initiation of HAART. The mean overall CD4 count at four months was 224.8 cells/mm^3 (± 128 cells/mm^3). The following outcomes were investigated: any increase in CD4 count by four months, a 100 cell increase in CD4 count response by four months and a 50% increase in CD4 count by four months. Differences between the genders are presented in Table 6 below.

Table 6: CD4 cell count responses four months after Initiation of HAART by gender

	Overall (n)	*N (%)*	**OR (95% CI)**
Frequency *N (%)* - males -females	4567 (100)	 1513 (33.1) 3054 (66.9)	
Any CD4 count response - males -females	4117 (93.6)	 1368 (93.1) 2749 (93.9)	 1 1.07 (0.97 – 1.19)
100 cell increase - males -females	2399 (54.6)	 719 (48.9) 1680 (57.4)	 1 1.32 (1.18 – 1.46)
50% increase CD4 cell - males -females	3452 (78.9)	 1146 (78.2) 2306 (79.1)	 1 1.06 (0.96 – 1.17)

Women had no significant advantage over men in terms of any positive CD4 count response at four months after adjusting for age and baseline CD4 count. However, women were 35% more likely to achieve a 100 cell increase in CD4 count [OR =1.35 (95% CI = 1.19 -1.54)] and 33% more likely to achieve a 50% increase in CD4 count [OR 1.33 (95% CI 1.11 – 1.59)] after four months of HAART when compared to men [OR = 1.14 (95% CI = 1.03 – 1.27)]. These odds ratios were adjusted for age and baseline CD4 count. Interaction terms were tested for but no significant interactions were found.

CD4 cell response at ten months after HAART initiation

3,594 individuals (59% of the cohort included in this analysis) had CD4 cell counts recorded at ten months after initiation of HAART. The proportion of men and women with CD4 counts recorded at 10 months is almost identical to the baseline gender distribution of the overall cohort. The overall mean CD4 count at ten months was 276 cells/mm^3 (± 140.5 cells/mm^3). The following three outcomes were again investigated: any increase in CD4 count by ten months, a 100 cell increase in CD4 count response by ten months and a 50% increase in CD4 count by ten months after initiation on HAART. Differences between the genders are presented in Table 9 below.

Table 7: CD4 cell count responses ten months after Initiation of HAART by gender

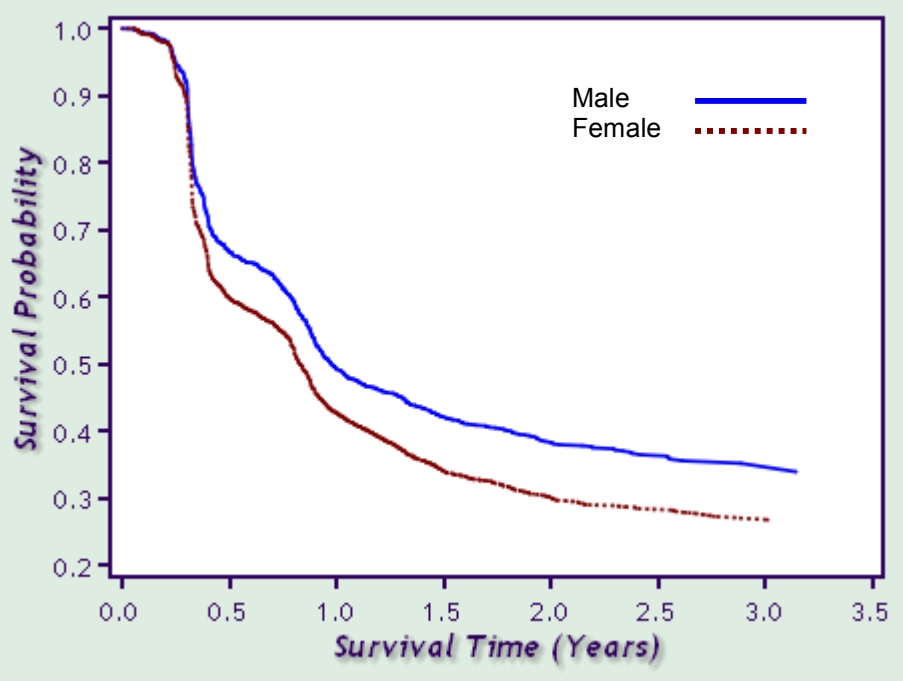
	Overall *n=3594*	**Males** *n= 1183 (33%)*	**Females** *n=2411 (67%)*	**χ2 (p value)/ z score (p value)**
Any CD4 count response - *N (%)*	3454 (95.5)	1083 (94.5)	2215 (96.0)	3.826 (0.050)
- $\bar{x}$, std	177.4 (127.8)	156.3 (111.9)	187.9 (133.8)	-6.898 (<0.0001)
100 cell increase - *N (%)*	2543 (73.6)	795 (69.4)	1748 (75.7)	15.975 (<0.001)
50% increase CD4 cell - *N (%)*	2948 (85.8)	960 (84.2)	1988 (86.6)	3.526 (0.060)

Women had significant advantages over men in terms of CD4 count response at ten months in all categories after adjusting for age and baseline CD4 count. Women were 42% more likely to achieve a 100 cell increase in CD4 count [OR =1.42 (95% CI = 1.20 - 1.68)], 55% more likely to achieve a 50% increase in CD4 count [OR 1.55 (95% CI 1.22 – 1.97)] and 73% more likely to show any CD4 response at ten months after initiation on HAART when compared to men [OR = 1.73 (95% CI = 1.19 – 2.52)]. These odds ratios

were adjusted for age and baseline CD4 count. Interaction terms were tested for but no significant interactions were found.

Time to 100 cell increase in CD4 count

Survival analysis was conducted using a 100 cell increase in CD4 count as the endpoint. Of the 6,617 individuals in the cohort, 290 did not have more than one CD4 count available and so were excluded from this stage of the analysis. Of the remaining 6,327 individuals, 3,905 (62%) achieved this endpoint before the censor date 31 October 2007. Of these, 1,208 (34.1%) were men and the remaining 2,697 (65.9%) were women. The proportion of females who achieved a 100 cell increase in CD4 count was significantly greater than the proportion of males who did so (χ^2 =44.81 p = <0.001). These subjects contributed 2,293,779 person days of observation for analysis. Gender differences in time to achieving a 100 cell increase in CD4 count were estimated using Kaplan-Meier (KM) survival curves and are depicted in Figure 6.



time	0	6mo	1 yr	18mo	2 yr	2.5 yr	3 yr
n at risk							
Male	2156	1439	839	512	309	179	59
Female	4171	2498	1460	860	517	279	89

Figure 6: Kaplan-Meier plots for time to achieving a 100 cell increase in CD4 count by gender

The log-rank test for equality of survivor functions showed that women achieved a 100 cell increase in CD4 count significantly sooner than their male counterparts ($\chi 2 = 40.83$ p= <0.0001). The median time to achieving this endpoint was 275 days for women and 299.5 days for men.

Factors associated with achieving a 100 cell increase in CD4 count were estimated using Cox proportional hazard models. Hazard ratios for each variable of interest were calculated and are presented in Table 8 for both univariate and multivariate analyses. No variables in the univariate analysis changed the hazard ratio for gender by 10% or more. Variables in the univariate analysis with $\alpha=0.20$ were entered into the multivariate analysis and retained at $\alpha=0.05$.

Table 8: Factors associated with a 100 cell increase in CD4 count after initiation of HAART

Factor	Univariate Model Hazard Ratio (CI) p - value	Multivariate Model Hazard Ratio (CI) p - value
Sex		
Males	1	1
Females	1.25 (1.16 - 1.33) <0.001	1.21 (1.13 - 1.29) <0.001
Age (years)	0.99 (0.98 - 0.99) <0.001	0.99 (0.98 - 0.99) <0.001
Baseline weight (kgs)	1.00 (0.99 - 1.00) 0.784	
Baseline CD4 count (cells/mm^3)	1.00 (0.99 - 1.00) 0.242	1.00 (0.99 - 1.00) 0.937
Baseline CD4 count (cells/mm^3)		
- > 100 cells/mm3	1	
- 50 – 100 cells/mm3	1.04 (0.96 - 1.13) 0.335	
- <50 cells/mm3	0.93 (0.87 - 1.00) 0.061	
Baseline BMI (kg/m^2)	1.00 (0.99 - 1.01) 0.065	
Baseline BMI (kg/m^2)		
- Normal (18.5 – 25)	1	
- Underweight (<18.5)	0.80 (0.73 - 0.88) <0.001	
- Overweight (>25)	0.98 (0.90 - 1.06) 0.623	
Employment status		
Unemployed	1	1
Employed	1.08 (1.01 - 1.15) 0.020	1.13 (1.05 - 1.20) 0.001
Initiating HAART regimen		
- 1a (3TC, efv, d4T/AZT)	1	
- 1b (3TC, d4T, nvp)	1.07 (0.95 - 1.22) 0.252	
- any first line incl lopinavir	0.86 (0.76 – 0.97) 0.013	
- 2^{nd} line (ddI, AZT, LPV/r)	1.06 (0.89 - 1.26) 0.493	
- other	1.05 (0.91 – 1.23) 0.477	
Year of initiation		
2004/2005	1	1
2005/2006	0.91 (0.85 - 0.98) 0.024	0.86 (0.79 - 0.93) <0.001
2006/2007	0.82 (0.76 - 0.89) <0.001	0.78 (0.72 - 0.84) <0.001

The hazard ratio for achieving a 100 cell increase in CD4 count was 21% greater for women when compared to men after adjusting for baseline CD4 count, age, employment status and year of initiation on HAART. Baseline CD4 count did not independently affect the hazard of achieving a 100 cell increase in CD4 count. Gender was the only covariate which did not violate the assumption of proportional hazards. Thus the final most parsimonious model included only gender. The variables included in the final model were

sex, age, baseline CD4 count and year of enrollment into the programme. Interaction terms were tested for but no significant interactions were found. Assumption testing for these models is presented at the end of the chapter.

Virologic Response

4,356 participants had HIV RNA viral load records for analysis. 34% (n= 1,480) of these people were male and the remaining 66% (n= 2,876) were female. This was almost identical to the gender distribution of the overall cohort. Virologic response was defined as a reduction of HIV viral load to less than 400 copies/ml. The objective was to determine if there were any gender differences in the odds of suppressing HIV viral load at two time periods - four months after initiation of HAART and ten months after initiation of HAART. The time to first ever HIV viral load suppression was also estimated and all three analyses are presented below.

HIV viral load suppression at four months after HAART initiation

3,441 individuals (79% of the cohort included in this analysis) had HIV viral loads recorded at four months after initiation of HAART. 1,178 (34.23%) of these participants were men and 2,263 (65.8%) were women. There was no significant differences in the proportion of women achieving virologic suppression at four months after initiating HAART when compared to men ($\chi 2 = 0.3834$ p=0.536). Factors associated with suppression of HIV viral load at four months after initiation of HAART were investigated using logistic regression. Odds ratios were calculated and are presented in Table 9 for both univariate and multivariate analyses.

Table 9: Factors associated with suppression of HIV viral load four months after initiation of HAART

Factor	Univariate Model Odds Ratio (CI) p - value	Multivariate Model Odds Ratio (CI) p - value
Sex		
Males	1	1
Females	1.08 (0.85 – 1.37) 0.536	1.07 (0.83 – 1.37) 0.621
Age (years)	1.00 (0.99 – 1.01) 0.894	1.00 (0.98 – 1.01) 0.793
Baseline weight (kgs)	1.01 (0.99 – 1.02) 0.307	
Baseline CD4 count (cells/mm^3)	1.00 (0.99 – 1.00) 0.143	1.00 (1.00 – 1.00) 0.156
Baseline CD4 count (cells/mm^3)		
- > 100 cells/mm3	1	
- 50 – 100 cells/mm3	0.90 (0.66 – 1.31) 0.668	
- <50 cells/mm3	1.13 (0.81 – 1.57) 0.481	
Baseline BMI (kg/m^2)	1.02 (0.99 – 1.05) 0.255	
Baseline BMI (kg/m^2)		
- Normal (18.5 – 25)	1	
- Underweight (<18.5)	0.93 (0.66 – 1.31) 0.668	
- Overweight (>25)	1.13 (0.81 – 1.57) 0.481	
Employment status		
Unemployed	1	
Employed	1.25 (0.98 – 1.58) 0.077	
Initiating HAART regimen		
- 1a (3TC, efv, d4T/AZT)	1	
- 1b (3TC, d4T, nvp)	0.88 (0.57 – 1.36) 0.571	
- any first line incl lopinavir	1.20 (0.76 – 1.89) 0.437	
- 2^{nd} line (ddI, AZT, LPV/r)	1.26 (0.65 – 2.43) 0.494	
- other	1.33 (0.73 – 2.42) 0.358	
Year of initiation		
2004/2005	1	
2005/2006	0.85 (0.61 – 1.18) 0.337	
2006/2007	0.89 (0.65 – 1.22) 0.472	

No significant association between gender and virologic response at four months after initiation of HAART was found in the univariate analysis. None of the other cofactors or covariates significantly predicted virologic response at four months after initiation of HAART in the univariate analysis either. Those variables in the univariate analysis which changed the odds ratio for gender by 10% or more were entered into the multivariate

analysis and retained at α=0.05. After adjusting for age and CD4 count in the multivariate analysis there was still no association between gender and virologic response at four months.

HIV viral load suppression at ten months after HAART initiation

2,900 individuals (67% of the cohort included in this analysis) had HIV viral loads recorded at ten months after initiation of HAART. 979 (33.8%) of these participants were men and 1,921 (66.2%) were women. The proportion of women achieving virologic suppression at ten months after initiating HAART was significantly greater than the proportion of males who did so ($\chi 2$ = 10.1560 p=0.001). Factors associated with suppression of HIV viral load at ten months after initiation of HAART were investigated using logistic regression. Odds ratios were calculated and are presented in Table 10 for both univariate and multivariate analyses. Those variables in the univariate analysis which changed the odds ratio of virologic suppression for gender by 10% or more were entered into the multivariate analysis and retained at α=0.05.

Table 10: Factors associated with suppression of HIV viral load ten months after initiation of HAART

Factor	Univariate Model Hazard Ratio (CI) p - value	Multivariate Model Hazard Ratio (CI) p - value
Sex		
Males	1	1
Females	1.45 (1.15 – 1.83) 0.002	1.54 (1.21 – 1.97) <0.001
Age (years)	1.01 (1.00 – 1.02) 0.216	1.01 (0.99 – 1.03) 0.111
Baseline weight (kgs)	0.99 (0.98 – 1.00) 0.102	
Baseline CD4 count (cells/mm^3)	1.00 (1.00 – 1.00) 0.300	1.00 (1.00 – 1.00) 0.530
Baseline CD4 count (cells/mm^3)		
- > 100 cells/mm3	1	
- 50 – 100 cells/mm3	1.03 (0.75 – 1.41) 0.875	
- <50 cells/mm3	0.81 (0.62 – 1.04) 0.103	
Baseline BMI (kg/m^2)	0.99 (0.97 – 1.02) 0.708	
Baseline BMI (kg/m^2)		
- Normal (18.5 – 25)	1	
- Underweight (<18.5)	1.20 (0.83 – 1.74)	
- Overweight (>25)	0.99 (0.73 – 1.35) 0.981	
Employment status		
Unemployed	1	
Employed	1.26 (0.99 – 1.60) 0.062	
Initiating HAART regimen		
- 1a (3TC, efv, d4T/AZT)	1	
- 1b (3TC, d4T, nvp)	0.79 (0.51 – 1.21) 0.277	
- any first line incl lopinavir	0.85 (0.52 – 1.16) 0.221	
- 2^{nd} line (ddI, AZT, LPV/r)	0.87 (0.49 – 1.55) 0.638	
- other	0.97 (0.56 – 1.68) 0.905	
Year of initiation		
2004/2005	1	
2005/2006	0.94 (0.70 – 1.25) 0.661	
2006/2007	1.14 (0.84 – 1.54) 0.390	

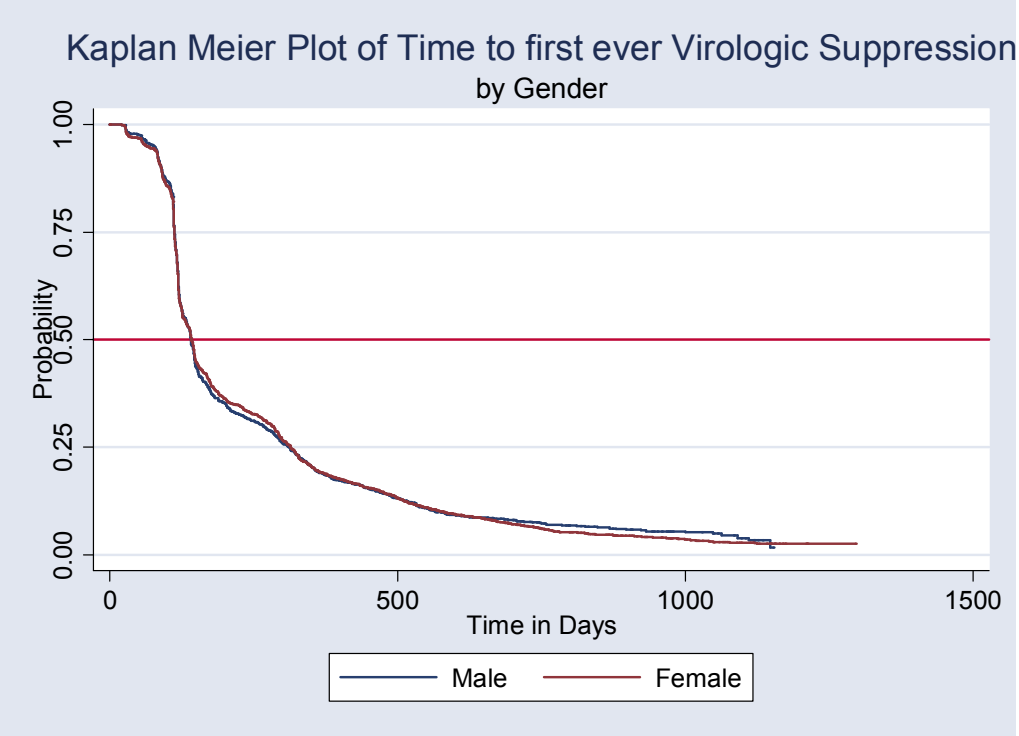
Gender significantly predicted virologic response at ten months after initiation on HAART in the univariate analysis. No other factor or covariate was significantly associated with risk of HIV viral load suppression at ten months in the univariate analysis. In the multivariate analysis women were 54% more likely to achieve HIV viral

load suppression after adjusting for CD4 count and age [OR =1.54 (95% CI =1.21-1.97)]. Neither age nor baseline CD4 count added significance to the model and the most parsimonious model included only gender. Interaction terms were tested for but no significant interactions were found.

Time to first ever HIV viral load suppression

Gender differences in time to first ever HIV viral load suppression were investigated. Of the 6,617 individuals in the cohort, 5,109 individuals had viral load dates and values recorded and were included in the survival analysis. Of these, 4,684 (92%) achieved this endpoint (HIV viral load suppression) before the censor date 31 October 2007. 1,532 (32.7%) were men and the remaining 3,152 (67.3%) were women. The proportion of females who achieved virologic suppression was significantly greater than the proportion of males who did so (χ^2 =5.15 p = 0.023). These subjects contributed 1,198,838 person days of observation for analysis. Gender differences in time to achieving HIV viral load suppression were estimated using Kaplan-Meier (KM) survival curves and are depicted in Figure 7 along with a risk table demonstrating the numbers at risk for selected follow-up durations,.

The log-rank test for equality of survivor functions confirmed that there were no significant differences in time to first virologic suppression between men and women (χ2=0.02 p= 0.8904). The median time to achieving this endpoint was 142 days for women and 141 days for men.



time	0	6mo	1 yr	18mo	2 yr	2.5 yr	3 yr
n at risk							
Male	1694	618	295	139	64	31	11
Female	3415	1309	603	202	146	62	19

Figure 7: Kaplan-Meier plots for time to first ever suppression of HIV viral load by gender

Factors associated with achieving first ever virologic response were estimated using Cox proportional hazard models. Hazard ratios for each variable of interest were calculated and are presented in Table 11 for both univariate and multivariate analyses. In the univariate analysis, there was no difference between men and women in terms of the likelihood of suppressing HIV viral load after initiation of HAART. Those who were employed were more likely to achieve virologic suppression at four months. No variables in the univariate analysis changed the hazard ratio for the relationship between gender

and hazard of virologic suppression at four months by 10% or more but age, baseline CD4 count and year of initiation on treatment were included in the multivariate analysis as they were believed to be important potential confounders.

Table 11: Factors associated with first ever HIV viral load suppression after initiation of HAART

Factor	Univariate Model Hazard Ratio (CI) p - value	Multivariate Model Hazard Ratio (CI) p - value
Sex		
Males	1	1
Females	1.00 (0.94 – 1.07) 0.891	1.03 (0.97 – 1.10) 0.313
Age (years)	1.00 (1.00 – 1.00) 0.887	1.00 (0.99 – 1.01) 0.277
Baseline weight (kgs)	1.00 (1.00 – 1.00) 0.525	
Baseline CD4 count (cells/mm^3)	1.00 (1.00 – 1.00) 0.815	1.00 (1.00 – 1.00) 0.851
Baseline CD4 count (cells/mm^3)		
- > 100 cells/mm3		
- 50 – 100 cells/mm3		
- <50 cells/mm3		
Baseline BMI (kg/m^2)	1.00 (1.00 – 1.00) 0.426	
Baseline BMI (kg/m^2)		
- Normal (18.5 – 25)	1	
- Underweight (<18.5)	1.00 (0.92 – 1.10) 0.924	
- Overweight (>25)	1.06 (0.98 – 1.14) 0.172	
Employment status		
Unemployed	1	
Employed	1.14 (1.07 – 1.21) <0.001	
Initiating HAART regimen		
- 1a (3TC, efv, d4T/AZT)	1	
- 1b (3TC, d4T, nvp)	0.88 (0.79 – 0.99) 0.036	
- any first line incl lopinavir	1.00 (0.89 – 1.11) 0.935	
- 2^{nd} line (ddI, AZT, LPV/r)	1.11 (0.95 – 1.29) 0.203	
- other	0.98 (0.86 – 1.13) 0.203	
Year of initiation		
2004/2005	1	1
2005/2006	1.28 (1.19 – 1.38) <0.001	1.29 (1.19 – 1.39) <0.001
2006/2007	1.62 (1.51 – 1.75) <0.001	1.66 (1.53 – 1.79) <0.001

The hazard ratio for achieving first ever HIV viral load suppression was not significantly different between the genders after adjusting for baseline CD4 count, age and year of initiation on HAART. Neither baseline CD4 count nor age independently affected the hazard of achieving first ever HIV viral load suppression. Gender was the only covariate which did not violate the assumption of proportional hazards. Thus the most parsimonious model included only gender. Interaction terms were tested for but no significant interactions were found. Assumption testing for these models is presented in Appendix E.

Weight Gain

5001 participants had baseline weight values for analysis. 1696 (33.9%) of these individuals were men and the remaining 3305 (66.1%) were women. This was similar to the gender distribution of the overall cohort. The mean baseline weight amongst these people was 60.1 kg (± 13.3 kg) and mean baseline BMI was 22.5 kg/m^2 (± 5.0 kg/m^2). Initially there appeared to be no significant differences between the baseline weight of these participants, but after stratifying by BMI, evidence of a significant difference in both baseline weight and baseline BMI emerged. Predictably, men weighed more at baseline (p=<0.0001) and women had a higher mean BMI than men at baseline (p=<0.0001). This apparent difference was consistent for both categories of BMI – overweight (BMI>25) and normal or underweight (BMI<=25). Only those with a low or normal BMI at baseline were considered in the remaining analysis as a gain in weight for persons with a high baseline BMI is probably not a sign of clinical improvement on HAART.

Weight gain four months after HAART initiation

Amongst those with normal or low BMI at baseline, the mean weight at four months was 62.5 kg (± 9.0 kg) for men and 57.1 kg (± 8.7kg) for women. This was significantly different ($p < 0.0001$). The following weight outcomes were investigated: any increase in weight by four months, a five kg increase in weight by four months and a 5% increase in weight by four months. Differences between the genders are presented in Table 12 below.

Table 12: Weight gain four months after initiation of HAART by gender

	Overall	**Males**	**Females**	**$\chi 2$ (p value)/ z score (p value)**
Weight gain (kg) ($\bar{x}$, std)	3.75 (5.9)	3.72 (6.0)	3.76 (5.8)	-0.206 (0.8365)
5 kg increase (*n, %)*	1141 (39.2)	438 (37.8)	703 (40.2)	1.5801 (0.209)
5% weight increase *(n, %)*	1585 (54.5)	607 (52.4)	978 (55.99)	3.3181 (0.069)

There was no evidence to suggest that the mean weight gain at four months was different comparing men and women. There were also no significant differences in the proportion of women who gained five kilograms or who increased their weight by five percent from baseline weight after four months on HAART when compared to men.

Factors associated with any weight gain four months after initiation on HAART were investigated with univariate and multivariate logistic regression models. Odds ratios for the relationship between weight gain at four months after HAART initiation and each variable of interest were calculated and are presented in Table 15. In the univariate analysis, women were 1.17 times more likely to gain weight four months after initiation

of HAART. Other significant predictors of weight gain included baseline CD4 count, baseline BMI and year of initiation on HAART.

Variables in the univariate analysis which altered the odds ratio for the relationship between sex and weight gain at four months after HAART initiation by 10% or more were entered into the multivariate analysis and retained at α=0.05. Factors included in the multivariate analysis were gender, baseline CD4 count and baseline BMI.

Table 13: Factors associated with weight gain four months after initiation of HAART

Factor	Univariate Model Odds Ratio (CI) p - value	Multivariate Model Odds Ratio (CI) p - value
Sex		
Males	1	1
Females	1.17 (1.01 - 1.35) 0.034	1.26 (1.07 - 1.49) 0.007
Age (years)	1.00 (0.99 - 1.01) 0.151	1.01 (1.00 - 1.01) 0.026
Baseline weight (kgs)	0.97 (0.96 - 0.97) <0.001	
Baseline CD4 count (cells/mm^3)	0.99 (0.99 - 0.99) <0.001	
Baseline CD4 count (cells/mm^3)		
- > 100 cells/mm3	1	1
- 50 – 100 cells/mm3	1.46 (1.21 - 1.74) <0.001	1.35 (1.12 - 1.63) 0.002
- <50 cells/mm3	2.10 (1.77 - 2.48) <0.001	1.82 (1.53 - 2.16) <0.001)
Baseline BMI (kg/m^2)	0.91 (0.89 - 0.92) <0.001	0.91 (0.89 -0.92) <0.001
Baseline BMI (kg/m^2)		
- Normal (18.5 – 25)	1	1
- Underweight (<18.5)	2.37 (1.88 - 2.97) <0.001	2.14 (1.68 - 2.70) <0.001
- Overweight (>25)	0.52 (0.44 - 0.60) <0.001	0.52 (0.44 - 0.61) <0.001
Employment status		
Unemployed	1	
Employed	1.09 (0.95 - 1.26) 0.218	
Initiating HAART regimen		
Regimen 1a	1	
Regimen 1b	0.49 (0.68 - 1.17) 0.411	
Regimen 2	1.00 (0.69 - 1.44) 0.997	
Other	0.94 (0.80 - 1.10) 0.449	
Year of initiation		
2004/2005	1	
2005/2006	1.21 (1.02 - 1.43) 0.025	
2006/2007	1.64 (1.38 - 1.95) <0.001	

Women were 26% more likely to have gained weight four months after initiation on HAART than their male counterparts after adjusting for age, baseline CD4 count and baseline BMI. Interaction terms were investigated and no significant interaction was found.

CHAPTER FOUR: DISCUSSION

The aim of this study was to determine and describe gender differences in clinical and immunological outcomes in a population of HIV infected South African adults. The results showed that women had advantages over their male counterparts in terms of both clinical and immunological outcomes. The risk of death and/or loss to follow up was greater for men when compared to women. Women were also significantly more likely to show an increase in CD4 counts, more likely to suppress HIV viral load (at ten months after initiation) and to gain weight after initiation on HAART.

Baseline Characteristics

The baseline characteristics of this cohort of HIV-infected individuals differed from the populations studied in previous research. There were a significantly greater proportion of women in this cohort compared to other European [16] and North American cohorts [8] which consisted largely of males. At baseline, the women in this cohort were more likely to be initiated on Regimen 1B (lamivudine, stavudine and nevirapine) or a regimen with a lopinavir/ritonavir substitution. This is largely explained by the fact that these drugs are preferred to efavirenz (part of the traditional regimen 1A) in women who are pregnant or planning to fall pregnant. Efavirenz is considered potentially teratogenic and concerns have been raised regarding the potential for neural tube defects in the unborn child if used in the first trimester [31]. The initiating HAART regimen did not appear to have any significant effect on any of the clinical or immunological outcomes analysed and this

baseline difference was thus unlikely to have been a confounding factor in the associations observed between gender and the outcomes of interest.

Several individuals in this cohort were recorded as being initiated on second line treatment despite being treatment-naïve at the time of initiation. This is an unlikely scenario and presumably these observations constitute either errors in the regimen dataset or the individuals were not naïve on entry into the cohort. As this is anonymised data, it was impossible to check the accuracy of these records. It is unlikely that these misclassification errors occurred in a non-random fashion and, as such, probably did not bias the outcome. To check the possibility of these errors influencing the results, those with a second line initiating regimen were excluded and the analysis repeated. The results were unchanged.

The gender distribution in this cohort is changing over time. Initially, there was more than double the number of females accessing treatment on this programme compared to males, but over time the rates of male enrollment has been increasing. Currently, women still outnumber the men, but by a much smaller margin. It is unlikely that this change can be attributed to a corresponding increase in incidence of new male HIV infections as the South African national HIV statistics do not suggest this [32]. This change may be due to changing perceptions and improved trust in the antiretroviral rollout programme.

One of the important reasons for fewer males accessing the treatment programme may be financial constraints. The services and treatment at the Themba Lethu Clinic is offered

free of charge but patients still need transport money to get to the clinic, which is often far from their homes or place of work. Additionally, the men were significantly more likely to be employed than the women in this cohort and difficulties getting time off work for regular clinic visits or loss of income due to days of work missed may prevent more men from accessing treatment. A visit to the clinic often involves a significant part of the day spent in queues although the recent addition of electronic live-capture of clinical data using TherapyEdge-HIV^{TM} during these clinical visits may be improving queue efficiency and speed of treatment collection. This may result in reduced waiting time and mean less time off work.

Death and Loss to Follow-up

The findings suggested there were little differences in survival for women after initiating HAART when considering the confirmed deaths only. However we can assume that a certain proportion of those lost to follow up are dead and previous work investigating causes for lost to follow up at the Themba Lethu Clinic showed that at least 27% of those individuals confirmed lost to follow up were actually dead [27]. When considering those confirmed dead or lost to follow up in this analysis, men were at a significant disadvantage even after adjusting for the potential confounders CD4 count and age.

Any difference in hazard of death alone between the genders was explained by the significantly lower baseline CD4 counts with which men presented. Previous research has suggested gender-specific normal ranges for CD4 counts in HIV-infected [11] and HIV uninfected individuals [28] and other studies have consistently reported women have

higher CD4 counts at time of seroconversion as well as maintaining slightly higher CD4 counts than men during the course of infection [19]. Treating CD4 counts as continuous variables may result in possible residual confounding after adjusting for baseline CD4 count if gender –specific normal ranges are in fact present. However, there is a lack of information regarding this normal "range" during HAART treated HIV infection and this may be a difficult to control for.

CD4 count response

The women in this study showed not only higher CD4 counts at baseline but also significantly greater CD4 count responses after initiating HAART. Women were more likely to have a 100 cell increase in CD4 count and were more likely to have increased their CD4 counts by 50% than the men. This finding was consistent at four months and ten months after initiating HAART. If the difference in baseline CD4 count is due to differences in gender-specific "normal ranges" for CD4 lymphocytes, then it may suggest that women should be started on antiretroviral therapy at higher CD4 counts than men. Alternatively, the baseline difference in CD4 counts may suggest that gender differences in help-seeking behaviour exist, with men seeking treatment later than women. This has certainly been the case in other African countries and advanced HIV disease at time of initiating HAART significantly contributed to mortality [6, 26]. Although not demonstrated in this study, if males are presenting later to treatment programmes, they are likely to receive limited benefits from HAART and suffer increased mortality even once receiving HAART.

Virologic suppression

Suppression of HIV viral load at ten months after initiating HAART was also more likely to occur in women than men. This is consistent with other findings [35, 36]. No short term advantages in suppression of viral load (after four months of HAART) were demonstrated for either gender in this cohort and this may suggest that if men can stay in treatment programmes and be adherent on treatment for long enough, the survival advantage demonstrated by women may disappear.

Weight Gain

Loss of less than ten percent of presumed or measured body weight is one of the WHO stage 2 criteria [29]. This single measure may be too simplistic as loss or gain of a certain percentage weight depends on the starting weight as well as the individual's body composition. Indeed there were no significant differences in baseline weight between men and women but the women presented with a higher mean baseline BMI. This suggests that the men in this study had lost more weight by the time that they presented for treatment when compared to the women. While body mass index (BMI) has been used by WHO as the standard for anthropometric statistics since the 1980s [30], its' use has limitations too, notably not accounting for distribution of muscle and bone mass. As such, BMI may not be an appropriate tool for assessing body composition and health across different populations. In the HIV infected population this may certainly be the case as individuals may suffer severe muscle depletion as part of the HIV wasting syndrome while others may have abnormal adipose tissue distribution due to antiretroviral toxicity.

Limitations

In considering the findings of this study, it is important to consider the following limitations. Selection bias may have arisen as only those who present for treatment were available for analysis. If there is a systematic difference between men and women in terms of help-seeking behaviour (which is suggested by the greater proportion of women accessing treatment and the earlier stage at which women present) then the results may be biased. As with all cohorts, high rates of loss to follow up can significantly bias the results if those who are lost to follow up are significantly different from those who remain in the study in terms of the exposure or outcome of interest. There was no evidence to suggest that there were any differences in gender distribution between those who were lost to follow up and those who remained in the study.

While a great amount of effort and care is put into collecting and capturing data on the Themba Lethu Clinical Cohort, the accuracy of the collected data could not be checked against any source due to the de-identified nature of the data. In particular, the accuracy of the death data is largely dependant on verbal reports from family members of the deceased and the inability to cross-reference this data with a national death register makes ascertainment of accurate death dates difficult. Additionally, if mortality is significantly higher for men than women as suggested in this project, then cause of death needs to be investigated for gender bias. Diseases such as Kaposi's sarcoma, which occurs fairly early in HIV infection, tends to occur more commonly in men [23] and could result in significantly earlier mortality for males. This information was not available to the researcher.

The clinical and immunological outcomes in this study were only considered up to 10 months after initiation of HAART in most of the analysis and it is possible that the advantages suggested by the data for women may not be significant or even possibly reversed should longer time periods on treatment be considered. Indeed as HIV-infected individuals are treated with antiretroviral therapy for longer periods, more research is needed to determine if gender differences in clinical and immunological outcomes persist on long-term therapy. Certainly there is evidence for female predominance in long-term toxicity on antiretrovirals such as lactic acidosis [33, 34] with the risk of lactic acidosis estimated to be 2.5 times greater for women than men [34].

This analysis used survival methods which considered achievement of defined outcomes in a time to first event manner. As such, recurrent events were not considered nor were such events accounted for. If women were more likely to relapse after achieving a particular end point, this would certainly lessen the impact of finding any difference between the genders in time to achieving the end point.

The violation of the assumptions and poor model fit in the lost to follow up analysis suggested that there may be significant predictors of loss to follow up which were not measured and thus not included in the models. One such factor may have been socio-economic status. Data was collected on employment status only which may be a poor proxy for socio-economic status. Socio-economic status and education levels have been shown previously to be associated with survival [24, 25] and failing to control for this in

the current study may have limited the usefulness of the findings. Additionally, information on baseline opportunistic infections amongst participants was not available and as such could not be controlled for in any of the analyses. Other studies which had a lower proportion of women with AIDS-defining conditions at or before their first clinic visit showed baseline illnesses to be an important confounder in the relationship between gender and disease progression [8].

Adherence to antiretroviral treatment is an essential component of a successful HAART regimen and poor compliance with therapy may lead to development of drug-resistant virus. Adherence is very difficult to measure and it may significantly influence clinical deterioration. Studies investigating adherence and loss to follow up have shown women to be more prone to poor adherence and at higher risk of loss to follow up [37]. Our study suggested men were at higher risk of becoming lost to follow up than their female counterparts. However, adherence could not be estimated from the data and may have confounded the effect of gender on clinical and immunological outcomes. It is possible that the true effect of gender on clinical and immunological outcomes will not be uncovered until adherence can be reliably measured.

There are no clear guidelines for South African patients regarding an acceptable weight gain within four months of initiating HAART. The studies reviewed showed mean weight gain of less than three kilograms within four months [21] but more than half of the individuals studied had baseline CD4 counts greater than 200/mm^3 while the vast majority of patients in the Themba Lethu Clinical Cohort had baseline CD4 counts below

200/mm^3 and thus may have been more likely to show more rapid weight gain initially. Additionally, using an absolute number as a cut-off for weight gain does not take into account an individuals starting weight or body type, consequently a weight gain of five percent or more within the first four months on treatment was chosen as the cutoff for weight gain as this corresponds with the weight loss that constitutes a WHO clinical stage 1 criterion. However this cutoff still may not be appropriate and this lack of knowledge may be a limitation. The database did not contain any information on skin fold thickness or other anthropometric measurements such as waist or arm circumference and so lipodystrophic changes which certainly may have gender differences were not accounted for.

CHAPTER FIVE: CONCLUSIONS AND RECOMMENDATIONS

The results of this study suggest that HIV-infected women may have an advantage over men with regard to clinical and immunological outcomes after initiation of antiretroviral treatment. In particular, men had higher mortality while women were more likely to show positive CD4 count response and to suppress HIV viral load after initiation on HAART.

Currently there are still a significantly greater proportion of women accessing the treatment programme. Although it seems that the proportion of men enrolling onto treatment programmes is increasing, the findings of this study suggest that men present later to treatment programmes than women do and when they do present they may have more advanced disease, presenting with lower CD4 counts and more significant weight loss. To improve this situation, it is important that voluntary counseling and testing (VCT) programmes target men in their publicity campaigns.

The establishment of "male-friendly" clinic practices may facilitate earlier VCT and access to antiretroviral therapy, and may also improve adherence amongst men. This could include after hours access, or weekend clinics as men were significantly more likely to be employed than women and work commitments may preclude regular visit to clinics for treatment. Workplace facilities for VCT and alternate locations for obtaining treatment, such as a post office medication collection points, as has been successfully implemented in the Direct AIDS Intervention programme [38] through the non-profit organization, Right To Care, may also be useful.

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While the women had higher baseline CD4 counts than the men, their mean CD4 counts at initiation were still very low and all HIV-infected persons should be encouraged to access treatment early so that they may have opportunist infections treated promptly and maximize the full benefit of antiretroviral therapy.

Attempts should be made to improve the lost to follow up rate once initiated on treatment and adherence promotion should occur regularly, particularly in the first six months after treatment initiation.

This study considered relatively short-term outcomes after initiation on HAART and as the antiretroviral rollout programme matures, further research is needed to establish if gender differences persist after long term therapy so that appropriate interventions can be instituted to ensure all individuals receive maximum benefit from antiretroviral treatment programmes.

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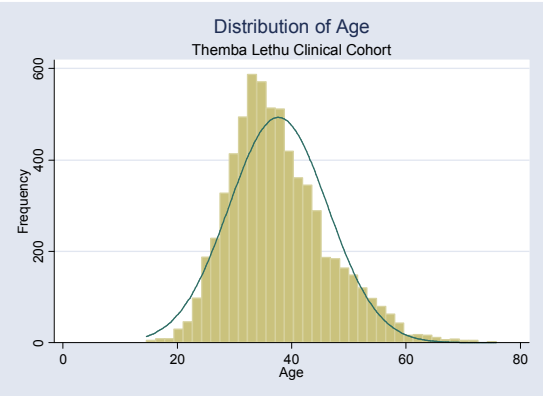
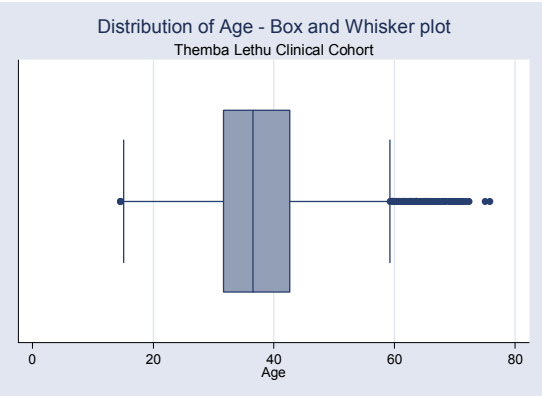
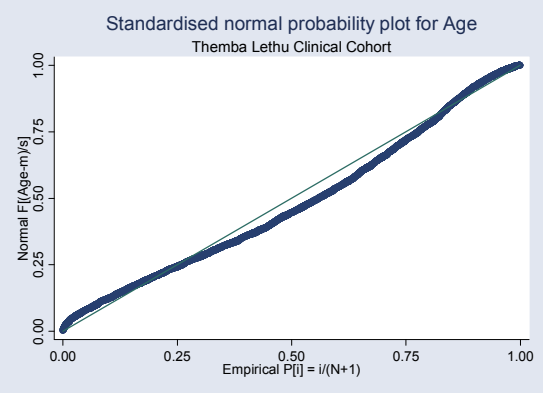
APPENDIX E

Assumptions testing:

Age distribution

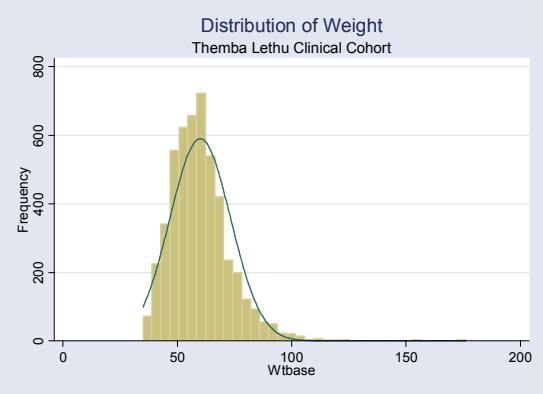


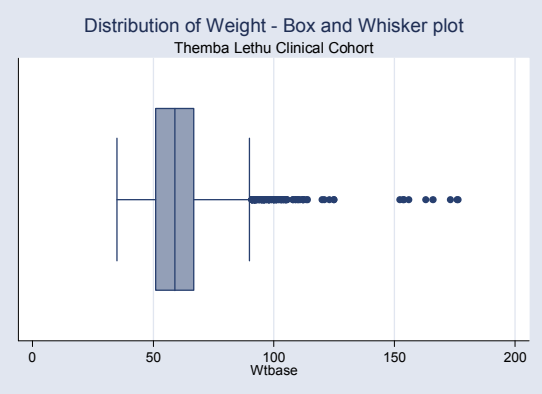


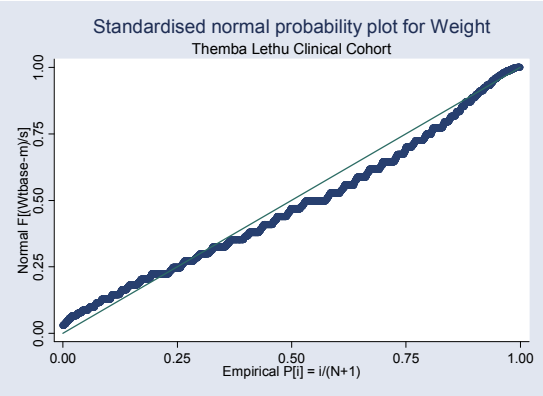


The histogram, box plot and normal probability plot all suggest a normal distribution of the continuous variables age (left) and weight (below).

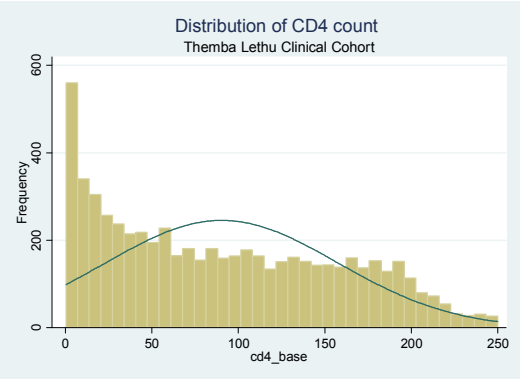
Weight distribution

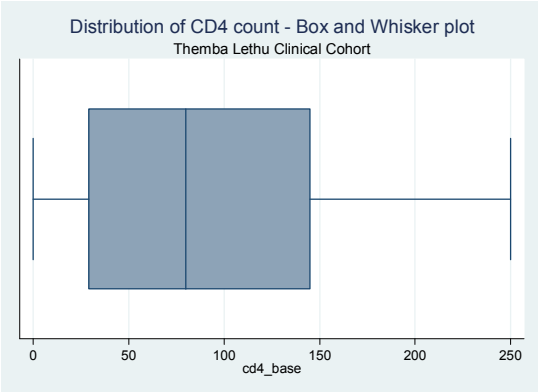


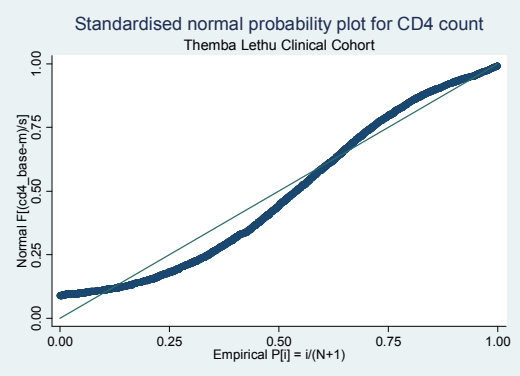




CD4 count distribution



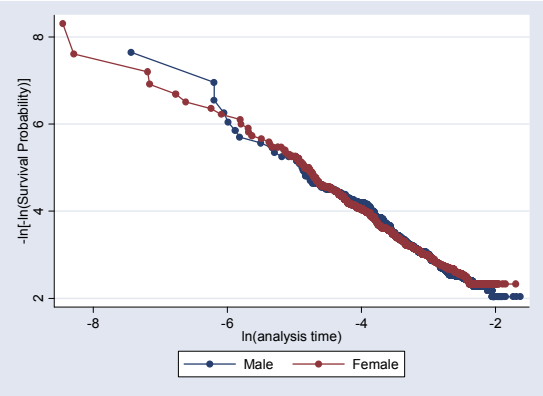




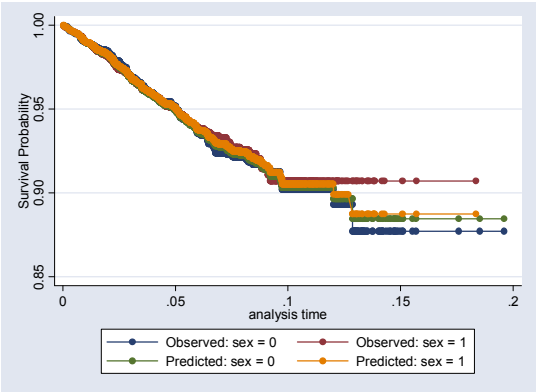
The histogram, box plot and normal probability plot all suggest the data is not of normal distribution for the continuous variable baseline CD4 count

Time to death analysis

Assumptions testing:
Two of the covariates (sex and baseline CD4 count) violated the assumption of proportional hazard when using Schoenfeld residuals assessed statistically (test of Proportional hazards assumption p value = <0.001). However the graphical output suggests that the assumption is not violated.



Graph 1: stphplot
Curve of category of sex versus log of analysis time. Parallel nature of plot suggests assumption of proportionality is not violated

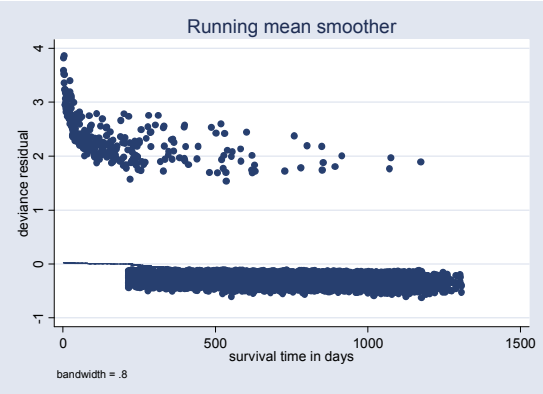


Graph 2 : stcoxkm
Kaplan-Meier curves plotted against Cox predicted values for sibling mortality. Observed values are close to predicted values thus it is unlikely that the assumption of proportionality has been violated.

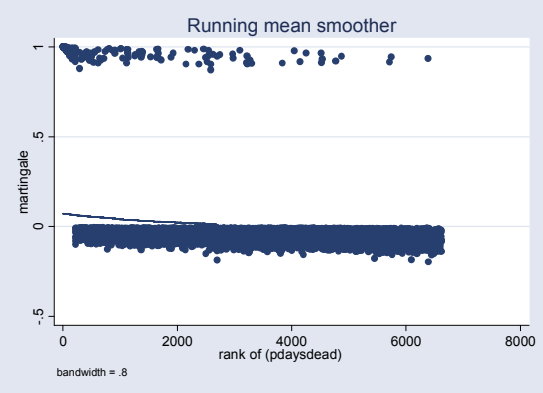
0 = male
1 = female

Overall Model Fit

The model was statistically significant and fit was tested. Martingale residuals and deviance residuals were calculated and plotted against survival time. Both confirmed that the Cox model fit the data fairly well.



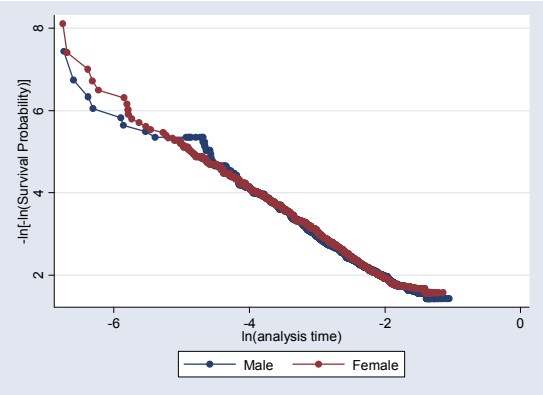
Deviance residuals versus survival time



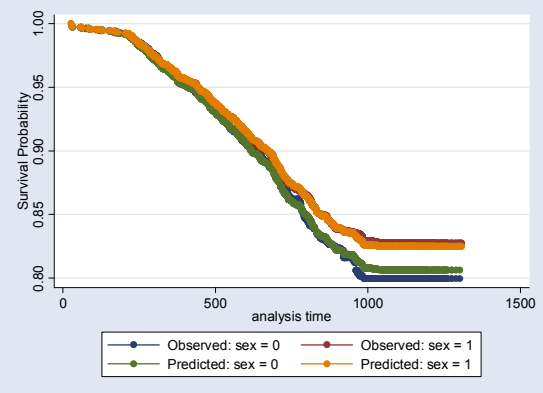
Martingale residuals versus survival time

Lost to Follow up Analysis

Assumptions testing:
None of the covariates in the model for those with normal baseline BMI violated the assumption of proportional hazard when using Schoenfeld residuals assessed statistically (test of Proportional hazards assumption p value = 0.8992). The graphical output confirms that the assumption is not violated.



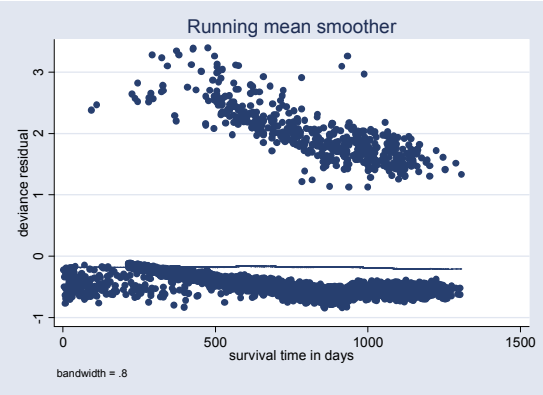
Graph 1: stphplot
Curve of category of sex versus log of analysis time. Parallel nature of plot suggests assumption of proportionality is not violated



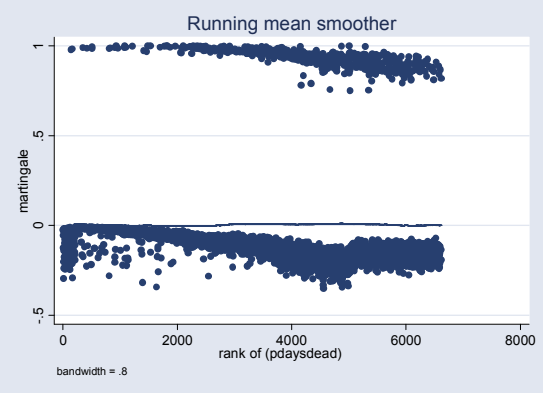
Graph 2 : stcoxkm
Kaplan-Meier curves plotted against Cox predicted values for sibling mortality. Observed values are close to predicted values thus it is unlikely that the assumption of proportionality has been violated.

Overall Model Fit

The model was statistically significant and fit was tested. Martingale residuals and deviance residuals were calculated and plotted against survival time. Both suggested that the Cox model fit the data fairly poorly.



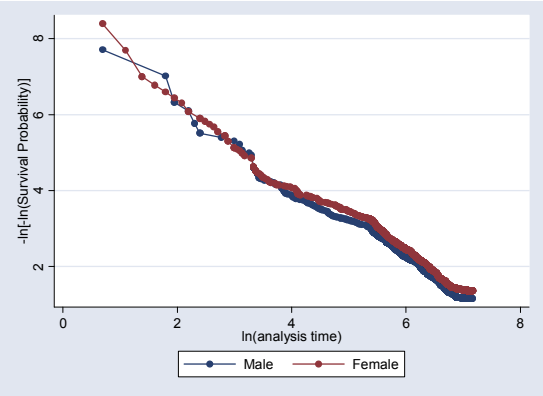
Deviance residuals versus survival time



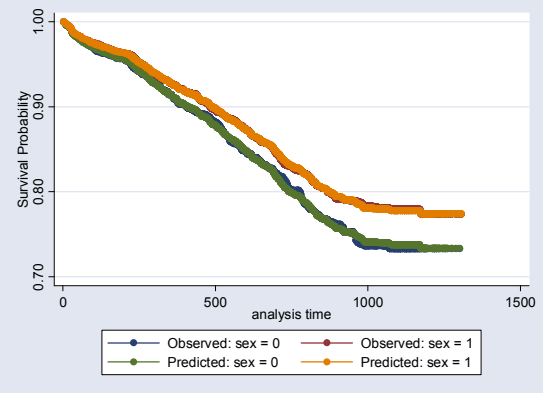
Martingale residuals versus survival time

Death or Lost to Follow up Analysis

Assumptions testing:
All of the covariates violated the assumption of proportional hazard when using Schoenfeld residuals assessed statistically (test of Proportional hazards assumption p value = <0.0001). However the graphical output suggests that the assumption is not violated.



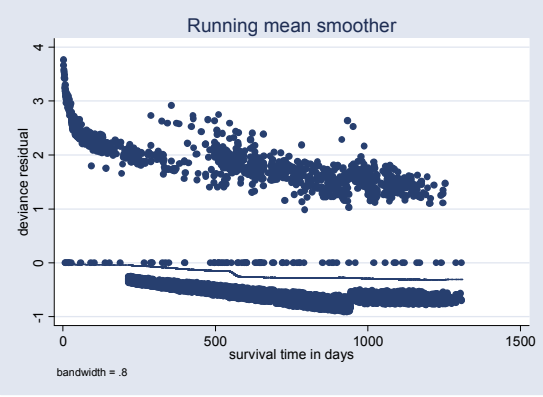
Graph 1: stphplot
Curve of category of sex versus log of analysis time. Parallel nature of plot suggests assumption of proportionality is not violated



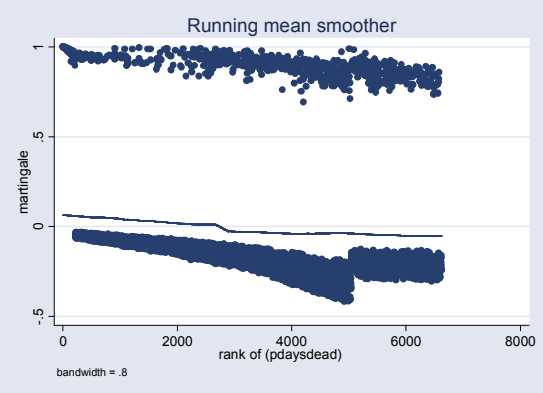
Graph 2 : stcoxkm
Kaplan-Meier curves plotted against Cox predicted values for sibling mortality. Observed values are close to predicted values thus it is unlikely that the assumption of proportionality has been violated.
0 = male
1 = female

Overall Model Fit

The model was statistically significant and fit was tested. Martingale residuals and deviance residuals were calculated and plotted against survival time. Both suggested that the Cox model fit the data fairly poorly.



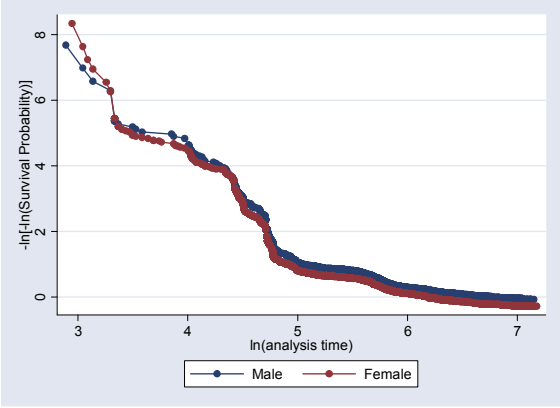
Deviance residuals versus survival time



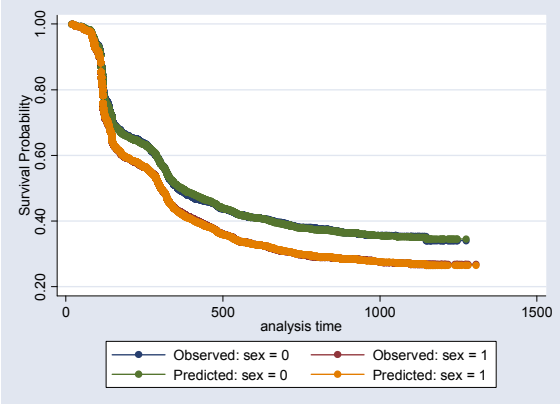
Martingale residuals versus survival time

Time to 100 cell increase in CD4 count analysis

Assumptions testing:
None of the covariates violated the assumption of proportional hazard when using Schoenfeld residuals assessed statistically (test of Proportional hazards assumption p value = 0.6315) and graphically. The graphical output is presented below.



Graph 1: stphplot
Curve of category of sex versus log of analysis time. Parallel nature of plot suggests assumption of proportionality is not violated

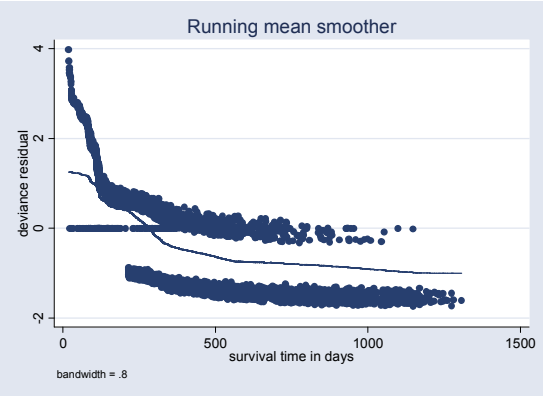


Graph 2 : stcoxkm
Kaplan-Meier curves plotted against Cox predicted values for sibling mortality. Observed values are close to predicted values thus it is unlikely that the assumption of proportionality has been violated.

0 = male
1 = female

Overall Model Fit

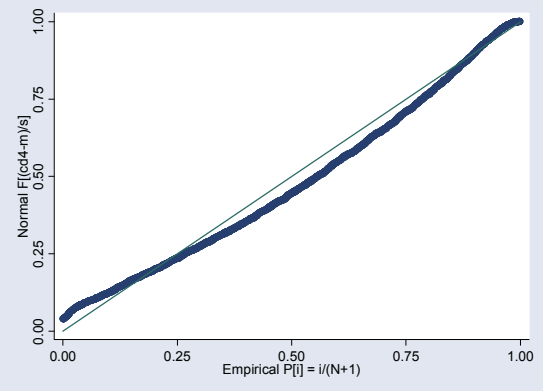
The model was statistically significant and fit was tested. Martingale residuals and deviance residuals were calculated and plotted against survival time. Both confirmed that the Cox model fit the data fairly well.

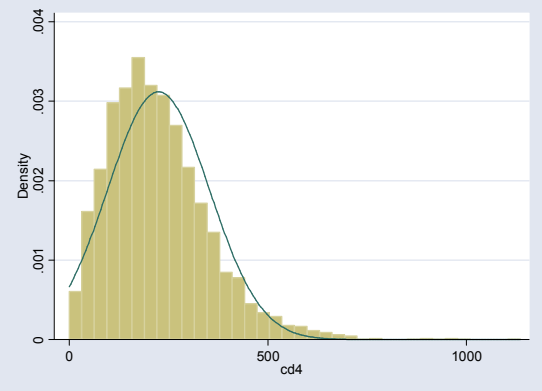


Deviance residuals versus survival time

Martingale residuals versus survival time

CD4 Cell count analysis



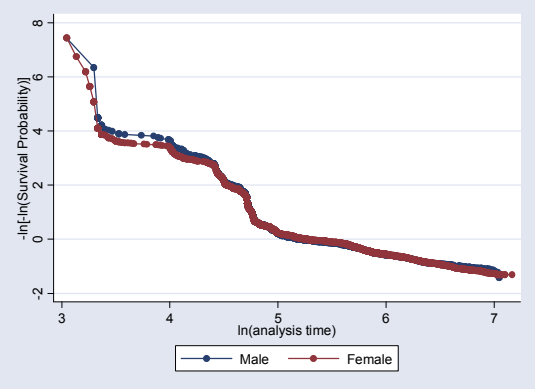


The Shapiro-Wilk test for normal data suggests that the CD4 count at 4 months was not normally distributed. However, the graphical output (histogram and normal distribution probability plots), suggested that the large sample size tends the data towards normal distribution.

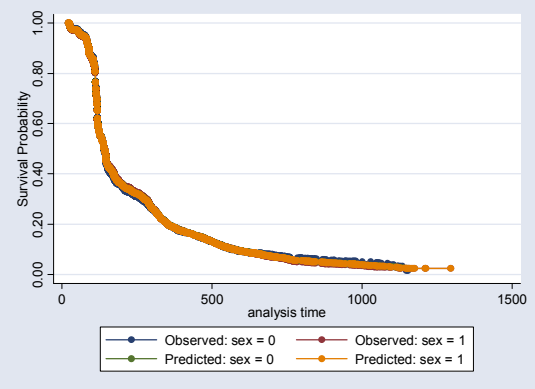
Time to first ever HIV viral load suppression analysis

Assumption testing

Assumptions testing:
None of the covariates violated the assumption of proportional hazard when using Schoenfeld residuals assessed statistically (test of Proportional hazards assumption p value = 0.4002) and graphically. The graphical output is presented below.



Graph 1: stphplot
Curve of category of sex versus log of analysis time. Parallel nature of plot suggests assumption of proportionality is not violated

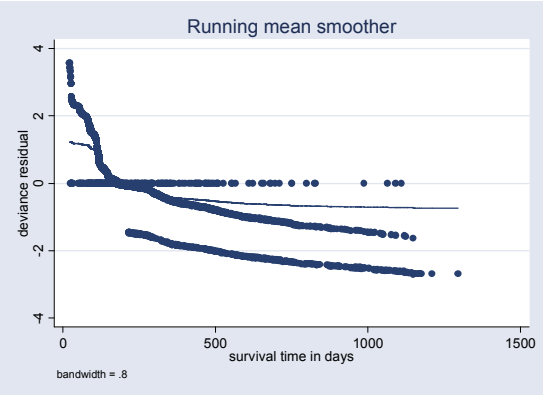


Graph 2 : stcoxkm
Kaplan-Meier curves plotted against Cox predicted values for sibling mortality. Observed values are close to predicted values thus it is unlikely that the assumption of proportionality has been violated.

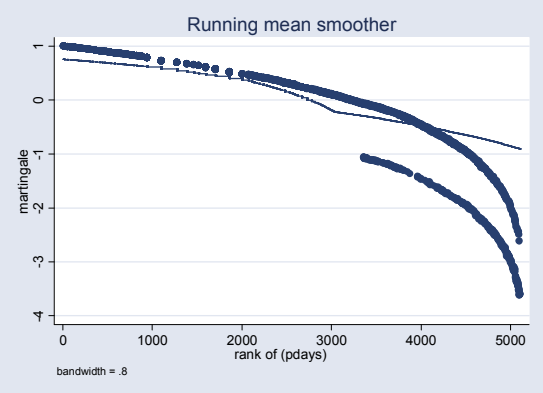
0 = male
1 = female

Overall Model Fit

The model was statistically significant and fit was tested. Martingale residuals and deviance residuals were calculated and plotted against survival time. These residual plots suggest the model fit could have been better.



Deviance residuals versus survival time



Martingale residuals versus survival time