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Comparison of treatment outcomes of HIV positive patients starting antiretroviral therapy in a private or public HIV clinic in Johannesburg, South Africa.

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A dissertation submitted in partial fulfilment of a degree of Master in Epidemiology in the field of Epidemiology and Biostatistics.

October, 2013

DECLARATION

I, Faith Moyo declare that this research report is my own work, compiled under the supervision of Dr. C S Chasela and Dr. D Evans. The report is being submitted to the University of the Witwatersrand in partial fulfilment of a degree of Master of Epidemiology in the field of Epidemiology and Biostatistics. There are no prior submissions of this material to other institutions for academic purposes.

Signature

F.Moyo

Date: 2013 October 30th

DEDICATION

To my daughter, Ruvarashe Pearl Ngwenya. May you be inspired to achieve your greatest dreams!!

****

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I would like to thank Tshepo Monaledi from De Beers and MMMF for their financial support towards my studies. I am forever indebted to your kindness and your belief and trust in me. May you continue extending this gesture to other people.

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I also thank my family and friends for their support and cheers when the going got tough. To Peter Nyasulu and the entire team in the School of Public Health, you were great!

Lastly, I thank God for carrying me through yet another journey.

ABSTRACT

Background Potential causes of poor antiretroviral therapy (ART) treatment outcomes can be patient or health system related. Data on the effect of health system on ART outcomes is scarce.

Objective: To compare treatment outcomes of HIV positive adults (≥18 years) initiating ART in either private or public HIV clinics in Johannesburg, South Africa.

Methods: A retrospective cohort analysis was conducted on HIV positive, ART naïve adults initiating ART at a public (Themba Lethu Clinic) or private HIV clinic in Johannesburg between 01 January 2005 and 31 December 2011. Treatment outcomes included mortality, loss to follow up (LTFU; defined as >90 days since last scheduled visit date), failure to suppress viral load (>400copies/ml) at 6 and 12 months and absolute change in CD4 count from baseline until 6 and or 12 months after ART initiation. Survival analysis was performed using Kaplan Meir curves. Multivariate Cox proportional hazards models were used to assess predictors of mortality and LTFU. Generalized estimation equations were used to determine predictors of failure to suppress viral load while absolute change in CD4 count was analysed using the Wilcoxon rank sum test.

Results: A total of 11690 patients initiated ART at the public clinic compared to 574 at the private clinic. Patients were similar in terms of age, gender and baseline viral load. Private clinic patients were less likely to die [aHR=0.39;95% CI 0.14-1.06] or to be retained on ART [aHR=1.59;95% CI 0.94-2.70], although both estimates lacked statistical significance. Public clinic patients presented with advanced HIV [WHO stage 3 or 4, p<0.001] compared to the private clinic. However, private clinic patients were 63% more likely to have a detectable viral load at 12 months of follow up [RR=1.63;95% CI 1.15-2.32]. There were no differences in the absolute CD4 changes between the private and public clinic at 6 months (median 99 IQR 43-78 vs. 103 IQR 52- 168; p=0.584) respectively.

Conclusion: This study demonstrates that health systems have an influence on ART outcomes. The private sector is commended for early initiation of treatment and the availability of a variety of ARV drugs. However there is need for standardization of prescribing practices and care. Better virological responses amongst public patients can be attributed to better adherence to treatment and reduced LTFU rates compared to the private

sector. Public-private partnerships are thus encouraged to address shortcomings of either sector.

Table of Contents

DECLARATION i

DEDICATION ii

ACKNOWLEDGEMENTS iii

ABSTRACT iv

LIST OF FIGURES viii

LIST OF TABLES ix

ABBREVIATIONS x

CHAPTER 1: INTRODUCTION 1

1.1 Background 1

1.1.1 Treatment and management of HIV/AIDS 1

1.2 Problem Statement 3

1.3 Justification of the study 4

1.4 Literature Review 5

1.4.1 Summary of literature review findings: 7

1.5 Study Aims and Objectives 7

1.5.1 Research Question 7

1.5.2 Aim of the study 8

CHAPTER 2: METHODOLOGY 9

2.1 Introduction 9

2.2 Study Design 9

2.3 Study Setting 9

2.3.1 Themba Lethu Clinic 10

2.3.2 Private Clinic 10

2.4 Study Population 10

2.5 Study Sample 11

2.5.1 Inclusion Criteria 11

2.5.2. Exclusion Criteria 12

2.6 Data Collection 12

2.7 Data Management and Analysis 13

2.7.1 Measurement of Exposure and Outcome 13
2.7.2 Data Management 14
2.7.3 Statistical Methods 16
2.7.3.1 Descriptive statistics 16
2.7.3.2 Inferential statistics 17
2.8 Ethics Clearance 18
CHAPTER 3: RESULTS 19
3.1 Organization of the study cohorts 19
3.2 Baseline demographic characteristics 21
3.3 Baseline clinical characteristics of patients 23
3.4 Programme Losses 25
3.4.1 Mortality 25
3.4.1.1 Time to Mortality 26
3.4.1.2 Predictors of mortality 28
3.4.1.3 Model Diagnostics for Mortality 31
3.4.2 Loss to Follow Up 32
3.4.2.1Time to LTFU 32
3.4.2.2 Predictors of LTFU 33
3.4.2.3 Model diagnostics for LTFU 36
3.5 Failure to suppress viral load 37
3.5.1 Proportion that failed to suppress viral load 37
3.5.2 Predictors of failure to suppress viral load at 12 months. 38
3.5.3 Model diagnostics for failure to suppress viral load at 12 months. 41
3.6 Immunological responses of patients to ART 41
3.7 Sensitivity Analysis Results 42
CHAPTER 4: DISCUSSION 44
4.1. Introduction 44
4.2 Mortality 44
4.2.1 Effect of type of health facility on mortality amongst ART patients. 45
4.2.3 Biological determinants of mortality 47
4.2.3 Socio demographic determinants of mortality 49
4.3 Loss to follow up 50
4.3.1. Effect of type of clinic on LTFU amongst ART patients 50
4.3.2 Biological determinants of LTFU 52
4.3.3 Socio-demographic predictors of patient retention in ART programs 53

4.4 Immunological and Virological responses **54**
4.4.1 Effect of type of clinic on immunological and virological responses **55**
4.4.2 Biological determinants of virological response of ART patients **56**
4.4.3 Socio demographic predictors of virological response **57**
4.5 Limitations of the study **57**
CHAPTER 5: CONCLUSION & RECOMMENDATIONS **60**
5.1. Introduction **60**
5.2 Conclusion **60**
5.3. Recommendations **61**
5.4 Potential areas of further research **63**
5.5 References **64**
5.6 Appendices **70**

LIST OF FIGURES

Figure 3.1 Cohort profile stratified by clinic type in December 2011……21

Figure 3.2 Baseline CD4 count of patients by health facility……..25

Figure 3.3 Survival estimates of mortality by sex of patients……..26

Figure 3.4 Survival estimates of mortality between the public and private health facility……...26

Figure 3.5 Model goodness of fit test using Cox-Snell residuals plot……30

Figure 3.6 Comparison of LTFU rates by health facility during the study period……31

Figure 3.7 Schoenfield residuals plot for LTFU……..36

Figure 3.8 Proportions of patients that failed to suppress viral load by clinic at 12 months……..39

LIST OF TABLES

Table 3.1: Baseline demographic characteristics of patients receiving antiretroviral treatment in the study sites……22

Table 3.2: Baseline clinical characteristics of patients by health facility……24

Table 3.3: Mortality rates by health facility over 24 months of exposure to ART.……27

Table 3.4**:** Factors associated with Mortality during the study period…….....30

Table 3.5: Factors associated with LTFU during the study period……35

Table 3.6: Factors associated with failure to suppress viral load (>400 copies /ml) at 12 months into the ART programme……40

Table 3.7 Immunological responses of patients to ART……42

Table 3.8.1: Sensitivity analysis results for mortality and LTFU ……...44

Table 3.8.2: Sensitivity analysis results for failure to suppress viral load at 12 months…….44

ABBREVIATIONS

ALT	Alanine aminotransferase
aHR	Adjusted hazard ratio
AST	Aspartate aminotransferase
ARV	Antiretroviral
ART	Antiretroviral therapy
AIDS	Acquired Immunodeficiency Syndrome
BMI	Body Mass Index
CCMT	Comprehensive Care, Management and Treatment
CI	Confidence Interval
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IRR	Incidence rate ratio
IQR	Interquartile range
Log	Logarithm
LTFU	Loss to follow up
NGO	Non-Governmental Organization
P	Probability
PEPFAR	United States President's Emergency Plan for AIDS Relief
RNA	Ribonucleic acid
SD	Standard deviation
TB	Tuberculosis
uHR	Unadjusted hazard ratio
UN	United Nations
SA	South Africa

WHO World Health Organisation

CHAPTER 1: INTRODUCTION

1.1 Background

1.1.1 Treatment and management of HIV/AIDS

Antiretroviral therapy (ART) is the treatment prescribed for HIV positive patients who meet the treatment initiation criteria[1]. Treatment involves a combination of antiretroviral drugs that suppress the HIV virus and thus minimize progression of HIV disease[1]. These drugs have proven successful in reducing HIV/AIDS morbidity and mortality[1] Globally, ART provision is implemented by government controlled programmes and by the private sector. The latter has a longer history, particularly in developing countries, through donor funded HIV projects[2]. The United Nations' call for universal access to HIV care and treatment prompted governments to scale up public ART programmes[3]. These time-bound commitments have resulted in the public sector becoming the major provider of HIV care and treatment worldwide.

South Africa's ART roll out programme was initiated in 2004 and is currently, the largest free ART programme in the world[4]. The country is the largest beneficiary of the United States President's Emergency Plan for AIDS Relief (PEPFAR)[5]. Over the years; ART provision was decentralized from referral hospitals to primary health care centres[6]. This was done to achieve improved access to HIV drug therapy through geographical equity[6].The South African government provides HIV care and treatment through its public Comprehensive Care, Management and Treatment (CCMT) sites. The sites are run by the

South African Department of Health in collaboration with non-governmental organizations (NGOs) and other stakeholders[4]. The provision of ART in the public sector is prescribed by National Guidelines adapted from the World Health Organization (WHO). Prior to April 2010, eligibility for ART was set at a CD4 count of ≤200 cells/mm^3 which has since gone up to ≤350 cells/mm^3[7]. Patients are given a first line or second line regimen of drugs recommended by the WHO. The first line regimen consists of two nucleoside reverse transcriptase inhibitors, (stavudine, lamiduvine) and one non-nucleoside transcriptase inhibitor (efavirenz)[7]. Pregnant women are given nevirapine in place of efavirenz[7]. The second line regimen consists of zidovudine, didanosine and lopinavor-ritonavor[7].

The private sector consists of health care providers operating outside the government ART programme[7]. Health care providers in the private sector can use the national guidelines but it is not mandatory[2]. Initiation criteria and treatment are generally the same. However the private sector has access to different drugs which are usually more expensive[2]. Private physicians offer services to clients who pay from their own pocket or through private company medical schemes[2]. The latter can be employees of companies or individual medical aid cover[2]. Patients do, however, have the option of enrolling either into a public or private HIV care and treatment centre. In the private sector, patients can initiate ART at an earlier WHO stage if they can afford to do so. The anticipated treatment outcomes of HIV management are virological suppression, increased CD4 counts, adherence to treatment and minimal attrition rates[8]. Poor treatment outcomes are a reflection of discrepancies at health facility level or amongst individual patients.

1.2 Problem Statement

The primary goal of any ART programme is to achieve good treatment outcomes. Adherence to treatment and patient retention to care are key to achieving good treatment outcomes in both the private and public sector. However, there are challenges to the attainment of desired treatment outcomes, some unique to either sector. There are concerns of poor monitoring in both sectors, particularly in the private sector where practitioners are often unregulated[7]. Thus, potential causes of poor clinical outcomes can be either health systems or patient related. The health systems factors include: clinical mismanagement, poor quality of HIV care, lack of standardization and poor regulation of services [2]. The major contributing patient related factor is non-adherence to treatment and this may be due to high costs of drugs especially in private clinics [9]. All these have negative impacts on treatment, leading to poor treatment outcomes. Attrition has been shown to be more common in private clinics [2, 9]. This suggests that patients in private clinics have a higher risk of developing viral resistance due to treatment interruptions than those in public clinics [9]. Ultimately, this may lead to hastened progression of the HIV disease and subsequent mortality. In the public sector, overload on staff compromises quality of HIV care e.g. counseling sessions are reduced or not done at all[9]. Lengthy queues at the clinic may deter patients from accessing drugs. Stigmatization, also common in the public sector, often leads to non-adherence to treatment and loss to follow up[9]. Poor monitoring and evaluation of services in the public is a concern, particularly in the wake of high incidence rates[5]. The additional cases have profound financial implications on the largely donor dependent public ART programme[5].

1.3 Justification of the study

This study was conducted to evaluate the differences (if any) in the treatment outcomes of patients initiating ART in private versus public clinics. Thus, findings would unearth strengths and weaknesses of the two health care systems with regards to HIV treatment outcomes. Subsequently, findings would provide a basis for potential counteractive measures eg. promotion of public-private partnerships.

Public-private partnerships are a relatively new phenomenon in South Africa that has been recommended to address challenges in either sector[2]. The collaboration can lead to task shifting which subsequently alleviates load on staff in public clinics. Contracting clinical HIV care to private physicians can also expose patients to alternative drugs that may not be readily accessible in the public sector. The partnerships have been shown to reduce stigmatization and increase patient retention in ART programmes[9]. The concept is also in line with the current re-engineering of primary health care initiative in South Africa[24]. The lack of integration of the different levels of care between the public and private sectors results in poor access to health care, poor quality of care and inefficient resource utilization[25].

Concerns have been raised over high rates of non-adherence to treatment in the private sector[9]. This study sought to investigate whether the survival of patients initiated on treatment in the private sector is reduced. Results of the study would then provide a platform for further research into factors associated with poor treatment outcomes in either sector.

Extensive studies have been done to assess HIV treatment outcomes in the public sector[16,17,19]. However, data on the differences in treatment outcomes between the public and private health care setting is scarce. This study was conducted to fill in the knowledge gap.

1.4 Literature Review

Despite the widespread expansion of ART programmes in South Africa, HIV continues to be a huge burden to the government. Gauteng province alone, constitutes the fifth highest burden of the disease in the country (prevalence of 15.2 %)[4]. The province has the second largest number of ART patients in South Africa, through government CCMTs. One of the study sites, Themba Lethu clinic is one of the public CCMTs in Johannesburg[4].

The aims of these public HIV programmes or any HIV programme are suppression of the virus to undetectable levels and improvement in immunological response[11]. These two are the backbone of clinical outcomes in HIV management. Adherence to treatment and loss to follow up are patient dependent variables that have direct impacts on the clinical outcomes. Most literature define HIV treatment outcomes in terms of the all the above mentioned variables. Consequently, the effectiveness of ART provision is measured by virological suppression, CD4 count improvement, adherence to treatment and loss to follow up of patients[11].

Earlier literature suggests that the private sector has a longer history of chronic clinical care than the public sector in South Africa for example TB services and ART provision[2,10]. However, HIV care and treatment is often unregulated and there are no prescribed standards of operation[9]. Private providers have the option of either following their country's guidelines or WHO recommendations[2]. There are two different paradigms regarding HIV care and treatment between the private and public sector. The latter adopts a predominantly curative approach rather than preventative, while the public sector is more focused on prevention[2]. Consequently, the private sector does not adequately address population level morbidity. Studies have also shown that, in developing countries, socioeconomic status determines the type of HIV clinic a patient attends as well as their access to ART[9,12].

Wealthier; educated and employed people are more likely to enroll in private clinics whereas poorer, uneducated and unemployed people will enroll in public facilities. It has also been suggested that gender plays an important role in the demographic characteristics of patients in the two clinic types. A South African study found that more employed women enroll in private clinics while, in India; males are more likely to enroll in private clinics than women[2,9]. This could be a result of the differences in women empowerment in the respective countries.

There is a general consensus that the high costs of drugs in the private sector are the major cause of loss to follow up and patients defaulting from treatment[2,9,12]. Financial barriers to ART access are thus skewed towards the private sector, particularly patients paying for the drugs from their own pockets. Cost becomes an impediment towards sustaining drug therapy in the private sector. The situation worsens in private patients who are co-infected with TB. TB drugs are also very costly in the private sector[2]. These patients are more susceptible to treatment defaults, subsequent viral resistance and hastened disease progression[9]. Virological suppression becomes difficult to achieve[7]. Some literature suggests that loss to follow up is often overestimated in the private sector due to lack of ascertainment of death[7]. In the public sector, stigmatization and lack of family support are some of the major contributors of non-patient retention[13,14]. Private clinics are perceived to be more sensitive to patients' privacy and confidentiality and less stigmatization than the public sector[9]. There are concerns over the poor quality of care due to clinical mismanagement and poor regulation in the private sector[2,7]. However, a systematic review of studies on general health outcomes between private and public urban settings showed that patients in the private sector are less likely to die than those in public clinics[15,18].

In developing countries, malnutrition has been found to be common in HIV positive people due to poor dietary intake[21]. Studies have been conducted to assess the impact of

malnutrition on the survival and immunological response of patients starting ART[20,21]. Results have shown that although malnutrition at ART initiation is associated with decreased survival, the effect is not mediated by impaired immunological reconstitution[20]. However, certain micronutrients (increased zinc and selenium levels) have been found to improve virological control[23].

1.4.1 Summary of literature review findings:

1. Extensive studies have been conducted on treatment outcomes in the public sector[17,18,19]. There is little knowledge on the comparison of HIV care and treatment outcomes between the public sector and private health institutions in South Africa. Results of this study will contribute towards filling this gap.

2. The above literature shows gaps in both the private and public sector. There is inconclusive evidence on which sector is giving optimum HIV care and treatment. Comprehensive research is thus needed to investigate treatment outcomes in both settings.

3. Concerns of clinical mismanagement in the private sector can have adverse effects on treatment outcomes, hence; this study will provide a basis for further research into causes of differences in treatment outcomes.

1.5 Study Aims and Objectives

1.5.1 Research Question

Are there differences in treatment outcomes amongst ART naïve patients starting treatment in a private or public HIV clinic in South Africa?

1.5.2 Aim of the study

To compare ART treatment outcomes in ART naïve patients starting treatment in private or public HIV health centres and to identify risk factors associated with poor treatment outcomes in South Africa.

1.5.3 Study Objectives:

1 To compare treatment outcomes (i.e. mortality, LTFU, failure to suppress viral load, CD4 count change) of HIV positive patients starting ART in private vs. public health care centres in Johannesburg between 01 January 2005 and 31 December 2011.

2 To assess risk factors associated with treatment outcomes (mortality, LTFU and failure to suppress viral load) in HIV positive patients starting ART in private vs. public health care centres in Johannesburg between 01 January 2005 and 31 December 2011.

CHAPTER 2: METHODOLOGY

2.1 Introduction

This chapter describes the methods used in the study as well as procedures undertaken to ensure validity of results. Components of the chapter include the design of the study, a description of the study population, data collection and study variables. The chapter ends with a detail of data management i.e. the statistical methods used and diagnostic tests conducted (e.g. confounding, interaction) to achieve validity of findings.

2.2 Study Design

A retrospective cohort study design was used to analyze routinely collected data from Themba Lethu Clinic and a private HIV clinic run by a local physician, whose name has been anonymized for ethical reasons. Findings were drawn from a retrospective review of respective cohort records from 01 January 2005 to 31 December 2011.

2.3 Study Setting

The study was conducted on data collected from a private and a public clinic. Data from both sites were obtained from Right to Care, a non-governmental organization that provides HIV care and treatment to government HIV care sites as well as private companies in Johannesburg. Both clinics are located in Johannesburg. The city is located in Gauteng province which as an HIV prevalence of 15.2%. An estimated 207 000 people were on ART

as of 2011at Themba Lethu[4]. Johannesburg has 40 public HIV CCMT sites. Below is a brief description of each health facility.

2.3.1 Themba Lethu Clinic

Themba Lethu is one of the public HIV CCMT sites in Johannesburg and thus constituted the public clinic of the study. The clinic is located at Helen Joseph Hospital and it is the largest ART site in South Africa[16]. Themba Lethu services are implemented and coordinated by Right to Care. Services include HIV testing and counseling, routine laboratory and clinical tests. Patients with a CD4 count of ≤350 cells/mm^3 are enrolled into the ART programme as of April 2010. Prior, the CD4 eligibility criterion was 200 cells/mm^3[26].

2.3.2 Private Clinic

The clinic is located in Brenthurst, Parktown Johannesburg. Records of patients from the clinic are captured in Right to Care's TherapyEdge-HIV™ electronic patient database management system. The clinic provides private HIV care and treatment i.e. patients pay for services and drugs from their pockets or through medical aid schemes. The clinic was selected to represent the private sector due to convenience of data availability to Right to Care.

2.4 Study Population

The Themba Lethu (public clinic) cohort of HIV positive patients began in 2004 following the government roll-out of the ART programme[17]. The cohort receives HIV/TB care and drug therapy free of charge at the site. As of October 2011, the cohort had 30 000

participants, with 19 800 (66%) on ART and 10 200 (44%) pre-ART[4]. The bulk of the cohort is from the Gauteng region. However some patients are from other parts of South Africa and outside its borders.

The private clinic has been operational since July 2007. As of January 2012, the clinic has 3191 patients, 2296 (72.0%) who are on ART and the rest are pre-ART patients. The majority of patients in the private clinic were females i.e. 2119 (66.4%). About 2562 (80.3%) of the patients are employed. Patients are mainly referred in from other sites. Cohort data from 01 January 2005-31 December 2011 was obtained from both sites.

2.5 Study Sample

A total of 12 264 patients were analyzed during the study period. Themba Lethu patients were 11 690 and 574 from the private clinic. The sample size was obtained from patients that met the eligibility criteria described below.

2.5.1 Inclusion Criteria

Study data were restricted to records of HIV positive patients who were ART naïve defined as:

- Initiating treatment at Themba Lethu or private clinic without prior exposure to ART.
- Baseline viral load >400 copies/µL and CD4 ≤350cells/mm^3
- WHO stage 3 or 4 regardless of CD4
- 18 years or older at the time of ART initiation.

The initiation start date was any time point between 01 January 2005 and 31December 2011. Data were censored on loss to follow up or death or at the end of the follow up period i.e. 31 December 2012.

2.5.2. Exclusion Criteria

Children and adolescents were excluded from the study to reduce bias from differences in ART regimens as well as physiological differences between adults and children[31]. Similarly pregnant women were excluded to minimize the effect of antenatal visits on LTFU[40]. In addition, pregnant women were excluded to prevent confounding effect of pregnancy (compromises immunity) on the immunological responses of patients to ART[34].

2.6 Data Collection

Observational data from Themba Lethu and the private clinic was used for the study. The data are stored in an electronic patient management system called TherapyEdge-HIV™. Information collected upon initiation includes demographics (such as sex, age and employment) and clinical data (conditions, treatment regimens and laboratory results) [4]. Data on clinical variables is collected on each medical visit. Laboratory analyses involve CD4 counts, viral load tests, regimen changes and other medical examinations. CD4+ T-cell lymphocytes counts are done using pan-leucogated CD4+ flow cytometry (FlowCount Fluorospheres, Beckman Coulter-Immunotech, France) while HIV-1 RNA viral load tests are conducted using NucliSENSEasyQ® HIV-1 assay (bioMérieux Clinical Diagnostics, France).

At Themba Lethu, treatment monitoring is done with CD4 counts and viral load tests between four and seven months after initiation of a new regimen, thereafter at six month intervals or as clinically indicated. All patient information is collected in real time at each visit by clinicians to ensure accuracy of clinical data. Staticians based on site manage the database for quality control purposes. Adherence to treatment is measured by self-reporting of patients

upon collection of drugs or medical visit. Patients collect their ARVs monthly or every two months. An electronic tracking system is used to manage patients' visits. Those who miss scheduled dates are actively traced telephonically or through home visits. Records of adverse events (loss to follow up or death) are also kept in the database.

In the private clinic, data collection is at the discretion of the physician. There is no standardized procedure for patient follow up and treatment monitoring.

2.7 Data Management and Analysis

2.7.1 Measurement of Exposure and Outcome

The following variables were used for the study:

Exposures:

1. **Type of Health centre**:

- Public clinic: a health facility offering HIV care and treatment free of charge using government funded resources
- Private clinic: a profit making health facility where patients pay for HIV care and treatment services from their pockets or through medical aid schemes

2. **Socio-demographic**:

- Age: age of patient in years at the time of ART initiation.
- Sex: sex of patient (male or female)
- Level of education: highest level of education of patient, categorized into below >primary or primary level≤.
- Employment: current employment status of patient

3. **Biological**

- Type of regimen: Department of Health recommended HIV drug therapy
- WHO stage: WHO classification of disease severity i.e. stage 4 being the highest clinically advanced form of disease and stage1 the reference stage of the disease.
- Nutritional Status: Albumin and Body Mass Index (BMI) were used as proxy measures for nutritional status of patients.

Study Outcomes:

1. Mortality: (all cause): death of a case enrolled onto the ART program between 01 January 2005 and 31 December 2011.
2. Loss to follow up (LTFU): referred to cases that ever fail to attend the clinic for more than 3 months since last scheduled visit during the study period.
3. Failure to suppress viral load: Referred to patients having a viral load of >400copies/ml at 12 months post-ART initiation.
4. CD4 count change: differences in number of T lymphocytes/mL at baseline and at 6 months or 12 months.

2.7.2 Data Management

Individual level data from both sites is prospectively collected for routine monitoring by site designated clinicians. Data are periodically updated onto TherapyEdge-HIV^{TM}. Data are continually cleaned for quality assurance and validity purposes. Data from each clinic was exported from TherapyEdge-HIV^{TM} as a comma separated values (csv) file and imported into SAS and then STATA 11^{TM} StataCorp LP for analysis. The eligibility criteria were used to select participants from each health facility. Thereafter, the individual datasets were merged into a composite dataset. The variable clinic type was generated to identify the type of health

facility patients belonged to. Normal quantile plots (Qnorm) and skewness tests (Shapiro-Wilk test; Ho: data is normally distributed; Ha: data is skewed) were conducted on continuous variables to test for normality. Non-parametric statistical tests were then performed on all skewed variables.

The demographic variables used in the study were age, gender, ethnicity, education and employment. As a result of fewer non-black ethnic groups, ethnicity was categorized into black and other ethnic groups. The nationality of patients was not included in the analysis because data on foreign nationals was sparse in both facilities. The educational level of patients was categorized into either ≥primary or <primary level, where primary level is Grade 7. The latter was considered as the basic level of education amongst patients from the public clinic who formed the bulk of the dataset. Similarly, employment was categorized into employed or unemployed based on the observation that approximately 50% of public patients were unemployed. Age was categorized into standard adult 10 year age groups i.e. 18-29.9, 30-39.9, 40-49.9 and ≥50.

Viral load tests were provided as quantified measurements reported as copies/mL. Baseline viral load measurements were log transformed and the mean determined for each health facility. However, at subsequent visits i.e. 6 months and 12 months, measurements were categorized into detectable (>400 copies/mL) and undetectable viral load (<400 copies/mL). Baseline CD4 cells/mL measurements were categorized into three categories with increasing immunity (≤100, 101-200, 201-350). Absolute CD4 measurements were analyzed at 6 months, and 12 months to determine median changes. The median change at 6 months was obtained by subtracting the CD4 count value at baseline from the CD4 value at 6 months. To determine the median change between 6 and 12 months, the CD4 count value at 6 months

was subtracted from the CD4 count value at 12 months. The WHO HIV disease classification system was used to determine stage of patients at baseline. Stages 1 and 2 were further categorized into early stage HIV and stages 3 and 4 categorized into clinically advanced HIV. The former was used as the reference group.

Government prescribed HIV drug regimens were used as standard drug regimens. Optional drugs combinations were categorized into their group and labeled as 'other' [26].

Anthropogenic measurements were recoded and categorized using WHO standards. BMI was categorized into underweight (<18.5 kg/m^2) and normal (≥18.5 kg/m^2). Patients were categorized into anaemic and normal (i.e.<10 g/dL and ≥10 g/dL respectively). Albumin was recoded into normal (≥33 g/dL) and hypoalbuminaemia (<33 g/dL) [46].

2.7.3 Statistical Methods

Statistical analysis was done using descriptive statistics and inferential statistics.

2.7.3.1 Descriptive statistics

Baseline demographic, clinical and immunological characteristics of patients enrolled in either clinic were compared. All continuous variables (e.g. age) were described using means and standard deviations for normally distributed data. Medians and IQR were reported for skewed data. Qnorm plots and skewness tests were used to test for normality of data. Continuous variables were compared using Student's t tests and Wilcoxon rank sum (Mann Whitney) for skewed data. Categorical data (e.g. gender) were described using proportions (N) and percentages (%). Pie or bar graphs were used to depict categorical data. Two way

comparisons of frequencies of categorical data were done using Pearson's Chi Square, while Fischer's Exact was used for sparse data.

2.7.3.2 Inferential statistics

- Outcome: Mortality and LTFU

Kaplan Meir estimates were used to compare mortality and LTFU between the two clinics. The Log rank test for equality of survival functions was used to test for statistically significant differences in mortality and LTFU between the two groups at the 5% level of significance. Person time for participants was determined from ART initiation to date of death or LTFU or censored at the end of the study period. Mortality and LTFU incidence rates per 1000 person months and associated 95% confidence intervals were calculated for each group at 6, 12 and 24 months after initiation of ART for each clinic. Cumulative incidence rates were also compared at the same time intervals between the two clinics. This method considered proportions of mortality and LTFU from the total sample in each clinic, while the incidence rates took into account number of patients available at each time interval.

Multivariate Cox proportional hazards models were used to assess predictors of poor treatment outcomes between the two facilities. Univariate analysis was used to select variables that were significant determinants of treatment outcomes at the $p < 0.20$ level of significance. These significant variables were then used to build the adjusted multivariate models. Priori variables (like age) were included in multivariate analysis despite lack of significance at univariate level. A $p \leq 0.05$ level of significance was used to select significant predictors of outcomes (mortality and LTFU) in adjusted multivariate analysis. Effect modification was assessed by introduction of interaction terms in the model, while the Mantel-Haenszel method was used to identify confounding. Log Likelihood ratio tests

(Lrtest) were used to select the final model using an Lrtest Chi-squared p ≤0.05. The results of the multivariate analysis were based on a statistical significant p value of p ≤0.05The assumption of proportionality of hazards was checked using Cox-Snell residuals plots and Schoenfield residuals tests. Model fit was tested using the goodness of fit test.

- Outcome: Failure to suppress viral load after 12 months.

Proportions and percentages were used to describe patients that failed to suppress viral load after 12 months of ART between the two facilities. Pearson's Chi squared test was used to test for associations between type of facility and virological failure. Generalized estimation equations (GEE) were used to assess predictors of virological failure between the two facilities. The GEEs were used to account for patient /within subject correlation, as such, an individual based approach was used. The components of the GEE method included a logit link function, robust standard errors, a binomial distribution and an exchangeable correlation structure. Models were built and diagnostic tests performed as described above.

- Outcome: CD4 count change

Medians and interquartile ranges were used to describe CD4 count changes in each facility. The Wilcoxon rank sum (Mann Whitney) was used to compare median CD4 count change between the private and public clinic at baseline to 6 months as well as from 6 months to 12 months.

2.8 Ethics Clearance

The use of de-identified datasets from Themba Lethu and the private clinic was approved by the Human Research Ethics Committee of the University of the Witwatersrand (clearance certificate number M120863).

CHAPTER 3: RESULTS

3.1 Organization of the study cohorts

As of December 2011, 25 803 patients were ever initiated on ART in Themba Lethu clinic. A total of 14 113 (54.7%) did not meet the inclusion criteria while 398 (1.5%) did not initiate ART at Themba Lethu clinic and 152 (0.6%) were below the age of 18 years. A total of 7811 (30.3%) initiated treatment outside the study period and 4052 (15.7%) were treatment experienced (i.e. an undetectable viral load and had a CD4 greater than 350 cells/mm^3). There were 1700 (6.7%) pregnant females. This left a total of 11690 (45.3%) eligible patients from Themba Lethu. By the end of the study period, 1618 (13.8%) died and 3239 (28.8%) were lost to follow up from Themba Lethu clinic.

The private clinic had 2296 patients ever initiated on ART by December 2011. Of these, 666 (29.0%) had initiated ART outside the study period. A total of 847 (36.9%) were treatment experienced and 19 (0.4%) were aged below 18 years. There were 189 (8.2%) pregnant females. This left a total of 574 patients eligible from the private clinic as shown in Fig 3.1. Baseline characteristics were separated and divided into demographic and clinical characteristics and they were presented in Table 3.1 and Table 3.2 respectively.

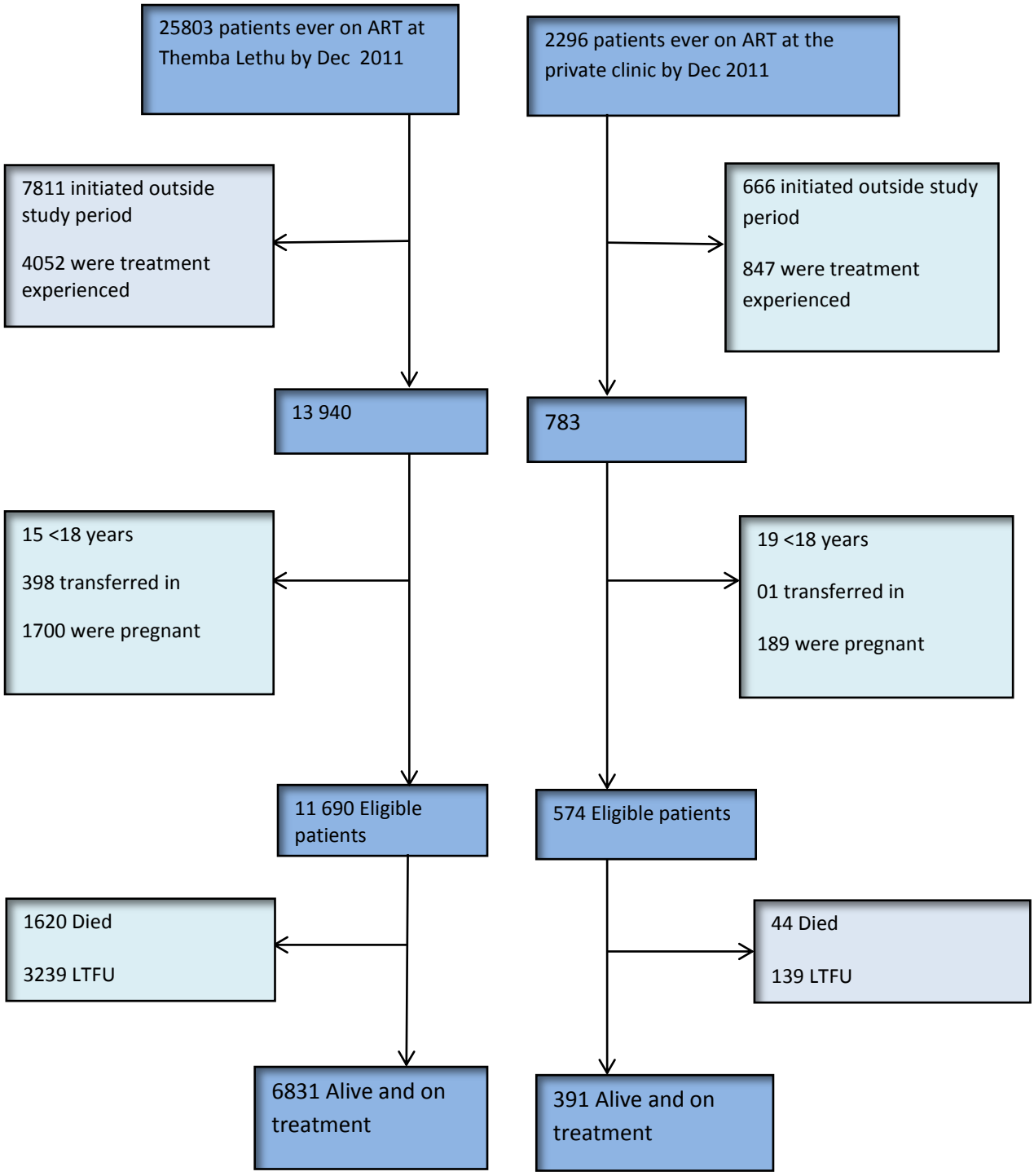


Fig 3.1. Cohort profile stratified by clinic type in December 2011. *Fig 3.1 is a structured flow chart of how the final eligible study cohort was obtained from the original datasets from each clinic. It is also shows the ART program losses (mortality and LTFU) of each health facility.*

3.2 Baseline demographic characteristics

Most of the baseline socio-demographic characteristics of patients between the two facilities were generally different as shown in Table 3.1. Patients were similar in terms of ethnicity, age and sex distribution. Significant differences were observed in the educational status and employment of patients. Patients in the private clinic were more educated, with about 70% having achieved education above primary level compared to 57.6% in the public clinic. This was consistent with the employment status of patients. From the private clinic, 85% of the patients were employed compared to about 50% in the public clinic. Employment type and educational level were associated with type of health facility ($p < 0.001$). In both facilities, the bulk of patients were South Africans (i.e. 92% at Themba Lethu clinic and 95.8% in the private clinic).

Table 3.1: Baseline demographic characteristics of 12 264 HIV positive patients receiving antiretroviral treatment; stratified by clinic.

Characteristic n (%)	Public N=11690	Private N=574	p-value
Gender			
Females	7166 (61.3)	383 (67.2)	0.05
Males	4524 (38.7)	187 (32.8)	
Age at initiation/years			
Median (IQR)	36.3 (31.1-42.8)	35.0 (31.41.0)	0.07
18-29.9	2338 (20.0)	103 (18.0)	
30-39.9	5283 (45.2)	307 (53.5)	
40-49.9	2899 (24.8)	130 (22.6)	
≥50	1169 (10.0)	34 (5.9)	
Race			
Black	11187 (95.7)	518 (90.2)	**<0.001**†
Other	511 (4.3)	24 (4.2)	
Unknown	0 (0.0)	32 (5.6)	
Education			
<Primary level	1912 (16.4)	9 (1.6)	**<0.001**
≥Primary level	6731 (57.6)	402 (70.0)	
Unknown	3047 (26.1)	163 (28.4)	
Employment			
Unemployed	5851 (50.1)	84 (14.6)	**<0.001**
Employed	5839 (49.9)	490 (85.4)	
Nationality			
South Africa	10751 (92.0)	550 (95.8)	**<0.001**†
Other	989 (8.0)	9 (1.6)	
Unknown	0 (0.0)	15 (2.6)	
Alcohol Use			
No	8772 (75.0)	215 (37.5)	**<0.001**
Yes	1867 (16.0)	84 (14.6)	
Unknown	1051 (9.0)	275 (47.9)	
Smoking status			
No	9120 (78.0)	269 (46.9)	**<0.001**
Yes	1513 (12.9)	30 (5.2)	
Unknown	1057 (9.1)	275 (47.9)	
ART Initiation by year			
2005	1445 (12.4)	35 (6.1)	**<0.001**
2006	2068 (17.7)	36 (6.3)	
2007	1881 (16.1)	68 (11.9)	
2008	1678 (14.4)	102 (17.8)	
2009	1884 (16.1)	119 (20.7)	
2010	1608 (13.8)	137 (23.9)	
2011	1126 (9.6)	77 (13.4)	

† Fischer's Exact p-value for sparse binary variables.

3.3 Baseline clinical characteristics of patients

Table 3.2 describes the clinical characteristics of patients by health facility. Baseline clinical characteristics were different for patients enrolled in the private and public clinic. The differences were statistically significant at the 5% level of significance; for example; the nutritional status of patients. Albumin tests and BMI were used as proxies for nutritional status of patients. The median albumin was 33g/L [IQR 29-38] compared to 30g/L [IQR 24-35] in the private and public facility respectively ($p < 0.001$). In the public clinic, 23% of patients were underweight (defined as BMI <18.5 kg/m^2) compared to 8% in the private clinic. Anaemic (defined as haemoglobin <10 g/dL) was common in the public clinic i.e. 26% compared to 14% in the private clinic. Patient liver damage was greater in the public clinic as shown in Table 3.2. There was an association between nutritional status and type of clinic at the 5% level of significance ($p=0.024$).

Patients in the private clinic were significantly associated with early initiation of ART (Early stage HIV: 78.2% compared to 55.8% in the public clinic). Also, the median baseline CD4 count was higher for patients in the private clinic compared to those in the public facility [median CD4:171 IQR (33-161) vs. 91 IQR (66-249)] respectively. However there was no evidence of significant differences in baseline viral load ($p=0.718$). Fig 3.2 shows the baseline CD4 count of patients by health facility. 70% of patients at Themba Lethu clinic were on d4T/3TC/EFV compared to 7.5% on the same regimen at the private clinic. The private clinic was the first to prescribe TDF/EMT/EFV to its patients. For example, 11% of private clinic patients were on this regimen in 2008 compared to less than 1% in the public clinic. Overall, type of ART regimen was significantly associated with type of health facility ($p < 0.001$).

Table 3.2: Baseline clinical characteristics of patients by health facility

Characteristic n (%)	Public N=11690	Private N=574	p-value
CD4 n (%)			
≤100	6271 (53.6)	188 (33.0)	**<0.001**
101-200	4074 (34.9)	151 (26.5)	
201-350	1345 (11.5)	231 (40.5)	
CD4 (cells/µL)			
Median (IQR)	91 (33-161)	171 (66-249)	**<0.001***
Log viral load			
Mean (SD)	11.32 (1.98)	11.19 (1.99)	[!]0.718
BMI (kg/m^2)			
<18.5	2684 (23.0)	45 (7.8)	**<0.001**
≥18.5	7146 (61.1)	279 (48.6)	
Unknown	1860 (15.9)	250 (43.6)	
Albumin(g/L)			
Median (IQR)	30 (24-35)	33 (29-38)	**<0.001***
<33	7800 (69.2)	77 (51.0)	
≥33	3474 (30.8)	74 (49.0)	
Liver Tests			
AST(IU/L)			
Median(IQR)	24 (16-37)	21 (15-29)	**0.0239***
ALT(IU/L)			
Median(IQR)	31 (24-48)	24 (20-34)	**0.0004***
Haemoglobin(g/dL)			
<10	3067 (26.2)	81 (14.1)	**<0.001†**
≥10	8623 (73.8)	489 (85.2)	
Unknown	0 (0.0)	4 (0.7)	
WHO stage			
Stage 1&2	6525 (55.8)	449 (78.2)	**<0.001**
Stage 3&4	5165 (44.2)	125 (21.8)	
Art regimen			
d4T/3TC/EFV	8221 (70.3)	43 (7.5)	**<0.001†**
3TC/TDF_EFV	2043 (17.5)	3 (0.5)	
AZT/3TC/EFV	245 (2.1)	40 (7.0)	
AZT/3TC/LPVr	16 (0.1)	41 (7.1)	
TDF/EMT/EFV	10 (0.01)	294 (51.2)	
d4T/3TC/LPVr	374 (3.2)	4 (0.7)	
[ǂ]Other	781 (6.7)	149 (26.0)	

*Wilcoxon rank sum test p value for skewed continuous variables †Fisher's exact test p value for sparse binary variables [!]Two sample Independent Student t test

[ǂ]Other: Abacavir sulphate, Atazanavir sulphate, Saquinavir mesylate, Amprenavir, Nelfinavir, Indinavir.

Table 3.2 Abbreviations:

BMI: Body Mass Index, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, d4T: Stavudine, AZT: Zidovudine, 3TC: Lamivudine, LPVr: Lopinavir, EFV: Efavirenz, EMT: Emtricitabane, TDF: Tenofovir Disoproxil Fumarate.

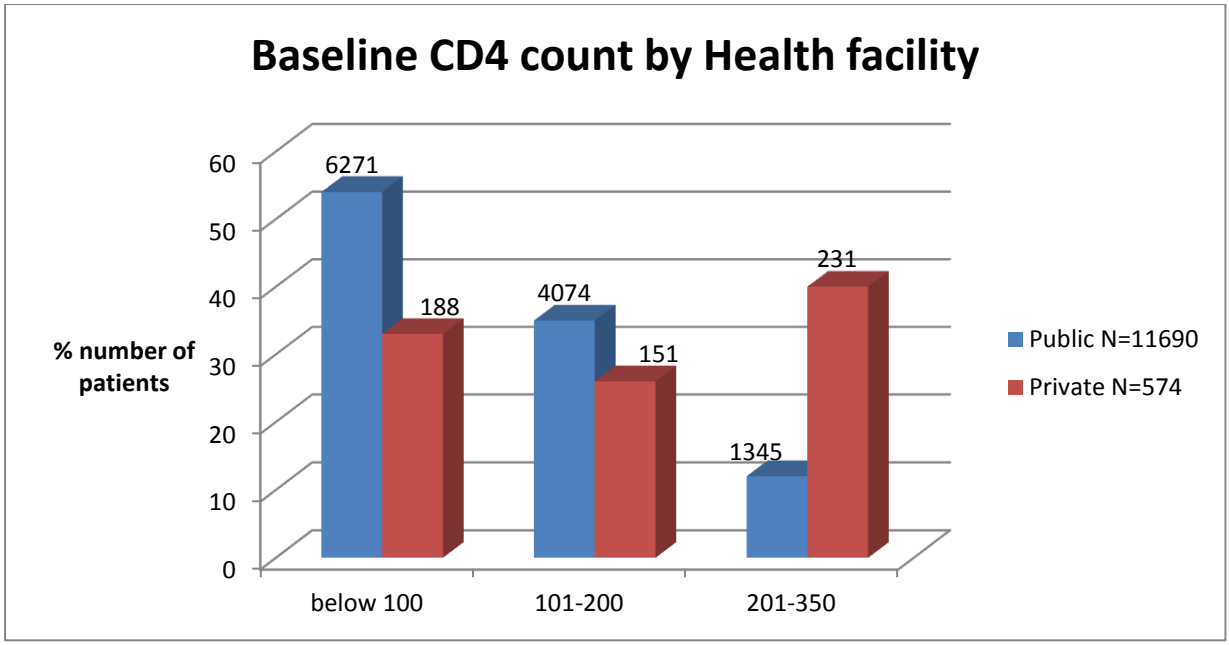


Fig 3.2 Baseline CD4 count of patients by health facility. *The majority of patients in the public clinic were initiating treatment with advanced HIV while those in the private clinic were initiating in the early stages of the disease.*

3.4 Programme Losses

3.4.1 Mortality

Statistically significant differences in the death of ART patients were observed between the two health facilities. Mortality was found to be higher in the public clinic compared to the private clinic; [1620 (13.8%) vs. 44 (7.7%)] respectively. Overall, initiating treatment in the private clinic was protective against mortality by approximately 40% and there was sufficient statistical evidence for this observation at the 5% level of significance i.e. [Incidence rate ratio=0.66, 95% CI: 0.48-0.89]. This finding was consistent with a significant Log rank p-value of non- equality of mortality between the two clinics (p=0.004). A significant association between the sex of participants and mortality was also observed (p <0.001) as shown in Fig 3.3 below.

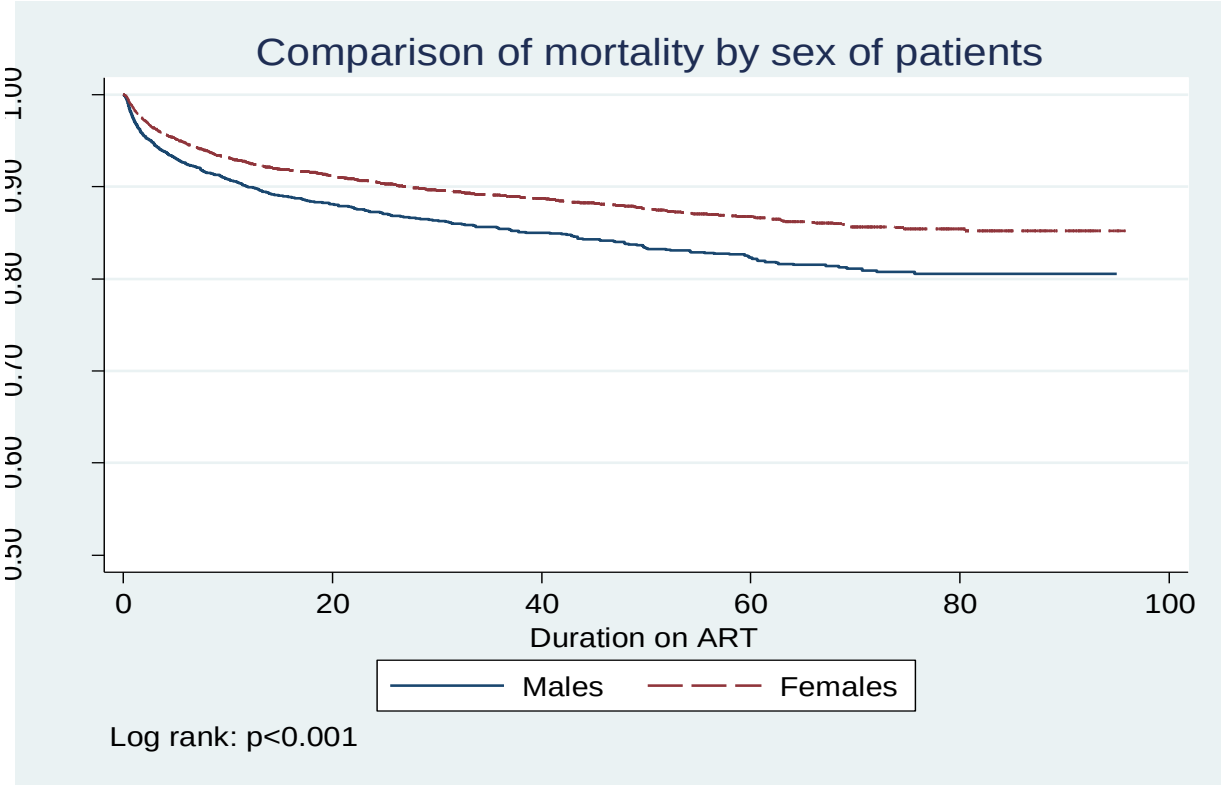


Fig 3.3 Survival estimates of mortality by sex of patients. *Male patients had a greater risk of dying compared to female patients.*

3.4.1.1 Time to Mortality

The cohorts were followed up for a period of 471 356.6 person months in total. Patients in the public clinic contributed a total of 452 671.6 person time in months with a median follow up period of 28.7 months IQR (14.7- 82.5). On the other hand, patients in the private clinic were followed up for 18 684.9 person months, with a median follow up period of 32.0 months IQR (9.2- 61.9). A total of 1664 deaths were observed throughout the duration of the study. Of these, 1620 were from the public clinic and 44 from the private clinic. The mortality rates over the entire study period between the two groups were (3.6 vs. 2.4 per 1000 person months) respectively. The risk of death was highest in the first 6 months of initiating ART for both facilities, decreasing steadily with prolonged exposure to ART as shown in Table 3.3.

The risk of death remained higher in the public clinic. Fig 3.4 shows the survival estimates of patients by clinic at 12 months. The number of deaths by clinic type until the end of the study has been provided in the appendix.

Table 3.3: Mortality rates by health facility over 24 months of exposure to ART.

	Public health facility			Private health facility		
Time/months	Person Time/months	Deaths	Incidence rate*	Person Time/months	Deaths	Incidence Rate*
0-6	76798.0	850	11.1	3177.3	16	5.6
7-12	66112.5	276	4.2	2989.4	6	2.0
13-24	108875.5	236	2.2	5015.0	8	1.5

*Incidence rates are per 1000 person months.

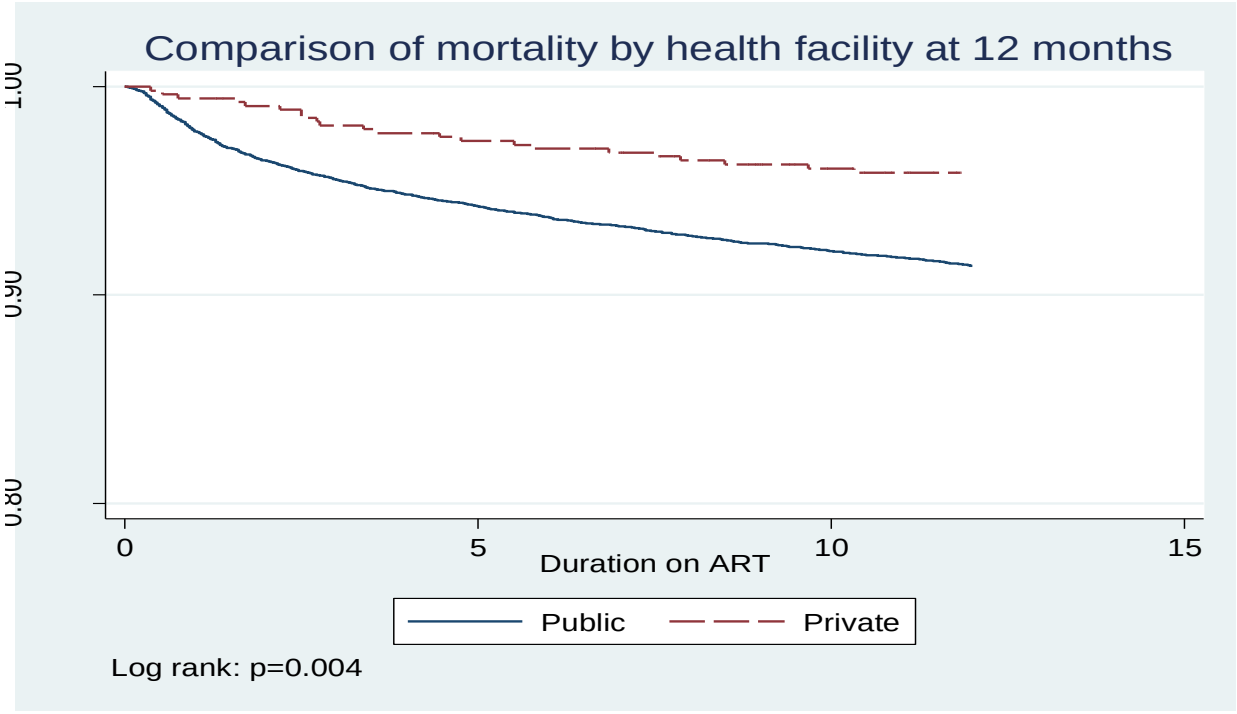


Fig 3.4 Survival estimates of mortality between the public and private health facility.
The graph shows that statistically significant differences in mortality were observed between the two clinics. Mortality was higher in the public clinic compared to the private clinic at 12 months.

3.4.1.2 Predictors of mortality

This analysis was performed on the composite dataset (public and private) to assess baseline characteristics which were associated with mortality during the study period (Table 3.1). The type of clinic in which patients enrolled into for ART was found to be a significant predictor of mortality. Patients in the private clinic were 61% less likely to die compared to public patients [aHR=0.39; 95% CI 0.14-1.06]. However; there was insufficient statistical evidence in support of this association at the 5% level of significance.

The age of patients at ART initiation was also found to be a significant predictor of death for ART patients. As expected, the risk of death increased with an increase in age. That is, patients aged above 50 years were two times more likely to die compared to young adults (18-29.9 years), [aHR=2.40; 95% CI 1.73-3.1]. However; the risk of death in the 30-39.9 year age group was comparable to the 18-29.9 year age group.

The survival of males and females on ART was found to be different i.e. the sex of patients was significantly associated with mortality. After adjusting for other baseline characteristics, the risk of death amongst males reduced 10%. However, the observation was not statistically significant [aHR=1.10; 95% CI 0.75-1.08].

A statistically significant association between hazard ratio and HIV stage was observed. The risk of death increased with an increase in HIV disease staging. Patients initiating ART late were 31% more likely die relative to those initiating treatment at the early stage of HIV [aHR=1.31; 95% CI 1.09-1.60]. Furthermore, an inverse relationship between the risk of death and CD4 count category was observed. The risk of death decreased with an increase in CD4 count category of patients. For example, there was statistical evidence at the 5% level that the risk of death increased by 77% in patients with the lowest CD4 count of less than 100 cells/mm^3 compared to those with a CD4 count between 250-350 cells/mm^3 [aHR=1.77;

95% CI 1.24-2.53]. Patients with below primary level education were more likely to die compared to those with above primary level education, although this association lacked statistical significance [aHR=1.12; 95% CI 0.76-1.02]). There was no evidence of ethnicity being a predictor of mortality at multivariate analysis. Unemployed patients were 8% more likely to die than unemployed patients despite lack of statistical evidence at the 5% level of significance [aHR=1.08; 95% CI 0.76-1.10].

There was strong evidence for association between nutritional status and mortality at both univariate and multivariate analysis. After adjusting for other covariates, the risk of death was three times more in underweight (BMI <18.5 kg/m^2) patients compared to patients with a normal weight (BMI ≥18.5 kg/m^2) [aHR=3.21; 95% CI 2.67-3.87]. Anaemic patients (Hb <10 g/dL) had 68% greater risk of dying compared to normal patients (≥10 g/dL), [aHR=1.68; 95% CI 1.38-2.04]. Similarly, patients who were hypoalbuminaemic (<33 g/dL) were also three times more likely to die compared to patients with normal albumin levels (≥33 g/dL), [uHR=3.10; 95% CI 2.68-3.40].

Table 3.4: Factors associated with Mortality during the study period.

	Unadjusted Hazard ratio (uHR)		[CI]	p-Value	Adjusted Hazard Ratio(aHR)	[CI]	p-Value
Baseline variables	**(++N=1664)**						
Health_facility							
Public	1620 (97.4%)	Ref			Ref		
Private	44 (2.6%)	0.65	[0.48-0.87]	0.004†	0.39	[0.14-1.06]	0.06
Age at initiation							
18-29.9	256 (15.4%)	Ref					
30.39.9	709 (42.6%)	1.20	[1.04-1.38]	0.012†	0.99	[0.76-1.31]	0.99
40-49.9	451 (27.1%)	1.44	[1.23-1.68]	<0.001†	1.51	[1.13-2.00]	0.005*
≥50	248 (14.9%)	2.08	[1.75-2.48]	<0.001†	2.40	[1.73-3.10]	<0.001*
Gender							
Female	920 (55.3%)	Ref			Ref		
Male	747 (44.7%)	1.27	[0.66-0.80]	<0.001†	1.10	[0.75-1.08]	0.25
Ethnicity							
Black	1559 (94.4%)	Ref			Ref		
Other	92 (5.6%)	1.32	[1.07-1.64]	0.009†	0.98	[0.65-1.47]	0.90
Education							
≥Primary level	675 (73.2%)	Ref			Ref		
<Primary level	247 (26.8%)	1.12	[0.76-1.03]	0.09†	1.02	[0.79-1.21]	0.97
WHO_stage							
Stage 1or2	682 (44.6%)	Ref			Ref		
Stage 3or4	847 (55.4%)	1.75	[1.58-1.94]	<0.001†	1.31	[1.09-1.58]	0.004*
CD4 count							
201-350	102 (6.1%)	Ref			Ref		
101-200	380 (22.8%)	1.53	[1.23-1.90]	<0.001†	1.25	[0.86-1.82]	0.24
<100	1182 (71.1%)	3.32	[2.71-4.07]	<0.001†	1.77	[1.24-2.53]	0.002*
Employment							
Employed	731 (45.0%)	Ref			Ref		
Unemployed	893 (55.0%)	1.27	[0.66-0.81]	<0.001†	1.07	[0.77-1.11]	0.36
BMI							
≥18.5	417 (48.8%)	Ref			Ref		
<18.5	438 (51.2%)	3.40	[3.00-3.93]	<0.001†	3.21	[2.67-3.87]	<0.001*
Haemoglobin							
≥10	996 (59.9%)	Ref			Ref		
<10	668 (40.1%)	2.23	[2.02-2.46]	<0.001†	1.68	[1.38-2.04]	<0.001*
Albumin							
≥33	207 (13.4%)	Ref			Ref		
<33	1289 (86.2%)	3.10	[2.68-3.40]	<0.001†	ǂNot included	ǂNot included	ǂNot included

† Variable significant at the 20% level of significance. Hazard Ratio of Reference=1 *Variable significant at the 5% level of significance. CI: 95% confidence interval BMI: Body mass index ǂ Including Albumin did not improve the final model i.e. lrtest p value = 0.96 Percentages derived from valid denominators (i.e. only for those for whom there are data for that variable)

3.4.1.3 Model Diagnostics for Mortality

The Cox- Snell residuals and goodness of fit diagnostics were used to assess the mortality model fit. Generalized Cox-Snell residuals were generated for each variable in the model to test for the proportionality of hazards assumption. That is; the hazard ratio comparing any two specifications of covariates is constant over time [51]. A graphical plot of the computed Cox-Snell residuals is used to assess model fit. An adequate model fit yields a straight line through the origin (gradient =1) as shown in Fig 3.5. All the covariates in the model satisfied the proportionality of hazards assumption. A non-significant p value (p=0.199) of the goodness of fit test was obtained showing that the model was suitable for explaining mortality during the study period.

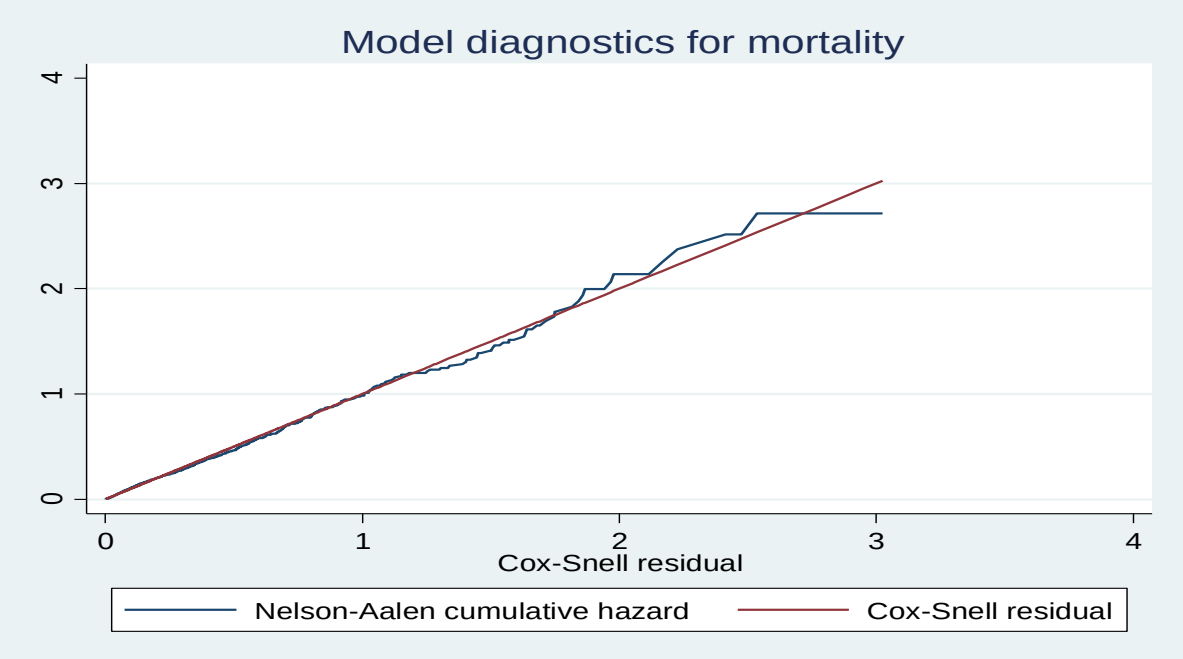


Fig 3.5 Model goodness of fit test using Cox-Snell residuals plot. *The model obtained was appropriate for explaining mortality.*

3.4.2 Loss to Follow Up

Patient retention was different between the two clinics. Patients in the public ART program were more stable compared to patients in the private clinic; [3239 (27.7%) vs. 139 (24.2%)] respectively. That is, patients that were lost to follow up were 63% more likely to be initiating ART in the private clinic and this observation lacked statistical significance [Incidence rate ratio: 1.63; 95% CI 1.41-1.87]. The Log rank test also proved that there was sufficient statistical evidence for non-equality of patient retention between the two ART clinics ($p < 0.001$).

3.4.2.1Time to LTFU

Patients followed up for a period of 471 356.7 person months in total. The public patients contributed a total of 452 671.6 person months with a median follow up period of 28.7 months IQR (14.7- 82.5). Patients in the private clinic were followed up for 18 684.9 person months, with a median follow up period of 32.0 months IQR (9.2- 61.9). A total of 3418 patients were lost to follow up from the two facilities during the study period. Although the absolute majority; 3239 (94.7%) were from the public clinic, LTFU was greater in the private clinic (Incidence rates: 7.2 vs. 11.7 per 1000 person months) respectively. It is worth noting that rates were initially higher in the public clinic in the first six months of ART initiation. Thereafter, there was a gradual decline in LTFU rates in the public clinic until the end of the study as shown by Fig 3.6. In the private ART program, LTFU rates increased steadily during the first year and remained higher than in the public ART program until the end of the study period.

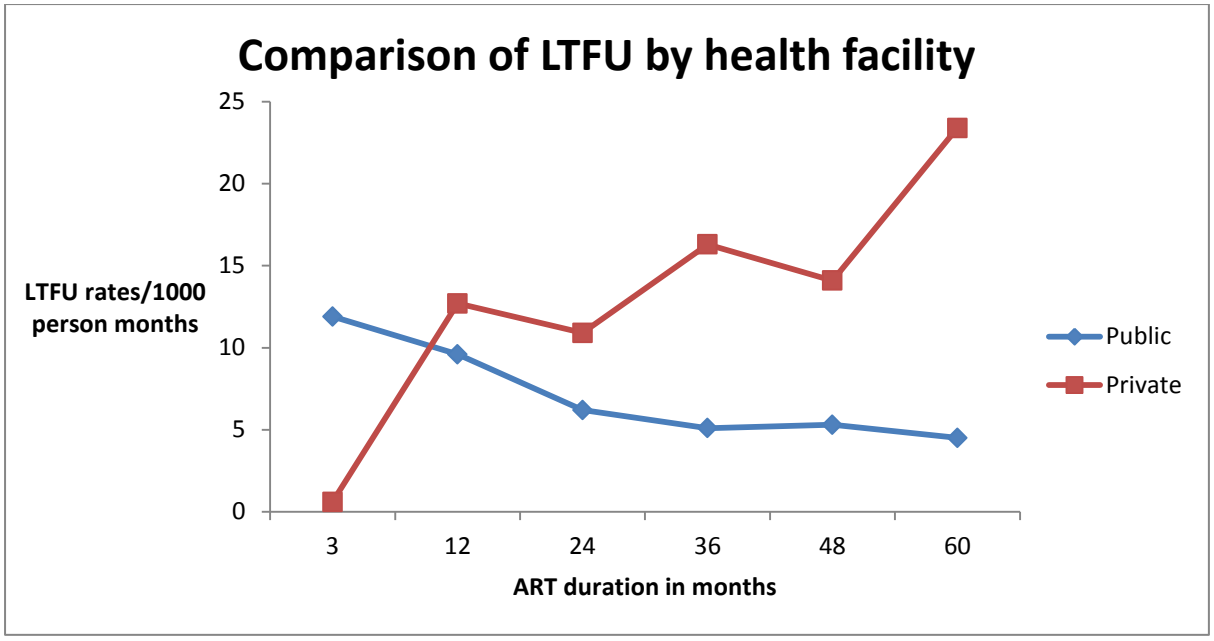


Fig 3.6 Comparison of LTFU rates by health facility during the study period. *LFTU was defined as >3months since last scheduled visit date. Overall; LTFU rates were higher in the private clinic, although patients were mostly lost from the public clinic in the first 6 months of ART.*

3.4.2.2 Predictors of LTFU

Similar to mortality, this analysis modelled baseline characteristics which were associated with loss to follow up throughout the study period on the composite cohort of 12 187 patients (Table 3.4). There was strong evidence at both univariate and multivariate levels that type of clinic had an influence on the retention of patients on the ART program. After adjusting for other covariates, patients receiving ART in the private clinic were 69% more likely to be lost from the private ART program compared to the public ART program [aHR=1.59; 95% CI 0.94-2.70].

The age of patients at ART initiation was also found to be a significant predictor of whether patients would be retained onto the program or not. An inverse relationship between LTFU and age was observed. Older patients were more likely to be retained on ART compared to

young adults. For example, the ≥ 50 age group were 36% less likely to be lost from the program compared to the 18-29 age group. Amongst the cohort, male patients were 21% more likely to be lost to follow up compared to female patients at multivariate level [aHR=1.21; 95% CI 0.70-0.89]. The risk of being lost to follow up increased by 21% among non-Black ethnic groups compared to the dominant Black ethnic group [aHR=1.21; 95% CI 0.94-1.56]). However there was no statistical evidence of this association at the 5% level of significance (p=0.14). Having a below primary level education increased the risk of LTFU at multivariate analysis, despite marginal statistically evidence [aHR=1.12; 95% CI 0.76-1.02].

An inverse relationship between LTFU and HIV-clinical stage was noted. Patients with advanced HIV (WHO Stage 3 or 4) were approximately 3% times less likely to be lost from the ART program compared to early stage patients (WHO Stage 1 or 2), [aHR=0.97; 95% CI 0.86-1.09]. However there was no evidence of this association as shown in Table 4.2. Similarly, patients with a CD4 count <100 cells/mm^3 were likely to be lost from ART compared to their healthier counterparts [aHR=1.09; 95% CI 0.98-1.20]. However there was no statistical evidence of an association between a patient's baseline CD4 count and LTFU.

After adjusting for other covariates, unemployed patients had a 14% greater likelihood of being lost from the ART program compared to employed patients and this was statistically significant [aHR=1.14; 95% CI 0.76-1.96]. The nutritional status of patients was found to be a strong predictor of patient retention on ART at both univariate and multivariate level. Anaemic patients (Hb <10 g/dL) were 20% more likely to be lost to follow up compared to normal patients (Hb ≥10 g/dL), [aHR=1.2; 95% CI [1.05-1.35]. Similarly, underweight patients (BMI <18.5 kg/m^2) were two times more likely to be lost to follow up compared to normal weight patients (BMI ≥18.5 kg/m^2), [aHR=2.0; 95% CI [0.72-2.19].

Table 3.5: Factors associated with LTFU during the study period.

Baseline variables	Unadjusted Hazard ratio (uHR) (++N= 3378)	[95% CI]	p-Value	Adjusted Hazard Ratio(aHR)	[95% CI]	p-Value
Health_facility						
Public	3239 (95.9%)	Ref		Ref		
Private	139 (4.1%)	1.49	[1.39-1.80]	<0.001†	1.59	[0.94-2.70]	0.08
Age at initiation						
18-29.9	846 (25.0%)	Ref		Ref		
30.39.9	1529 (45.3%)	0.78	[0.72-0.85]	<0.001†	0.76	[0.66-0.88]	<0.001*
40-49.9	747 (22.1%)	0.73	[0.66-0.80]	<0.001†	0.65	[0.54-0.77]	<0.001*
≥50	257(7.6%)	0.68	[0.59-0.78]	<0.001†	0.64	[0.50-0.82]	<0.001*
Gender						
Female	1968 (58.3%)	Ref		Ref		
Male	1410 (41.7%)	1.20	[0.75-0.86]	<0.001†	1.21	[0.70-0.89]	<0.001*
Ethnicity						
Black	3198 (94.7%)	Ref		Ref		
Other	180 (5.3%)	1.26	[1.09-1.47]	<0.001†	1.21	[0.94-1.56]	0.136
Education						
≥Primary level	1640 (71.7%)	Ref		Ref		
<Primary	646 (28.3%)	1.18	[0.75-0.90]	<0.001†	1.12	[0.76-1.02]	0.08
WHO_stage						
Stage 1or2	1716 (55.8%)	Ref		Ref		
Stage 3or4	1361 (44.2%)	1.13	[1.05-1.22]	<0.001†	0.97	[0.86-1.09]	0.608
CD4 count						
201-350	448 (13.3%)	Ref		Ref		
101-200	1163 (34.5%)	1.02	[0.92-1.14]	0.095†	1.10	[0.90-1.35]	0.362
<100	1763 (52.2%)	1.09	[0.98-1.20]	0.632	0.92	[0.75-1.12]	0.390
Employment						
Employed	1540 (46.0%)	Ref		Ref		
Unemployed	1809 (54.0%)	1.24	[0.71-0.81]	<0.001†	1.14	[0.76-0.96]	0.008*
BMI						
≥18.5	1476 (64.4%)	Ref		Ref		
<18.5	817 (35.6%)	1.98	[1.82-2.16]	<0.001†	2.00	[1.72-2.19]	0.143
Haemoglobin						
≥10	2419 (71.6%)	Ref		Ref		
<10	959 (28.4%)	1.38	[1.27-1.48]	<0.001†	1.20	[1.05-1.39]	<0.007*
Albumin						
≥33	745 (26.7%)	Ref		Ref		
<33	2041 (73.3%	1.41	[1.29-1.53]	<0.001†	1.07	[0.94-1.22]	0.302

† Variable significant at the 20% level of significance. Hazard Ratio of Reference=1 *Variable significant at the 5% level of significance.

++Percentages derived from valid denominators (i.e. only for those for whom there are data for that variable)

3.4.2.3 Model diagnostics for LTFU

The proportionality of hazards assumption (hazard ratio comparing any two predictors is constant over time) was tested on all the variables in the final model. Scaled Schoenfield residuals were used to assess the proportionality of hazards property of the model. An adequate fit yields a flat line (gradient = 0) in the regression of residuals against time[51]. The assumption was met for all the variables. Fig 3.7 shows a graphical display of scaled Schoenfield residuals plot for one of the variables i.e. type of clinic.

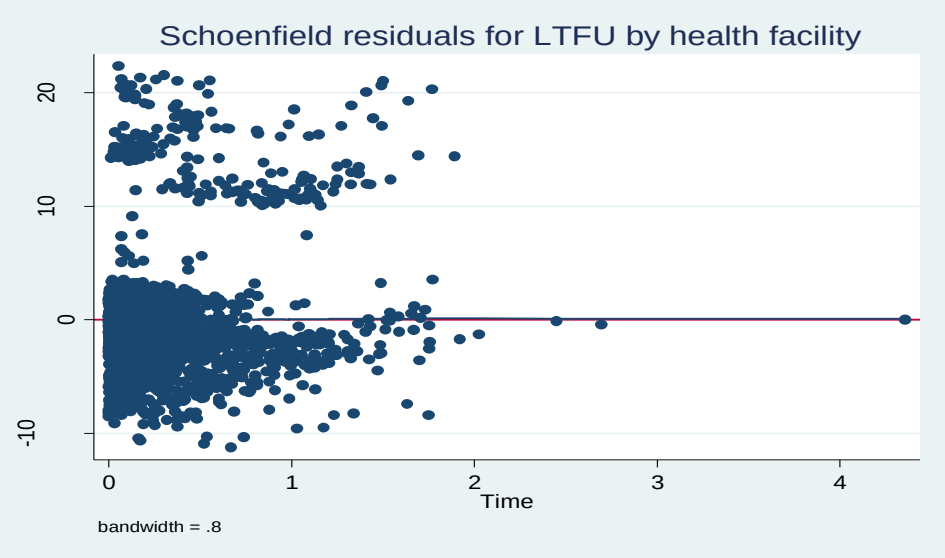


Fig 3.7 Schoenfield residuals plot for LTFU. *The variable clinic type met the proportionality of hazards assumption.*

3.5 Failure to suppress viral load

Patients receiving treatment in the public clinic had better virological outcomes compared to patients receiving treatment in the private clinic. The proportion of patients that failed to achieve virological suppression in the private clinic was twice the equivalent in the public clinic at 6 months i.e. 98 (28.6%; N= 342) compared to 1250 (14.4%; N =8685) respectively. Virological failure still remained higher in the private clinic after 12 months of follow up. The differences in the cumulative incidence of virological failure between the two facilities were statistically significant.

3.5.1 Proportion that failed to suppress viral load

The proportion of patients that failed to virological suppress at 12 months (cumulative incidence) were analysed between the two health facilities using the intent to treat approach. Analysis was based on the proportion that failed to suppress viral load out of the total with a viral load result at 12 months.

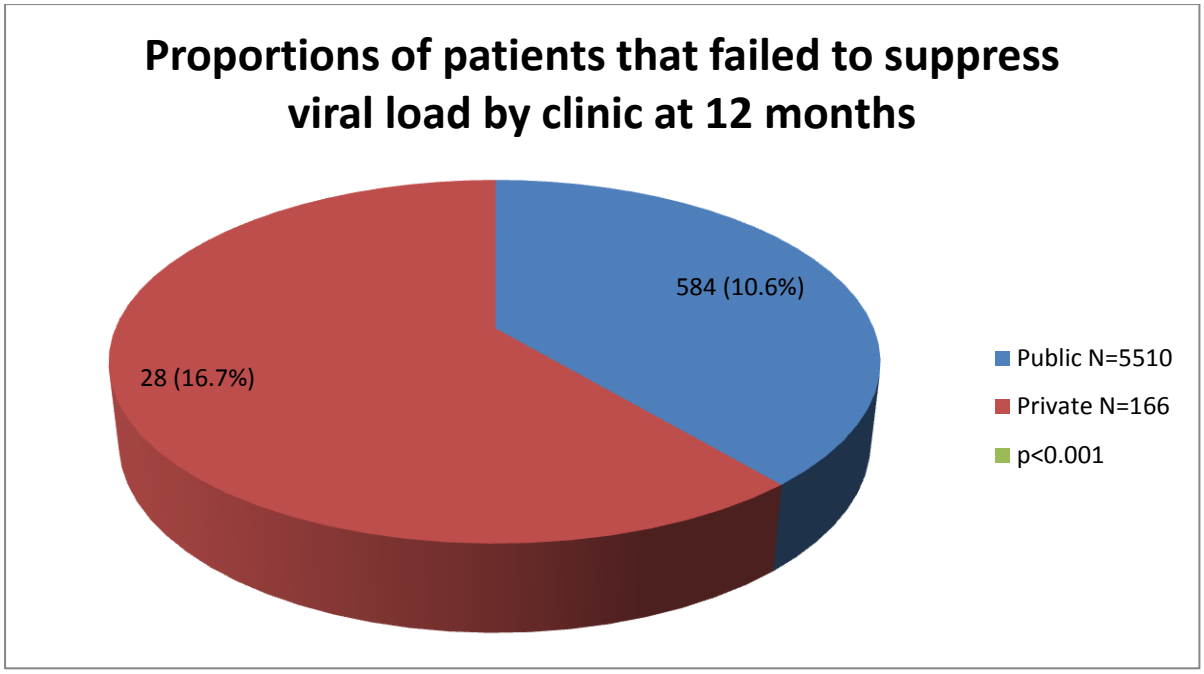


Fig 3.8 showing proportions of patients that failed to suppress viral load by health facility at 12 months. *Patients on the public ART program exhibited better virological outcomes compared to patients in the private ART program.*

3.5.2 Predictors of failure to suppress viral load at 12 months.

Patients in the private clinic were 63% more likely to have a detectable viral load at 12 months compared to public patients and this observation was statistically significant (p=0.007). Gender was also found to be a significant predictor of the virological response of ART patients. Males were 20% more likely to have a detectable virological load at 12 months of ART initiation [RR=0.80; 95% CI 0.68-0.94]. Patients initiating treatment with advanced HIV (WHO Stage 3 or 4) had a 9% greater risk of failing to virologically suppress at 12 months than patients with early stage HIV (WHO Stage 1 or 2). However this observation was not statistically significant (p=0.302). In contrast, patients with low CD4 counts were associated with good virological responses. For example patients with a CD4 count between 101-200 cells/mm^3 were 11% less likely to have a detectable viral load compared to those with a CD4 count in the range of 201-350 cells/mm^3.

Education was found to be protective against having a detectable viral load. That is, patients with below primary level education were 17% more likely to have a detectable viral load. However there was no statistical evidence in support of this observation at the 5% level of significance. The nutritional status of patients was found to be highly associated with their virological response to treatment at univariate level. Underweight patients (BMI <18.5 kg/m^2) were 20% more likely to have a detectable viral load compared to patients with a BMI ≥18.5 kg/m^2 [aRR=1.20; 95% CI 0.93-1.36]. However this observation was not statistically significant. Similarly, anaemic patients (Hb <10 g/dL) had a 14% greater risk of having a detectable viral load at 12 months compared to normal patients (Hb ≥10 g/dL), despite a lack of statistical evidence (p=0.181).

Table 3.6: Factors associated with failure to suppress viral load (>400 copies /ml) at 12months into the ART programme.

	Unadjusted Risk ratio (uRR)	[95% CI]	p-Value	Adjusted Risk Ratio (aRR)	[95% CI]	p-Value
Baseline variables	**(++N= 612)**					
Health_facility						
Public	584 (95.4%)	Ref		Ref		
Private	28 (4.6%)	1.59	[1.13-2.26]	0.009†	1.63	[1.15-2.32]	0.007*
Age at initiation						
18-29.9	138 (22.5%)	Ref		Ref		
30-39.9	280 (45.8%)	0.87	[0.72-1.06]	0.159†	0.81	[0.66-0.99]	0.038*
40-49.9	145 (23.7%)	0.90	[0.72-1.12]	0.355	0.85	[0.67-1.07]	0.159
≥50	49 (8.0%)	0.80	[0.59-1.09]	0.166†	0.78	[0.57-1.08]	0.136
Gender						
Female	365 (59.6%)	Ref		Ref		
Male	247 (40.4%)	1.17	[0.71-0.96]	0.84	1.20	[0.68-0.94]	0.008*
Ethnicity						
Black	580 (95.6%)	Ref				
Other	27 (4.4%)	1.14	[0.79-1.63]	0.481	Not included	Not included	Not included
Education						
≥Primary level	348 (73.4%)	Ref		Ref		
<Primary	126 (26.6%)	1.16	[0.69-1.01]	0.068†	1.17	[0.67-1.05]	0.114
WHO_stage						
Stage 1or 2	213 (56.6%)	Ref		Ref		
Stage 3or 4	240 (43.4%)	1.12	[0.96-1.32]	0.155†	1.09	[0.92-1.29]	0.302
CD4 count						
201-350	81 (13.2%)	Ref		Ref		
101-200	204 (33.3%)	0.90	[0.74-1.03]	0.417	0.89	[0.69-1.18]	0.413
<100	327 (53.5%)	1.03	[0.82-1.30]	0.795	0.97	[0.75-1.25]	0.788
Employment						
Employed	307 (50.9%)	Ref			Not included	Not included	Not included
Unemployed	296 (49.1%)	0.92	[0.79-1.07]	0.267			
BMI						
≥18.5	439 (76.9%)	Ref					
<18.5	132 (23.1%)	1.20	[0.93-1.36]	0.227	Not included	Not included	Not included
Haemoglobin						
≥10	464 (75.8%)	Ref			Ref		
<10	148 (24.2%)	1.19	[1.00-1.45]	0.06†	1.14	[0.94-1.38]	0.181

† Variable significant at the 20% level of significance. Risk Ratio of Reference=1 *Variable significant at the 5% level of significance

++Percentages have been derived from valid denominators (i.e. only those for whom there are data for that variable)

3.5.3 Model diagnostics for failure to suppress viral load at 12 months.

The Linktest method was used to assess the model for any specification error, (i.e. availability of irrelevant variables in the model). A non-significant p value (p= 0.152) was obtained confirming that model contained meaningful predictors of failure to suppress viral load. Additional tests were conducted using goodness of fit test. A non-significant p-value (>0.10) of this tests suggests that the model is adequate; whereas a small p-value (< 0.05) suggests otherwise [51]. The model passed the goodness of fit test marginally (p=0.08), suggesting that the non-significant predictors in the model may have been irrelevant with respect to explaining the outcome (failure to suppress viral).

3.6 Immunological responses of patients to ART

Table 3.7 describes the immunological responses of the cohorts to ART at 6 and 12 months of treatment. The immunological responses of patients to ART between the two clinics were generally comparable. At six months of exposure to ART, the median CD4 count change of patients was the same between the two clinics (p=0.58). In both facilities, the median CD4 change at 12 months was significantly lower than the prior median change at 6 months. At health facility level, statistically significant differences in CD4 change were noted in the 6-12 month time interval (p=0.017) as shown in Table 3.7. The immune responses of patients receiving treatment in the private clinic were very diverse as shown by the wide IQR (at 12 months) compared to the public clinic.

Table 3.7: Immunological responses of patients to antiretroviral therapy

Characteristic	**Public N=11690**	**Private N=574**	**p-Value***
CD4 change(cells/µL/): Median (IQR)			
6 months	**Public N=9009**	**Private N=364**	**p-Value**
	103 (52-168)	99 (43-178)	0.584
12 months	**Public N=5598**	**Private N=183**	**p-Value**
	48 (0-101)	68.5 (-2.5-135.5)	**0.017**

*Wilcoxon rank sum test p value for skewed continuous variables

3.7 Sensitivity Analysis Results

As stated in the eligibility criteria, pregnant women were excluded from the study. However, sensitivity analysis was conducted on all the final models of study outcomes to investigate the effect of including pregnant women on inference quantities (i.e. p-values and confidence intervals). The sensitivity analysis results showed that although there were slight differences on the inference quantities, the same conclusions were drawn for the study outcomes when pregnant women were included in the models (Table 3.8.1).

Sensitivity analysis was also performed to investigate the effect of including missing values on the estimates of predictors of failure to suppress viral load. In this study, missing values were excluded from the model. Subsequent models were inclusive of missing values. In model 1, missing values were assigned a viral load of <400 copies/ml of blood. In model 2, they were assigned a viral load of ≥400 copies/ml of blood. In all three models, the direction of the effect was the same. LTFU remained higher in the private clinic as shown in Table 3.8.2.

Table 3.8.1 Sensitivity analysis results for mortality and LTFU

		Excluding pregnant women		Including pregnant Women	
Outcome	Health facility (main exposure)	**Adjusted Hazard Ratio**	**95% CI**	**Adjusted Hazard Ratio**	**95% CI**
Mortality	Public	Ref			
	Private	0.39	[0.14-1.06]	0.50	[0.18-1.37]
LTFU	Public	Ref			
	Private	1.59	[0.94-1.56]	1.24	[0.61-2.52]
Failure to suppress viral load	Public	Ref			
	Private	1.63	[1.15-2.32]	1.66	[1.12-2.48]

Table 3.8.2 Sensitivity analysis results for failure to suppress viral load.

Model	**Health facility (main exposure)**	**Adjusted Hazard Ratio**	**95% CI**
Excluding missing values	Public	Ref	
	Private	1.63	[1.15-2.32]
Including missing values[1]	Public	Ref	
	Private	1.59	[1.12-2.52]
Including missing values[2]	Public	Ref	
	Private	1.16	[1.10-1.21]

[1]missing values defined as viral load <400 copies/ml of blood [2] missing values defined as viral load ≥400 copies/ml of blood

CHAPTER 4: DISCUSSION

4.1. Introduction

This chapter is an overview of the study's findings for each outcome. A detailed outline of factors associated with each outcome follows, starting with the main exposure of the study i.e. type of health facility. The other covariates were grouped into either biological or sociodemographic. Possible explanations of the findings' standing are given relative to existing literature. In addition, the chapter gives an overview of the relevance of the findings in the treatment and management of HIV, while taking cognisance of the study's limitations. The chapter also describes potential areas of research to be pursued as further research from this study.

4.2 Mortality

The overall rate of mortality in the study was 10.7 per 1000 person months. Clinic level mortality rates showed that mortality was higher in the public clinic compared to the private clinic i.e. (3.6 vs. 2.4 per 1000 person months) respectively. Patients enrolled in the private ART programme were 60% less likely to die compared to those in the public ART programme. The risk of death was highest in the first 6 months of ART in both facilities, more so in the public clinic.

4.2.1 Effect of type of health facility on mortality amongst ART patients.

While factors that lead to poor treatment outcomes are often at patient level, some may be health system related. There is limited literature on the comparison of HIV treatment outcomes between the private and public sector. The bulk of the available research has been on treatment outcomes in the public sector. This is mainly due to availability of routine data collected for monitoring and evaluation purposes in public HIV clinics. This is a requirement from the Department of Health[31]. The private sector is not mandated to keep routine data.

The major objective of this study was to assess whether the type of health facility in which patients enrol for treatment has an effect on treatment outcomes and their survival. The data show that the type of health facility in which HIV patients enrol into for ART has an effect on their survival. The study showed that patients initiating treatment in the private clinic were more likely to survive compared to those receiving treatment in the public clinic. Comparable mortality results between the two sectors were recorded by another study[7]. This may be because the private practitioners were operating under South African HIV guidelines and based on centrally managed work place programme hence mortality rates were similar between the public and private ART programmes[7].

In this study, mortality was higher in the public clinic versus the private clinic. This may be because the patients were initiating treatment with early HIV and were healthier (good nutritional status) compared to those in the public clinic. Also, there was possibly a very low risk of death associated with treatment interruptions due to financial constraints. In this study, 85% of the patients were gainfully employed (at baseline) hence they could afford private sector HIV services from their pockets or expenses were covered by company medical aid

schemes. Consequently, they may have had access to tertiary level care and superior drugs compared to their counterparts. The expensive alternative HIV drugs were administered more frequently in the private clinic than in the public clinic i.e. 26% to 7% respectively ($p < 0.001$ Table 3.2).

This finding shows that the private sector provides an opportunity for ART patients to access alternative HIV drugs which may be even superior to existing standard regimens. However, concerns have been raised over issues of non-compliance and poor regulation of prescribing standards in the private sector[9,47]. Drugs that are reserved as second line regimens in the public sector are often used as first line regimens in the private sector. The variations in prescribing practices in the private sector may be determined by relations between pharmaceutical companies and physicians, and not necessarily in the best interests of patients[47].

Given the foregoing, there is urgent need for standardizing HIV care and treatment in both sectors. Public-private partnerships can address issues of non-compliance and lack of standardized care in the private sector. This coalition has also has the potential to address inadequacies of the public sector. For example public-private partnerships can alleviate staff shortages in the public through task shifting. Patients can access drugs from these collaborations to minimize drug shortages in the public sector. In addition, patients may feel more comfortable receiving care in a more 'private' setting compared to public clinics where there are often many other patients.

It is important to acknowledge the fact that the attributes of the private clinic cohort are not always representative of all private sector ART patients. There are concerns of increased risk of death amongst patients due to eventual failure to sustain treatment in the private sector[9]. Initially, patients are generally able to pay for their medication in the early phase of ART but

the cost of drugs can impede continuity of treatment for some patients in the private sector. Also, the employment status was recorded at baseline. Patients may have switched their employment status as the programme continued. As such, mortality rates may be quite different from what was observed in this study.

For both facilities, mortality rates were highest in the first six months of ART initiation. This observation is consistent with available literature, with some authors reporting peaks in the first year of ART[27,28,29]. This emphasizes the need for adequate screening of patients at baseline to identify high risk groups to prevent early mortality, especially in the public sector where majority of patients initiate with advanced HIV.

The overall mortality rate reported in this study was relatively high compared to other studies in the same setting[28,29]. This difference can be attributed to the different study periods. Also, this could be due to ascertainment of death through linkage of Themba Lethu clinic data with the national death registry since 2010. This may have elevated the proportions of ART patients dying, particularly at Themba Lethu clinic where there are properly established linkages to the national death registry[42].

4.2.3 Biological determinants of mortality

A wide range of studies have been conducted on the significance of more proximate biological determinants on survival and treatment outcomes of ART patients. This study found CD4 count, WHO clinical stage 4 of HIV and BMI to significant predictors of mortality upon ART initiation. These findings have also been reported elsewhere[27,29,30,32,33,49]. Patients from the private clinic initiated ART with early stage HIV

(WHO Stage 1 or 2, CD4 count: 201-350 cells/mm^3) compared to public patients who initiated treatment with advanced stage HIV (WHO Stage 3 or 4, CD4 count: <100 cells/mm^3). This could explain why mortality was very high in the public clinic in the first six months of ART initiation. Other studies allude to early mortality due to undiagnosed opportunistic infections, drug related complications as well as Immune Reconstitution Inflammatory Syndrome (IRIS)[30,48].

Significant variations in the nutritional status of patients were noted between the private and public facility. The baseline tests showed that private patients were healthier than their counterparts. BMI and albumin tests were used as proxies for the nutritional status of patients. For example, 23% of public clinic patients were underweight (BMI <18.5 kg/m^2) compared to 8% in the private clinic and this difference was statistically significant ($p < 0.001$). Underweight patients were three times more likely to die compared to normal patients. This probably explains the higher rates of mortality in the public clinic since it had more underweight patients. Malnourished patients may have had a higher risk of death due to deficiency of essential micronutrients[30].

Liver damage (at baseline) was also more common in the public clinic. This could have contributed to the high mortality rate in the public clinic. The potential causes of liver damage may have been existing underlying conditions like hepatitis or HIV disease itself. Alcohol related causes could not be ascertained due to under-reporting in both facilities.

The findings of the study emphasize the need to maintain and enhance voluntary counselling and testing campaigns so that people become aware of their HIV status and initiate treatment early; particularly in the public health sector. For example, initiation criteria will be reviewed to a CD4 count of <500 copies/mm^3[48]. The 'test to treat' hypothesis provides a potentially effective way of managing HIV to the point of elimination in South Africa[49]. However; the

major drawback of this model is that at present the country is not financial capable of implementing it[49].

To complement ART, provision of low cost nutrient supplements must be intensified in the public sector where the majority of patients were malnourished. This may be because most of the patients were unemployed hence did not have the financial means to eat healthy. A follow up study needs to be done to better understand causes of higher liver damage at Themba Lethu compared to the private clinic.

4.2.3 Socio demographic determinants of mortality

A direct relationship between the age of patients and mortality was observed. The data show that the hazards of death increased with an increase in age. The more senior patients (≥50 years) were 2.5 times more likely to die compared to young adults. The same conclusion was drawn elsewhere[36]. Older patients were more likely to have poor treatment outcomes than young adults in the first two years of treatment[36]. The higher risk of death in the older patients is attributed to progressive physiological decline. For example, naturally, older people tend to have lower CD4 counts compared to young people. The risk of death was in keeping with the latter. Patients with a low CD4 count were more likely to die compared to their healthier counterparts. This may also explain the poor immunological response in the older age groups. The successful provision of ART has ensured that HIV patients live longer and age into senior citizens, who may require additional care to improve treatment outcomes (i.e. managing pre-existing conditions like hypertension, diabetes and cancers).

In this study, male patients were 10% more likely to die compared to females. Although, this association was not statistically significant it has serious bearings on the survival of male

HIV patients. Their increased risk of death has been attributed to late treatment seeking behaviour and non-adherence to treatment[30,48]. As a result there is need for programmes that encourage early testing and ART initiation particularly among elderly males. Concerns have been raised over the impact of intergenerational sex on the spread of HIV in South Africa. Elderly males are blamed for infecting young girls mainly during transactional sex[37]. This exacerbates the burden of HIV in the country and has huge financial implications on the sustenance of public HIV programs in the future.

4.3 Loss to follow up

Patient retention on ART was poor in the private clinic. These patients were 63% likely to be lost from the ART programme [Incidence rate ratio: 1.63; 95% CI 1.41-1.87]. The overall LTFU incidence rates were 7.2 vs. 11.7 per 1000 person months in the public and private clinic respectively. LTFU was highest in the first 6 months of ART in the public clinic and declined steadily until the end of the study. In the private clinic, there was a progressive increase in LTFU rates after the first year of ART initiation.

4.3.1. Effect of type of clinic on LTFU amongst ART patients

The study found that ART patient retention was different between the two clinics. Attrition was higher in the private clinic, with rates increasing with ART duration. Research has shown that loss to follow up is very common in the private sector, where HIV patients often have to pay for all HIV related services as well treatment[2,9,12]. In the public clinic, LTFU was generally higher in the first 6 months of ART, stabilizing at 24 months. Similar findings have

been documented[28,36,39]. Possible explanations for attrition in the public sector are unrecorded early deaths or patient transfer-out to other ART programmes.

Despite, the widely documented success of ART in HIV management, the non-retention of patients in ART programmes is one of the challenges faced by physicians and health care providers. Out of all patients that are recruited for treatment, about 40% are lost from ART programs within two years of initiating treatment and they are likely to die within 1 year if they do not access alternative care[38]. This seriously undermines efforts aimed at achieving optimum treatment outcomes in ART programmes. High attrition rates imply that a few of the patients that enrol into an ART program will remain alive and still be on treatment in that program, i.e. an indirect measure of program failure. The private sector must encourage patients to transfer out into public ART programmes in the event that they cannot sustain ART in this sector, an initiative that is feasible if there are private-public partnerships.

It is important to take cognisance of the fact that LTFU rates are often inflated in the private sector due to lack of ascertainment of death of patients with death registries. This may be a result of lack of valid identification numbers. Unlike in the public sector where patients are usually obliged to go to one clinic, patients in the private sector may move to a different doctor for various reasons and it doesn't necessarily mean that they are failing their treatment. This could also explain the high rates of patient loss from the private clinic in this study. In the public sector, intensive efforts are made to follow up on patients before they are confirmed lost from the programme. At Themba Lethu clinic, for example, linkage to death registries is used to determine the final status of patients lost from the program and some end up being retained. Some researchers recommend working closely with the national vital statistics to ascertain death of patients that disappear from ART programs[38]. Such efforts are aimed at addressing attrition, an area which is often overlooked in the private sector. Public ART programmes have established linkages to death registries to improve quality of data for

monitoring and evaluations purposes. However, the cost of locating lost patients is the major setback of such endeavours. This subsequently raises questions of which initiative should receive more funds; recruiting more people into ART or ensuring retention rates are high in these life-long programmes. The ideal is to recruit as many eligible patients onto treatment and ensure they are retained in the program.

4.3.2 Biological determinants of LTFU

In this study, BMI and haemoglobin were the only biological factors which were statistically significant predictors of LTFU. Patients with a normal weight (BMI ≥18.5 kg/m^2) were two times more likely to be lost from the program compared to underweight patients (BMI <18.5 kg/m^2). Those with anaemia (Hb <10 g/dL) were 20% more likely to be lost from the ART program as well. The healthier patients may have been asymptomatic and did not feel sick hence did not see the need for them to remain on the programme. The nutritional status of patients' needs to be given special attention and monitored closely. Abnormal weight loss may be an indication of underlying medical conditions like tuberculosis or HIV wasting. As a result, such patients may be in need of more than ARV drugs. As mentioned earlier, provision of nutritional supplements may lead to better patient retention.

In this study, having a higher CD4 count was associated with being lost to follow up. That is, patients in the advanced stage of HIV (WHO Stage 3 or 4) were more likely to be retained into the program than those in WHO stage 1or 2, despite lack of statistical evidence at the 5% level. This is could be because the latter may not see the need to remain on treatment if they do not have opportunistic infections. On the other hand, those in the advanced stage of treatment will remain on treatment to improve their health status, on condition they do not die

from opportunistic infections. Data from several studies show that patients attrition rates are high in programs with a high number of patients that initiate treatment with low baseline CD4 counts or advanced WHO Stage 3 or 4 [32,40,41]. The major explanation for this is that in these studies, attrition is inclusive of LTFU and mortality.

4.3.3 Socio-demographic predictors of patient retention in ART programs

The study established that males were 17% more likely to be lost from the ART program compared to females. This finding has also been documented elsewhere[48]. The high risk of attrition amongst males may be attributed to poor health seeking behaviour of males or unconfirmed mortality. It has been suggested that the proportion of males that access treatment and remain in ART programs is small compared to females in both developed and developing countries[48]. These findings suggest the need for designing gender based HIV programmes that encourage health seeking behaviour amongst males. For those that have been successfully recruited onto treatment, further counselling and monitoring are required to improve treatment outcomes amongst men.

Age was also found to be a significant predictor of patient retention in this study. Retention rates were significantly associated with an increase in age. In other words, young adults are more likely to be lost from ART programs than older patients. Similar findings were reported by other studies[36,48]. The risk of LTFU increased by 14% in unemployed patients (at baseline) compared to those who were employed. This is consistent with the observation that younger, unemployed patients are likely to be lost from programmes. The adults are likely to

be working and can sustain financial requirements associated with treatment. This trait is particularly important in the private health sector where there is a profound need for financial stability in ART provision. In the public sector, young unemployed adults may be lost due to lack of transport money to ART clinics. However, decentralization of care initiatives seems to be addressing such issues[42]. Also, the older patients may be retained more in ART programmes because they are used to taking life-long medication due to age related chronic conditions like hypertension. Young adults on the other hand may have difficulties adhering to treatment or remaining in the program due to lack of discipline that is required when life-long medication. As a result, there is need for corporate sector involvement in financing programs that are in keeping with latest technology to increase youth retention in ART. For example, mobile network funded programs of reminding patients about treatment schedules.

The dominant ethnic group amongst patients were blacks i.e. >90% in both clinics. The minority groups had a greater risk of being lost from the programme than South Africans. This was expected as some minority groups may be stigmatized or feel ostracized, particularly foreign nationals. Access to health care is often a major challenge especially to minority groups and foreigners[48]. Consequently, there is need to integrate foreign nationals to minimize local transmission.

4.4 Immunological and Virological responses

Statistically significant differences in the median baseline CD4 count of patients was observed between the two clinics. Patients in the private clinic had a higher median baseline CD4 count compared to patients in the private clinic i.e. (171 IQR: 66-249 vs. 91 IQR:33-161, $p < 0.001$). There was no difference in the median CD4 count change between the clinics

at 6 months, only after 1 year of treatment. Virological comparisons showed that baseline viral load was analogous between the health facilities. However, after 12 months of treatment, public clinic patients exhibited better virological responses.

4.4.1 Effect of type of clinic on immunological and virological responses

Different immunological and virological responses were observed for patients receiving treatment in either clinic. Private patients were significantly associated with initiating treatment with high baseline CD4 counts. These patients do not have to wait until they reach the national HIV eligibility criteria; which is a prerequisite in the public sector. The public clinic patients tended to wait until late stage before seeking treatment. This could also explain why being in the private clinic was protective against mortality. However, median CD4 changes at various time points were generally comparable (Table 3.7).

The virological responses of patients were also compared after 12 months of treatment. Private clinic patients were 63% more likely to have a detectable viral load compared to public patients. This could be a result of poor adherence to treatment amongst patients. This is despite the fact that above 70% (1703 missing) patients reported total adherence. The latter may have been subject to bias as it was self-reported in both facilities. As a result, adherence could not be accurately ascertained.

4.4.2 Biological determinants of virological response of ART patients

In this study, the nutritional status of patients was found to be a significant predictor of virological responses. Underweight (BMI <18.5 kg/m^2) patients had a greater risk of failing to reach virological suppression at 12 months (<400 copies/ml of blood). Although there was no statistical evidence for this observation, WHO stage 4 patients were 10% more likely to have a detectable viral load than those in WHO stages 1 or 2. The same findings were documented elsewhere[39,48]. This finding speaks to the need for patients to initiate treatment early to improve treatment outcomes. In addition, there is further emphasis on the need for providing nutrient supplements to patients to improve overall virological outcomes. It has been shown that some micronutrients improve virological response in ART patients[23].

The sex of patients was also found to be a significant predictor of virological response at 12 months. The males were 20% more likely to have a detectable viral load compared to females. This finding was in keeping with reports from other researchers[48]. Evidence has been provided that males generally exhibit poor HIV treatment outcomes than females. This is due to differences in rates of HIV disease progression as well as virological and immunological responses amongst the sexes[43,48]. Consequently, HIV positive males require close monitoring to improve overall treatment outcomes. Males that have sex with other males may require even more attention as they may not access treatment in fear of stigmatization, thereby creating a reservoir of new infections.

4.4.3 Socio demographic predictors of virological response

In this study, virological responses were poor in young patients. That is, a viral load decline with an increase in age was observed, but the observation lacked statistical significance. Similar findings have reported[36]. Good virological response in the elderly patients is possibly attributed to good adherence to treatment relative to young people. Patients with above primary level education had a 17% reduced chance of having a detectable viral load compared to those that were less educated. This implies that during counselling sessions, patients need to be educated on how they must take their medication and the importance of adherence. Educated patients may have exhibited better treatment outcomes because they have better understanding.

4.5 Limitations of the study

The data used during the study was from one public ART clinic and one private ART clinic located in Johannesburg. Neither clinic is fully representative of the sector that they represent. Themba Lethu is a tertiary clinic supported by experts in HIV management. Hence, generally outcomes would be expected to be better than in the average public sector HIV clinic. Similarly the private sector clinic is not representative of the entire private sector clinic. This clinic is a dedicated HIV clinic run by an experienced HIV clinician whereas most patients in the private sector are treated by general practitioners with little HIV experience, treating only a few HIV positive patients amongst all their other patients. Also, treatment prescribing practices are very different in the private sector[71].

Selection bias was one of the major limitations of the study. Systematic differences between patients at baseline were noted as shown in Table 1. It is important to note that statistical

significance in differences may have been a result of absolute differences, that is, a function of large numbers in one category. However, this bias was minimized by conducting multivariate analysis and adjusting for confounders. In addition, HIV management in the developed world is different from limited resource countries. Consequently, generalizability of findings to all settings is limited.

In both clinics, the data are collected to manage patient information and not for empirical research. As a result, the quality of the data may have been compromised. For example, there were a lot of missing data and other important covariates were not available e.g. type of employment and sexual behaviours of patients, alcohol and smoking status. Such information would have shed light on the treatment outcomes of high risk groups like sex workers and homosexual males. Information on treatment adherence was self-reported increasing risks of information bias. Other potential confounders like frequency and length of visits, provider patient relationships were not measured. The employment status of patients was only recorded at baseline. Patients may have switched their employment and subsequent economic status during the course of the ART programme.

The findings of the study also need to be interpreted with caution due to the small sample size of private patients relative to the public patients. A comparable size may have given a better indication of true treatment outcomes. Further research involving several private clinics is recommended to provide more conclusive results.

Loss to follow up may have been overestimated due to lack of ascertainment of death particularly in the private clinic. This may have underestimated mortality in the study. On the other hand; all-cause mortality was estimated instead of HIV-related death. This may have led to misclassification mortality. Lastly, this study was observational. Hence despite

adjusting for potential confounders, the possibility of residual confounding cannot be overlooked.

CHAPTER 5: CONCLUSION & RECOMMENDATIONS

5.1. Introduction

The following conclusion and recommendations are drawn from the discussion in the preceding chapter. This chapter also proposes potential areas of further research emanating from this study.

5.2 Conclusion

Currently, the dominant paradigm towards HIV treatment is centred on a chronic disease management approach. As a result, stakeholders are resorting to initiatives that can sustain this life-long ART programs. The study demonstrates that the type of health facility in which patients access ART has an effect on treatment outcomes. While both the private and public sectors face challenges, they also have desirable attributes that can be optimized for the improvement of treatment outcomes amongst HIV patients.

The private sector is commended for the availability of a wide variety of treatment options for HIV. This may expose patients to possibly superior and efficacious drugs. However, the lack of standardization over prescribing practices can also place patients at risks of poor quality service and unnecessarily high treatment costs. The high cost of health services is the major cause of treatment interruptions and subsequent loss to follow up. As a result, poor treatment outcomes are common in the private sector. The

private sector is encouraged to move from an acute, curative approach towards HIV treatment to a chronic disease care framework.

Better immunological and virological responses were observed in the public clinic. The possible explanation for this is that patients are followed up more in the public sector, there is standardized counselling and treatment. The private sector should seek to be guided by the same approach. However there are concerns of very early mortality in the public sector. This is attributed to late initiation of ART. Most of the public patients were initiating treatment with advanced HIV. As a result, mortality rates were high in the first six months of treatment. Also, the overload to staff may compromise the quality of service that patients get in the public sector.

5.3. Recommendations

- Public-private partnerships

There is need for promotion of public-private partnerships. This will lead to improved standardization of care in HIV management. This initiative will also be in line with re-engineering of primary health care in South Africa, i.e. private sector working with communities to address primary health care associated with HIV. This collaboration will address inequalities in health service delivery between the two sectors and lead to efficient resource utilization in the long run. Currently, the private sector is blamed for wasting health resources and that it only serves a small fraction of the entire population. 46% of health expenditure is said to be spent on medical aid schemes which only serve less than 15% of the population[45]. Public-private partnerships can cater for people across different social strata and have the potential to complement efforts of either

sector. For example stable HIV patients from public clinics can be down referred to private physicians to alleviate overload to staff. Private physicians can also work with nurses to monitor nurse managed ART programmes. This will also reduce concerns of poor regulation of the private sector as the nurse managed ART programmes operate under national HIV guidelines.

- Nutritional supplements in the public sector

The nutritional status of patients at baseline was found to be a significant predictor of treatment outcomes. This finding highlights the need for patient screening at baseline. Malnutrition was common in the public sector, where most of the poorer patients enrol for treatment. Low cost nutritional supplements may be administered to these patients to improve treatment outcomes. Liver damage at baseline was also common in the public clinic. This could be an indication of serious underlying medical conditions that require additional care besides HIV treatment Consequently, screening of patients at baseline is essential for overall improvement of the well-being of patients.

- Reduction of LTFU rates

The study found that young adults were likely to be lost from ART programs compared to the elderly patients. Consequently there is need to invest in targeted LTFU rate reduction strategies. For example the promotion of mobile network supported treatment schedule reminders can improve retention of young people in ART programmes.

As mentioned earlier, public-private partnerships can help alleviate LTFU that originates from high cost of sustaining ART in the private sector. Private patients who can no longer afford treatment can access drugs from these collaborations at government

subsidized rates. Also, stable private patients can be down referred to public-private HIV clinics at minimal costs to the patient.

5.4 Potential areas of further research

As mentioned earlier, it is worthwhile to take cognisance of the fact that neither clinic used in the study is fully representative of the sector it represents. Consequently, the results obtained may not be generalizable to either sector. This study thus provides a step into further research, involving different private clinics to give more conclusive results.

Follow up studies are needed to investigate issues of drug toxicity particularly in the public clinic where liver damage was more common. The cause of higher liver damage (at baseline) in the public clinic could not be established. Alcohol and substance abuse are potential causes but could not be ascertained because they were poorly reported in both facilities. As a result there is need for further investigation.

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5.6 Appendices

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

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Ms Faith Moyo

CLEARANCE CERTIFICATE	**M120863**
PROJECT	Comparison of HIV Treatment Outcomes among Patients Starting Antiretroviral Therapy in a Private or Public Clinic in Johannesburg, South Africa
INVESTIGATORS	Ms Faith Moyo.
DEPARTMENT	School of Public Health
DATE CONSIDERED	31/08/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

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

DATE 28/09/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr C Chasela

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

Faculty of Health Sciences
Medical School, 7 York Road, Parktown, 2193
Fax: (011) 717-2119
Tel: (011) 717-2076

Reference: Ms Salamina Segole
E-mail: salamina.segole@wits.ac.za
21 August 2012
Person No: 569935
PAG

Miss F Moyo
104 Champaigne Castle
Cnr Claim & Jagger, Hillbrow
Johannesburg
2001
South Africa

Dear Miss Moyo

Master of Science in Epidemiology in the field of Biostatistics and Epidemiology: Approval of Title

We have pleasure in advising that your proposal entitled "*Comparison of treatment outcomes of HIV positive patients starting ART in a private or public clinic in Johannesburg, South Africa*" has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

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

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Professor Patrick MacPhail

CLEARANCE CERTIFICATE	M110140
PROJECT	Analysis of Clinical Data Stored on the Therapy Edge HIV Database from HIV Comprehensive Care Clinics Associated with Right to Care (Previously M060626 R14/49 P MacPhail)
INVESTIGATORS	Professor Patrick MacPhail.
DEPARTMENT	Clinical HIV Research Unit
DATE CONSIDERED	27/01/2012
M1101400DECISION OF THE COMMITTEE*	Annual Renewal Approved (January 2012-January 2013)

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

DATE 27/01/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof AP MacPhail

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

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

xM110140

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

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Professor Patrick MacPhail

CLEARANCE CERTIFICATE	**M110140**
PROJECT	Analysis of Clinical Data Stored on the Therapy Edge HIV Database from HIV Comprehensive Care Clinics Associated with Right to Care (Previously M060626 R14/49 P MacPhail)
INVESTIGATORS	Professor Patrick MacPhail.
DEPARTMENT	Clinical HIV Research Unit
DATE CONSIDERED	26/01/2011
DECISION OF THE COMMITTEE*	Renewal approved

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

DATE 26/01/2011 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written "informed consent" attached where applicable
cc: Supervisor : Prof AP MacPhail

DECLARATION OF INVESTIGATOR(S)

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

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 MacPhail

CLEARANCE CERTIFICATE **PROTOCOL NUMBER MO60626**

PROJECT Analysis of Clinical Data stored on the TherapyEdge HIV database from HIV Comprehensive Care Clinics associated with Right to Care

INVESTIGATORS Prof AP MacPhail

DEPARTMENT Clinical HIV Research Unit

DATE CONSIDERED 06.06.30

DECISION OF THE COMMITTEE* Annual Renewal Approved

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

DATE 18/02/2010 **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof AP MacPhail

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Professor Patrick MacPhail

CLEARANCE CERTIFICATE	M110140
PROJECT	Analysis of Clinical Data Stored on the Therapy Edge HIV Database from HIV Comprehensive Care Clinics
Associated with Right to Care	(Previously M060626 R14/49 P MacPhail)
INVESTIGATORS	Professor Patrick MacPhail
DEPARTMENT	Clinical HIV Research Unit
DATE CONSIDERED	30/11/2012
DECISION OF THE COMMITTEE*	Annual Renewal Approved (January 2013 - January 2014)

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

DATE 30/12/2012 CHAIRPERSON .....
(Professor P E Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc Supervisor : Prof AP MacPhail

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.

I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES