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A RESEARCH REPORT SUBMITTED TO THE SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG, IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN MEDICINE FOR THE YEAR 2010

TITLE:

A RURAL-URBAN COMPARISON OF PATIENT CHARACTERISTICS AND HIV TREATMENT OUTCOMES IN SOUTH AFRICA.

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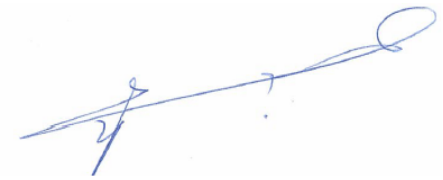
DECLARATION

I, Ekrikpo Udeme declare that this research report work is my own work. It is being submitted for the degree of Master of Science in Medicine in the field of Epidemiology and Biostatistics in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signature.. 

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29th September, 2010

DEDICATION

I dedicate this work to Almighty God who remains faithful to His word through the years and to my mentor Prof Emmanuel Ekanem for believing in me.

ABSTRACT

Background: Few studies have compared the sociodemographic characteristics and treatment outcomes of HIV/AIDS patients in rural and urban South Africa.

Aim: This study compared the baseline socio-demographic characteristics and treatment outcomes (time to mortality, immunologic and virologic response) of HAART-naïve patients in urban and rural South Africa.

Methodology: A secondary analysis of data obtained from the Themba Lethu Clinic, Helen Joseph Hospital, Johannesburg (urban site) and the ACTS clinic, Mpumalanga (rural site) from January 2005 to December 2008 was used to make comparison of baseline socio-demographic and clinical characteristics of patients in both cohorts. The survival experience and predictors of mortality was performed using Kaplan – Meier survival analysis and Cox proportional hazards models while effects on immunologic and virologic responses to HAART were modeled using logistic regression.

Results: At initiation of HAART, the rural cohort had similar CD4 count and body mass index, but lower haemoglobin levels, compared to the urban cohort. The median follow up time for both cohorts was 566 days with the urban cohort having a mortality rate of 5.6/100 person-years compared to the 4.8/100 person-years of the rural cohort. CD4 count, BMI and WHO stage were predictors of mortality in both cohorts. Logistic regression models for virologic and immunologic response did not show any difference by site in the multivariate models.

Conclusion: Though there are differences in the baseline sociodemographic and clinical characteristics of rural and urban patients starting HAART for the first time, achievement of immunologic and virologic response at 6 months of therapy were similar in both cohorts. Continued public health enlightenment campaigns and nutritional support programs should be undertaken to ensure patients present early and benefit from treatment.

ACKNOWLEDGEMENT

My deepest gratitude goes to God for making this aspiration come to fruition through His grace.

My special thanks to my supervisor, Prof. Matthew Fox and co-supervisor Dr Mhairi Maskew for their supervision, expert guidance and support given throughout this research. My sincere appreciation goes to Right to Care for providing data that was used for this research.

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Finally, my special thanks to my parents, my beautiful wife, Edidiong and Inyene my son who endured my absence and labored in prayer for this venture to be successful.

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DEFINITION OF TERMS

1. EARLY MORTALITY: Death occurring within 6 months of commencing highly active retroviral therapy.

2. Highly Active Antiretroviral Therapy: Antiretroviral drug combination consisting of two nucleoside reverse transcriptase inhibitors and one non-nucleoside reverse transcriptase inhibitor or boosted protease inhibitor.

3. Immunologic response: This is defined in this study as an increase of CD4 count, from initiation of HAART, of at least 50 cells/µl, within 6 months of therapy.

4. Virologic response: A reduction in viral load to undetectable levels (<400 copies/ml) at 6 months after HAART initiation.

LIST OF ACRONYMS AND ABBREVIATIONS

ABL – Advanced Biological Laboratories

ACTS – AIDS Care Training and Support

ALP – Alkaline phosphate

ALT – Alanine transaminase

AST – Aspartate transaminase

AIDS – Acquired Immune Deficiency Syndrome

ARVs – Antiretrovirals

BMI – Body Mass Index

CD4 – Cluster Designation 4

HAART – Highly Active Antiretroviral Therapy

HIV – Human Immunodeficiency Virus

HIV RNA – HIV Ribonucleic Acid

ROC – Receiver Operator Characteristic curve

TB/HIV – Tuberculosis/HIV co-infection

TLC – Themba Lethu Clinic

VCT – Voluntary Counseling and Testing

WHO – World Health Organization

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CHAPTER ONE: INTRODUCTION AND LITERATURE REVIEW

INTRODUCTION

1.1 BACKGROUND

The Human Immunodeficiency Virus (HIV) has created a formidable opposition to the achievement of health for all globally. Sub-Saharan Africa has been most affected – as at end of 2007, about 22 million people were living with HIV. There is an estimated 1.9 million new infections annually and about 1.5 million deaths (1).

South Africa has the largest number of people living with HIV in the world with an estimated 5.7 million people living with HIV in the country at the end of 2007, including 3.2 million women. The adult (15 – 49 years) HIV prevalence is 18.1% and HIV accounted for 350,000 deaths in 2007 only (1). Among antenatal care attendees the HIV prevalence is believed to be reducing (2). The national antenatal prevalence of 28.0% recorded in 2007 was a 1.1% reduction from the 2006 figure (2).

The South African government decided to provide public access to HIV treatment in November 2003 and 85,000 people were on treatment in the public sector as at September 2005 (3) . At the end of 2007, the World Health Organization (WHO) estimated 460,000 South Africans were on antiretroviral (ARV) treatment, 28% of those in need of treatment in South Africa(1).

In addition to the issue of health care personnel in rural areas, the distance of the health centres from the homes of the rural dwellers may be a deterrent to regular follow up visits. Information about HIV/AIDS may also be more limited in the rural areas thereby creating a

state of ignorance about the disease and encouraging its spread. Differences may also exist in the demographic, educational and economic characteristics of those in the rural and urban areas which may have an effect on the prevalence, rate of spread and outcome of treatment of HIV/AIDS patients.

Antiretroviral therapy is now established in urban and rural South Africa but rural-urban differences in treatment outcomes have not been adequately studied. As access to antiretroviral therapy in the rural areas is being enhanced, it is important to determine if the rural patients are faring as well as those receiving treatment in the urban centres.

If differences in treatment outcomes exist between these groups of patients, then it would be important to identify the characteristics responsible for this difference with the aim to modify these factors to ensure better treatment outcome.

1.2 PROBLEM STATEMENT

Sentinel surveillance has shown a steady increase in the HIV prevalence among pregnant women outside major urban areas in South Africa (1). It has been shown that death is a major reason for cohort exit in rural South African HIV patients on treatment (4). What we do not know is whether the mortality rates in these rural cohorts are the same as that obtained among the urban cohorts and what could account for such difference. There also has not been an extensive documentation of the differences that exist between rural and urban cohorts in South Africa, especially at the initiation of HAART.

1.3 JUSTIFICATION FOR THE STUDY

Prevalence studies have been done in rural areas which have shown increasing prevalence of HIV/AIDS over the years (4, 5). There is little evidence indicating a difference in the treatment outcomes of HIV infected individuals in rural areas in South Africa compared to those in the urban areas. If the outcome of highly active antiretroviral therapy (HAART) is different in rural areas from that obtained from the urban areas (10), it would be important to identify the factors behind these differences and institute intervention programmes so as to ensure better HIV/AIDS treatment outcomes in South Africa.

There is also the possibility that a difference in treatment outcome may arise from differences in baseline characteristics of the patients in the rural and urban areas. Such baseline characteristics may be the focus of an intervention program that will enhance treatment outcome.

The findings of the study could help in planning more effective health service delivery to the HIV/AIDS patients in both urban and rural areas. Comparing the characteristics and treatment outcomes of the rural cohort with those in the urban centres would also potentially help inform policy makers of methods to optimize results in antiretroviral therapy and care for people with people with HIV/AIDS in all parts of South Africa.

1.4 LITERATURE REVIEW

The HIV epidemic in South Africa was initially believed to be more pronounced in the urban areas in sub-Saharan Africa compared with rural areas but recently, studies in the Kwa-ZuluNatal province of South Africa have demonstrated a rising prevalence of HIV/AIDS in rural communities.

The changes in HIV prevalence in urban and rural South Africa

The prevalence of HIV infection in women attending ante natal clinic in Hlabisa, Kwa-Zulu/Natal was noted to have significantly increased from 4.2% (95%CI, 3.0 - 5.7) in 1992 to 7.9% (95%CI, 6.0 – 10.1) in 1993 and further to 14.0% (95%CI, 10.4 – 18.4) in 1995. At this time (1995), the seroprevalence in Durban antenatal clinics was estimated at 19% (95%CI, 16.5 to 21.7) (5). Though the prevalence remained higher in the urban area, the rate of rise in the rural area has been a reason for concern. By 1997, the antenatal HIV seroprevalence in rural Hlabisa had risen to 26% with the highest prevalence occurring in women aged 20-24 years (6). Frohlich et al noted that HIV prevalence among ANC attendees increased from 26% (2001) and, 34% (2002) to 41% in (2003) in rural KwaZulu Natal (7). This finding may not be generalized to other parts of South Africa.

Rural-urban migration has been implicated as one of the reasons for the increasing prevalence in rural areas. This was shown in a study in Carletonville, South Africa where the HIV prevalence among migrant women was significantly higher than non-migrant women; 46% vs. 34.7% (odds ratio 1.61, 95%CI of 1.11 – 2.3) (8). Also settlements that have a highly mobile population may

also be at increased risk of higher prevalence of HIV infection. This point is emphasized by a study in Tanzania which showed a two fold increase of HIV prevalence in a trading centre compared to an area 2 Km from the trading centre. It was shown that there was greater population mobility in those living in the trading centre than those inhabiting the villages only 2 Km away from it (9).

Others have suggested that differences in rural-urban HIV estimates may be because of the differences of the perceptions of health needs among these two groups. Work done in KwaZulu Natal suggests that knowledge about HIV/AIDS was relatively low and HIV and other sexually transmitted diseases were not perceived as a health priority among those in the rural areas (10).

Sociodemographic, clinical and psychosocial differences between rural and urban HIV patients

The difference between the rural and urban HIV populations is not limited to prevalence but may also include differences in sociodemographic characteristics. In a study of HIV patients in New England, it was shown that individuals with HIV in rural areas were older; the rural men were more likely to have sex with other men and had longer travelling time to their HIV care centre than individuals in urban areas (11). Though the rates of intravenous drug abuse and CD4 counts were the same at the onset of treatment, the mortality rate of individuals in the rural group was higher than that in the urban group (12). A similar study in the United States showed proportionately more males being infected in the urban areas than the rural area (13).

These differences may also be psychosocial in nature. Heckman et al documented a significantly lower social and family well being in rural HIV patients in the USA (12). These rural patients also had more medical and psychological barriers preventing them from accessing treatment. They had greater fear of community stigma and less support from family and friends. The fear of discovery was also higher in patients in the rural area. There was no difference in the rate of denial in the two groups. Rural persons with HIV disease were noted to have longer distances to travel to access medical care, shortage of facilities and trained medical personnel in the hospitals they used, a lack of personal and public transportation and community residents' stigma toward people living with HIV (13).

Stigma has become a major problem in the provision of care for HIV/AIDS patients in Africa (14) and urban – rural differences exist in the magnitude of effect stigmatization has on the need to seek for care and remain adherent to HAART with rural dwellers experiencing less of the ill effects of stigma because of the communal lifestyle they have (15).

There is little data on the geographical differences in the characteristics of HIV patients in South Africa. One of the few available studies compared the characteristics of patients on pre – ART care and on HAART for less than 6 months in 3 centres – one urban (the Helen Joseph Hospital in Gauteng); one semi-urban (Witkoppen health and welfare centre) and one rural centre (ACTS clinic at Mpumalanga) (16).

This study showed a higher mean age at commencement of ARV in the rural area than the urban area. Also, the mean CD4 count at initiation of treatment was significantly lower in the rural area than urban centre. The educational status difference mirrored what is expected in

the rural-urban divide – the urban dwellers were generally better educated than the rural dwellers. There were significantly more women than men on ARV treatment in the rural cohort. Only 13% of those in the rural area had a formal sector job compared to 27% of those in the urban area. Those in the rural area were more unlikely to disclose their HIV status to their partners (16). The emotional support given to these patients by their partners could encourage adherence to therapy and therefore better treatment outcomes.

The relatively easier availability of health personnel and infrastructure in the urban areas indicate that there is better access to HAART in the urban than the rural centres (17). This could lead to worse treatment outcomes among the rural patients who are more likely to report late when complications of the disease have set in.

Risk factors for mortality

Several studies have identified predictors of poor outcome in varying patient cohorts. These factors range from sociodemographic characteristics to clinical factors present at or before initiation of HAART or occurring during the course of treatment.

A South African study showed pulmonary tuberculosis and diarrhoeal disease to be common causes of mortality in HIV/AIDS patients living in rural South Africa (4). Late access to ARV program and subsequent advanced immunodeficiency (18), wasting syndrome, malignancy, acute bacterial infections and immune reconstitution syndrome (19) have been found to risk factors for early mortality among HIV patients in South Africa.

Anaemia, thrombocytopenia and severe malnutrition have been shown to be independent predictors of mortality in rural cohorts of HAART naïve patients in rural Tanzania (20). HIV infected patients with low BMI on commencement of HAART, clinical stage IV disease and commencement of HAART with a stavudine-based therapy were associated with significantly lower increases of CD4 count after 6 months of therapy (21). The patients' age at initiation of therapy, WHO clinical stage IV, a higher baseline HIV RNA, a body mass index less than or equal to 21 Kg/m^2, low socioeconomic status and erythrocyte sedimentation rate greater than or equal to 60mm/hr have been found to be predictors of mortality (22, 23).

Anaemia has been determined to be an independent predictor of mortality in HIV patients on HAART (24). Some are now arguing that this finding may not only be related to a reduced oxygen carrying capacity due to a low haemoglobin level but may also be associated with increased iron stores that occur when anaemia is present and genetic differences in the iron storage and iron carriage protein genes (25-27). Elevated transferrin, ferritin and a combined iron status index have been shown to be associated with increased risk of mortality (26). Anemia can also be a feature of opportunistic infections like Mycobacterial and parvovirus infections (20). Other mechanisms for anemia in HIV patients include impaired erythropoietin production in HIV associated nephropathy, micronutrient deficiencies, immunologic myelosuppression and chronic blood loss from intestinal helminthes (20).

The nutritional status of patients also plays a significant role in predicting mortality in HIV patients. Body mass index (BMI) is used as a proxy for measuring nutritional status. Moderate to severe malnutrition (body mass index less than 17Kg/m^2) has been found to be an

independent predictor of mortality (28) and there may be up to a six-fold increase in the risk of mortality among HIV patients with moderate to severe malnutrition compared to those with normal BMI (29).

Immunologic response

Immunologic response during HAART has been defined in various studies as an increase in CD4 count of at least 50 cells/μL from baseline values after six months of HAART (30), attainment of CD4 cell count of greater than 200 X 10^6 /L in those who had counts less than 200 X 10^6 /L before commencement of HAART (31) and the achievement of at least 20% increase in the CD4 count in those who had greater than 200 X 10^6 /L at commencement of HAART (31).

Sustained immunologic response following use of HAART is regarded by most as a useful marker of good response to use of antiretrovirals. Studies have attempted to elucidate the factors that determine HIV patients that would achieve immunologic response. Baseline CD4 count, baseline plasma HIV RNA level, use of protease inhibitors and WHO clinical stage at commencement of HAART have been noted as predictors of immunologic response (32, 33). Other immunological markers like the early CD8+ cell increase may be an indicator of sustained immunologic response in some HIV cohorts (34).

An initial immunologic response may be followed by decline in CD4+ cell counts later in the course of treatment. The risk of immunologic failure following an initial immunologic response may be associated with the baseline CD4 count, ongoing viral replication (usually a manifestation of resistance to HAART), and intravenous drug use (35). A complex relationship

exists between viral replication and CD4 count changes and it is possible to have a discordant immunologic and virologic response (36-38).

Virologic response

The attainment of an undetectable viral load within 4 – 6 months of HAART (39, 40) defines virologic response to therapy. Virologic response at six months is usually the norm in the absence of resistance to HAART.

The number of baseline reverse transcriptase inhibitors plus protease inhibitor – resistance mutations may predict virologic response in advanced HIV disease (41). Also, virologic rebound after an initial virologic response has been associated with low adherence to therapy, previous use of an antiretroviral drug before the commencement of a protease inhibitor based triple regimen, younger age at initiation of HAART and a higher baseline viral load level (42). Differences in the viral load at initiation of HAART and resistance patterns between the rural and urban patients may also be responsible for differences in treatment outcomes.

Outcome differentia in rural and urban HIV patients

Differences in urban and rural HIV patients in resource limited countries may be similar to differences documented between resource poor and developed countries. A large study comparing baseline characteristics and treatment outcome of HAART-naïve patients in resource poor and resource rich countries has shown that the low income countries have a lower median CD4 count at initiation of HAART, a greater proportion of females, with equal CD4 count

increases and equal HIV RNA reduction; mortality was nevertheless found to be significantly higher among those in the low income countries than the high income regions (43).

The studies discussed above have shown that there usually exists a difference in the baseline sociodemographic characteristics of HIV patients in urban and rural centres which may impact on the treatment outcomes of the patients. It is therefore important to investigate these differences in the urban and rural cohort of patients and proceed to investigate if differences exist in their treatment outcomes.

1.5 AIM OF THE STUDY:

To compare the sociodemographic and clinical characteristics of patients commenced on HAART in the rural and urban areas of South Africa and assess differences in the treatment outcomes (mortality, immunologic and virologic response) in these areas.

1.6 OBJECTIVES

1. To compare the baseline sociodemographic and clinical characteristics of HIV patients initiated on HAART in urban and rural areas from January 2005 to December 2008.
2. To compare the treatment outcomes (mortality, immunologic and virologic response) of HIV infected patients receiving HAART in rural and urban South Africa from January 2005 to December 2008.

CHAPTER TWO: METHODOLOGY

This study is a secondary analysis of data obtained during initiation of treatment and follow up of HIV patients receiving treatment at the Themba Lethu clinic, Helen Joseph Hospital, Johannesburg and the AIDS Care Training and Support (ACTS) Clinic at the Masoyi tribal area, Mpumalanga.

2.1 Study Population

The urban centre is located in Johannesburg, the large cosmopolitan city in Gauteng province of South Africa. The rural centre is at the foot of the Legogote mountains in the Masoyi tribal area of Mpumalanga province of South Africa.

FIG 1: MAP SHOWING JOHANNESBURG AND THE MPUMALANGA PROVINCE WHERE THE RURAL SITE IS LOCATED. (COURTESY GOOGLE MAPS)

The urban centre is at the Themba Lethu clinic, a comprehensive Care Management and treatment facility based in Helen Joseph Hospital in Johannesburg. It has a large patient base serving almost 20,000 HIV patients. Individuals who are HIV positive and meet the criteria for commencement of HAART are given two weeks of adherence counseling before treatment is commenced. At enrollment, important socio-demographic and clinical data is collected from the patient. The socio-demographic data includes age, gender, occupation, tobacco smoking and alcohol history. The clinical data includes history of tuberculosis, HIV related opportunistic infections and non-HIV related conditions. Others are patients' vital signs and anthropometric measures (weight and height for BMI computation). If female, pregnancy status is ascertained.

Follow up medical visits are done four months after commencement of HAART and 6 monthly thereafter. In each follow up visit, clinical data is obtained from the patient to assess for response to therapy. A CD4 count and viral load is done and patients' adherence to therapy is assessed. When indicated, patients deemed to be doing poorly are given more frequent follow up visits to enhance success of therapy.

The study population from the rural area constitutes all patients seen at the AIDS Care Training and Support Clinic (ACTS) located at the Masoyi tribal area of Mpumalanga from January 2005 to December 2008. The Masoyi tribal area has a population of 250,000 and the centre provides high quality HIV treatment and support for those infected and affected by the virus. About 1,000 patients are seen monthly in the outpatient clinics and training of community care givers is also undertaken to care for AIDS patients at home (44).

Patients who visit the ACTS clinic usually would have voluntary counselling and testing (VCT). Individuals who test negative are counseled on adoption of a lifestyle that will ensure they stay negative. A case file is opened for individuals that test positive and have a positive confirmatory test. They then begin adherence and counseling clinic visits. At the second adherence visit, the counselor establishes if the patient has accepted his/her HIV status and is psychologically ready for HAART, if other indications for commencement of HAART are present. The adverse side effects and benefits of the use of antiretroviral therapy is discussed and the patient's CD4 count, viral load and other baseline tests including liver function and renal function tests performed. The importance of adherence to therapy is emphasized.

Patient follow up is initially at 2 weeks after commencement of HAART, thereafter, if no complications occur, follow up is done every 3 months. At both sites, the patient can visit the clinic at any time in between follow up periods if any adverse health event occurs.

The rural clinic also has strong support groups, where individuals commenced on HAART are encouraged to join one of the groups. The groups are formed along age group lines and have meeting time tables (see Appendix A). The caregivers in this centre believe these support groups are the key to maintaining a high level of patient adherence to therapy and curbing loss to follow up.

Both sites use Therapy edge™ to capture patients' data from initiation of therapy to all the follow up visits. Therapy edge™, developed by Therapyedge Inc USA and marketed by Advanced Biological Laboratories, is a web based decision support system for the treatment of HIV. It

graphically tracks and processes patient clinical information and helps the clinician in making decisions about patient care.

2.2 STUDY DESIGN FOR SECONDARY DATA ANALYSIS

This is a retrospective cohort study. Using data collected over a period of four years (January 2005 – December 2008) in these HIV treatment sites, comparison of HIV treatment outcomes was performed for these two sites.

STUDY OUTCOMES

Three treatment outcomes were defined for this study, since any single outcome is not sufficient in itself to be used as a solitary measure of HIV treatment outcome.

The outcomes measured include immunologic response, virologic response and time to mortality.

- **Immunologic response:** This is defined in this study as an increase of CD4 count, from initiation of HAART, of at least 50 cells/µl, by 6 months of therapy (30).
- **Virologic response**: A reduction in viral load to undetectable levels (<400 copies/ml) by 6 months after HAART initiation (39).
- **Mortality** – Confirmed death as documented on the database of the study sites in the period of study.

2.3 Study variables

Other variables extracted from the databases included:

- **Socio-demographic data:** Age at initiation of treatment (years); gender (male, female); educational level (years of formal education); history of tobacco and/or alcohol use, ethnicity (black or non-black), employment status (employed or unemployed).

- **Clinical data:** CD4 count at commencement of therapy (number of cells/µL) and on follow up visits; viral load (copies/µL) on follow up visits; liver function tests; complete blood count; presence and type(s) of AIDS defining illnesses, nutritional status at commencement of therapy (measured using body mass index, BMI and serum albumin levels as proxy measures); presence of associated tuberculosis; initial HAART regimen the patient was commenced on; WHO stage of disease at the time of commencement of therapy.

The laboratory tests were performed at initiation of therapy and at six month intervals at the urban centre if the patient is responding well to treatment. For patients with adverse effects of HAART or with complications of the disease, follow up is done at shorter intervals.

Inclusion Criteria: All HIV positive adults aged 18 years and above commenced on ARV treatment in the study sites for the period January 2005 to December 2008.

Exclusion Criteria:

- All patients on pre-ARV care.
- All those who had received antiretroviral drugs prior to enrollment at the clinics.
- All pregnant women at initiation of therapy because the increased blood volume during pregnancy tend to cause an underestimation of the CD4 count and viral load. After pregnancy, there is usually a sharp rise in the viral load. These fluctuations in the parameters used to assess outcome may affect my result, hence the exclusion of these subset of patients. Also, during pregnancy, the combination of antiretroviral drugs used changes.

2.4 DATA ANALYSIS

Data for all eligible patients were extracted from TherapyEdge-HIV™, a patient management and clinical decision support system developed by Advanced Biological Laboratories (ABL) and converted to .dta format for analysis using STATA.

All analysis was done using STATA 10 statistical software (Stata Corp, Texas, USA). During data cleaning, duplicate entries were identified and removed. All individuals who were pregnant (93 patients) or had used any combination of antiretroviral drugs (1038 patients) before presentation at these clinics were excluded. The frequency and proportion of missing values for each variable was examined. For each of the numeric variables, data entry errors were assessed for using the 'summarize' command in STATA and graphical display to locate outliers and

exclude those that were not biologically possible. All individuals with CD4 count at baseline greater than 550 cells/ µl were excluded from the study. These potentially corresponded to individuals who were not HAART-naïve.

The datasets containing sociodemographic variables was merged with that containing the clinical variables for the two sites. Data from the rural site was appended to the urban site dataset to produce a single master dataset used for the analysis.

A binary outcome was defined for mortality and time to death was determined from the initiation of HAART to the earliest of death, loss to follow up or end of the follow up period. For the purpose of modeling immune response, a new variable 'immunres' was created and coded "1" for those who were able to achieve at least 50 cells/ µl increase in their CD4 count at 6 months of therapy and "0" for those who did not achieve this CD4 increase.

To model virologic response, a new variable 'vires' was created and coded "1" for those that had a viral load level of < 400 copies/ml at 6 months of therapy and "0" for those who did not achieve this level of reduction in their viral load levels.

The baseline sociodemographic and clinical characteristics of the two cohorts were compared. For the numeric (continuous) variables – age, CD4 count at baseline, viral load at baseline, years of formal education, body mass index – the Wilcoxon rank sum test was used to test the equality of the median values of these variables in the two cohorts since these variables were not normally distributed. Normality was assessed both graphically (using box and whisker plots and histogram plots) and statistically (using the Shapiro-Wilk test).

The liver function tests, renal function tests and haemoglobin levels were categorized into normal and elevated (or deficient) categories and the Chi square was applied to test for association between the treatment site and these categorical variables.

To compare the survival experience of both cohorts, Kaplan – Meier curves for both cohorts by gender were created and the equality of both curves tested using the log-rank test. Two Cox proportional hazard models were used to elucidate factors that predict mortality and to adjust for other factors that may have an effect on mortality. A direct comparison of the mortality rates in both cohorts was avoided because of the risk of mortality-ascertaining bias caused by the lack of updating of the rural mortality with the South African mortality database. Instead a comparison of the predictors of mortality was done.

In building the multivariate model, variables are included singly into the model containing gender as the only predictor. All variables that change the point estimate of 'gender' on the outcome by at least 10% were retained in the model. This is continued till all the important variables are in the model. Interaction terms were then included into the model to assess for statistical interaction. An interaction term was deemed important in the model if the P – value of its Wald statistic was <0.05. The assumption of proportional hazards was then checked and if violated, time varying covariates were investigated and included into the model to obtain the final model.

Logistic regression models were used to model both immunologic response and virologic response. Univariate analysis was first performed and crude odds ratios for the association of these variables with immunologic and virologic responses noted. Multivariate models were

built and interaction issues assessed for. The assumption of linearity in the logit scale was also assessed and the Hosmer – Lemeshow goodness of fit test was used for model diagnostics. Also the sensitivity of the model was obtained and a receiver operator characteristic (ROC) curve for each of the logistic regression models was plotted so as to calculate the area under the curve and assess the functionality of the model.

2.5 ETHICAL CONSIDERATIONS

Ethical clearance was obtained from the University of Witwatersrand Committee for Research on Human Subjects (medical) for permission to carry out this study (Protocol number M090943, approved 02/10/2009), Appendix B. The Clinical HIV Research Unit of the Themba Lethu Clinic at the Helen Joseph Hospital also granted approval for the use of the primary datasets (Appendix C1 and C2).

The dataset was anonymized before I had access to it and there was no contact between the patients and myself.

CHAPTER 3: RESULTS

3.1 DESCRIPTIVE ANALYSIS

A total of 10,451 observations were included in the analysis. 1992 (19.1%) were from the rural site while 8459 (80.9%) received treatment in the urban centre. Table 1 gives a description and comparison of the baseline socio-demographic characteristics of the cohorts.

TABLE 1: DESCRIPTION AND COMPARISON OF BASELINE SOCIO-DEMOGRAPIC CHARACTERISTICS*

SOCIODEMOGRAPHIC FACTORS	URBAN (N=8459)	RURAL (N=1992)	RELATIVE RISK (95% CI)
Age at initiation of HAART [year; median (IQR)] N	37.1 (31 – 42.2) 8459	38.3 (31.1 – 43.6) 1992	µ
Female gender n/N (%)	5351/8459 (63.3)	1252/1992 (62.9)	1 (0.98 – 1.02)
Black ethnicity n/N (%)	8088/8459 (95.6)	1728/1992 (86.8)	2.47 (2.27 – 2.68)
Employed n/N (%)	3793/8307 (45.7)	342/1778 (19.2)	1.21 (1.19 – 1.23)
Smoking history n/N (%)			
Current smoker	886/8067 (11.0)	118/1769 (6.7)	1.09 (1.06 – 1.12)
Prior history	459/8067 (5.7)	55/1769 (3.1)	1.10 (1.07 – 1.14)
Never smoked	6722/8067 (83.3)	1596/1769 (90.2)	1
Alcohol Use n/N (%)			
current user	944/8086 (11.7)	128/1766 (7.3)	1.09 (1.07 – 1.12)
Prior history	744/8086 (9.2)	55/1766 (3.1)	1.08 (1.05 – 1.11)
Never used	6398/8086 (79.1)	1596/1766 (90.2)	1
Years of formal education n/N (%)			
≥ 6 years	7030/8111 (86.7)	515/960 (53.7)	1.32 (1.27 – 1.36)

*the categorical variables were compared using the Chi-square while the Wilcoxon rank sum test was used to compare the medians of the numeric variables.

μ = P-values <0.05.

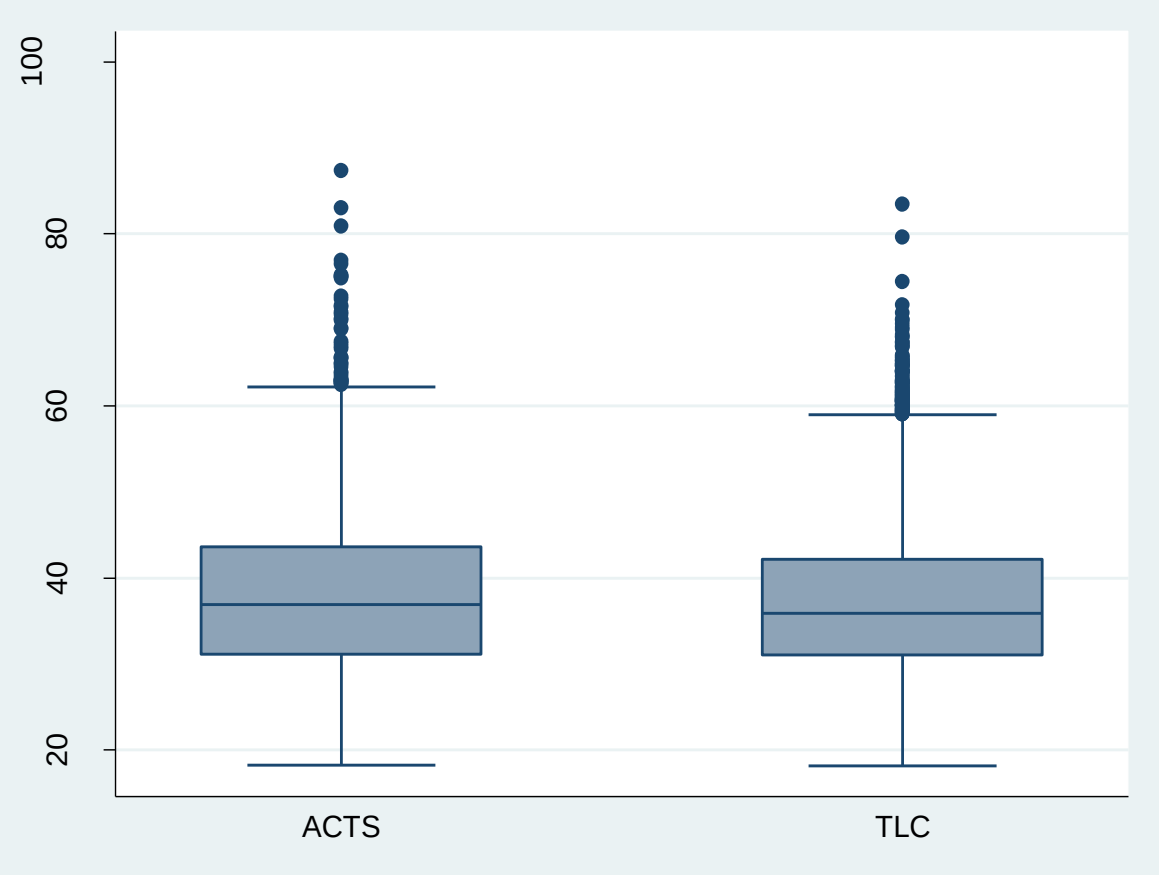

FIGURE 2: BOX AND WHISKER PLOTS COMPARING THE AGE DISTRIBUTION OF TREATMENT COHORTS

The patients from the rural site have a higher proportion of non-black patients than those in the urban site. The sex distribution was similar across the sites. A greater proportion of the urban patients were employed, smoking tobacco actively and taking alcohol regularly. There was 32% increased likelihood for a patient in the urban cohort to have at least six years of formal education (95% CI, 1.27 – 1.36). Figures 2 and 3 compare graphically, the age and gender distribution of both cohorts.

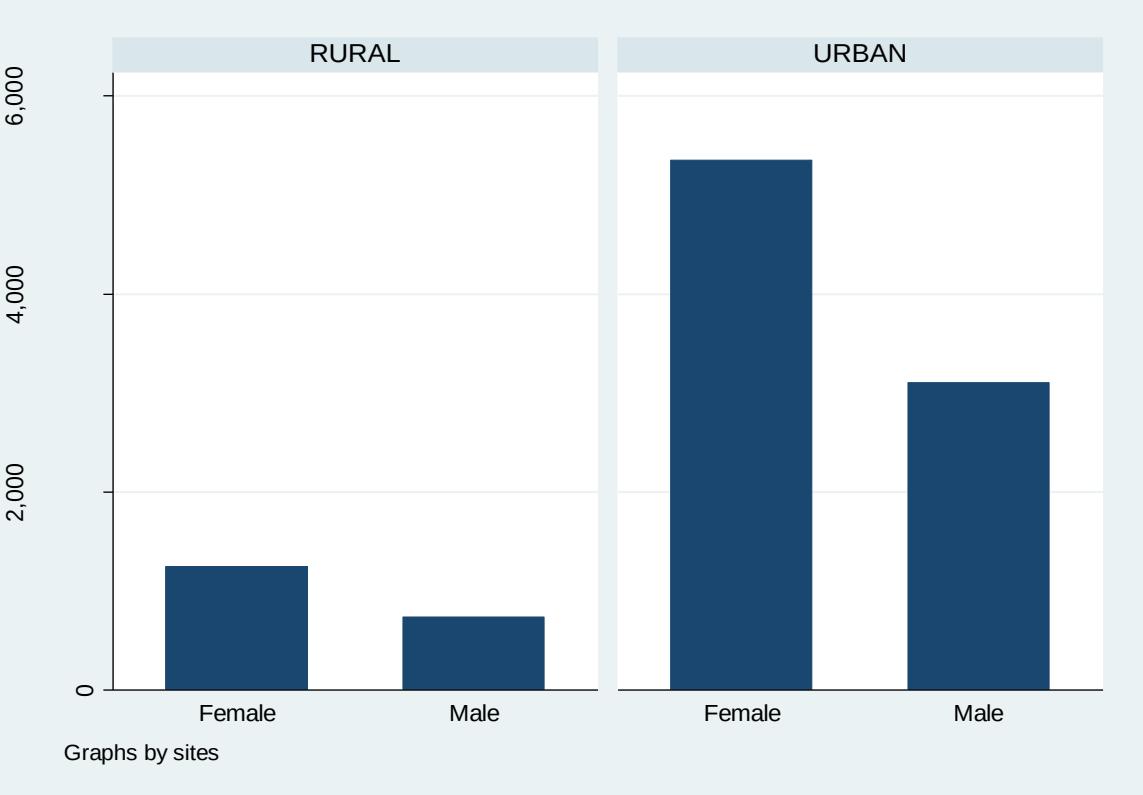

FIGURE 3: BAR CHART SHOWING THE SEX DISTRIBUTION BY TREATMENT SITE

Table 2 compares the baseline clinical characteristics of the patients in both sites.

The urban cohort had higher median CD4 counts but a lower proportion (83.0% vs. 88.8%) was commenced on the stavudine – lamivudine – efavirenz combination as first line therapy instead of the stavudine – lamivudine – nevirapine comination. The urban cohort also had a higher proportion of patients with early stages of HIV disease and lesser proportion with anaemia.

TABLE 2: COMPARISON OF BASELINE CLINICAL CHARACTERISTICS

CLINICAL CHARACTERISTIC	URBAN (N = 8451)	RURAL (N = 1992)	RELATIVE RISK (95% CI)
Baseline CD4 count [cells/UL; median (IQR)]N	89 (32 – 158) 8451	78 (25 – 159) 1992	μ
Initial regimen n/N (%)			
d4T/3TC/EFV*	6897/8299 (83.0)	1703 (88.8)	1
d4T/3TC/NVP**	553/8299 (6.6)	61 (3.1)	1.12 (1.09 – 1.15)
Others	977/8299 (10.4)	220 (9.1)	1.02 (0.99 – 1.05)
Baseline BMI [kg/m2; median (IQR)] N	21.5 (19 – 24.7) 7304	20.3 (18 – 23.7) 1237	μ
TB at initiation of HAART	1285 (15.2) 8451	282 (14.2) 1992	1.02 (0.99 – 1.04)
WHO stage n/N (%)			
I	4451/8451 (52.67)	979/1992 (49.15)	1
II	147/8451 (1.74)	26/1992 (1.31)	1.07 (0.97 – 1.11)
III	3081/8451 (36.42)	761/1992 (38.20)	0.98 (0.96 – 0.99)
IV	780/8451 (9.22)	226/1992 (11.35)	0.95 (0.91 – 0.98)
Anaemia n/N (%)	2026/7766 (26.1)	693/1574 (44)	<0.001

*stavudine-lamivudine-efavirenz combination. **stavudine-lamivudine-nevirapine combination

μ = P-values <0.05. These were statistically significant because of the large sample size but with no clinically significant difference.

Anaemia was defined as haemoglobin of less than 10g/dl. The proportion of TB cases at initiation of HAART for both cohorts was similar.

3.2 COMPARISON OF THE SURVIVAL EXPERIENCE OF BOTH COHORTS

1009 patients died in both cohorts during the period of study, putting the average mortality risk during the period of follow up at 9.65%. 141 (7.1%) died among the rural cohort while 868 (10.3%) died among the urban patients throughout the follow up period. 592 people, overall, died within 6 months of commencing HAART. This constitutes 58.7% of the total number of people that died during the 4 years of the study period. This means more than half of the deaths experienced after HAART commencement occur within the first 6 months of commencing HAART.

The median follow up time for the study was 566 days. The mortality rate was 4.8 per 100 person-years for the rural cohort and 5.6 per 100 person-years for the urban cohort. An investigation into the incidence rates in the two cohorts for specific periods during follow up was done and this is represented in table 3 below.

TABLE 3: MORTALITY RATES FOR SPECIFIC PERIODS FOR BOTH COHORTS

PERIOD	**URBAN**		**RURAL**	
	NO. OF DEATHS	**MORTALITY RATE PER 100 PERSON-YEARS (95% CONFIDENCE INTERVAL)**	**NO. OF DEATHS**	**MORTALITY RATE PER 100 PERSON-YEARS (95% CONFIDENCE INTERVAL)**
0 – 6 MONTHS	496	12.6 (11.5 – 13.8)	95	10.3 (8.5 – 12.7)
6 – 12 MONTHS	174	5.6 (4.8 – 6.5)	27	4.0 (2.7 – 5.8)
12 – 24 MONTHS	125	2.8 (2.3 – 3.3)	14	1.7 (1.0 – 2.9)
24 MONTHS +	69	1.7 (1.4 – 2.2)	5	1.0 (0.4 – 2.5)

In all the specific time periods, the mortality rate appeared to be higher in the urban cohort than the rural cohort. It is also observed that the highest rates of mortality were recorded in the first six months after commencing HAART and the mortality rates were reducing progressively with time in both cohorts.

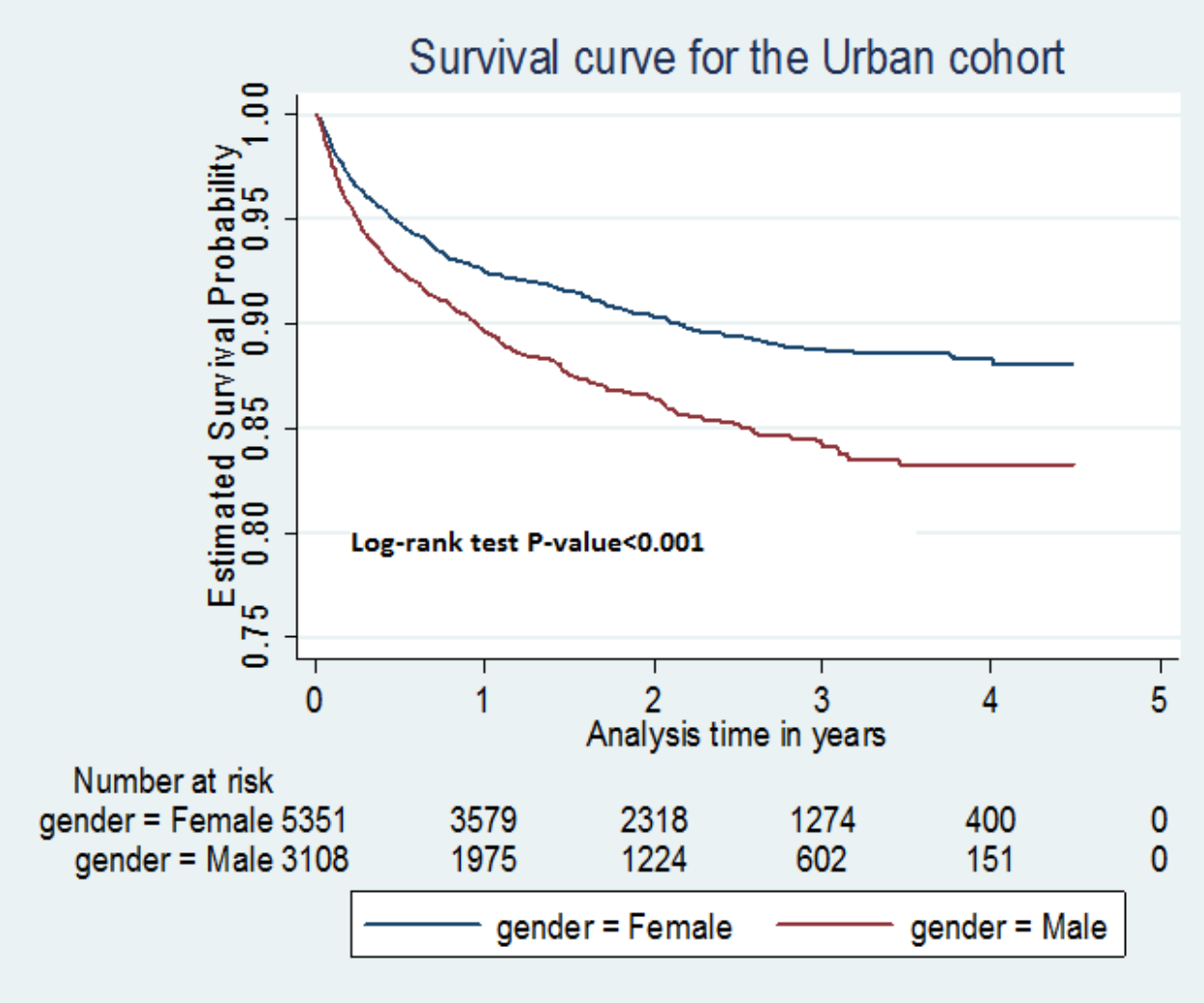

FIGURE 4: KAPLAN-MEIER GRAPH SHOWING THE SURVIVAL EXPERIENCE OF BOTH GENDERS IN THE URBAN COHORT.

Figure 4 shows the survival experience of both genders in the rural cohort. The females appear to have a better survival experience than the males in the urban cohort during the period of study unlike the rural cohort where both genders have similar survival experience (see figure 5). Two Cox models were built to investigate the predictors of mortality in both treatment cohorts.

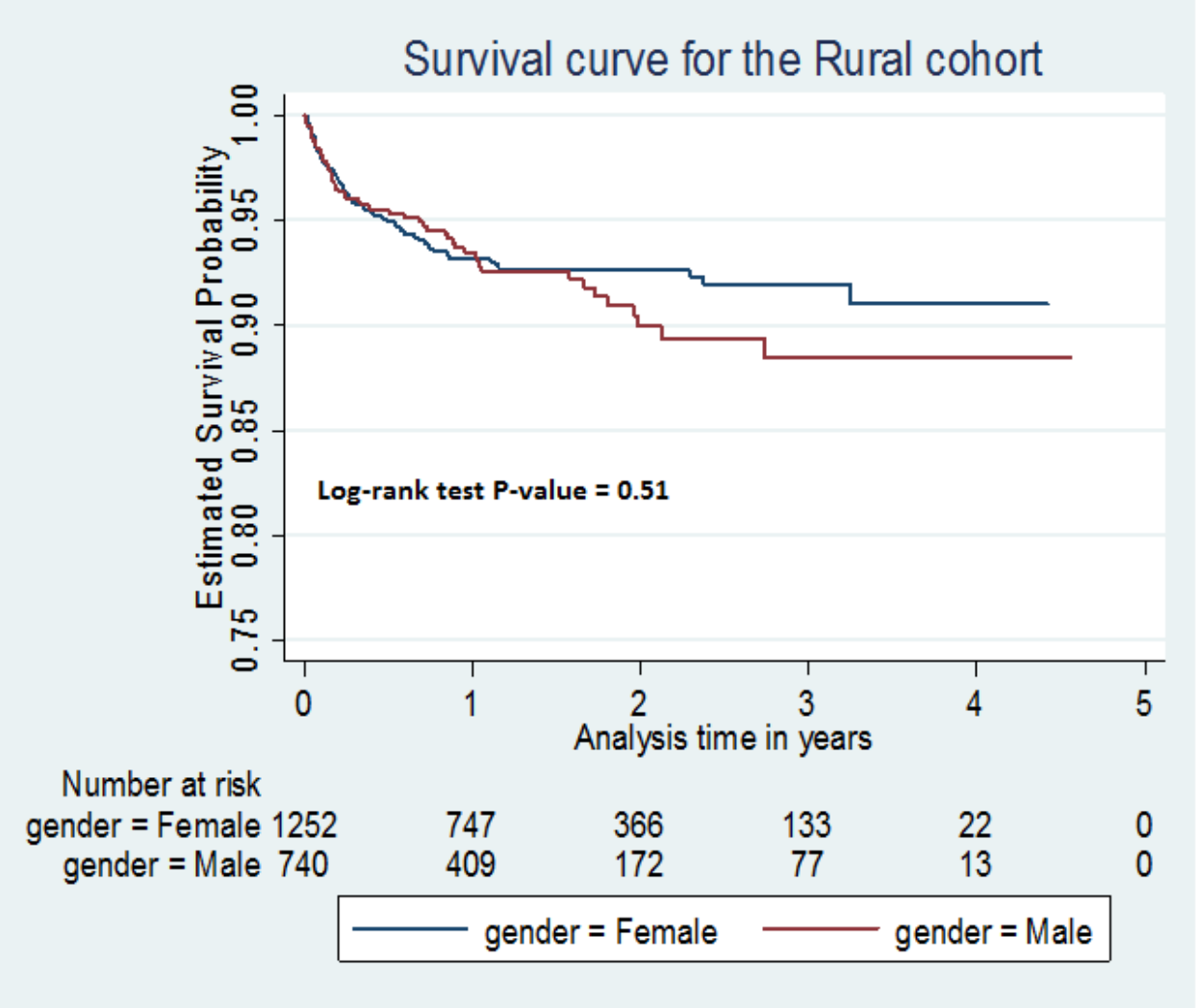

FIGURE 5: KAPLAN – MEIER CURVES SHOWING THE SURVIVAL EXPERIENCE OF BOTH GENDERS IN THE RURAL COHORT.

3.3 MODELLING THE SURVIVAL EXPERIENCE IN BOTH COHORTS

Two Cox proportional hazard models were used to investigate the factors that predict mortality in the rural and urban cohorts. The age at initiation of therapy, male gender, body mass index, CD4 count, haemoglobin and WHO disease stage at the beginning of treatment, predicted mortality in the urban cohort. BMI was categorized into underweight (<18 kg/m^2), normal (18 – 24.9 kg/m^2), overweight (25 – 29.9 kg/m^2) and obese (≥ 30 kg/m^2).

TABLE 4: UNIVARIATE AND MULTIVARIATE COX REGRESSION MODELS FOR THE URBAN COHORT

VARIABLE	UNIVARIATE HAZARD RATIO (95% CI) P-value	MULTIVARIATE** HAZARD RATIO (95% CI) P-value
Age (5 years)	1.09 (1.05 – 1.13) <0.001	**1.10 (1.06-1.15) <0.001**
Male gender	1.45 (1.27 – 1.66) <0.001	**1.34 (1.16-1.56) 0.006**
BMI (Kg/m^2)		
Underweight	1	**1**
Normal	0.44 (0.37 – 0.72) <0.001	**0.60 (0.50 – 0.72) <0.001**
Overweight	0.29 (0.22 – 0.38) <0.001	**0.50 (0.37 – 0.67) <0.001**
Obese	0.70 (0.58 – 0.84) <0.001	**1.00 (0.82 – 1.23) 0.97**
CD4 count (per 10 cells/UL)	0.94 (0.91-0.94) <0.001	**0.95 (0.94-0.96) <0.001**
Haemoglobin (g/dl)	0.83 (0.81 – 0.86) <0.001	**0.87 (0.84 – 0.90) <0.001**
WHO Stage		
I	1	1
II	1.48 (0.91 – 2.42) 0.11	1.33 (0.76 – 2.32) 0.31
III	1.68 (1.45 – 1.95) <0.001	1.12 (0.95 – 1.31) 0.17
IV	2.43 (1.98 – 2.97) <0.001	**1.37 (1.10 – 1.71) 0.01**

**Note: 7774 patients were included in the final multivariate Cox model.

Univariate analysis for the urban cohort showed males had a hazard ratio of 1.45 (95%CI of 1.27 – 1.66); for every 5 year increase in age, the risk of mortality increased by 9%. Other covariates that significantly predict mortality at the univariate level of the analysis include BMI (there was lower mortality for individuals who were normal or overweight compared to those who were underweight at initiation of therapy); the higher the CD4 levels at baseline, the lower the risk of mortality; WHO Stage 3 and 4 HIV disease; serum creatinine at baseline; serum alanine and aspartate transaminases levels at baseline, serum albumin level at initiation of HAART and haemoglobin levels.

The final multivariate model for the urban cohort (Table 4) showed a 37% increased rate of mortality for patients in WHO stage 4 disease at the onset of treatment compared to those in

Stage 1. Anaemia was also a predictor of mortality with a hazard ratio of 0.87 (95%CI 0.84-0.90) for every g/dl increase in hemoglobin if other factors are kept constant. The other protective factors against mortality included BMI. There was a 40% reduction in the risk of mortality for the normal weight individuals compared to the underweight patients. Those overweight at initiation of therapy also had a lower risk of mortality compared to the underweight. The obese individuals did not show any difference in their risk of mortality compared to the underweight. For every 10 cells/µL increase at baseline, the risk of mortality reduced by 5%. Males in the urban cohort were more likely to die and for every 5 year increase in age, the risk of mortality in the urban cohort increased by 10%.

TABLE 5: UNIVARIATE AND MULTIVARIATE COX REGRESSION MODELS FOR THE RURAL COHORT

VARIABLE	UNIVARIATE HAZARD RATIO (95% CI) P-value	MULTIVARIATE** HAZARD RATIO (95% CI) P-value
BMI (Kg/m^2)		
Underweight	1	**1**
Normal	0.44 (0.37 – 0.72) <0.001	**0.64 (0.41 – 1.02) 0.06**
Overweight	0.29 (0.22 – 0.38) <0.001	**0.16 (0.03 – 0.66) 0.01**
Obese	0.70 (0.58 – 0.84) <0.001	**0.79 (0.51 – 1.20) 0.26**
CD4 count (per 10 cells/UL)	0.95 (0.93-0.97) <0.001	**0.94 (0.93-0.99) <0.001**
No history of Pulmonary TB	0.79 (0.47 – 1.33) 0.39	**0.33 (0.15 – 0.72) 0.006**
WHO Stage		
I	1	1
II	2.72 (0.84 – 8.76) 0.11	2.13 (0.29 – 15.82) 0.46
III	2.21 (1.50 – 3.24) <0.001	**2.44 (1.44 – 4.15) 0.001**
IV	3.27 (2.03 – 5.27) <0.001	**2.14 (1.10 – 4.17) 0.026**

**Note: 1992 patients were included in the final multivariate Cox model.

BMI, CD4 count at baseline and WHO stages at commencement of HAART were also important predictors of mortality in the rural cohort as they were for the urban cohort (Table 5). After adjusting for CD4 count, history of pulmonary TB and WHO stages, there is 84% reduction in the

risk of mortality in the overweight compared to the underweight. Unlike the urban cohort, those with normal weight did not show any difference in their risk of mortality compared to the underweight individuals at initiation of HAART. The obese, like in the urban cohort, did not have a different mortality risk compared to the underweight. The higher the CD4 count at initiation of HAART, the lesser the risk of mortality. Those in the rural cohort without a history of co-infection with tuberculosis have a 67% reduced mortality rate after adjusting for BMI, CD4 count at initiation of HAART and WHO stage of the disease. Individuals in WHO stage 3 and 4 at commencement of HAART are also more likely to die compared to those in stage 1 after adjusting for BMI, CD4 count and co-infection with tuberculosis.

3.4 IMMUNOLOGIC RESPONSE

10451 patients met the inclusion criteria for analysis. Of these, 2182 (20.9%) were lost to follow up during the first 6 months after commencement of HAART. 592 (5.7%) died within 6 months of therapy. 77% of the patients who were still alive and not lost to follow up at 6 months had achieved immunologic response. This constitutes 80.5% of the patients in the rural site and 76.3% of the urban patients. Figure 6 shows the patient flow for both cohorts combined and Figure 7 shows graphically the increase in CD4 count in both cohorts over 6 months of therapy.

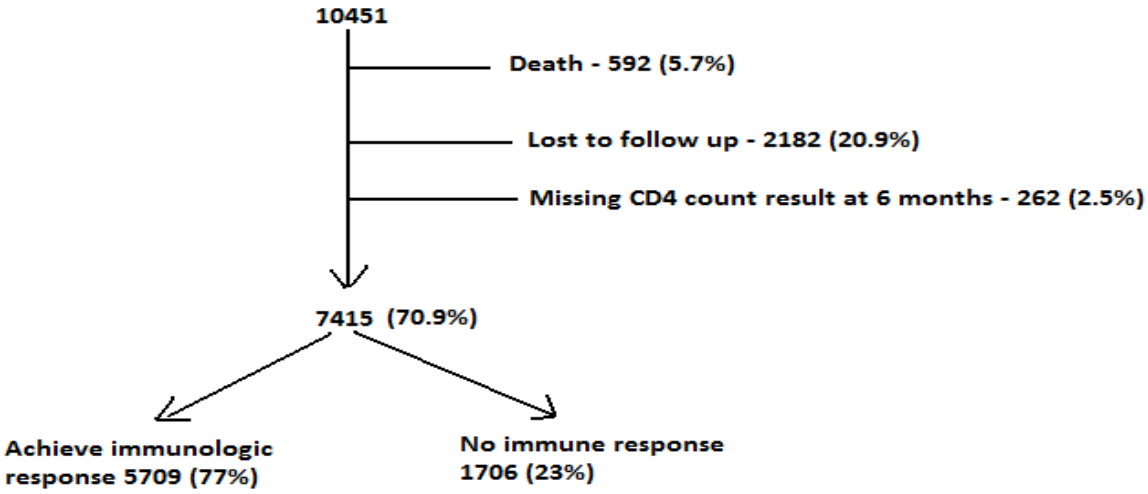

FIGURE 6: PATIENT FLOW CHART AT 6 MONTHS OF THERAPY

The mean change in CD4 count was 149 cells/ µL and 122 cells/µL for the rural and urban site respectively. The difference in CD4 count for both cohorts was 27 cells/ µL (95% CI, 15 – 40 cells/ µL).

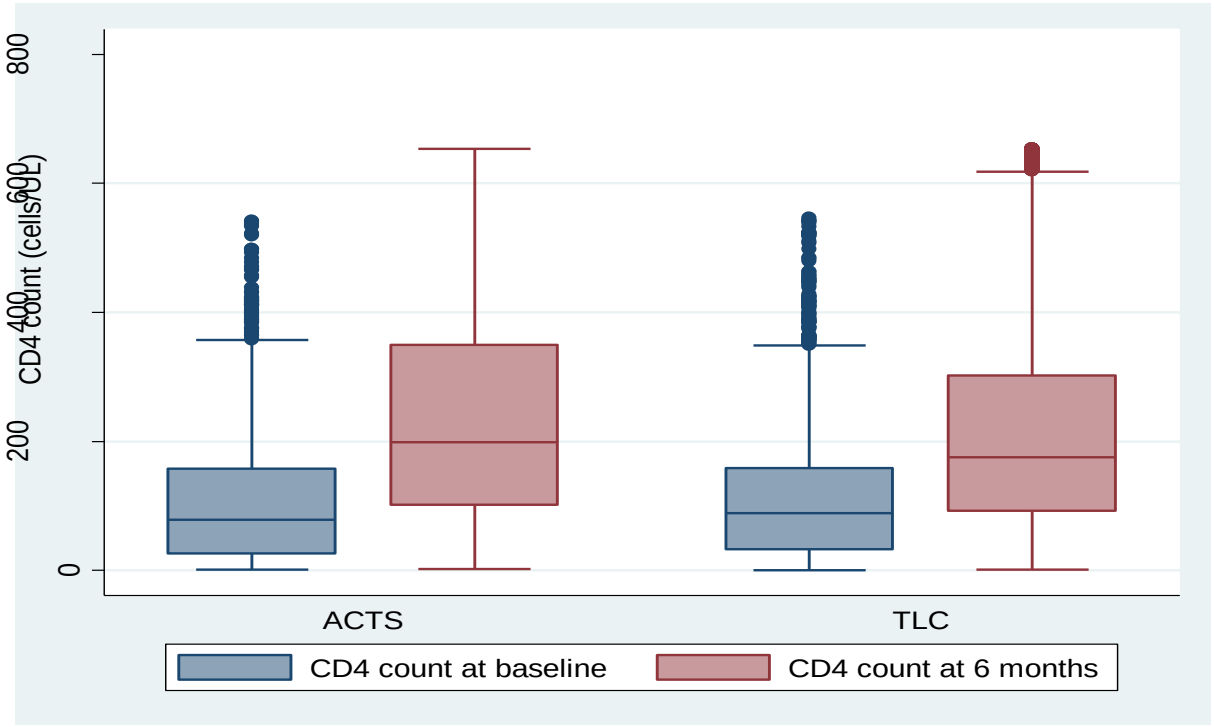

FIGURE 7: BOX PLOTS SHOWING DISTRIBUTION OF CD4 COUNT AT BASELINE AND 6 MONTHS AT BOTH SITES

Both univariate and multivariate logistic regression models were used to compare the treatment site effect on the achievement of immunologic response and to assess other factors that predict immunologic response. This is summarized in table 6 below.

TABLE 6: UNIVARIATE AND MULTIVARIATE LOGISTIC REGRESSION MODELS FOR IMMUNOLOGIC RESPONSE

VARIABLE	UNIVARIATE ODDS RATIO (95% CI, P-value)	MULTIVARIATE** ODDS RATIO (95% CI, P-value)
Sites		
Rural	1	1
Urban	0.78 (0.67-0.91, 0.001)	0.94 (0.73 - 1.22, 0.66)
Age (5 years interval)	0.91 (0.88-0.94, <0.001)	**0.92 (0.89-0.96, <0.001)**
Gender*		
Female	1	1
Male	0.72 (0.65-0.81, <0.001)	1.28 (0.83-1.99, 0.27)
CD4 count at baseline (10 cells/UL)	0.68 (0.64-0.72, <0.001)	**0.65 (0.60-0.70, <0.001)**
BMI at baseline (kg/m^2)	1.00 (0.95-1.07, 0.86)	**1.11 (1.03-1.19, 0.005)**
Haemoglobin at baseline (g/dl)	0.92 (0.89-0.94, <0.001)	**0.96 (0.93-0.99, 0.01)**

*statistical interaction exists between patient's gender and treatment site.

**5694 observations were included in the model.

The final multivariate logistic regression model suggests that both urban and rural cohorts have equal chances of achieving immunologic response.

For every five year increase in age at initiation of treatment, patients are 8% less likely to achieve immune response. The higher the CD4 count at initiation of therapy, the less likely (35% less for every 10 cells/UL increase) that an individual will achieve a CD4 appreciation of at least 50 cells/µL after 6 months of therapy.

There is an 11% increase in the odds of achieving immune response for every Kg/m^2 of BMI increase at baseline and a 4% decrease in the odds of achieving immune response for every g/dl increase in haemoglobin level all other factors being held constant.

The final multivariate model did not violate the assumption of linearity in the logit scale. Goodness of fit of the model was assessed using the Hosmer – Lemeshow goodness of fit test. A P – value of 0.68 for the Hosmer –Lemeshow test suggests the model has a good fit. The sensitivity of this multivariate model in predicting immunologic response as defined in this study is 99.6% with a positive predictive value of 77.2% and a negative predictive value of 51.3%.

A receiver operator characteristic (ROC) curve was plotted to assess the area under the curve for this model. The area under the curve for the model is 62.6%. Please see appendix D for the ROC curve tracing.

3.5 VIROLOGIC RESPONSE

Of the 10451 patients available for analysis after application of the inclusion and exclusion criteria, 592 (5.7%) died within 6 months of commencing HAART, 2182 (20.9%) had been lost to follow up and 972 (9.3%) had no data recorded for their viral load at 6 months. 6705 (64.2%) were available for modeling of virologic response. 6123 (91.3%) of the patients had achieved virologic response by 6 months, comprising 914 (90.3%) of the rural patients and 5209 (91.5%) of the urban patients. This patient flow is shown in figure 8.

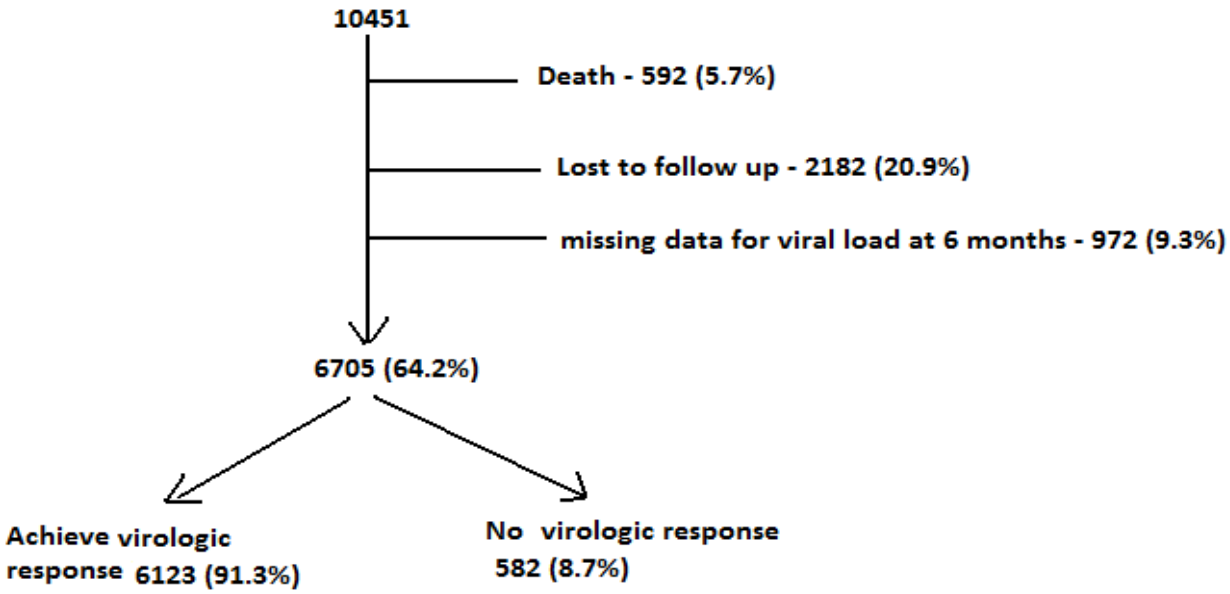

FIGURE 8: PATIENT FLOW FOR INDIVIDUALS USED IN VIROLOGIC RESPONSE MODELLING

A logistic regression model was fitted to compare the effects of the two treatment sites on the achievement of virologic response and elucidate factors that predict virologic response. Table 7 gives a summary of the univariate and multivariate models.

Both the univariate model and the final multivariate model show that there is no difference in the proportion of individuals in the cohort attaining virologic response. Age at initiation of therapy is important in predicting virologic response like its effect on predicting immunologic response and time to mortality. The odds ratio of achieving virologic response for every five year increase in age is 1.08 (95% confidence interval of 1.03 – 1.15). Patients who were unemployed at the time of initiation of HAART were 33% less likely to achieve immune response compared to those employed, all other factors remaining unchanged.

For every 10 cells/µL increase in CD4 count at initiation of HAART, there is a 16% increase in the odds of achieving virologic response, all other factors held constant.

No interaction issue was significant in the model. Model diagnostics were then performed.

TABLE 7: UNIVARIATE AND MULTIVARIATE LOGISTIC REGRESSION MODELS FOR VIROLOGIC RESPONSE

VARIABLE	UNIVARIATE ODDS RATIO (95% CI, P-value)	**MULTIVARIATE ODDS RATIO (95% CI, P-value)
Sites		
Rural	1	1
Urban	1.15 (0.92-1.45, 0.22)	1.08 (0.85 – 1.38, 0.54)
Age*	1.02 (1.01-1.03, 0.001)	1.08 (1.03-1.15, 0.02)
Employment status		
employed	1	1
Unemployed	0.69 (0.57-0.82, <0.001)	0.67 (0.54-0.82, <0.001)
CD4 count (per 10 cells/μL)	1.19 (1.06 – 1.32, 0.002)	1.16 (1.04 – 1.30, 0.007)

*In Units of 5 years.

**6551 observations included in the model.

The assumption of linearity on the logit scale was assessed for and ensured that it was not violated. The fit of the model was adjudged to be good by the Hosmer – Lemeshow goodness of fit test.

The model has 100% sensitivity and an area under the ROC curve of 58.8%. The ROC curve for the model is shown in appendix E.

Three HIV treatment outcomes – time to mortality, immunologic response and virologic response – have been used to compare the success of HIV treatment in an urban and a rural HIV treatment site in South Africa.

The four models used to predict these outcomes suggest that both urban and rural cohorts share similar predictors of mortality and there is no difference in the proportions achieving virologic and immunologic response at six months of therapy.

CHAPTER 4: DISCUSSION, LIMITATIONS OF THE STUDY AND CONCLUSION

4.1 DISCUSSION

This comparison of HIV treatment outcomes in urban and rural South Africa was done on HAART-naïve patients to eliminate the possibility of previous HAART therapy being a confounder in the study. Also, the exclusion of pregnant women from the study helped avoid the confusion that may arise from fluctuations in CD4 count that occur during pregnancy and in the immediate post-partum period.

Patients from the rural site started treatment with a lower CD4 count and a more advanced HIV disease as evidenced by a greater proportion of patients with WHO stage 3 and 4 disease. This finding is supported by a similar study in South Africa comparing the clinical and sociodemographic characteristics of patients commencing HAART in an urban and a rural centre (16). This study also corroborated the finding of better formal education and formal employment in the urban centre compared to the rural centre. The assumption is that the rural patients, having fewer years of formal education and living in rural settings, may not be able to access information on HIV/AIDS, therefore they tend to present late as evidenced by the lower median CD4 count and a greater proportion of more advanced HIV disease in the rural cohort. The rural cohort also had a significantly lower proportion of patients in formal employment, therefore, lower earning power. This comes as a disadvantage to early presentation to ARV centres for care and compliance to clinic visits after commencement of HAART. Unfortunately, the rural centre charges a token fee for every clinic visit. This token fee, though small, may have a profound effect on default of patients due to financial constraints. The unemployed were less

likely to achieve virologic response at 6 months of HAART. This point emphasizes the need to provide a source of livelihood for people living with HIV/AIDS.

Both sites saw more females commencing HAART than males but there was no difference in the gender proportions by site. Though the CD4 count in the rural cohort was lower at initiation of therapy than the urban cohort, both cohorts had similar HIV RNA load at initiation of HAART. This finding is important to note as it may have an influence on the likelihood of the patients to achieve immunologic and virologic response. It is also possible to achieve virologic response without having a concomitant immunologic response and vice-versa. Some studies have reported the finding of discordance between the viral load and the CD4 count response following HAART (37).

Another baseline clinical characteristic that merits discussion is the nutritional state of the patient. In this study, the BMI and serum albumin were used as proxies for measuring nutritional status as these were the best available parameters collected in this retrospective analysis. The merits and demerits of BMI as an indicator of nutritional status has been noted (45). Many hold the view that the BMI is a complicated tool for use in public health studies and should be reserved for clinical studies (34). Another disadvantage of using BMI may be the issue of standardization of the scales used for weight measurement in both centres. Despite these few demerits, the BMI is still one of the best available tools in measuring nutritional status (34). This study showed a higher BMI in the urban patients than the rural patients. The lower BMI of the patients in the rural centre may be an indicator of malnutrition due to the prevailing

unfavorable socioeconomic state caused by a lower proportion of patients in formal employment.

58.7% of those who died on commencement of HAART died within the first six months. This finding is supported by a number of papers written in different climes (46-48). Research has identified a number of factors that lead to early mortality after commencing HAART. These include late diagnosis of HIV infection in Sub-Saharan Africa (48), tuberculosis, acute sepsis, cryptococcal meningitis, wasting syndrome, malignancy and immune reconstitution syndrome (48-50). The concern of immune reconstitution syndrome (IRIS) as a major cause of early mortality following the initiation of HAART does not appear to be very important in Sub-Saharan Africa, rather our problem is late diagnosis of HIV infection characterized by patients with low CD4 count at initiation harboring a number of AIDS defining conditions (49). A nested case-control study done with an urban African cohort to determine the incidence and elucidate the risk factors for IRIS found the cases of IRIS to be mild and not leading to mortality and put the incidence of IRIS at about 10% (51). Other risk factors for early mortality include male sex and oesophageal Candidiasis and the risk of mortality in the first six months could be as high as 70% in some settings (52).

Other predictors of mortality in these cohorts include BMI at initiation of therapy, WHO stage, baseline CD4 count, anaemia and age at HAART initiation. The presence of malnutrition at the onset of HAART reduces the chances of survival while on therapy (28, 53). The Cox models for both cohorts showed that higher BMI at initiation of HAART is associated with reduced hazards of mortality. Those with better nutritional status at initiation of treatment were also more likely

to achieve immunologic and virologic response at six months. This finding demonstrates the importance of optimizing patients' nutritional status as an important component of pre-ARV care. The adverse effect of malnutrition on HIV treatment outcomes has been documented extensively (28, 54, 55). The older a patient is at the time of initiating HAART, the more likely the individual is to die, the less likely to achieve immunologic response and the more likely to achieve virologic response.

The patients in both cohorts were equally likely to achieve immunologic and virologic response at 6 months of therapy. The finding of better immunologic response in those with lower CD4 cell count at initiation of HAART merits further discussion here. It appears it is easier for patients with lower CD4 counts at baseline to have a 50 cell/µL increase than those with higher baseline CD4 counts, though they still have higher mortality rates as shown in the Cox hazards model. This may be due to the fact that they take a longer time to achieve a CD4 cell count of > 200 cells/µL, hence still susceptible to opportunistic infections (37).

Having discussed the findings above, it is important to state the limitations of the study since all interpretations of these findings must be done with these limitations in mind.

4.2 LIMITATIONS OF THE STUDY

It is possible that the centres chosen to represent the urban and rural areas of South Africa may not be representative of other centres. Therefore, the results of this study may not be generalizable. Different centres use different treatment protocols and may even differ by the predominant WHO stage at which the patients present. There may also be differences between government run and non-governmental sites.

About 21% of the patients were lost to follow up in the first six months of the study. The high proportion of individuals lost to follow up has a potential of creating bias in the study if those lost to follow up are systematically different from the rest of the cohort. A number of those classified as “lost to follow up” in the rural cohort may actually have died without being properly documented. This ‘loss to follow up’ level corresponds with what has been observed in many HIV treatment centres resource-poor settings (56, 57).

The urban cohort mortality data used for this study, but not the rural cohort data had been updated with the South African national mortality database. This suggests the possibility of missing records of mortality among the rural cohort. This has made the direct comparison of mortality rates in the two cohorts liable to mortality-ascertaining bias. This necessitated comparing the predictors of mortality in both cohorts instead of a direct comparison of mortality rates in both cohorts.

This study, being a retrospective analysis of data, may have the problem of not collecting data on all the possible variables that may have an effect on mortality, immunologic and virologic response. It would be desirable to have information on the hepatitis B and C status of the patients and the presence or otherwise of chronic diseases like hypertension and diabetes mellitus that may have an impact on mortality. This introduces the likelihood of residual confounding into the study.

Despite the limitations outlined above, this study has a number of strengths. The large sample size affords an opportunity to find a difference in outcomes if there really is one. There is a

paucity of studies comparing treatment outcomes in urban and rural Africa; therefore, this study will serve as a foundational study for such research.

4.3 CONCLUSION

HIV treatment outcomes – immunologic response and virologic response – do not differ between rural and urban South Africa. CD4 count, WHO stage at initiation of HAART and BMI are the factors that predict mortality in both cohorts.

4.4 RECOMMENDATIONS

Good nutritional support programs should be put in place in the pre-ARV clinics in both urban and rural areas to optimize patients' nutritional status before commencement of HAART. This may help in reducing mortality, especially in the first six months of therapy. Majority of patients die within the first 6 months of commencement of HAART as shown in this study which correlates with late stage of HIV/AIDS. Continued public health enlightenment campaigns should be undertaken to ensure patients present early and benefit from treatment. This will not only enhance HAART but also significantly reduce the burden of disease in sub-Saharan Africa.

Early diagnosis of HIV disease and early initiation of HAART at CD4 count of 350 cells/µL or lower instead of the 200 cells/ µL may also improve survival in HIV patients in Sub-Saharan Africa.

The vital status of patients in the rural cohort should be updated with the South African national mortality database and this analysis repeated.

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APPENDIX A – ACTS support group roster

Mon	Tue	Wed	Thu	Fri	Sat	Sun
9/Nov/09	10/Nov/09	11/Nov/09	12/Nov/09	13/Nov/09	14/Nov/09	15/Nov/09
0	20	32	9	9	0	0
0	10	12	17	8	0	0
0	30	44	26	17	0	0
New	Young Women 1	Older Women 3	Young Men 2	Pregnant Moms Mixed Teenagers	0	0
Patients Only	Teenagers 12+ Older	Toddlers 6 + younger	Primary School 7 - 11 years	Young Women 5	0	0
0	M	N	O	P	0	0
Mon	**Tue**	**Wed**	**Thu**	**Fri**	**Sat**	**Sun**
16/Nov/09	17/Nov/09	18/Nov/09	19/Nov/09	20/Nov/09	21/Nov/09	22/Nov/09
1	23	17	20	4	0	0
3	9	33	10	10	0	0
4	32	50	30	14	0	0
New	Couples	Old Men 1	Older Women 2	Pregnant Moms	0	0
Patients Only	Teenagers 12+ Older	Toddlers 6 + younger	Primary School 7 - 11 years	Couples 2 MHBC	0	0
0	A	Lulu Creche	C	D	0	0
Mon	**Tue**	**Wed**	**Thu**	**Fri**	**Sat**	**Sun**
23/Nov/09	24/Nov/09	25/Nov/09	26/Nov/09	27/Nov/09	28/Nov/09	29/Nov/09
0	16	7	15	11	0	1
0	22	17	22	7	0	0
0	38	24	37	18	0	1
New	Moms & Babes 1	Young Women 3	Young Women 2	Pregnant Moms	0	0
Patients Only	Teenagers 12+ Older	Toddlers 6 + younger	Primary School 7 - 11 years	Young Men 3 MHBC	0	0
0	E	F	G	H	0	0
Mon	**Tue**	**Wed**	**Thu**	**Fri**	**Sat**	**Sun**
30/Nov/09	1/Dec/09	2/Dec/09	3/Dec/09	4/Dec/09	5/Dec/09	6/Dec/09
0	18	9	8	5	0	0
1	6	20	18	5	0	0
1	24	29	26	10	0	0
New	Young Men 1	Older Women 1	Young Women 4	Pregnant Moms	0	0
Patients Only	Teenagers 12+ Older	Toddlers 6 + younger	Primary School 7 - 11 years	Older Women 3	0	0
0	I	J	K	L	0	0
Mon	**Tue**	**Wed**	**Thu**	**Fri**	**Sat**	**Sun**
7/Dec/09	8/Dec/09	9/Dec/09	10/Dec/09	11/Dec/09	12/Dec/09	13/Dec/09
0	4	2	4	1	0	0
0	2	7	8	0	0	0
0	6	9	12	1	0	0
New	Young Women 1	Older Women 3	Young Men 2	Pregnant Moms Mixed Teenagers	0	0
Patients Only	Teenagers 12+ Older	Toddlers 6 + younger	Primary School 7 - 11 years	Young Women 5	0	0
				P	0	0
Mon	**Tue**	**Wed**	**Thu**	**Fri**	**Sat**	**Sun**
14/Dec/09	15/Dec/09	16/Dec/09	17/Dec/09	18/Dec/09	19/Dec/09	20/Dec/09
0	4	0	0	1	0	0
0	2	0	2	2	0	0
0	6	0	2	3	0	0
New	Couples	Day of	Older Women 2	Pregnant Moms	0	0
Patients Only	Teenagers 12+ Older	Reconciliation	Primary School 7 - 11 years	Couples 2 MHBC	0	0
0	A	0	C	D	0	0
Mon	**Tue**	**Wed**	**Thu**	**Fri**	**Sat**	**Sun**
21/Dec/09	22/Dec/09	23/Dec/09	24/Dec/09	25/Dec/09	26/Dec/09	27/Dec/09
0	0	0	0	0	0	0
0	2	0	0	0	0	0
0	2	0	0	0	0	0
New	Moms & Babes 1	Young Women 3	Young Women 2	Christmas	0	0
Patients Only	Teenagers 12+ Older	Toddlers 6 + younger	Primary School 7 - 11 years	Day	0	0
0	E	F	G	H	0	0

APPENDIX B – Wits ethical clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Ekrikpo U Ekpenyong

CLEARANCE CERTIFICATE	**M090943**
PROJECT	A Rural-Urban Comparison of Patient Characteristics and HIV Treatment Outcomes in South Africa
INVESTIGATORS	Ekrikpo U Ekpenyong.
DEPARTMENT	School of Public Health
DATE CONSIDERED	2009/10/02
DECISION OF THE COMMITTEE*	Approved unconditionally

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

DATE 2009/10/02 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr M Maskew

DECLARATION OF INVESTIGATOR(S)

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

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

APPENDIX C1

Clinical HIV Research Unit, Department of Medicine

Helen Joseph Hospital, Themba Lethu Clinic, Perth Road, Westdene, Johannesburg 2092, South Africa
Postnet Suite 176, Private Bag X2600, Houghton 2041, South Africa • Tel: +27 11 276-8800 • Fax: +27 11 482-2130

02 November 2009

Dr NL Hlongwane
Senior Superintendent
Helen Joseph Hospital
Perth Road
Westdene

By Hand

Dear Dr Hlongwane

RE: Mr Udeme Ekrikpo: ETHICS REF NO: M090943

"A Rural-Urban Comparison Of Patient Characteristics And Hiv Treatment Outcomes In South Africa"

This letter serves to confirm that Mr Udeme Ekrikpo researcher at the Epidemiology and Biostatistics, Right To Care wishes to conducted research here at Helen Joseph Hospital.

The research has already been approved by the Human Research Ethics Committee (University of the Witwatersrand) under protocol M090943.

As the proposed study is purely research and will not impact on the hospital in anyway.

Yours sincerely,

Mrs Marlene Naidoo
Regulatory Manager
Clinical HIV Research Unit
Themba Lethu Clinic
Helen Joseph Hospital
Perth Road, Westdene, Johannesburg
Tel: +27 11 276 8809

APPENDIX C2

Gauteng Department of Health

Helen Joseph Hospital

PERMISSION FOR RESEARCH

DATE: 02 November 2009

NAME OF RESEARCH WORKER: Mr Udeme Ekrikpo

CONTACT DETAILS OF RESEARCHER (INCLUDE ALTERNATE RESEARHER):
Epidemiology and Biostatistics, Right To Care: Tel: 083 953 6372

TITLE OF RESEARCH PROJECT A Rural-Urban Comparison Of Patient Characteristics And Hiv Treatment Outcomes In South Africa

OBJECTIVES OF STUDY (Briefly or include a protocol):

- To compare the baseline sociodemographic and clinical characteristics of HIV patients initiated on HAART in urban and rural areas from January 2005 to December 2008.
- To compare the treatment outcomes of HIV infected patients receiving HAART in rural and urban South Africa from January 2005 to December 2008.

METHODOLOGY (Briefly or include a protocol):
To compare the sociodemographic and clinical characteristics of patients commenced on HAART in the rural and urban areas of South Africa and assess for differences in the outcomes of treatment in these areas.

Prevalence studies have been done in rural areas which have shown increasing prevalence of HIV/AIDS over the years. There is little evidence indicating a difference in the relative outcomes of treatment of HIV infected individuals in rural areas in South Africa compared to those in the urban areas. If the outcome of highly active antiretroviral therapy (HAART) is different in rural areas from that obtained from the urban areas, it would be important to identify the factors behind these differences as this will add to the body of knowledge of the HIV epidemic in South Africa.

There also is the possibility that a difference in treatment outcome may arise from the difference in the baseline characteristics of the patients in the rural and urban areas.

The findings of the study may also help in planning more effective health service delivery to the people in the rural areas considering their unique characteristics. Comparing their characteristics and treatment outcomes with those obtained in the urban centres would also help modify the service delivery to maximize results in antiretroviral therapy and care for people with people with HIV/AIDS in rural South Africa.

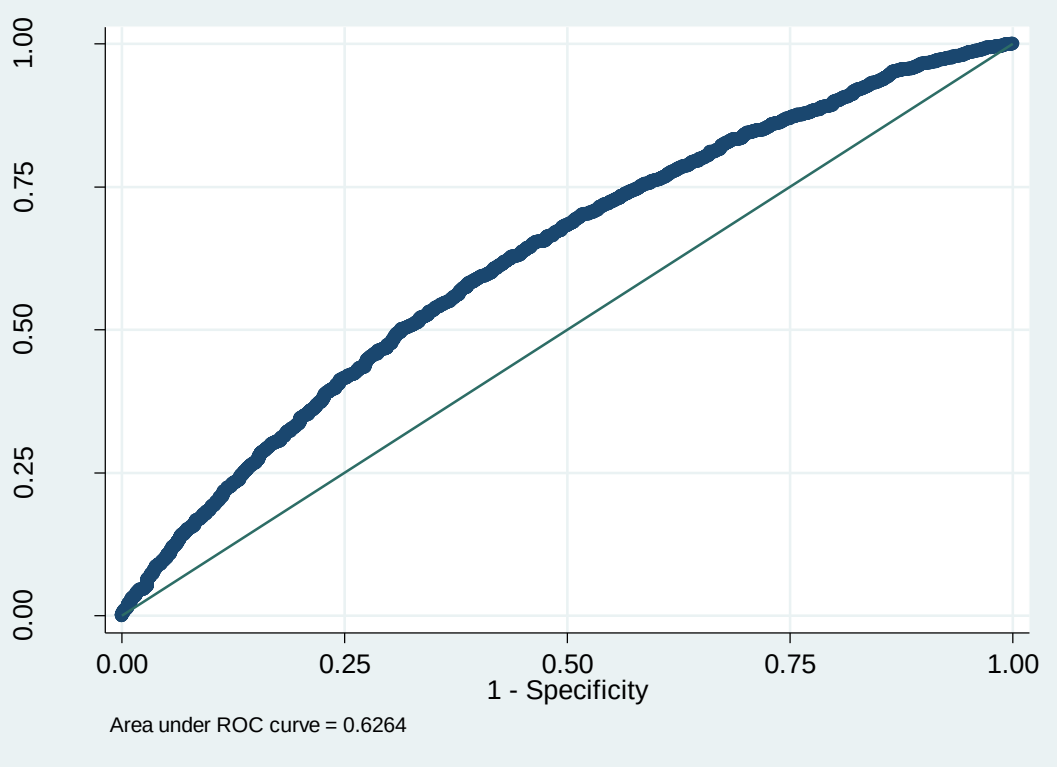
CONFIDENTIALITY OF PATIENTS MAINTAINED: Yes
COSTS TO THE HOSPITAL: NIL
APPROVAL OF HEAD OF DEPARTMENT:
APPROVAL OF CRHS OF WITS UNIVERSITY: Yes

SUPERINTENDENT PERMISSION:

Signature: _____ Date: 4/12/2009

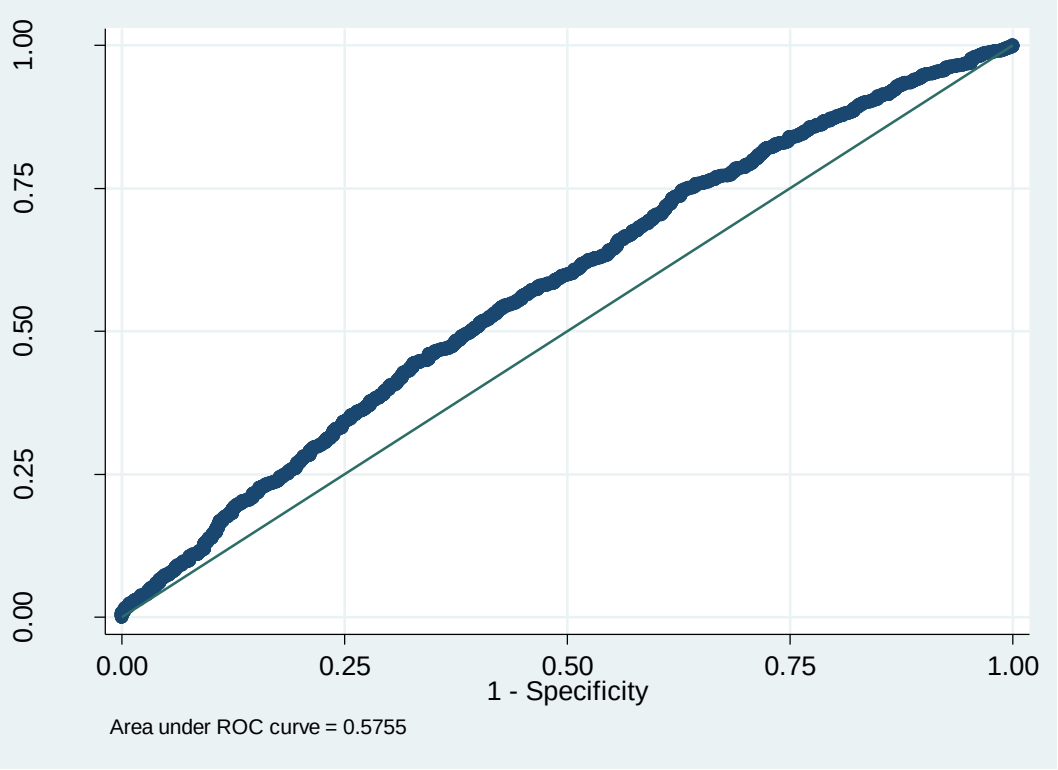
Subject to any restrictions: _____

APPENDIX D



RECEIVER OPERATOR CHARACTERISTIC (ROC) CURVE FOR THE MULTIVARIATE LOGISTIC MODEL PREDICTING IMMUNOLOGIC RESPONSE.

APPENDIX E



ROC CURVE FOR THE VIROLOGIC RESPONSE MODEL