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`POTENTIAL CONTRIBUTORS TO HOSPITAL ADMISSIONS AMONG HIV-POSITIVE PATIENTS IN SOUTH AFRICA IN THE ERA OF HAART.

By

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DECLARATION

I declare that the Master's script, which I hereby submit for the degree MSc Clinical Epidemiology at the University of Pretoria, is my own work and has not been previously submitted by me for a degree at another university

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ABSTRACT

AIM

The objective of this study is to determine factors that may contribute to hospital admissions in a cohort of medically insured South African patients in the era of HAART.

METHODS

This was a retrospective cohort of all HIV-positive adult and paediatric patients enrolled on a medical aid disease management programme in South Africa over a period of three years. Patient-specific demographic and clinical information were obtained from the medical aid records.

Survival analysis was used to analyse time to first admission looking at admissions occurring after enrolment to the programme, during the study period of between 01 January 2006 and 31 December 2008. Only the right censored cases were included in the analyses. Descriptive analyses were conducted on the key prognostic factors. Variables that were significant in the univariate were considered in the multivariate Cox proportional hazards model.

RESULTS

A total of 8440 patients were included in the analysis. Half of these patients had at least one admission during the observation periods with 43.28% having had 2 or more admissions. The average admission rate was 2 admissions per patient over the 36 month observation period.

Young children, adolescents and the very old (> 60 years) were significantly more likely to be admitted than the middle age groups, HR = 1.30 [95%CI 1.21 -1.40] p<0.01, 1.24 [95%CI 1.10 – 1.41] and 1.13 [95% CI 1.10 – 1.27] p<0.01 respectively.

Low CD4 cell counts of < 200 cells/ µL were significantly associated with a higher likelihood of hospitalizations with hazard ratios even greater for CD4 cell counts of less

than 100 cells/ µL, HR= 1.34 [95%CI 1.29 – 1.39], p<0.01.

Cases were more likely to be admitted by a clinical haematologist or gynaecologist than by other specialist categories.HR =1.58 [95%CI 1.29 – 1.94] and 1.17[95%CI 1.08 – 1.27] respectively with p<0.01.

CONCLUSION

Factors that are associated with hospital admissions in this private sector, medically insured population are a younger and older age, low CD4 cell counts and admission by a clinical haematologist and gynaecologist.

These results suggest that disease management strategies should be intensified for the younger and older age groups.

All HIV-positive patients should be closely monitored for CD4 deterioration so that treatment is initiated timeously.

Routine haematological investigations should be recommended for all HIV-positive patients in order to pick up and treat haematological conditions before they result in a hospital admission.

Evidence based guidelines, outlining the place of caesarian section deliveries in the HIV population, should be developed for use by gynaecologists specifically in the private sector.

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ABBREVIATIONS

AIDS – Acquired Immune Deficiency Syndrome

ART- Antiretroviral therapy

ARVs –Antiretrovirals

CMV - Cytomegalovirus

COPD – Chronic Obstructive Lung Disease

HAART – Highly Active Antiretroviral Therapy

HCV – Hepatitis C virus

HIV – Human Immune Virus

ICU – Intensive Care Unit

IRIS – Immune Reconstitution Inflammatory Syndrome

MAC – Mycobacterium Avium Complex

MTCT – Mother To Child Transmission

PCP - Pneumocystis Carinii Pneumonia

PJP - Pneumocystis Jiroveci Pneumonia

PMTCT –Prevention of Mother To Child Transmission

UNAIDS –Joint United Nations Programme on HIV/AIDS

TB - Tuberculosis

WHO – World Health Organization

CHAPTER 1

INTRODUCTION AND BACKGROUND

Introduction

Sub-Saharan Africa continues to bear the brunt of the global HIV epidemic. Almost 25 million people are living with HIV in sub-Saharan Africa accounting for two thirds (68%) of all adults and children living with HIV globally. In 2009, 1.3 million deaths were reported globally, 72% of which occurred in sub –Saharan Africa. [1]

In South Africa an estimated 5.6 million people are reported to be living with HIV and AIDS.[1] South Africa has 0.7% of the world population but accounts for 28% of the world's HIV and TB population and 33% of the cases in sub-Saharan Africa.[2] Of the 50 million South Africans, only 16% have access to medical aid allowing them access to better healthcare services and treatment.[2-4] Thus of the 5.6 million people living with HIV, only a small percentage have access to quality services for management of their disease through private health facilities. The rest use public health facilities with limited resources. In the public sector most facilities have staff shortages with high patient volumes. There is an increased demand for medical services with limited resources while the private sector is well resourced and offers medical services to fewer patients. Until recently, the clinical protocols used in the different sectors were not the same. The private sector was initiating treatment for all patients at CD4 counts below 350 cells\µL while the public sector still used the CD4 cut off of 200 cells\µL. This CD4 cut off for the public sector has since been revised to 350 cells\µL for all patients, resulting in further increase in patient volumes as more patients now meet criteria for ART initiation. This

further puts pressure on these already over-burdened public sector facilities. The well resourced private sector remains inaccessible to the majority of the population as they cannot afford to pay for these private medical services.

Problem Statement

The immunopathogenesis of HIV is characterized by the gradual depletion of CD4 cells during the progression of the disease to AIDS, accompanied by widespread dissemination of the virus, resulting in increased susceptibility to opportunistic infections. As a result of progressive immunosuppression, infected individuals may start presenting with a range of opportunistic conditions. [5, 6]

Paediatric patients are usually the hardest hit by HIV because of their already vulnerable and weak immune systems. They are particularly vulnerable in their first year of life when their immune systems are weakest.[7, 8]

The South African paediatric guidelines have been revised to align with international guidelines that advocate initiation of HAART to all infants younger than 1 year regardless of CD4 percentage or count and clinical stage, to reduce mortality and morbidity in this age group.[9]

The introduction of antiretroviral therapy and effective prophylaxis of opportunistic infections has however dramatically changed the natural history of HIV.

The role of antiretroviral therapy is to reduce mortality and morbidity relating to opportunistic infections. Patients are treated with HAART, a combination of three or more drugs, to minimize the emergence of drug resistance. The beneficial effects of ART result from gradual restoration of pathogen-specific immune responses mediated by suppressed viral replication and increased CD4 cell count.[10] HIV is now a manageable chronic condition with an improved life expectancy.

However, in developing countries such as South Africa, many patients still have no access to treatment. Others initiate ART at a late stage when they already have advanced immunodeficiency. Lower CD4 cell counts (less than 200 cells\µL) are

particularly related to higher HIV mortality and morbidity.[11, 12]

The challenges relating to access to treatment are mainly observed in the public sector while initiation of treatment at low CD4 cell counts still remains a setback in both the public and private sectors. Access is however improving, as shown in the WHO 2008 progress report and the UNAIDS 2009 global report.[1,2] In 2009 alone, 1.2 million people received HIV antiretroviral therapy for the first time, a 30% increase in the number of people receiving treatment in a single year. [1]

Overall, the number of people receiving therapy has grown 13-fold, to more than five million people in low- and middle-income countries, since 2004. Expanding access to treatment has contributed to a 19% decline in deaths among people living with HIV between 2004 and 2009. This is just the beginning: 10 million people living with HIV who are eligible for treatment under the new WHO guidelines are still in need of treatment. [1]

All medically insured HIV-infected patients have access to routine monitoring tests, antiretroviral therapy and treatment of related opportunistic infections and hospitalization where necessary. They also have access to HIV testing to allow early detection of HIV, timely enrolment into wellness programmes and access to ART where necessary.

What, then, are the factors that still contribute to hospital admissions among the medically insured population in this era of HAART?

Research objectives

The aim of this study is to determine the demographic and clinical determinants of hospital admissions among HIV-positive patients enrolled in a medical aid disease management programme in South Africa in the era of HAART.

CHAPTER 2

LITERATURE REVIEW

The introduction of HAART has led to a decline in the overall hospital admissions as well as a reduction in the morbidity and mortality associated with HIV infection.

HAART initiation at very low CD4 cell counts is however associated with immune reconstitution inflammatory syndrome, which characteristically results in deterioration in the patient's clinical picture due to the restoration of immune function. The clinical picture includes paradoxical worsening of treated opportunistic infections or the unmasking of previously subclinical, untreated infections. This may often warrant a hospital admission.[10, 13-16]

IRIS is a common complication in patients starting ART, particularly those with a history of cytomegalovirus retinitis, cryptococcal meningitis, and tuberculosis and in those with low CD4 cell counts. Other conditions include mycobacterium avium complex (MAC), Pneumocystis Jiroveci Pneumonia (PJP) previously known as Pneumocystis Carinii Pneumonia (PCP), and auto-immune conditions. [10, 13-15]

In an article by Weinstein, in the era of ART, patients with HIV infection admitted to ICU fell into 3 general categories: those with AIDS-related opportunistic infections, those who are experiencing complications related to ART, and those with medical problems unrelated to HIV.[17,18]

A study conducted by Kumar et al in Barbados showed that opportunistic infections were the commonest discharge diagnosis, followed by serious bacterial infections, anaemia and HIV nephropathy.[12]

Low CD4 cell counts (less than 200 cells\µL) and no use of HAART were found to be strongly correlated with hospitalizations due to opportunistic infections. Most admissions were in patients who were known to be infected prior to the current admission, whereas first-time diagnosis of HIV infection was made during the admission for the rest. Over two thirds of the known HIV-infected patients were already on HAART at the time of hospitalization. According to the authors, poor adherence and drug resistance resulting in treatment failure were the most likely reasons for immunological failure in those patients already on HAART. A growing trend towards increasing admissions related to HAART toxicity and non-AIDS related conditions was also noted.

Another study looking at hospitalizations in HIV-positive patients enrolled in a treatment programme was conducted by Weber et al in British Columbia.[19]
Their results showed that hospital admissions were related to unemployment, being an intravenous drug user, a poor health status and having a physician experienced in the management of HIV and AIDS. Prior admission to hospital was also found to be a determinant for future admissions.
The authors associated unemployment and intravenous drug use with low socio-economic status and referred to a study that was done in cardiovascular and cancer patients that linked a low socio-economic status to increased mortality and morbidity.
Physicians with more experience were thought to have a wider spectrum of illness severity in their practices, hence a higher rate of hospital admissions.

Manavi and McMillan looked at immunosuppression in patients who were already receiving HAART. [20] They noticed that 30% of hospital admissions happened in patients with detectable viral loads who had CD4 T-cell counts of less than 200 cells\ µL. They also noted that having CD4 cell counts of less than 200 cells/ µL despite undetectable viraemia for at least 6 months accounted for 21% of hospital admissions. The immunosuppression in the treated patient group was as a result of slow CD4 T-cell recovery, and this was related to failure of HAART regimens but could still occur in patients with full viral suppression. [20]
Mugavero et al looked at the predictors of AIDS–related morbidity and mortality in a

southern U.S. Cohort. The aim of this study was to look at sociodemographic, psychological and clinical factors contributing to hospital admissions. Seventy five percent of patients included in this study did not have private health insurance.
Younger age, lack of private health insurance, psychosocial trauma, depressive symptoms, lower baseline CD4 cell count and less time on antiretroviral therapy during follow-up were associated with HIV-related events.[11]

A retrospective review of hospital admissions of all HIV-infected patients admitted in a hospital in Madrid between January 1998 and December 2004 was carried out by Núněz et al. Fifty four percent of these patients were not on ART.[21]
This study found that being on HAART, female gender, older age, lower CD4 cell counts and hepatitis C virus (HCV) co-infection were associated with hospital admissions.
This study also looked at the impact of antiretroviral treatment-related toxicities on hospital admissions in HIV-infected patients of whom 45% were on ARV therapy. ARV-related toxicities were found to be the main or secondary reason for hospital admissions in 7% of the patients.
Liver toxicity was the most frequent complication, of which one-third was associated with nevirapine use and 80% occurred in subjects with underlying chronic hepatitis C virus (HCV) infection. Other main ARV-related toxicities were bone marrow toxicity due to zidovudine (17%), pancreatitis (13%), and indinavir-associated nephrolithiasis (6%). Eight patients presented with symptomatic hyperlactatemia, two of whom had lactic acidosis.
The authors of this study concluded that ARV-related toxicities accounted for less than 10% of all hospital admissions in HIV-infected patients. Although the morbidity was not regarded as negligible, given the large number of patients on ARV therapy the results suggested that most ARV adverse events are moderate and can be well managed in outpatient clinics.
A study by Gardner et al included a population of predominantly African-American HIV-positive women and it aimed to determine the rates and risk factors for overall and condition-specific hospitalizations in the era of HAART.

There were increased rates of hospitalization associated with several “non-AIDS” conditions and these included renal laboratory abnormalities, hypertension, and HCV antibody positivity. This study also showed a decline in AIDS defining illnesses due to HAART and suggested that the reduction in HIV-1 viral burden or improvement in CD4 cell count may not significantly reduce non–AIDS related hospitalizations.[22]

The summary of the findings from the studies reviewed show that low CD4 counts (<200 cells/ µL), prior admission, no use of HAART or poor adherence on HAART, a low socio-economic status and having a physician experienced in the management of HIV and AIDS, younger and older age, lack of private health insurance, psychosocial trauma, female gender; older age, and HCV co-infection were associated with hospital admissions.

All the studies reviewed above included participants with different characteristics to the population being studied in this paper. They mainly focused on public sector patients who did not have private health insurance.
The results from these studies can therefore not be entirely generalized to the South African medically insured private sector population, hence the importance of performing this proposed study.

CHAPTER 3

MATERIALS AND METHODS

Study Population

This is a retrospective cohort study of HIV-positive patients enrolled on a medical aid disease management programme in South Africa between 01 January 2006 and 31 December 2008.

Disease management programmes aim to assist with the co-ordination of patient care between the treating doctor, pharmacy and laboratory services, and to ensure access to correct benefits. This co-ordination of care is intended to assist in improving the patient's clinical outcomes.

Only data collected after enrolment to the disease management programme was used. Any prior admissions outside the programme were not documented. Permission to carry out the study was granted by the senior management of the relevant medical aid company. The clinical protocol was approved by the Ethics committee of the University of Pretoria.

Inclusion Criteria

All active medical aid HIV-positive adult and paediatric enrolled patients between the periods of 01 January 2006 and 31 December 2008. Only HIV-related admissions were taken into account. These were identified using the ICD-10 coding system. These admissions included HIV-specific codes and all other related conditions including but not limited to infectious diseases, haematological conditions, obstetric conditions, malignancies and neuropsychiatric conditions.

Exclusion Criteria

All patients who were not active members of the medical scheme at the time of data collection and all those who were active members but not part of the disease management programme at the time of data collection were excluded from the study.

Data collection

Medical aid records including demographic and clinical information were reviewed for 8440 HIV-enrolled patients. This information included the admitting doctor details and admission diagnosis.

Statistical analysis

The data captured in Excel and converted into STATA for statistical analysis. STATA version 10.0 was used for statistical analyses. The main outcome of the study was time from enrollment into the program from 01 January 2006 to first admission to hospital. Those that already had an admission before 01 January 2006, thus left censored were excluded from analyses. The main event was admission to hospital between 01 January 2006 and 31 December 2008. Those that were enrolled but never had an admission at the end of the study were right censored at the end of the study, including those that left the management program between the observation periods.

Survival analysis techniques specifically Cox proportional hazards models were used to analyze these data. Descriptive analysis of key prognostic factors was conducted. All variables that were considered statistically significant at p-value less or equal to 5% in the univariate analyses were considered in the multivariate Cox proportional hazards model.

Medical aid plan type was used as a proxy for socio-economic status. The top plans represent a higher socio-economic status while the lower plans represent a low socio-economic status. The limitation of this assumption is that there are some patients who should be classified as high socio-economic status who have bought cover on the lower plans and are therefore misclassified.

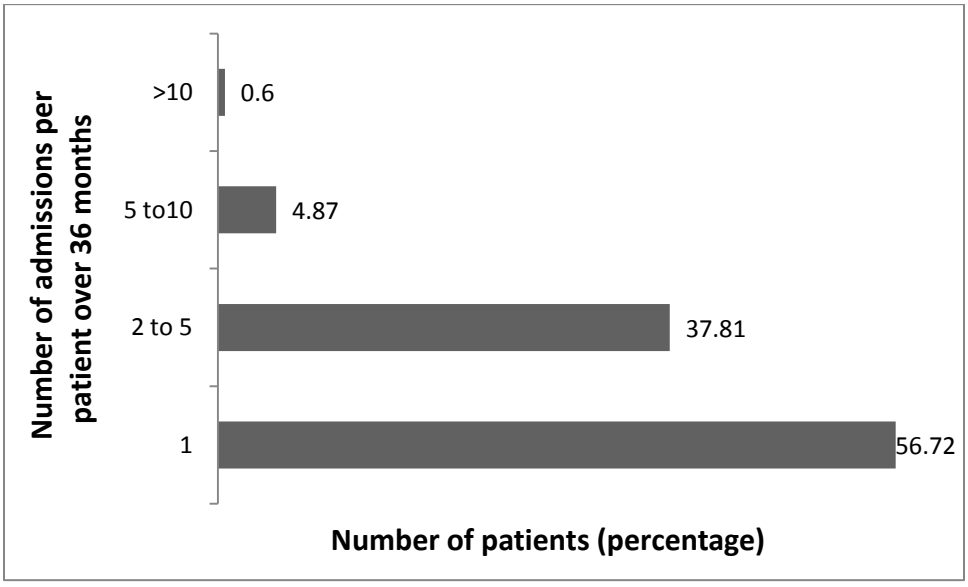
CHAPTER 4

RESULTS

Descriptive Statistics

A total of 8440 patients were followed up in the study. Among these patients, half of them had at least one admission during the observation period. Of those that had an admission, 56.72% had one admission while 43.28% had more than one admission, 37.81% had 2 to 5 admissions, 4.87% had between 5 and 10 admissions, while 0.60% had 10 to 16 admissions with an average of 2 admissions per patient over the 36 month period. The highest number of admissions was 16 admissions over the 36 month period.

Figure 1: Number of admissions per patient for the 4220 study participants who were hospitalized during the 36 months study period



Three percent of participants were aged 2 to 10 years, 1% aged 11 to 20 years, 55% aged 21 to 40, 38% aged 41 to 60 years and 3% aged 60 years or more. There were

slightly more females than males in the study. The average age of patients in the study was 38 years.

Figure 2: 8440 study participants split by age bands

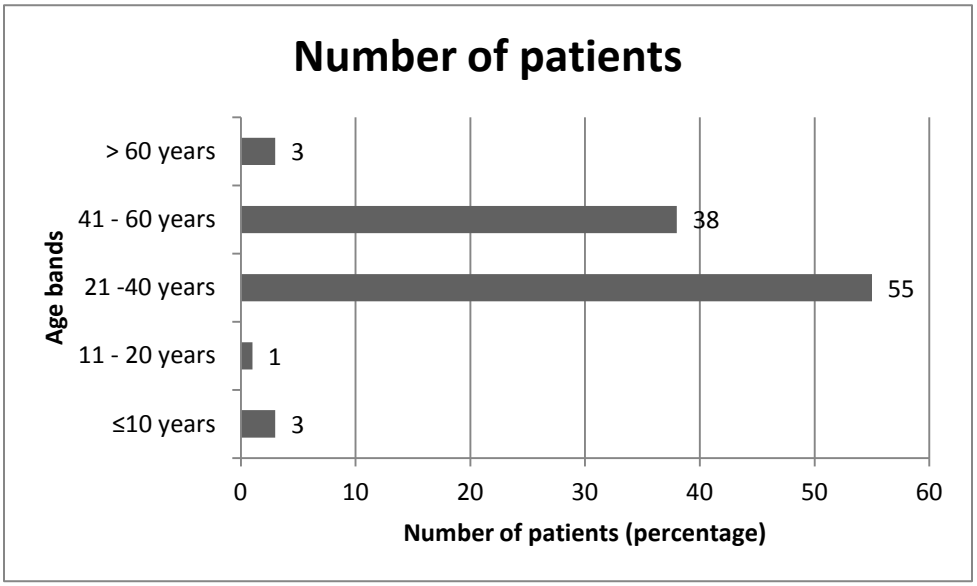


Figure 2 shows that most patients are in the 21-40 year age group followed by the age group 41-60 years. The South African HIV prevalence data also show that the age group 21-40 has the highest HIV prevalence, especially among women. This is the time that they are highly sexually active, since many are in the age group that is planning to start families. This is also illustrated in figure 9. [23, 24]

There were more females than males (72.6% versus 27.4%) in the 21–40 year age group while there were more males than females (57.5% versus 42.5%) in the 41-60 year age group. The median CD4 cells/µL was 245 ranging from 1 to 6386 cells/µL. Most patients had CD4 cell counts of less than or equal to 200, indicating severe immune suppression. A considerable proportion of participants started treatment after admission indicating that a sizeable percentage probably did not know their HIV status until they were admitted to hospital.

Table 1: Basic characteristics of the study participants

Characteristic N=8440	n (%)
Age in years (min –max)	38 (2 -83 years)
≤10 years	253(3)
11-20 years	84(1)
21-40 years	4642 (55)
41 -60 years	3207(38)
>60 years	253(3)
Gender	
Male	3460(41)
Female	4980(59)
Had event (admission)	
Yes	4220(50)
Single admission	2405(57)
Multiple admissions	1815(43)
No	4220(50)
Participants with available CD4 count records	7258(86)
Participants with no CD4 count records	1182(14)
CD4 cell count (median)	245(1 -6386)
CD4 cell count ≤ 200	3048(42)
CD4 > 200 and ≤ 350	1452(20)
CD4> 350	2758(38)
ART started	
Before admission	1688(40)
After admission	2532(60)

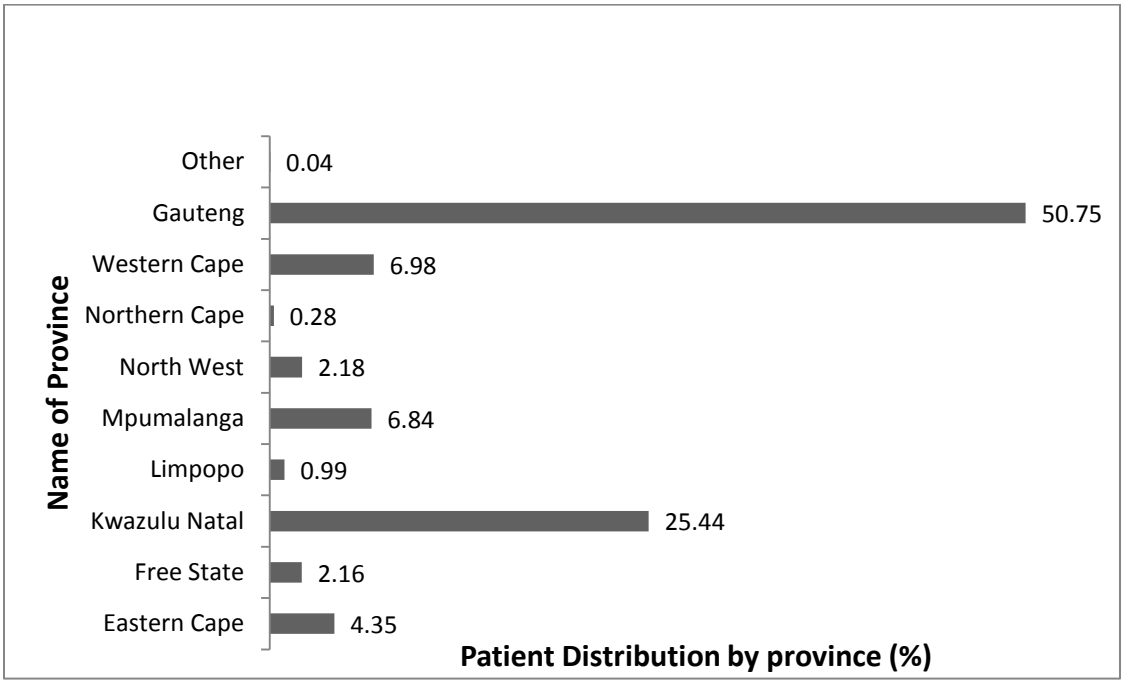
88% of patients in the study were on ART. Among the patients on ART, 40% started ART before first admission whilst 60% started ART after admission.

Figure 3 illustrates the distribution of patients by province. Seventy six percent of patients included in the study are living in Gauteng and Kwazulu-Natal while 24% live in other provinces.

“Other “refers to individuals who have addresses falling outside of South Africa. These patients reside in Southern Africa (e.g. Lesotho, Namibia, Zimbabwe) but not in South Africa. They were included in the analysis because most of their medical care is still provided in South Africa.

The South African provincial prevalence data published by the Human Sciences Research Council (HSRC) in 2009 identified KwaZulu-Natal, Mpumalanga and Free State as having a high HIV prevalence of over 20% among people of reproductive age. The Western Cape and Northern Cape provinces had the lowest prevalence of below 10% and the rest of the provinces including Gauteng had a prevalence of between 14% and 17.7%.[23] Other publications have also shown similar prevalence patterns. [24]

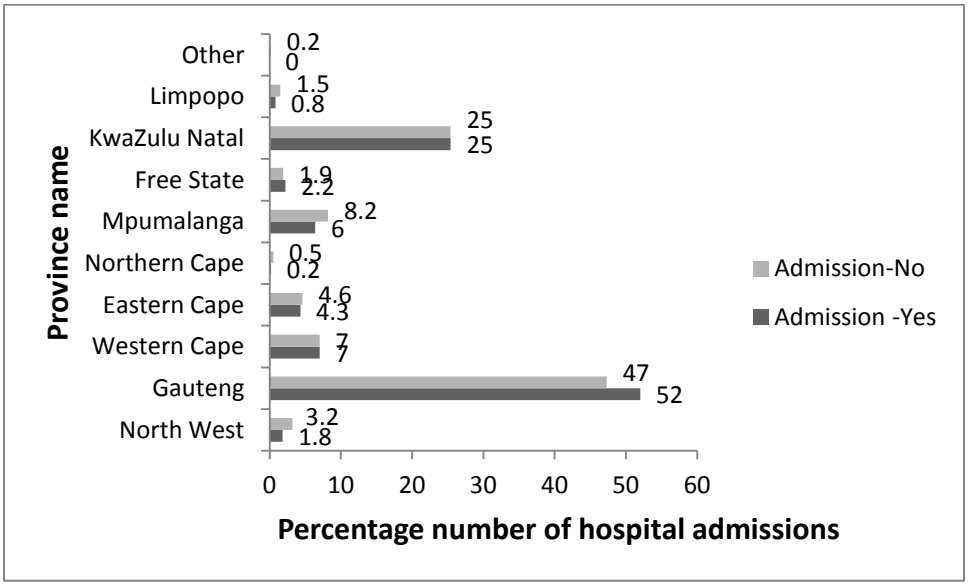
Figure 3: 8440 study participants by provincial distribution



The patient distribution seen in Figure 3 is therefore not completely aligned to published provincial prevalence figures since the patients under study are mainly from urban

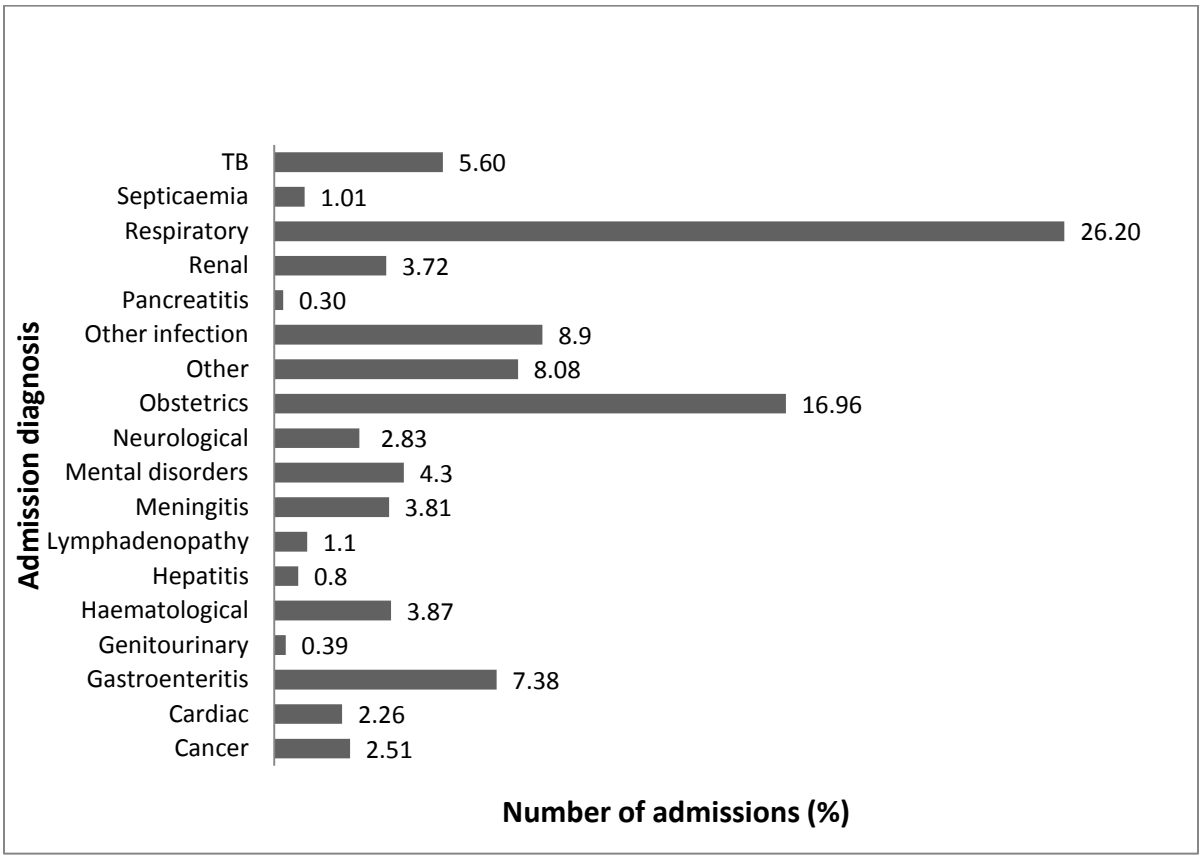
provinces. Access to medical aid cover is more common to people in urban areas than those in rural areas. The admissions are also highest in Gauteng and Kwazulu-Natal where most of the HIV-positive patients enrolled in the medical aid scheme are concentrated. This is illustrated in Figure 4. This also correlates with the South African population statistics where more that 40% of the general population lives in Gauteng and Kwazulu-Natal.[4]

Figure 4: Comparison of the provincial distribution of the 4220 study participants who had an admission versus the 4220 study participants who did not have an admission.



The most common admission diagnoses for this patient population are presented in Figure 5.

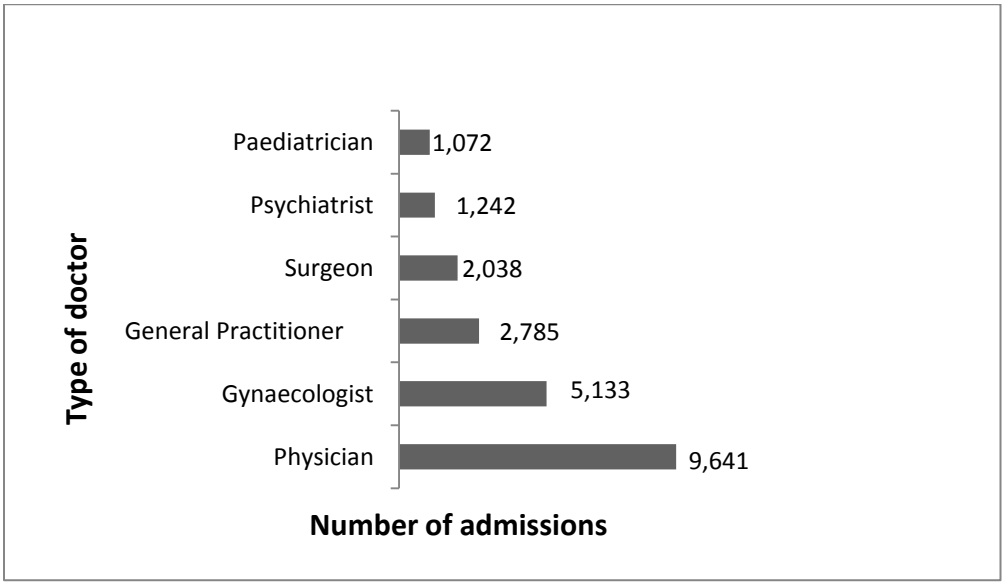
Figure 5: Admission diagnosis for the 4220 study participants generated from codes submitted on hospital claims



The results show that respiratory admissions were the commonest followed by obstetric admissions. These diagnoses refer to bronchopneumonia and childbirth via caesarian section respectively. Cases that were specifically coded as tuberculosis were not included under the respiratory admissions; all tuberculosis-related admissions were grouped together. It is however important to note that some tuberculosis cases fall within the bronchopneumonia diagnosis but may not have been coded as such. The third commonest admission diagnosis is “Other infection” and it includes a variety of infections such as abscesses, cellulitis, and peritonitis.

Figure 6 illustrates the top 6 doctor types that accounted for 82.4% of all admissions. Physicians and gynaecologists were the top 2, correlating with the admission diagnoses of bronchopneumonia and childbirth respectively. General practitioners were the third most common admitting doctor type. Most patients visit their general practitioners for routine primary care. Admission candidates are most likely to be picked up at this stage.

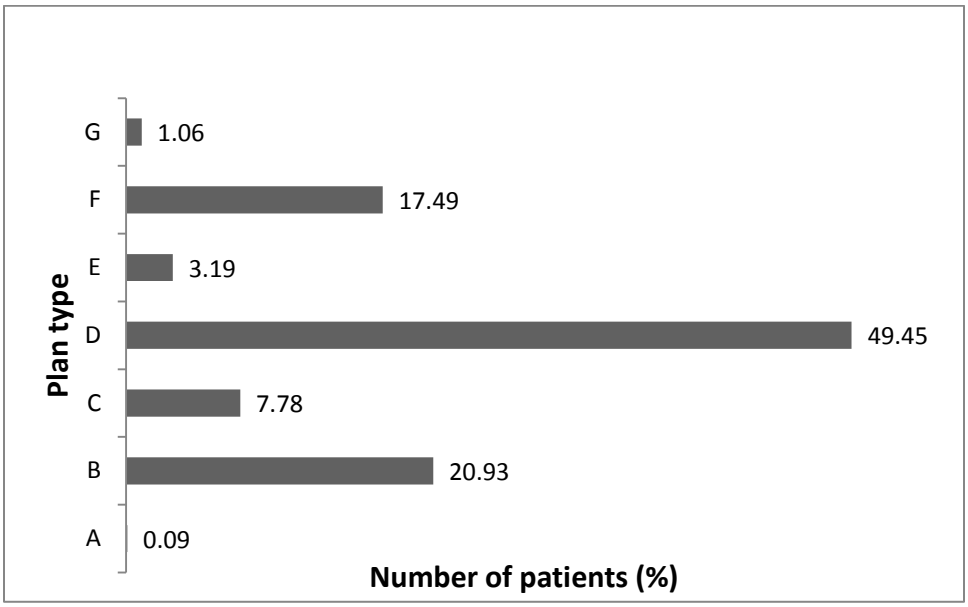
Figure 6: Admitting doctor type for the 4220 study participants who had a hospital admission



Medical aid plan type is used in this study as a proxy for socio-economic status.

Forty nine percent of patients were on plan D followed by 20.93% and 17.49 % for plans B and F respectively.

Figure 7: Distribution of the 8440 study participants by Medical Aid Plan Type



Plans A, B and C = top plans, **Plan D and E** = middle premium plans, **Plan F and G** = low premium plans

Figure 8: Comparison of the Medical Aid Plan Types of the 4220 study participants who had an admission versus the 4220 study participants who did not have an admission.

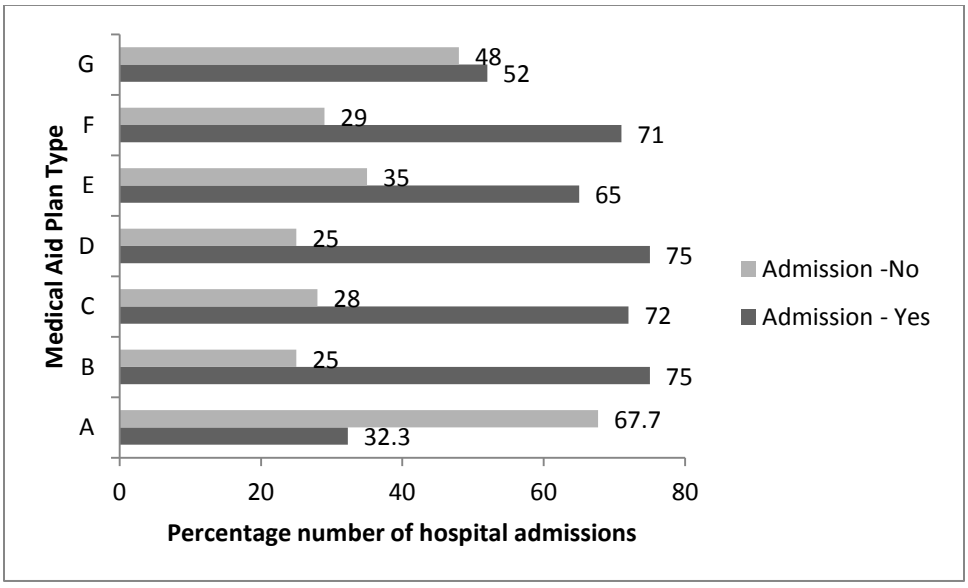


Figure 8 also illustrates admissions by plan type. Plan types D, B, C and F had 75%, 75%, 72% and 71% admissions respectively, with plan type A having the least admissions (32.3%). Plan type A was a relatively new plan with fewer members at the time of the study. Interpretation of the results relating to socio-economic status will take this into account.

Survival Analysis

Univariate analysis

Dates of enrolment and admissions were used to create the survival outcome which requires follow up time and an indicator of whether the event occurred or not. The analysis focuses on time to first admission to hospital since the beginning of observation period during the three year follow up period.

Age and CD4 cell count were categorized into groups with similar biological features when it relates to the outcomes variable.

Age was categorized into the very young (≤10years), older children and teenagers (10 to 20 years), reproductive age group (21-40 years), late adult life (41-60 years) and the elderly (>60 years).

CD4 count was categorized according to level of immune suppression with <100 cells/μL for very severe immune suppression, ≥100 but < 200 cells/μL for severe immune suppression, ≥200 but < than 350 cells/μL for moderate immune suppression, ≥350 but < 500 cells/μL for mild immune suppression and > 500 cells/μL for immunocompetence.

Figure 9 presents the Kaplan-Meier estimate of time to event during a period of 36 months follow up. The figure shows that 50% of patients have had an event, that is, have been admitted in hospital within 10 months of recruitment whilst 75% have had an event just over 24 months of recruitment. This is an indication that most people enroll rather late in the infection when their immunity is severely compromised.

Figure 9: Survival curve illustrating time to first admission for the 8440 study participants followed over a period of 36 months. Study participants who did not have any admission during the study period were censored at the end of 36months

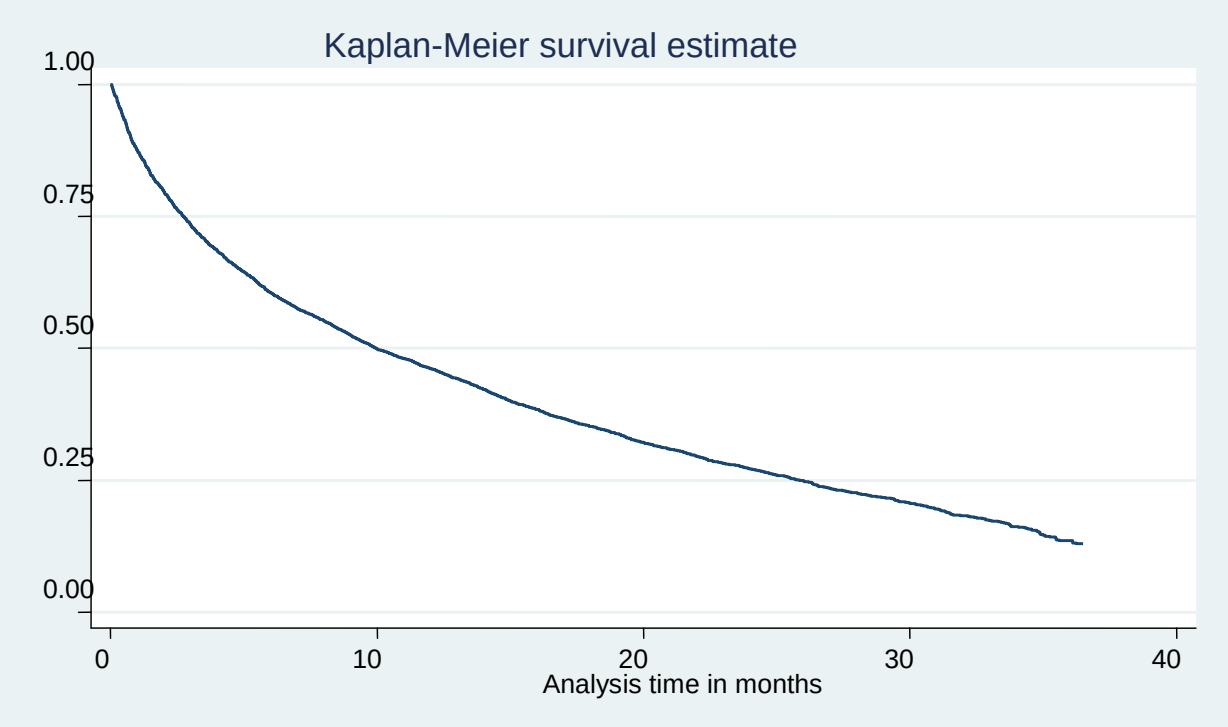


Figure 10 represents the survival curve by gender. The results show that females are more likely to be admitted much earlier than males. It has already been observed that obstetric admissions are the second commonest admission diagnoses for this population (Figure 5). These diagnoses are common among women than men. A Log-rank Test was performed to compare the survival between the two curves. The results show a statistically significant difference in the admission rates between males and females ($p<0.01$) with females being more likely to be admitted earlier than males.

Figure 10: Survival curve showing admissions by gender for the 8440 study participants followed over a period of 36 months.

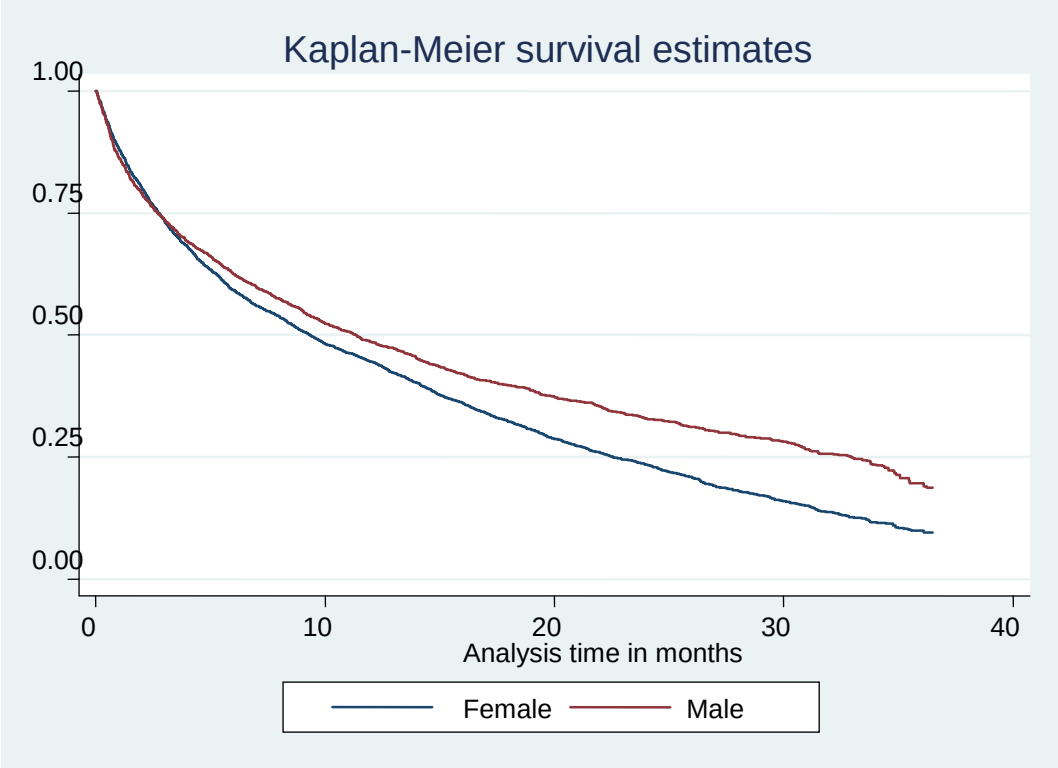
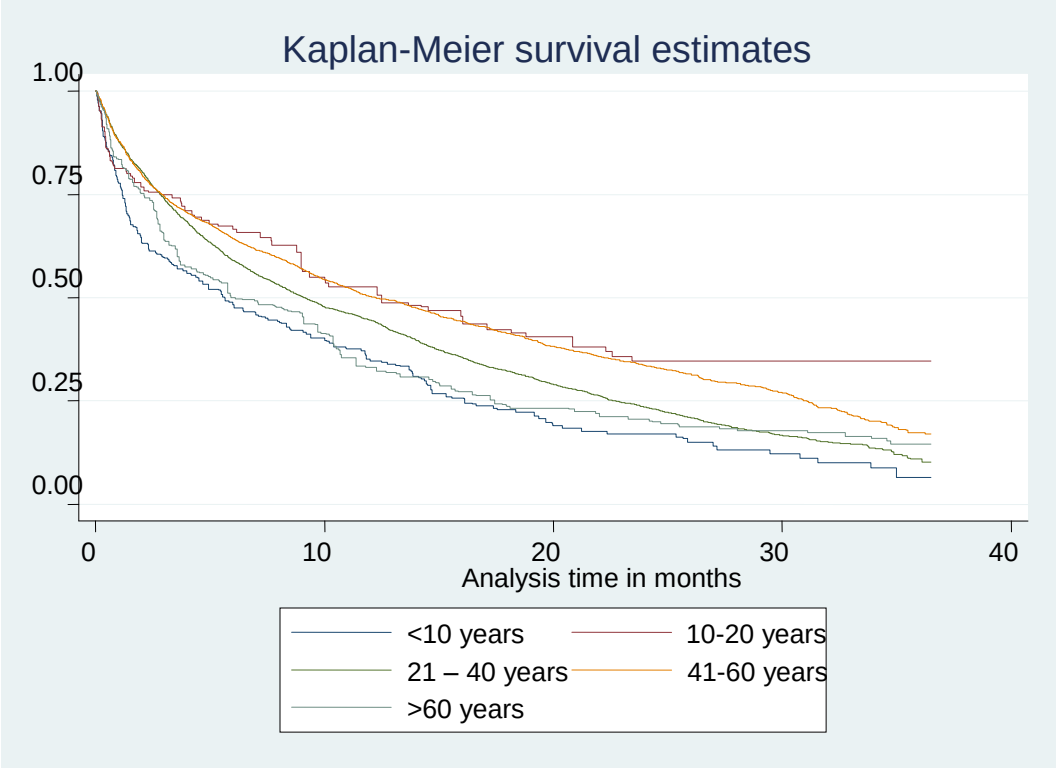


Figure 11 illustrates that admission rates are lowest for age group10–20 yrs while age groups < 10years and >60 years show the highest admission rates.

Age group 21-40 years initially showed lower admission but towards the end of the analysis time, the survival curve crossed over, approaching that of < 10year olds. The 21-40 year age band is within the reproductive age group and obstetric admissions for the female patients could be responsible for this picture. Low CD4 cell counts could also be a driver of admissions in this age band.

Figure 11: Survival curve by age bands for the 8440 study participants followed over a period of 36 months.



A Log-rank test for equality of survivor functions was performed to compare the survival between the different age bands. The results show statistically significant difference between the survival curves by age groups (P<0.01).

Figure 12 also shows that the national HIV prevalence is higher among those aged between 21 and 40 year, especially among females. Figure 12 is taken from the South African HIV Survey 2008 published by HSRC**.**[23]

Figure 12: HIV prevalence, by sex and age, South Africa 2008

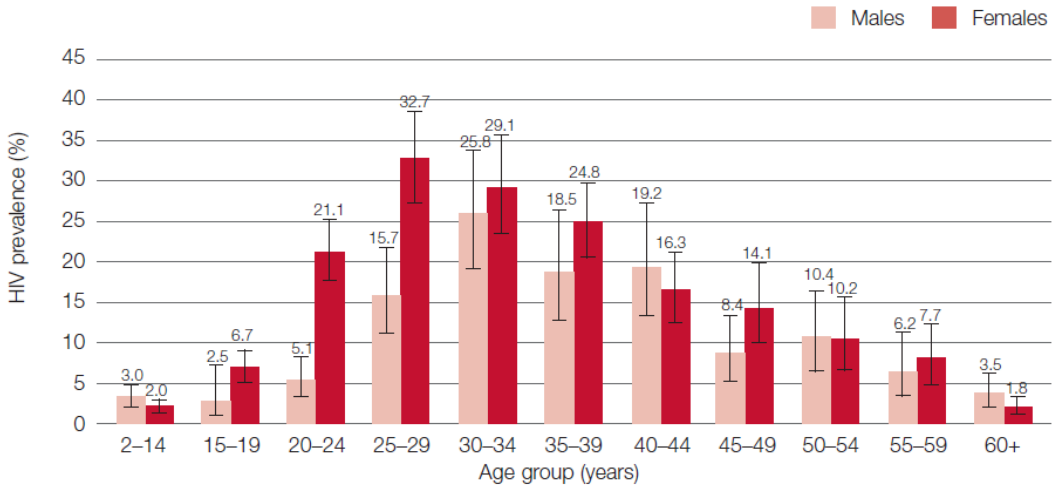
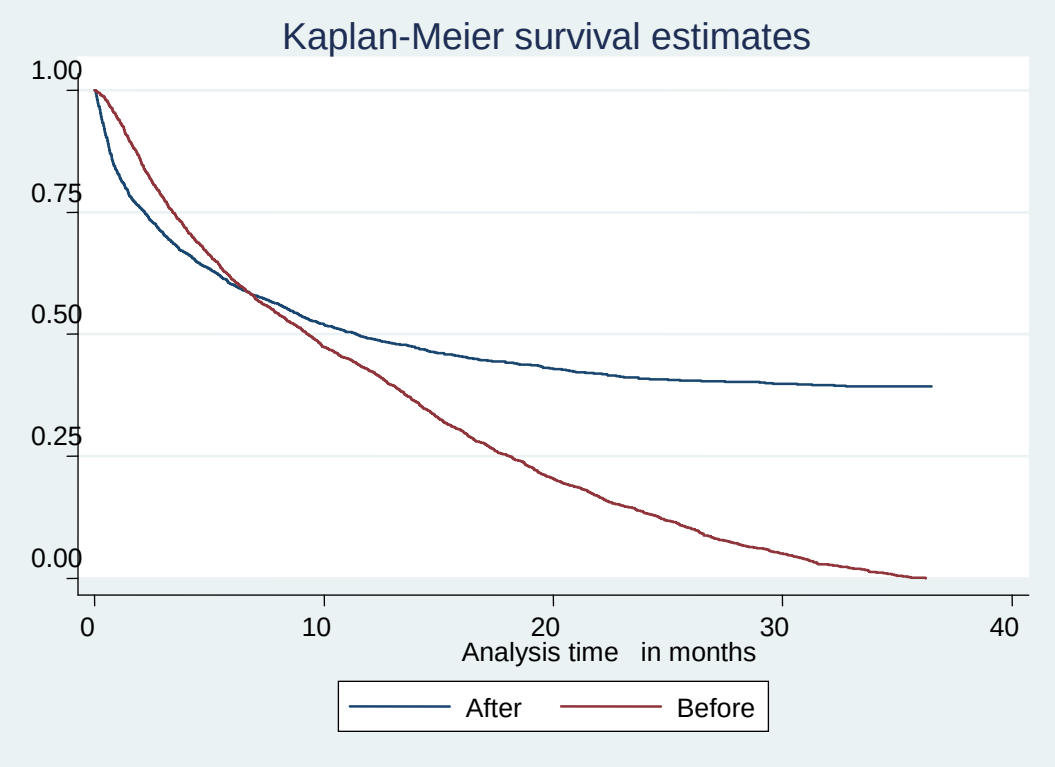


Figure 13 shows survival based on whether the patients were on treatment or not at the time of their first admission. It appears that the survival is initially better for those who started treatment before their first admission. Around month 7 the curve crosses over and shows a poorer picture for these patients. There could be several reasons contributing to this including the possibility that patients who are already on antiretroviral therapy might be failing treatment due to poor adherence to therapy.

A Log-rank test was performed to compare the survival experience between those who started treatment before and those who started treatment after admission. The results show a statistically significant difference in the admission rates between those who initiated antiretroviral therapy before the first admission versus those who initiated treatment after their first admission ($p<0.01$) with the patients starting treatment before first admission showing faster rates of admission.

Figure 13: Survival curve comparing admissions for the 4220 study participants' who started ART either before or after their first admission



These results need further analyses that control for the duration of treatment. Table 2 shows the distribution of CD4 bands for patients initiating antiretroviral therapy "Before" and "After" their first documented admission. In the "After" group, 42% of the CD4 counts were below 200 while in the "Before" group 45% were in this category. This is not a significant difference between these groups and it does not explain the findings seen in figure 13.

Table 2: Comparison of CD4 bands for the 4220 participants who had admission "Before" versus "After" initiation of ART

	CD4 bands					
	<100	**≥ 100 to <200**	**≥ 200 to <350**	**≥ 350 to <500**	**≥ 500**	**Total**
After	5,500(25%)	3,741(17%)	4,873(22%)	3,511(16%)	4,261(19%)	21,886
Before	4,384(30%)	2,151(15%)	2,789(19%)	2,226(15%)	2,846(20%)	14,396
Total	9,884	5,892	7,662	5,737	7,107	36,282

Table 3 shows the distribution of age bands for patients initiating antiretroviral therapy "Before" and "After" their first documented admission. There were no significant differences between these two groups especially when looking at the ≤ 10 year and > 60 year age bands.

Table 3: Comparison of age bands for the 4220 participants who either had an admission "Before" or "After" initiation of ART

	Age bands in years					
	<10	**11 – 20**	**21- 40**	**41 – 60**	**>60**	**Total**
After	640(3%)	291(1.3%)	11,475(52%)	8,749(40%)	731(3.3%)	21,886
Before	420(3%)	101(0.7%)	8,613(60%)	4,928(34%)	334(2.3%)	14,396
Total	1,060	392	20,088	13,677	1,065	36,282

Figure 14 illustrates that 64.6% of members still have CD4 cell counts that are below 350 cells/µL, and 43.48% of patients have severe immunodeficiency with CD4 cell counts below 200 cells/µL. Thirty five percent of the patients have CD4 cell counts above 350 cells/µL with only 19.59% of patients with CD4 counts above 500 cells/µL. Literature clearly associates lower CD4 cell counts below 200 cells/µL with increased morbidity and mortality.[11, 14, 18, 19]

Figure 14: CD4 cell count bands for the 7258 study participants who had available CD4 records

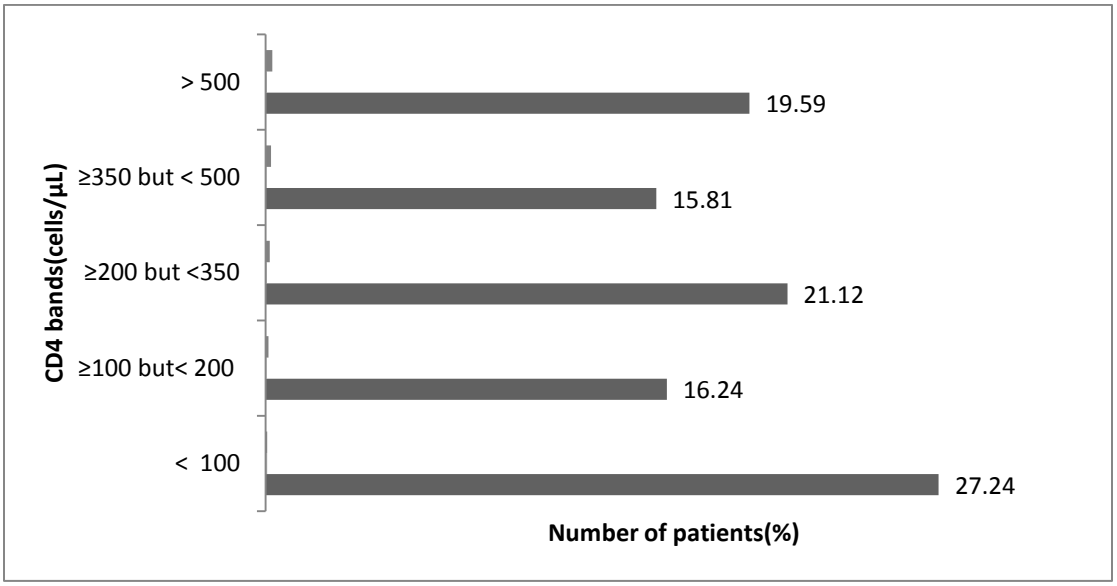


Figure15: Survival curve illustrating admissions by CD4 band for the 7258 study participants with available CD4 records showing admissions by CD4 category

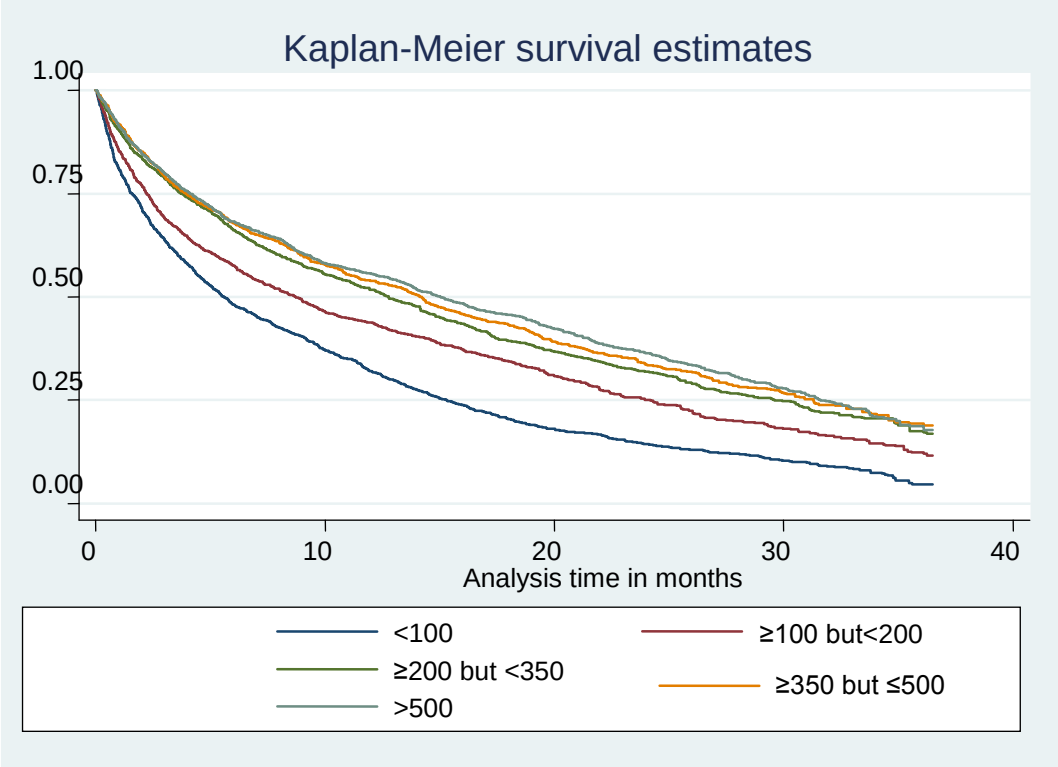


Figure 15 further confirms that lower CD4 cell counts are associated with poor survival outcomes compared to patients with higher CD4 cell counts. This means that the time to first admission was quicker for patients with lower CD4 cell counts compared to the higher CD4 bands. Thus it is important that HIV is diagnosed early whilst CD4 counts are still higher to reduce the possibility of a hospital admission. A Log-rank test for equality of survivor functions was performed to compare the survival between the different CD4 categories. The results show statistically significant difference between the survival curves by CD4 bands ($p<0.01$).

Figure16: Survival curve by doctor type for the 8440 study participants

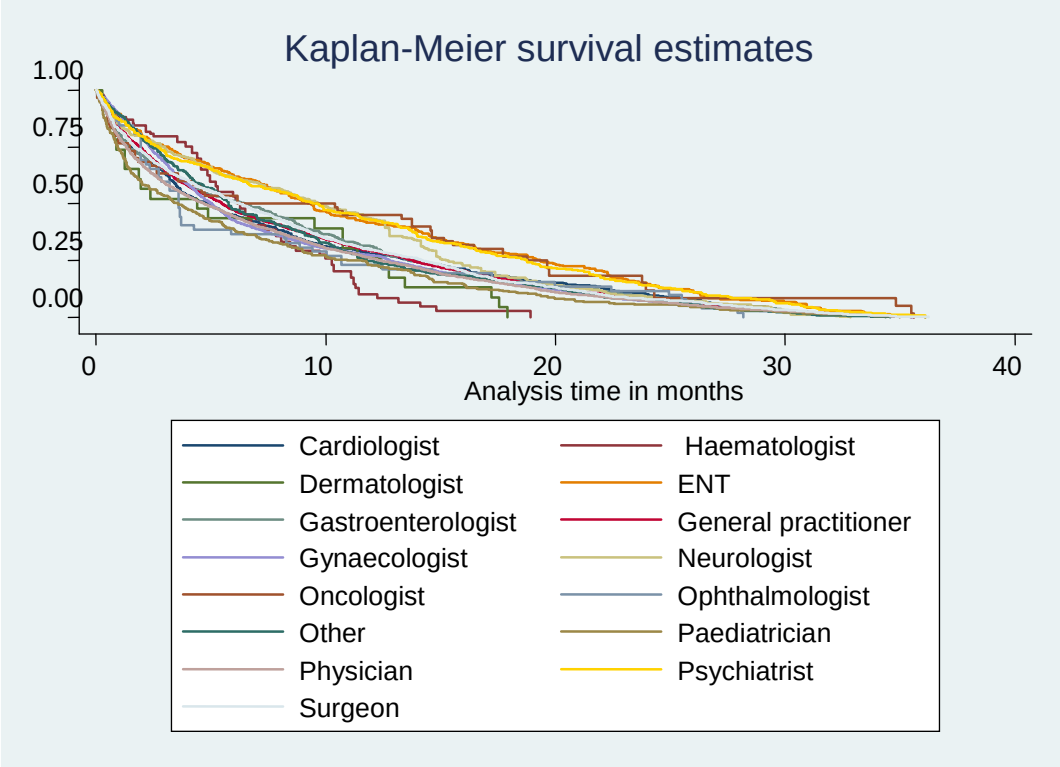


Figure 16 illustrates admissions by doctor type. The survival curves for most of the doctor types appear to be close to one another implying no significant difference in admission rates between different doctor types. Around month 11, the clinical haematologist curve does however seem to be worse off than the rest. This means that this doctor type is associated with more admissions. Survival curves for psychiatrists, oncologists and ENT specialists initially appear to be better than the rest of the doctor types but become statistically insignificant towards the end of the analysis time.

A Log-rank test was performed to compare the survival curves of the different doctor types. The results show a statistically significant difference in the admission rates between the different doctor types ($p<0.01$).

Figure17: Survival curve by Medical Aid Plan type for the 8440 study participants

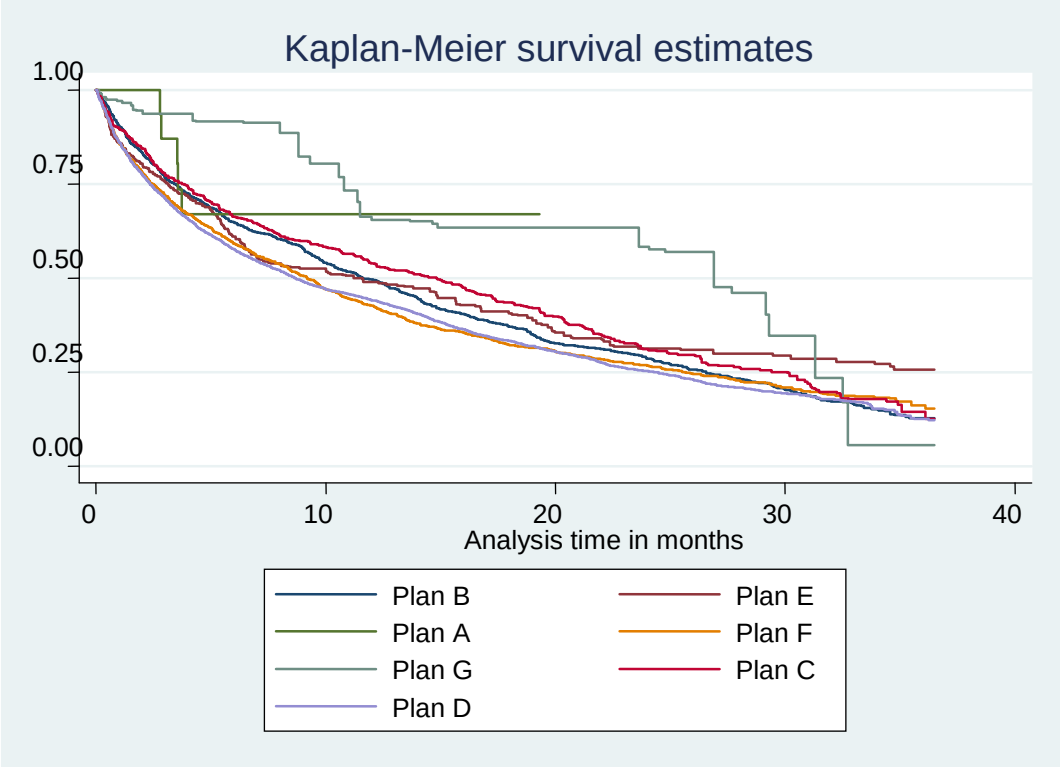


Figure 17 looks at survival (admission) by plan type. Better survival is associated with plan A and plan G. Plan A had very few patients compared to other plans and therefore these results may not be a true representation. Towards the end of the analysis time, the survival curve for plan G crosses over the rest, ending off as the plan type with poorest survival. Survival curves for plans D and F show poorer survivals but at the end there is no difference when compared to plans B and C and they actually look better than the curve for plan G. Plan D is a middle income plan and most of the patients included in this study belong to this plan type. Plan F is one of the low income plans with relatively limited benefits and is associated with a low socio-economic status.

A Log-rank test was done and it showed a statistically significant difference in the admission rate between plan types ($p<0.01$)

Figure18: Survival curve by province for the 8440 study participants

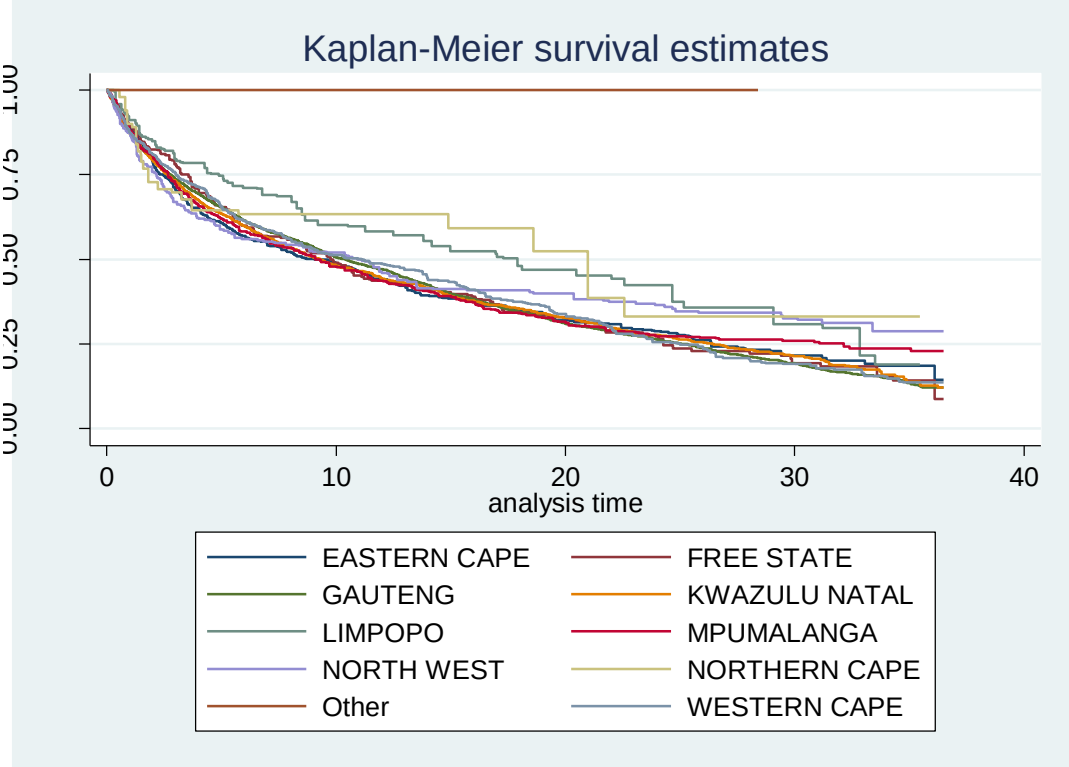


Figure 18 illustrates survival by province. There were no admissions associated with patients from the “Other” province.

Limpopo and Northern Cape are associated with better survivals while there does not appear to be a significant difference between the rest of the provinces. From around 15 months North West province also seems to show better survival. These provinces are among the provinces with a lower HIV prevalence according to the South African provincial prevalence data published by the Human Sciences Research Council (HSRC) in 2009.

There are also very few patients from these provinces in this study.

A Log-rank Test was performed to compare the survival curves of the different provinces. The results show a statistically significant difference in the admission rates between the different provinces ($p<0.01$).

Table 4: Summary of the Univariate Analysis

Variable	Test	Outcome
Age	Log-rank	p<0.01
Gender	Log-rank	p<0.01
CD4	Log-rank	p<0.01
Antiretroviral start	Log-rank	p<0.01
Plan type	Log-rank	p<0.01
Doctor type	Log-rank	p<0.01
Province	Log-rank	p<0.01

Seven variables were tested and found to be significantly associated with the outcomes variable (admissions).The log-rank test were used to test for the significance of the observed association. These variables were all included in the multivariate analysis. A stepwise approach to include them in the model was followed.

Multivariate analysis

Seven variables were included in the multivariate analysis using a stepwise method. A forward selection of variables was adopted.
Variables were introduced one by one into the model, if a variable did not show statistical significance it was then dropped off the model. This allowed only statistically significant variables to be included in the final model. The variable “province” was dropped and was not included in the final model as it did not show any statistically significant association with the outcomes variable in the process of model development. All the other six variables were kept and included in the final model as they continued to show significance during the stepwise inclusion.
The reference categories for age, gender, CD4 count, plan type were changed and the first category was not used as a reference for these variables.
Reference categories with a lower prevalence of the failure variable were used instead and these were age category 41-60, male gender, CD4 category >500 cells/µL and plan type C.

Table 5: A Summary of the multivariate output for the 6 variables that showed statistical significance in the univariate analysis

_t	Haz. Ratio	Std. err.z	P>z	[95% Conf. Interval]
Age				
<10yrs	1.30	.048	0.01	1.21 - 1.40
10 -20years	1.24	.084	0.01	1.10 - 1.42
21 -40 years	1.10	.015	0.01	1.10 - 1.13
41-60 years	1.00			
> 60years	1.13	.044	0.01	1.10 - 1.27
CD4 count				
<100	1.34	.026	0.01	1.30 - 1.39
≥100 to <200	1.22	.027	0.01	1.17 - 1.27
≥200 to < 350	1.08	.022	0.01	1.04 - 1.13
≥350 to <500	1.10	.025	0.01	1.05 - 1.15
>500	1.00			
Gender				
Female	.97	.013	0.01	.94 - .99
Male	1.00			
Plan Type				
Plan B	1.07	.03	0.01	1.02 - 1.13
Plan E	1.40	.06	0.01	1.28 - 1.52
Plan A	4.08	1.30	0.01	2.19 - 7.61
Plan F	1.33	.04	0.01	1.26 - 1.40
Plan G	.75	.06	0.01	.64 - .87
Plan D	1.21	.03	0.01	1.15 - 1.27
Initiation of ART				
Before	.41	.005	0.01	.40 - .42
After	1.00			
Doctor type				
General Practitioner	1.14	.033	0.01	1.07 - 1.20
Medical Specialist	1.17	.028	0.01	1.12 - 1.23
Surgical Specialist	1.15	.029	0.01	1.10 - 1.21
Other specialists	1.00			

The analysis showed that lower CD4 counts (< 200 cells/ µL were associated with high hospital admissions. CD4 cell counts lower than 100 cells/ µL showed an even greater association with hospital admissions with HR = 1.34 [95%CI 1.30 – 1.39] for CD4 band < 100 cells/ µL while the HR = 1.22 [95%CI 1.17 – 1.27] for ≥ 100 to ≤200 CD4 band. Age groups ≤ 10 years, 10 to 20 years and the older age group (>60 years) were significantly more likely to be admitted than the middle age groups, HR = 1.30 [95%CI 1.21 -1.40] (p<0.01) 1.24[95%CI 1.10 – 1.42] and HR=1.13[95% CI 1.10 – 1.27]

(p<0.01) respectively

The hazard ratio for gender was closer to 1 showing no statistical significance.

Prior to inclusion of the doctor type variable, initiating ART before the first admission had strong association with admissions HR =1.73, p<0.01. The association of plan type with admissions was statistically significant for plan type D with HR=1.22 and for plan type F with HR=1.16, p<0.01 and it showed a protective effect for plan type G with HR=0.64, p<0.01.The inclusion of the variable doctor type resulted in a change in hazard ratios for plan type and initiation of antiretroviral variables. Plan type A became highly statistically significant HR=4.08, [95% CI 2.19 - 7.61] followed by plan types E, F and D with HR=1.40, 1.33, 1.21, p<0.01 respectively. It is important to note that there were very few patients in plan type A with fewer admissions which is also suggested by the wide confidence interval. The doctor type variable is a potential confounder as its inclusion resulted in a change in hazard ratios for the other variables.

The initiation of antiretrovirals variable had HR =1.72[95%CI 1.68 – 1.77] before the doctor type variable was included in the model. On inclusion of the doctor type variable the HR = 0.41, [95% CI 0.40 – 0.42] p<0.01.

The doctor type variable was associated with admissions, with medical specialists having a higher HR =1.17[95% CI 1.12 – 1.22], p<0.01 followed by the surgical specialists HR=1.15 [95% CI 1.10 – 1.21], p<0.01 and general practitioners HR=1.14[95% CI 1.07 – 1.20] p<0.01. On further analysis, the type of doctor that showed statistically significant association with admissions within the medical specialist and the surgical specialist groups were the clinical haematologist and gynaecologist with HR =1.58 [95% CI 1.29 – 1.94] p<0.01 and 1.17[95% CI 1.08 – 1.27] p<0.01 respectively.

In the final analysis, variables that showed a statistically significant association with hospital admissions were the age of a patient, CD4 cell count and doctor type. Even though the plan type showed significance this was for a very small group of patients with very few admissions and thus these results will need to be confirmed in a bigger population group.

CHAPTER 5

DISCUSSION

This study specifically looked at private sector patients who had medical insurance. These are patients who have access to better quality of health care services when compared to patients who use public sector facilities in South Africa. Public sector patients face challenges such as having to wait in long queues to access HIV care due to staff shortages.

The findings of this study confirm the results shown in other studies that demonstrate that CD4 cell counts of < 200 cells/µL are risk factors for HIV-related hospital admissions. The lower the CD4 counts get (<100 cells/µL), the greater the hazards for an admission. It is therefore very important to monitor CD4 cell counts for all HIV-positive patients, especially those not yet on antiretroviral therapy. This will ensure timely initiation of ART before the CD4 cell count drops too low. Antiretroviral therapy reduces the occurrence of opportunistic infections and thus reduces the incidence of hospital admissions.

It is evident from the reviewed literature that initiation of ART at very low CD4 cell counts is associated with IRIS which is also associated with increased mortality and morbidity.

In this private sector population, such low CD4 counts were not expected as patients have access to HIV testing and treatment benefits. Awareness of the importance of HIV counseling and testing needs to be intensified in this population.

Knowledge of HIV status allows patients to access HIV care timeously, and not wait until they get sick or are hospitalized.

The South African government in partnership with the private sector has since 2010, jointly embarked on an HIV testing campaign aimed at improving the numbers of those who know their status. Knowing ones status is also coupled with transition to care programmes that assist those patients who test positive to access HIV care and

treatment.

Early knowledge of HIV status is therefore crucial, as this will ensure that patients are kept healthy for longer and that they are closely monitored for deteriorating CD4 cell counts. CD4 counts below 200 cells/µL should therefore not be seen in this patient population. Initiation of treatment for all adult patients, as per the South African private sector treatment guidelines is for anyone with a CD4 cell count that is below 350 cells/µL regardless of clinical stage. [31]

There were more females than males (72.6% versus 27.4%) in the 21 – 40 year age group while there were more males than females (57.5% versus 42.5%) in the 41-60 year age group. This means that the older men are either married to or are engaging in sexual relationships with the younger ladies. Intergenerational sex has been implicated in the spread of HIV infection between younger ladies and older men.[23]

In the univariate analysis, the female gender has also been associated with an increased risk of admissions which could be related to child birth. This also ties in with admissions associated with gynaecologists. In South Africa the private sector caesarian section rate is high, at more than 60% for all women regardless of HIV status.[32] In the HIV-positive population, it is important to investigate the drivers of this behavior and to ensure that the caesarian section rate is not related to lack of provision of ART to the pregnant mother.

Literature relating to the mode of delivery for HIV-positive mothers indicates that the role of caesarian section deliveries in patients receiving HAART and achieving undetectable viral loads has become unclear and controversial. The optimal use of HAART during pregnancy and an undetectable viral load at least 4 weeks before delivery has been associated with MTCT rates of 1%. Elective caesarian section in these patients might not offer additional benefit over vaginal delivery. Vaginal delivery should still be offered to women on optimal antiretroviral therapy with an undetectable viral load 4-6 weeks before delivery. Caesarian section deliveries are however still recommended for women not taking HAART during pregnancy, women with a detectable viral load at delivery, women on zidovudine monotherapy and women with HIV/hepatitis C co-infection. [27-31]

Younger patients need close monitoring to ensure early initiation of treatment. It is however not always easy to manage this age group as the compliance is always dependant on the commitment of the caregiver. PMTCT programmes need to be strengthened both in the public and private sectors to ensure eradication of paediatric HIV in South Africa and in Africa as a whole. This is a battle that developed countries have already won.

Older patients are also a vulnerable age group and usually present with other co-morbidities. Taking ARVs can also be a challenge for this age group especially due to forgetfulness.

Haematological complications like anaemia are commonly seen in HIV-infected patients and are related to several causes. HIV infection may lead to anaemia in many ways such as changes in cytokine production with subsequent effects on haematopoiesis; decreased erythropoietin concentrations; opportunistic infectious agents, such as Mycobacterium avium complex and parvovirus B; administration of chemotherapeutic agents such as zidovudine, ganciclovir, and trimethoprim sulfamethoxazole and myelophthisis caused by cancers such as lymphosarcoma. Other mechanisms for HIV-associated anaemia, although uncommon, include vitamin B12 deficiency and the autoimmune destruction of red blood cells. [33]

The univariate analysis also showed a faster rate of admissions for patients initiating treatment before their first admission. The possible explanation would be that that those patients who initiated their ART before their first documented admission could have already been failing treatment due to possible non-adherence. Further analysis of this group would be recommended specifically looking at how long they have been on ARV's prior to their first admission.

The prevalence of anaemia in the HIV-positive population has been estimated at 63% to 95%, making it a very common haematological complication. Anaemia has also been associated with progression to AIDS and shorter survival.[33, 34]

The association of clinical haematologists with hospital admissions in this study is therefore very important, in light of the above.

Physicians are generally associated with all medical admissions including all the

different opportunistic infections that HIV-positive patients present with.

Respiratory conditions predominantly coded as bronchopneumonia were the commonest admission diagnosis in the respiratory category in this study.

The spectrum of HIV-associated opportunistic pneumonias is broad and includes bacterial, mycobacterial, fungal, viral and parasitic pneumonias.[35, 36, 37, 38]

Pulmonary complications of IRIS are also common and are associated with bacterial (MAC and TB), fungal (Cryptococcus and Pneumocystis) and viral (CMV).

TB is amongst the commonest causes of IRIS particularly in sub-Saharan Africa where there is a high burden of this disease.

Medical aid benefits vary according to plan type. As the disease progresses most patients require more and more benefits which can be limited on the lower plan types.

The strong association between Plan A and hospital admissions could therefore be related to the fact that even though there are fewer patients and fewer admissions in this plan type, these patients could already be having advanced disease or could have other chronic co-morbidities.

Even though starting ART before or after the first admission did not show significance in the multivariate analysis, adherence to treatment is very important for patients already receiving ART to prevent treatment failure that will further result in morbidity and mortality.

Limitations of this study

Data were collected from medical aid records that relied on correct coding by the admitting doctors and admitting hospitals. The results may be skewed by incorrect coding. Not all patients had recorded CD4 cell counts and therefore only the available data was included and analysed. Use of medical aid plan type as a proxy for socio-economic status has its own limitation as there are some high income earners who have bought medical aid cover on the lower plans. The membership in the lower plans still comprises mainly of low income earners.

CHAPTER 6

CONCLUSIONS AND RECOMMENDATIONS

Factors that are still associated with hospital admissions in this private sector medically insured population are a younger and older age, low CD4 cell counts and admission by a clinical haematologist or gynaecologist.

The results of this study confirm what has previously been documented in other studies with regard to the association of hospital admissions with low CD4 counts, younger and older age groups.

The association with clinical haematologist and gynaecologist were not previously documented in the reviewed literature.

Patient education about early HIV testing needs to continue and patients must also be made aware of their medical aid benefits so that they can access them early. HIV testing assists patients to know about their status early on in the disease. This allows for close monitoring for disease progression and early intervention when indicated.

Patients must be started on treatment at relatively higher CD4 cell counts of at least 350 cells/µL. This is important especially for prevention of IRIS and the related complications that are often seen at lower CD4 cell counts. Routine monitoring of CD4 counts and viral loads for all HIV-positive patients at least bi-annually is therefore crucial. Where a rapid decline in CD4 cell count is noted, more frequent monitoring is recommended with a recommendation to initiate treatment when necessary.

Screening of all patients for opportunistic infections prior to initiating HAART is also important especially in patients with CD4 counts lower than 200 cells/µL as the risk of IRIS is higher in this patient population.

All pregnant women must be offered an HIV test as part of the routine antenatal screening. All those who test positive for HIV must be offered PMTCT timeously in order to achieve undetectable viral loads at the time of delivery. This will assist in eradicating paediatric HIV in Africa.

Paediatric HIV is a complex disease. There are however very few clinicians with experience in this field. In order to improve clinical outcomes in this patient population, up-skilling of private and public health sector clinicians is very important. Disease management should be intensified for the paediatric population in order to achieve better clinical outcomes.

Care-giver support is also important coupled with intense education on the importance of compliance.

An HIV-positive status of the mother should no longer be the sole reason for offering a caesarian section. Vaginal delivery should be offered to women who are fully covered with HAART and who have an undetectable viral load 4-6 weeks before delivery, where there are no other known contraindications.

In this era of HAART, clinicians need to be aware of the changing face of HIV and need to be educated about related co-morbidities, especially in the older patient population.

Patients are now living longer, opportunistic infections are declining and other chronic non-infectious conditions are emerging. Screening for these non-infectious conditions is therefore important and should be incorporated in the HIV benefits of all medical aid schemes for HIV-positive elderly members.

Medical aids should share data with the treating clinicians in order to alert them to these issues. This could be channeled through Continuing Medical Education (CME) sessions and must be coupled with intensified member education relating to HIV benefits.

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