

Morbidity and mortality in the modern antiretroviral treatment era in a tertiary teaching hospital in Durban, South Africa.

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Abstract

Background

Worldwide despite the availability of antiretroviral therapy, Human Immunodeficiency Virus / Acquired immunodeficiency syndrome still causes morbidity and mortality among patients. This study aimed at identifying the determinants of morbidity and mortality in the era of modern antiretroviral treatment (ART).

Methods

A retrospective study was conducted; data were obtained from medical records of all HIV infected patients admitted to King Edward medical wards from January to December 2018. This included demographic profile, clinical attributes and laboratory records. Data were analysed using R software where descriptive and inferential statistics were presented. The inferential statistics were five numbers summaries, box plot, Chi square, all fisher exact test and t test or rank some test.

Results

A total of 577 (50.6%) females and 564 (49.4%) males aged 12 years old and older infected by HIV were included in the study. The mean age of all the patients was 39.6 ± 12.2 , 506 (44.3%) patients had CD4 less than 200 cells /mm³ and 273 (23.9%) had VL \geq 1000 copies/ml. Association between CD4 cell count and Viral load ($p < 0.05$) was found. Male gender [OR 1.39(1.07–1.8) $p = 0.015$], Age [OR1.02 (1.01–1.03) $p < 0.001$], CD4 < 200 cells/mm³ [OR 2.14(1.37–3.45) $p = 0.001$], VL \geq 1000 copies/ml [OR 1.93(1.08–3.63) $p = 0.032$] were associated with mortality in our cohort. Tuberculosis was the most common diagnosis on admission and the leading cause of death.

Conclusion

These findings illustrate that advanced HIV disease remains significant among inpatients despite the roll-out of ART. There is a need for raising the awareness of early appropriate treatment.

Introduction

Worldwide, Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS) pandemic is a challenging public health concern.¹ In 2017 five low- or middle-income countries, India (84%), Eritrea (83%), Djibouti (78%), Malawi (78%) and Togo (75%), achieved or exceeded the target of a 75% reduction in TB deaths among people living with HIV.² South Africa bears the highest number of people living with HIV/AIDS.³ In 2018 an estimation of 7.7 million people was living with HIV in South

Africa.⁴ In the same year, 240,000 new HIV infections appeared, and 71,000 South Africans died from AIDS-related illnesses.⁵ In South Africa cryptococcal meningitis (CCM) continues to have significant mortality among HIV infected patients with low CD4 count, ranking between 30% and 50%.⁴ Approximately 95 of HIV-infected patients develop anaemia during their disease.⁴ The cause of anaemia in HIV-infected patients is often multifactorial.⁴ South Africa implemented the National HIV/AIDS and Sexually Transmitted Infections (STI) National Strategic Plan (NSP) to tackle the HIV/AIDS epidemic. The primary objectives of this plan were to reduce HIV incidence by 50% and to expand the availability and access to ART to 80% of all HIV infected patients in the country.⁶ The target of the Joint United Nations Programme on HIV/AIDS (UNAIDS) is to have 90% of all people tested for HIV, 90% treated, 90% virologically suppressed by 2020 and to end HIV infection.⁷ Early access to antiretroviral therapy (ART) to all people living with HIV regardless of CD4 count improve life expectancy.⁷ Due to the modern antiretroviral therapy which has enhanced the survival of HIV patients⁸, HIV infection is no longer a fatal illness but a chronic disease which is now manageable.⁹ The antiretroviral therapy (ART) suppresses viral replication, restores immune function, reduces HIV associated morbidity and mortality.¹⁰ Despite these gains, 8–26% of African patients die in the first year of initiating ART, with most deaths occurring in the first three months.¹¹ Mortality is attributed to late initiation of ART when patients have advanced disease with increased risk of opportunistic infections and immune reconstitution inflammatory syndrome.¹² Currently, antiretroviral treatment is freely available and modern, there is a fixed-dose combination, drugs are less toxic unlike in the past where most of the drugs were toxic with multiple treatment-related complications.⁸ Based on advances made in treatment, AIDS-defining illnesses related should no longer be observed, however up until today HIV infected patients still suffer and die from AIDS. Many barriers to adherence to ART had been revealed by several studies, among them socio economic factors (such as poverty, food insecurity, unemployment and transport costs) education, cultural, political factors, stigma, discrimination, lack of social support^{13,14,15} The objective of this study is to identify the reason of hospitalization and cause of death in this population.

Methods

We conducted a retrospective study of HIV infected patients who had been admitted in the medical wards at King Edward Hospital, Durban South Africa. All records of patients admitted to the medical wards from January to December 2018 were reviewed. Those included in the study were all HIV infected patients aged 12 years old and older who had been hospitalized in the medical wards at King Edward Hospital during the study period. Non-HIV patients and children were excluded. Data collected from medical records included socio-demographics, clinical parameters, admission date, discharged date, deceased date, causes of death, causes of hospitalization, laboratory data (CD4 cell count, RNA viral load, based on the HIV test) and ART. The reasons for admission were based on the final diagnostic on discharge. The final diagnostic on discharge was obtained after the patients had carried out laboratory examinations. It was based on similar standardized terminology. Causes of death were reported as they were written on death certificate. R statistical computing software was used for data analysis. Tables and graphical

displays were used to present the results. In addition, the association between the covariates was tested either with the Chi-Square test, Kruskal Wallis or Wilcoxon rank-sum test depending on the type of variables. A p -value < 0.05 was used as a benchmark for determining the level of statistical significance.

Ethical consideration.

We obtained full Ethical approval from the Biomedical Research and Ethics Council (BREC) under reference number BE 345/19.

Results

Four thousand (4000) records of patients of 12 years and older admitted to the medical wards at King Edward hospital from January to December 2018 were examined. This study included 1 141 patients diagnosed or known HIV positive. Out of the 1 141 patients, 564 (49.4%) were males and 577 (50.6%) were females. The mean age for the entire cohort was 39.6 ± 12.2 , with a range of 12 to 92, 506 (44.3%) patients had CD4 count < 200 cells /mm³, 253 (22.2%) patients had a viral load more than 1000 copies/ml. Among the included patients 301 (26.3%) died, while 840 (73.6%) were discharged home alive (Table 1). Age, male gender, CD4 cell and Viral load were associated with mortality ($p \leq 0.05$) (Table 2). Association between CD4 cell count and viral load was found (Table 3). Tuberculosis was the most common diagnosis reported at admission and accounted for 257 (22.5%) of the admissions, followed by kidney disease 83 (7.2%), anaemia 75 (6.6%), cryptococcal meningitis 62 (5.4%). Tuberculosis was also the number one cause of death with 62 (20.6%) followed by acute or chronic kidney disease 38 (12.6%), Pneumonia 19 (6.3%). Other conditions that were responsible for admission 166 (14.5%) and death 43 (14.3%) are shown in Table 4 and Table 5, respectively. There was no significant difference in the duration of hospital stay between males and females (Fig. 1). It was noticed that 70% of patients were reported to be on ART, among them, 53.1% was discharged and 16.9% died (Fig. 2).

Table 1
Comparison of HIV patients in medical wards at King Edward hospital by disposition at discharge and characteristic of 1141 patients

Characteristic	Discharged	Died	p-value	Overall
	(n = 840)	(n = 301)		(n = 1141)
Gender			0.014	
Male (Ref)	397 (47.3%)	167(55.5%)		564(49.4%)
Age			0.007	
Mean ± SD	38.9 ± 11.7	41.8 ± 13.1		39.7 ± 12.1
CD4(cells /mm ³)			0.001	
< 200	363 (43.2%)	143 (47.5%)		506 (44.3%)
200-<350	126 (15.0%)	34 (11.3%)		160 (14.0%)
350-<500	100 (11.9%)	20 (6.6%)		120 (10.5%)
500+	141 (16.8%)	26 (8.6%)		167 (14.6%)
Missing	110 (13.1%)	78 (25.9%)		188 (16.5%)
Length hospital stay(days)			0.003	
Mean ± SD	9.46 ± 9.43	8.65 ± 10.5		9.25 ± 9.72
Viral load (copies/ml)			0.049	
< 50	104 (12.4%)	16 (5.3%)		120 (10.5%)
50-<1000	94 (11.2%)	17 (5.6%)		111 (9.7%)
1000+	195 (23.2%)	58 (19.3%)		253 (22.2%)
Missing	447 (53.2%)	210 (69.8%)		657 (57.6%)
The p-values are from table Stack and based on non-missing cases only.				

Table 2
Factors associated with Mortality among HIV infected patients admitted at King Edward hospital

Explanatory	OR(Univariable)	OR(Multivariable)
Gender:	1.39 (1.07–1.81, p = 0.015)	1.12 (0.68–1.84, p = 0.647)
Male (Ref)		
CD4 (cells /mm ³)	2.14 (1.37–3.45, p = 0.001)	4.45 (1.96–11.62, p = 0.001)
< 200		
200- <350	1.46 (0.83–2.59, p = 0.186)	2.41 (0.87–7.16, p = 0.097)
350-<500	1.08 (0.57–2.04, p = 0.803)	1.00 (0.24–3.64, p = 0.999)
Age(years)	1.69 (0.74–4.57, p = 0.250)	2.67 (0.40-54.12, p = 0.389)
20–40		
40–60	1.88 (0.82–5.09, p = 0.169)	2.93 (0.29–71.84, p = 0.413)
60+	3.94 (1.55–11.48, p = 0.007)	8.02 (0.38–304.00, p = 0.204)
Duration(weeks)	0.60 (0.42–0.85, p = 0.005)	0.49 (0.20–1.11, p = 0.095)
1–2		
2–3	0.70 (0.43–1.11, p = 0.142)	0.25 (0.06–0.89, p = 0.038)
3	0.80 (0.52–1.21, p = 0.308)	0.43 (0.05–2.79, p = 0.389)
Viral load (copies/ml)	1.18 (0.56–2.48, p = 0.667)	1.08 (0.48–2.44, p = 0.857)
50-1000		
1000+	1.93 (1.08–3.63, p = 0.032)	1.36 (0.70–2.74, p = 0.380)

Table 3
Relations between Viral Load and sex, age, CD4, duration of stay, outcome.

Viral load (copies/ml)	< 50	50<1000	1000+	p-value	Overall
	(n = 120)	(n = 111)	(n = 253)		(n = 1141)
Gender				0.609	
Male (Ref)	58 (48.3%)	49 (44.1%)	126 (49.8%)		564 (49.4%)
Age				0.675	
Mean ± SD	39.4 ± 11.4	39.5 ± 10.5	39.1 ± 12.5		39.7 ± 12.1
CD4(cells/mm3)				< 0.001	
< 200	39 (32.5%)	47 (42.3%)	165 (65.2%)		506 (44.3%)
200-<350	11 (9.2%)	25 (22.5%)	38 (15.0%)		160 (14.0%)
350-<500	17 (14.2%)	19 (17.1%)	18 (7.1%)		120 (10.5%)
500+	51 (42.5%)	19 (17.1%)	28 (11.1%)		167 (14.6%)
Missing	2 (1.7%)	1 (0.9%)	4 (1.6%)		188 (16.5%)
				0.909	
Duration of stay(days)					
Mean ± SD	10.0 ± 9.13	9.41 ± 8.36	10.4 ± 10.3		9.25 ± 9.72
Outcome				0.049	
Discharged	104 (86.7%)	94 (84.7%)	195 (77.1%)		840 (73.6%)
Died	16 (13.3%)	17 (15.3%)	58 (22.9%)		301 (26.4%)

Table 4
Reasons for admissions among HIV patients in medical wards at King Edward hospital

Diagnosis	Frequency	Percentage
Tuberculosis	257	22.50%
Kidney disease	83	7.20%
Anaemia	75	6.60%
Cryptococcal meningitis	62	5.40%
Pneumonia	56	4.90%
Gastroenteritis	42	3.70%
Parasuicide	35	3.10%
Lymphoma	32	2.80%
Sepsis	31	2.70%
Congestive cardiac failure	29	2.50%
Cerebrovascular accident	25	2.20%
Unspecified meningitis	25	2.20%
Liver failure	24	2.10%
Bronchopneumonia	19	1.70%
Viral meningitis	19	1.70%
Hypertension	18	1.60%
Psychiatric	14	1.20%
Diabetic ketoacidosis	13	1.10%
Diabetes mellitus	10	0.90%
Headache	10	0.90%
Deep vein thrombophlebitis	9	0.80%
Epilepsy	9	0.80%
Adult onset seizures	8	0.70%
Asthma	8	0.70%
Bronchiectasis	7	0.60%
Heart failure	7	0.60%

Diagnosis	Frequency	Percentage
Kaposi's sarcoma	7	0.60%
Pneumocystis pneumonia	7	0.60%
Drug-induced liver injury	6	0.50%
Nephrotic syndrome	6	0.50%
Thrombocytopenia	6	0.50%
Cholelithiasis	5	0.40%
Gastritis	5	0.40%
Hepatocellular carcinoma	3	0.30%
Toxoplasmosis	3	0.30%
Other medical illnesses non HIV related	166	14.50%
TOTAL	1141	100%

Table 5
Causes of death among HIV patients in medical wards at King Edward hospital

Diagnosis	Frequency	Percentage
Tuberculosis	73	24.30%
kidney disease	38	12.60%
Pneumonia	19	6.30%
Liver failure	14	4.70%
Anaemia	13	4.30%
Congestive cardiac failure	13	4.30%
Gastroenteritis	12	4.00%
Cryptococcal meningitis	10	3.30%
Lymphoma	10	3.30%
Sepsis	10	3.30%
Bronchopneumonia	9	3.00%
Unspecified meningitis	9	3.00%
Cerebrovascular accident	8	2.70%
Viral meningitis	8	2.70%
Kaposi's sarcoma	6	2.00%
Diabetic ketoacidosis	3	1.00%
Hepatocellular carcinoma	3	1.00%
Other medical illnesses non-HIV related.	43	14.30%
TOTAL	301	100.00%

The p-values are more than 5% implying that there was no significant difference in the duration of stay between males and females' patients. This applies to both the duration of stay before discharged or demising.

Only 70% of patients had been reported to be on antiretroviral treatment (ART) on admission or discharge.

Discussion

This study aimed to identify the determinants of morbidity and mortality among HIV infected patients in the modern era of antiretroviral treatment (ART) at King Edward Hospital from January to December

2018. In this study tuberculosis was reported to be the most cause of hospitalization and of death accounting to 22.5% and 24.3%, respectively (Table 4, Table 5). Similarly, in Uganda, a study reported 18% of admissions and 24% of death due to tuberculosis.¹⁶ Other studies conducted in Nigeria¹⁷, in Gabon¹⁸ and in South Africa⁴¹ had similar findings. This may be as a result of lack of or poor TB preventative strategies, inadequate HIV counselling and testing services, also delays in referral and ART initiation are all potential reasons for late consultation and increase of TB. Other issues include, the poor infection control measures in most public spaces, lack of active case finding (ACF) and contact tracing. A study conducted in the Ivory Coast showed that access to antiretroviral therapy alone or early antiretroviral treatment with isoniazid preventive therapy (IPT) respectively, decrease the risk of mortality among HIV patients.²¹ Another study conducted in Rio de Janeiro revealed that TB prevalence and mortality of HIV patients were significantly reduced by increasing TB screening and the implementation of IPT.²² In addition, as in majority (44.3%) of the patients included in this study, CD4 counts were ≤ 200 cells /mm³ and VL ≥ 1000 copies/ml, that is a risk for developing an opportunistic infection. Other studies conducted in Gondar and India reported a high risk of developing opportunistic infection among this group.^{19,20} Anaemia and Cryptococcal meningitis were also frequently diagnosed during admission. Anaemia accounted for 6.6% of admission. This was less than what had been found in Ghana.²³ In this study, iron deficiency, vitamin B12 deficiency, folate deficiency and side effect of zidovudine are suspected to induce anaemia. Many patients had been admitted at the late stage of their disease which implied a delay in their initiation to antiretroviral treatment. Anaemia is known to be a significant problem among patients with HIV infection.²⁴ Even though anaemia can occur at any stage of HIV infection, its frequency and severity are positively correlated with progression of the disease.²⁵

Providing an early antiretroviral treatment, in general, is known to decrease anaemia among HIV patients by inhibiting the progress of the diseases, however zidovudine an element of some antiretroviral treatment regimens is identified as the commonest cause of drug-associated anaemia in low-income countries.²⁶ A study conducted in Ethiopia showed that overall, ART exposure reduced anaemia prevalence among HIV patients.²⁷ Cryptococcal meningitis accounted for 5.4% of admission among HIV patients included in this study. Similarly, the same findings were also found in Latvia.²⁸ and in Uganda.³⁵ This may result as most of the HIV infected patients included in this study had lack of information about preventive therapy among those with low CD4 cell counts. Some of the patients had delayed initiation to ART. Cryptococcal meningitis is an opportunistic infection which occurs in HIV patients in their late stage of disease.³⁰ Screening of cryptococcal antigenemia among persons living with HIV can allow early identification of symptomatic cases and improve health outcomes. The early access to antiretroviral treatment had improved the immune system of many HIV patients so that they do not become vulnerable to infection with Cryptococcus.²⁹ Studies conducted in the United States³¹ and in Thailand³² showed how fluconazole prophylaxis reduced the incidence of cryptococcal disease among HIV patients. After tuberculosis, kidney disease (acute or chronic) was found the second reason for admission and second cause of death. Among HIV infected patients admitted to King Edward, 7.2% accounted for admission and 12.6% for death, which is comparable to what had been reported in Zambia.⁴¹ Renal failure in HIV

infection is associated with increased morbidity and mortality.³³ Patients who were admitted at the late stage of the disease and had low CD4 of less than 200 cells /mm³ that also contributed to renal impairment. A study reported that chronic renal failure usually occurs only in advanced disease and mostly in patients with a CD4 count of fewer than 200 cells / mm³.³⁴ The early access to antiretroviral treatment may improve impaired renal function among HIV patients.³⁵ In the ART regimen, Tenofovir (TDF) is the first-line treatment of HIV infection, however, it is associated with a higher risk of kidney disease.⁴⁵ The other cause of death was pneumonia with 6.3% after kidney disease. A study conducted in Uganda found almost the same prevalence of pneumonia among HIV patients³⁶, however, another study conducted in Malawi³⁷ found a high prevalence of pneumonia than this study. According to the findings of this study, pneumonia might be a result of lack preventive therapy among HIV patients who had been admitted to the hospital and most of them starting late antiretroviral treatment. It had been found that ART is independently and statistically significantly associated with decreased mortality and morbidity in pneumonia patients.³⁸ Some patients were admitted at the hospital with acute symptoms, such as an acute respiratory failure, a study shows that it is a complication of pneumonia and it is associated with a high risk of death among HIV patients.³⁹ Even though there were more women than men included, more men died while admitted to the hospital than women with ($p \leq 0.05$). This is comparable to that reported from another study conducted in Nigeria.⁴⁰ In this study, male gender was admitted with lower CD4 cell counts and more severe opportunistic infection. Men may be presenting into care later than women with more advanced disease. Age, male gender, CD4 cell count less than 200 cells /mm³, HIV viral load more than 1000 copies/ml were reported to be associated with mortality in patients. These findings indicate that patients who died during hospitalization were more likely to present with poor performance status and more advanced and severe disease. A study conducted in Ethiopia reported almost the same, they found CD4 count ≤ 200 cells/mm³ as a prediction of mortality.⁴³ This study found an association between CD4 cell count and HIV viral load ($p \leq 0.05$), low CD4 cell count implies high viral load, and this might result as most of the patients had been admitted in the advanced status of the disease. However, a study conducted in Europe had contrary findings.⁴⁴

Limitation Of The Study

We noticed missing data such as ART treatment, viral load and CD4 count cell of some HIV patients.

Conclusion

Regarding the modern era of ART, there have been many improvements. Despite this improvement in treatment, people living with HIV are still hospitalised and die of AIDS. This study found that many patients were admitted with a low CD4, an indication of advanced disease. Age, male gender, CD4 cell count less than 200 cells /mm³, and HIV viral load more than 1000 copies/ml were reported to be associated with mortality in patients. Tuberculosis remains the most common cause of morbidity in patients with HIV infection in South Africa. Health care professionals should take measures to strengthen

the early diagnosis, prevention and treatment of the common opportunistic infections by investing effort into the improvement of education, screening, initial diagnosis and treatment in the community.

Declarations

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Competing interests

The authors declare that there are no conflict of interests

Authors' contribution

Manimani Riziki Ghislain, Sindy Gumede and Nombulelo Magula conceptualised and designed the study. Manimani Riziki Ghislain prepared the first draft. Manimani Riziki Ghislain and Sindy Gumede did data collection and analysis. Nombulelo Magula assisted with the manuscript preparation. All authors reviewed draft versions of the manuscript and gave their final approval of the manuscript.

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Data Availability

All data generated or analyzed during this study are included in this article.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency.

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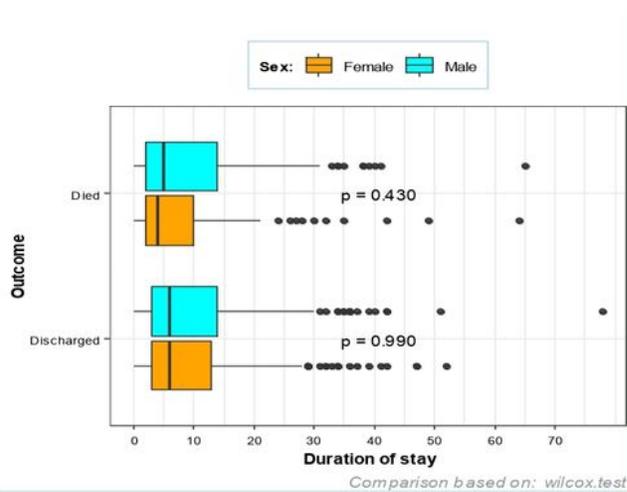
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Figures

Figure 1. Length of hospital stay

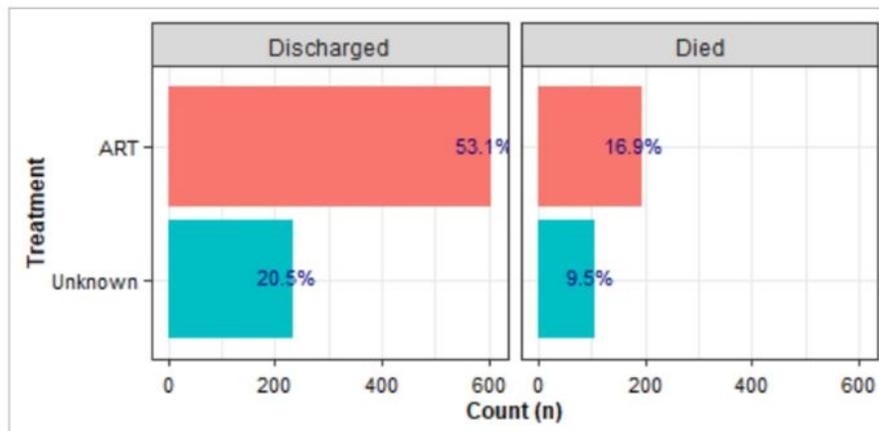


The p-values are more than 5% implying that there was no significant difference in the duration of stay between males and females' patients. This applies to both the duration of stay before discharged or demising.

Figure 1

Length of hospital stay. The p-values are more than 5% implying that there was no significant difference in the duration of stay between males and females' patients. This applies to both the duration of stay before discharged or demising.

Figure 2: Relation between ART treatment and outcome



Only 70% of patients had been reported to be on antiretroviral treatment (ART) on admission or discharge.

Figure 2

Relation between ART treatment and outcome. Only 70% of patients had been reported to be on antiretroviral treatment (ART) on admission or discharge.