

Survival Analysis of AIDS In-Patients at Joint Clinical Research Centre, Uganda

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Abstract

The study compares survival between ARV-experienced and ARV-naïve in-patients of JCRC and determines prognostic factors related to their survival. The majority of the patients were in WHO disease Stage 4. Tuberculosis was most prevalent in the ward while cryptococcal meningitis was the leading cause of death.

The median survival time in the ARV group was 180 days while that of the ARV-naïve group was 36 days. ARV use reduced the risk of dying by a factor of 0.5 in patients in Stage 4 but did not significantly affect survival in other stages of the disease. The older patients were more likely to die than the younger one if in earlier disease stages.

It is concluded that ARV patients survived longer than ARV-naïve in-patients and that ARV use is a prognostic factor for Stage 4 patients. Age is a prognostic factor but only for patients in lower stages of the disease.

1.0 Introduction

JCRC receives patients from all over Uganda and neighbouring countries. The Centre admits severely ill AIDS patients and dispenses both antiretroviral drugs and other drugs for opportunistic infections from its pharmacy.

Although morbidity and mortality due to HIV/AIDS is decreasing because of introduction of antiretroviral therapy (ART), hospitalizations of infected patients are very frequent as the beneficial effects of potent anti-retroviral regimens are eroded due to toxicity and emergence of drug resistance (Harrington, 2002).

Sub-Saharan Africa saw the first introduction of antiretroviral (ARV) drugs in an organized manner at the Joint Clinical Research Centre (JCRC) in Uganda as early as 1992 when it conducted the first ART trial in Africa. By June 2002 there were 16 commercially available antiretroviral medications (WHO, 2002) and JCRC is following the biggest number of patients on ARVs in Uganda and the rest of Africa (Mugenyi, 2003). The goals of ART are to prevent immunological decline and clinical progression and in so doing prolong survival and improve quality of life by suppressing viral load for as long as possible.

Although studies have shown that opportunistic infections are significantly reduced with ART (Carrieri et al, 2002), there is little documentation on the post ARV prognosis of HIV especially in its late stages. This stage, which is characterized by many hospitalizations, is crucial for AIDS care as it is the last stage of treatment and is presenting a challenge in the ARV era.

The survival of AIDS in-patients depends on opportunistic infections. Ward patients, usually in WHO disease Stage 4 are vulnerable to common opportunistic infections like cryptococcal meningitis, pneumocystis carinii pneumonia (PCP), toxoplasmosis and extra-pulmonary tuberculosis (PTB). In the developed world, these AIDS defining illnesses have been shown to be related to the number and year of

hospitalizations, CD4 counts, ART and sex (Arasteh et al, 2002). In resource poor settings the level of income or even the educational level of the patient could also be associated with these illnesses. In order to determine whether or not a patient will develop a particular condition or health related event, we need to know some characteristics of the patient. The most important conditions (Risk Factors) will guide management of HIV/AIDS patients. This study contributes to HIV/AIDS care through determining prognostic factors associated with survival in the ARV era. It also highlights the benefits of ART in a ward in a resource poor setting.

2.0 Problem statement

The introduction of ART and the development of a wide range of potent drugs for opportunistic infections have inevitably improved HIV/AIDS care. But the impacts of these changes on AIDS in-patient's survival have not been adequately characterized. In the developed world where there is easy access to both ARVs and other drugs, new problems have arisen in the management of HIV such that even the most adherent population can only sustain viral load suppression for not too long and the risk of cardiovascular diseases has been reported on the increase. In Africa, apart from the low per capita incomes that have partially caused poor adherence, other problems include lack of information, for even the few who can access antiretroviral drugs and the problem of self-administered ARVs obtained by patients from relative's abroad who are not trained in dispensing and administering them.

Because of the widespread use of ART, the prognosis of HIV/AIDS in the population has changed that both ARV experienced and ARV-naïve patients are being hospitalized with the same kind of illnesses. To expound on the importance of ART, one needs to determine the prognosis of HIV/AIDS in the ARV era and contribute to post ARV era treatment guidelines.

3.0 Objectives of the study

The general objective of this study was to determine the prognostic factors related to survival of AIDS in-patients in the ARV era. The specific objectives were to compare the survival of ARV-naïve and ARV-experienced AIDS in-patients and identify prognostic factors related to survival time of AIDS in-patients.

4.0 Justification

Studies on survival during ARV period is limited. In fact, there are no studies which looked at this period in Uganda. Since JCRC pioneered ARV administration in sub-Saharan Africa, the wealth of data generated is itself a justification for studying survival in order to provide useful information for the broad introduction of ART to the rest of Africa and for building a framework for developing HIV/AIDS guidelines for treatment of severely immunosuppressed patients. It would also provide input for specialized training for health care providers and for new cadres of specialized clinicians in the field of HIV/AIDS.

5.0 Hypotheses

There is no difference between ARV-naïve and ARV-experienced AIDS in-patients in terms of survival and illness.

Age is not a prognostic factor associated with survival of AIDS in-patients.

WHO staging is not a prognostic factor associated with survival of AIDS in-patients.

ARV drug use, is not a prognostic factor associated with survival of AIDS in-patients.

6.0 Literature Review

HIV/AIDS disease progression results in hospitalizations from opportunistic infections owing to a collapse of the patients immune system. The inadequacy of specialized facilities for AIDS and the cost of drugs and treatment render treatment to only those who can afford. Patients with low incomes interrupt therapy while others only present themselves at the late stages of the disease unfortunately when some conditions are difficult to handle. ARV-experienced patients are a common phenomenon in the wards and yet the expectation would be that of reduced morbidity among this group of patients.

The natural history of HIV infection as well as the spectrum of HIV associated diseases has profoundly changed in areas where there is broad use of ART. Mugenyi (2002) observes that the AIDS epidemic in most countries has moved from the “out of control” phase through the “effective control” phase to the ‘bottoming out’ phase. He says this stage has been possible through various programs including massive awareness programs, voluntary counseling and testing and more recently the introduction of ART and prophylactic treatment. Prophylactic treatment against PCP for example has been very helpful in curbing the disease that was rampant in these patients. Recent provision by Pfizer of free Fluconazole as prophylaxis against cryptococcal meningitis is also yet a positive step in curbing the killer opportunistic infections. And the provision of free Tuberculosis (TB) drugs was a positive move by government that contributed to a drop in the morbidity of AIDS patients.

6.2 Prognostic factors

Egger et al, (2001) collected retrospective information from patients and identified characteristics such as sex, disease staging, initial treatments used, baseline CD4 counts and HIV RNA at 6 months after starting therapy as determinants of survival. Their investigation identified 10 potential prognostic factors. These were age, Intravenous Drug abuse (IVDA), CDC disease stage, CD4 counts and baseline HIV RNA. They found that the probability of an event-free survival was higher with higher CD4 counts and higher with lower HIV RNA and that CD4 counts was the dominant prognostic factor. Also predictive was old age above 50, history of intravenous drug use (IDU) and Stage C of the disease. Although this work provided an insight into variables relevant to prognosis of HIV/AIDS, it remained general on the disease staging, which is not universal.

In poor resource settings, income is a big factor in HIV/AIDS and patients seek treatment and hospitalization when in advanced stages of disease. In another study, Chaisson et al, (1995) found that HIV progress to full-blown AIDS and survival, are not related to sex, race, injection drug use or socioeconomic status. Rather, HIV disease progression depends on CD4 cell count, receipt of ART and age. The study showed that HIV-infected persons were twice as likely to progress to AIDS or die from their infection if they had a low CD4 cell count (201 to 350 cells per ml compared with a normal cell count of about 1,000 per ml) and were symptomatic at enrollment. They had nearly twice the risk (1.7) if they had received ART before and an increased risk of 2 percentage points per year of age. This study also found that CD4 cell count was the most important predictor of survival.

7.0 Methodology

A total of 906 patients were admitted to the JCRC ward in Kampala between 19th January 1999 and 18th January 2003. These patients were subsequently discharged having improved or were referred to other hospitals while others died on the ward. This was a one-year follow up study of survival among a cohort of AIDS in-patients.

Information was obtained on age of patient, sex of patient, date of admission, date of discharge, date of death, medications taken by patient, cause of death (if the patient died), date of readmission and CD4 counts of the patient.

Stratified Cox regression was used to study the survival. The stratification variable was chosen as disease staging as it violated the proportionality assumptions. In the Cox regression model the dependent variable was taken as time to death and the covariates were disease staging, age, and ARV use.

The Cox model usually expressed in hazard form called the proportional hazards model is written as

$$h(t) = [h_0(t)e^{\beta_1x_1+\beta_2x_2+\dots+\beta_px_p}$$

Where $x_i, i = 1, \dots, p$ x_1 to x_p are the covariates

$h_0(t)$ is the baseline hazard which depends only on time.

$h(t)$ is the hazard function

The model for analysis proposed is written in its linear form as:

$$\ln \left[\frac{h(t)}{h_0(t)} \right] = \beta_1x_1 + \beta_2x_2 + \dots + \beta_px_p$$

8.0 The findings

About 56% of the patients were male. The mean age was 36.5 years. By sex, the mean age for the females was 35.4 years and it was males 37.3 for males. This relation was not statistically significant ($F_{1,905,0.538} = 0.380$).

The majority of the patients were in the age bracket of 30-39 (48.5%) while the least admitted were those less than 18 years (6.0%). About 27% of the patients fell in the age group 40-49. In general 64.9 % of the patients were less than 39 years of age.

8.1 Patient readmissions

About 29 % of in-patients had ever been admitted before and about 30% of them were readmitted 3 or more times over the follow up period. About 23% of patients had 2 or 3 admissions while 4% had 4 or 5 admissions during the study period. About 2% of the patients had at least 6 admissions. This could be due to chronic illnesses related to HIV, treatment failure or resistance to ARVs. Treatment failure is said to be caused by prolonged usage of ARV and OI drugs which may lead to renal failures. ARV-experienced patients who developed resistance and those non-compliant to drug combinations experienced a rebound in opportunistic infections. Non-compliance can be due to high drug cost, dose complexities and side effects of treatment. For patients on AZT containing regimens e.g. Combivir+3TC readmissions were commonly due to anaemia.

Tuberculosis was the commonest diagnosed OI with a prevalence of 16.6% while cryptococcal meningitis had 10.5% and PCP 8.1%. Conditions like toxoplasmosis,

candidiasis and anaemia had prevalence of 5.9%, 6.5% and 6.9% respectively. Gastroenteritis had a prevalence of 4.2% while malaria had 4.0%. Other significant conditions included other community-acquired pneumonias (4.3%), kaposi sarcoma (1.8%), encephalitis (1.8%), upper respiratory tract infections (1.7%), urinary tract infections (1.6%) and peripheral neuropathy (1.3%). Table 1 shows the prevalence of 8 most common conditions at admission.

Table 1: Prevalence of most common conditions at admission

Opportunistic Infection	Prevalence (%)
Tuberculosis	16.6
Cryptococcal meningitis	10.5
Toxoplasmosis	5.9
PCP	8.1
Candidiasis	6.5
Anaemia	6.9
Gastroenteritis	4.2
Malaria	4.0

8.2 Past medical history of admitted patients

The past medical history of patients was used to document infections previous to their hospitalization. The records showed that in-patients had suffered from several opportunistic infections, which were classified in terms of body systems as in the Table 2.

Gastro intestinal infections constituted 32.3% of the infections. Respiratory infections constituted 20.5%. Diseases of the Nervous System contributed 16.9% and fevers (12.4%). Patients had also suffered from diseases affecting other systems like genital urinary, skin, and cardiovascular. Ailments such as disseminated candidiasis, diabetes and malaise that could not be categorized into systems contributed 9.4%. Among the gastro intestinal infections, vomiting contributed 11.3%, diarrhoea (7.5%), and anorexia (5.0%). Others included acute abdominal pain and liver disease; each had less than 2% prevalence. Respiratory infections included cough with 7.7%, tuberculosis with 5.9%, dyspnoea (2.5%), chest pain (1.4%) and PCP (1%). Other respiratory infections contributed less than 1% and included bronchopneumonia caused by haemophilus.

Diseases of the central nervous system included headaches with 5.3%, cryptococcal meningitis (4.5%), dizziness (1.3%) and convulsions (2%). Others included encephalopathy, CMV, autonomic nervous dysfunction, and dysarthria with less than 1% contribution to the morbidity of the patients.

Table 2: Prevalence of past illnesses among in-patients by body systems

System	Frequency	Prevalence %
Nervous system	242	16.9
Gastro intestinal	462	32.3
Genito urinary	12	0.8
Respiratory	294	20.5
Skin	26	1.8
Eye	4	0.3
Lymph nodes	18	1.3
Anaemia	30	2.1
Musculoskeletal	26	1.8
Fever	89	12.4
Others	134	9.4
Cardiovascular	6	0.4
Total	1432	100.0

Cardiovascular diseases included heart failure and diseases of the lymph nodes included lymphadenopathy. Skin infections were herpes zoster and mucocutaneous kaposi sarcoma (KS). Patients experienced some of these diseases in early stages of infection and progressed to advanced stages of the infection. Recurrence of this infection was very common due to improper treatment as a result of poor diagnosis and poor adherence and inhibitive drug cost.

The results show that 79% of the patients were admitted for the first time with CD4 counts < 100 cells/mm³. About 15% of the patients presented with CD4 counts in the range 100-199. These patients were classified into CDC Stage C and constitute patients who are severely immunosuppressed and mostly in acute phase of illnesses and are prone to several of the killer. Patients admitted at better levels of CD4 counts were in stage 3 of HIV progression and these patients qualify for ART, which would remove them from the risks of common opportunistic infections. The distribution of CD4 counts also shows that patients sought hospitalization at the JCRC in their last stages of HIV disease when their immunity is severely compromised.

About 32% of admitted patients had ever been on ART or at least started ART while in the ward. The drug combinations taken by patients included NRTI+NNRTI, NRTI+PI containing regimen. The other was a regimen with one NRTI and other antiretrovirals e.g. Hydroxyurea. The NRTI included Combivir, 3TC, DDI, D4T, Abacavir and AZT. The NNRTIs included Nevirapine and Efavirenz. The PIs included Saquinavir, Crixivan, Kaletra and Nelfinavir. Hydroxyurea was classified in a separate group of antiretrovirals. Many patients were found to be inconsistent in taking their drugs and some had stopped taking them for extended periods of time.

Patients who had taken ARVs for a long time changed therapy in the course of treatment probably because of treatment failure.

Table 3 shows the survival data of in-patients grouped in intervals of 1 month. The probability density function and the hazard rate are also given. The median survival time was 115.57 days and the highest frequency of death occurred in the first month of hospitalization with a hazard rate of 0.012.

Table 3: Survival data and estimated survival functions of in-patients

Interval Start Time	Number Entering This Interval	Number Withdrawn During Interval	Number Exposed To Risk	Number Of Terminal Events	Proportion Terminating	Cumulative Proportion Surviving At End	Hazard Rate
0	906	511	650.5	202	0.311	0.690	0.0123
30	193	22	182.0	27	0.148	0.587	0.0053
60	144	11	138.5	15	0.108	0.524	0.0038
90	118	9	113.5	6	0.053	0.496	0.0018
120	103	8	99.0	5	0.051	0.471	0.0017
150	90	5	87.5	5	0.057	0.444	0.0020
180	80	3	78.5	3	0.038	0.427	0.0013
210	74	3	72.5	3	0.041	0.409	0.0014
240	68	10	63.0	3	0.048	0.390	0.0016
270	55	2	54.0	0	0.000	0.390	0.0000
300	53	2	52.0	1	0.019	0.382	0.0006
330	50	2	49.0	1	0.020	0.375	0.0007
360	47	9	42.5	0	0.000	0.375	0.0000
390	38	38	19	0	0.000	0.375	**

The hazard rate shows a decreasing trend, reaching 0.001 by the 6th month. Out of 271 patients who died during the follow up period, about 75% were in the first month and about 92% in the first 3 months of hospitalization. Hence, the prognosis of a patient who has survived 1 month after admission is better than that for newly hospitalized patients if factors such as age and sex are not considered.

8.4 Time to death by causes

Causes of death among ward patients were recorded from death certificates and their times to death recorded against underlying causes of death. The data showed that the mean survival time registered among patients hospitalized with a diagnosis of toxoplasmosis was about 137 days. This was also the case for patients with a diagnosis of bronchopneumonia.

Cryptococcal meningitis had a mean survival time of about 16 days, encephalitis 12 days and those diagnosed with severe anaemia lasted at most 29 days after first admission. For this population patients diagnosed with PCP had a mean survival time of 22 days after first admission. Table 4 shows the mean survival times by causes of death.

Table 4: Mean survival times by causes of death

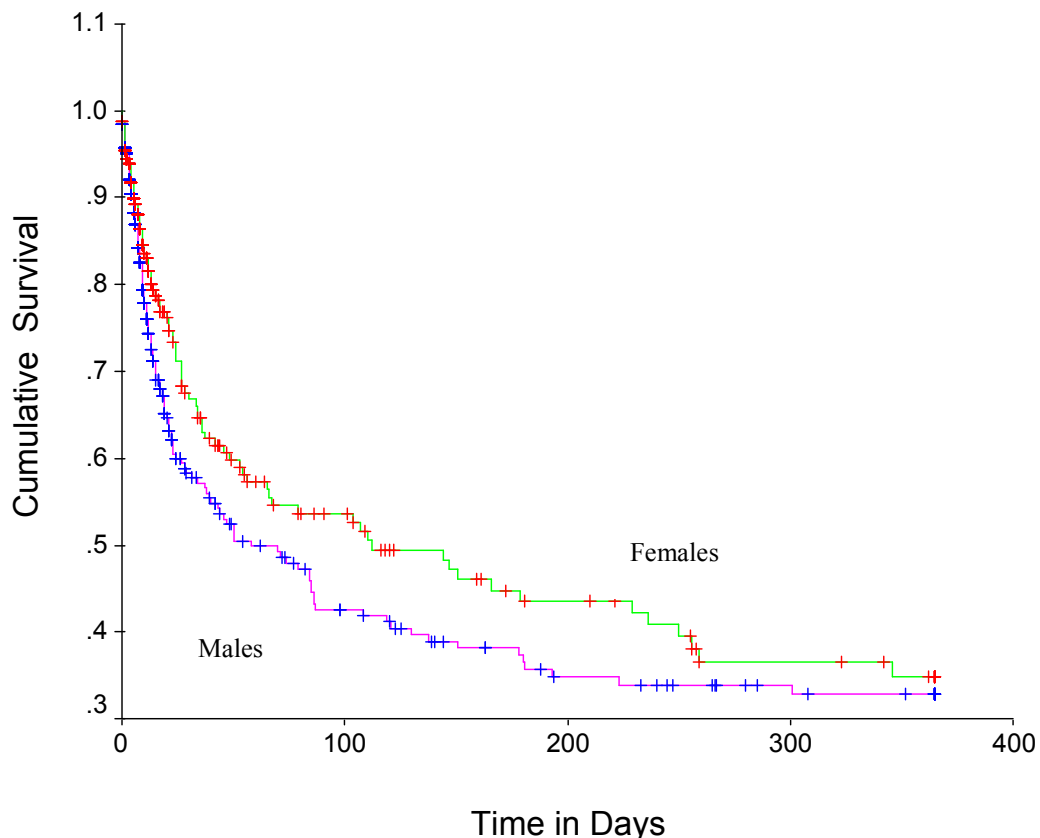
Causes of death	N	Mean (days)
Enteritis	23	212.3
Anaemia	22	29.0
PCP	35	22.1
Cryptococcal meningitis	84	15.9
Tuberculosis	40	1.0
Toxoplasmosis	44	136.8
Encephalitis	23	12.3
Total	271	57.0

8.5 Survival and patient characteristics

8.5.1 Sex

Patients were stratified by sex. The median survival among the females was 112 days while that among the males was 58 days. The log rank test was used to test the equality of the survival distributions between females and males. The log rank ($\chi^2=3.10$, $df=1$, $p=0.0784$) showed that there was no significant difference in survival between females and males in the ward.

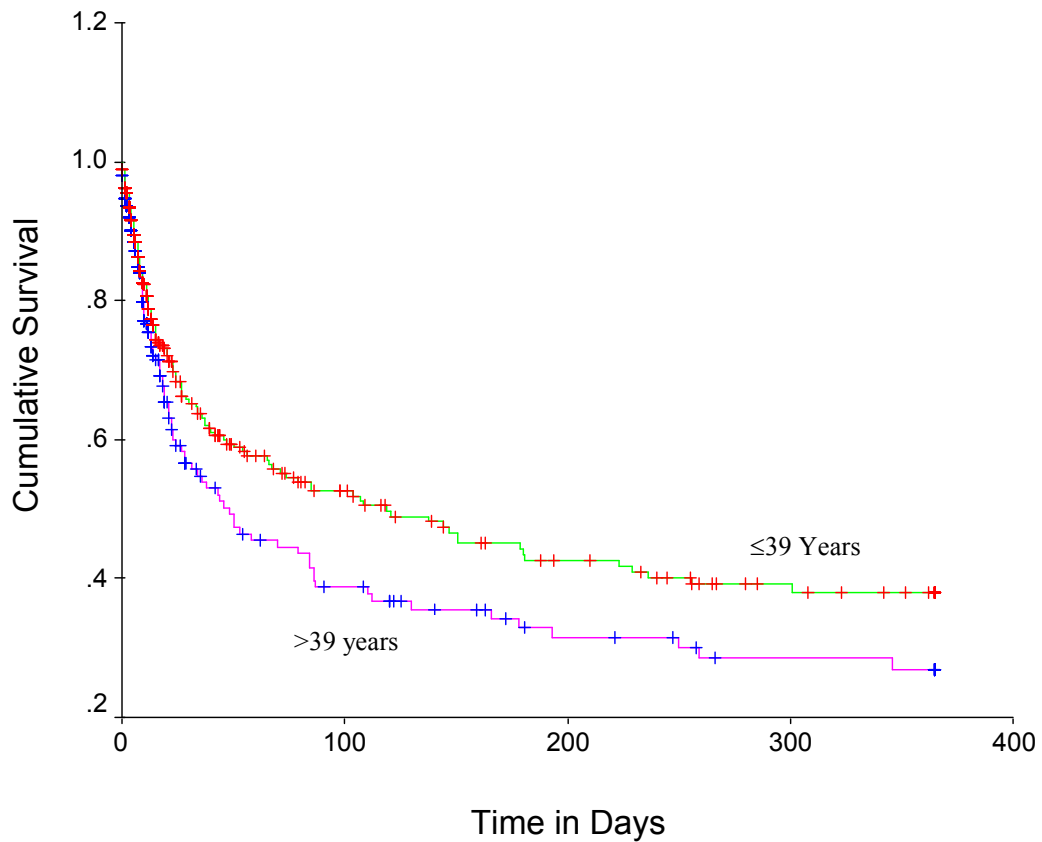
Figure 1: Survival curves by Sex



8.5.2 Age

Patients were stratified into those older and those younger than 39 years of age. The median survival time in the lower stratum was 119 days while that on the upper stratum was only 48 days. Testing the equality of survival distributions between the two strata, the log rank test showed a significant difference ($p=0.031$). In fact patients in the lower strata survived longer than those in the upper strata.

Figure 2: Survival curves by age group

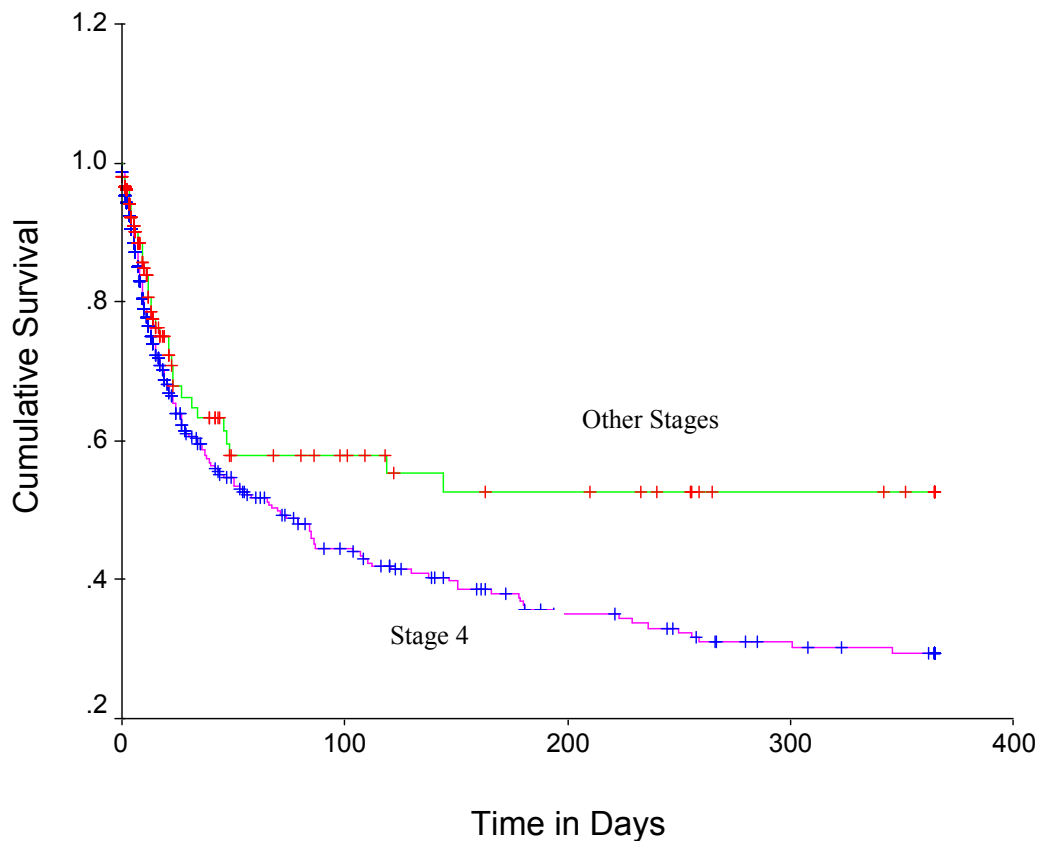


8.5.3 Opportunistic infections

The in-patients were stratified into whether their primary diagnosis was a WHO HIV stage 4 defining illness or otherwise.

The log rank test was used to test for the equality of survival distributions between patients admitted with HIV Stage 4 and those in other stages of disease. The test showed that HIV Stage 4 was significantly associated with death (log rank 5.32, df = 1, p=0.0211).

Figure 3: Survival curves of in-patients by disease staging

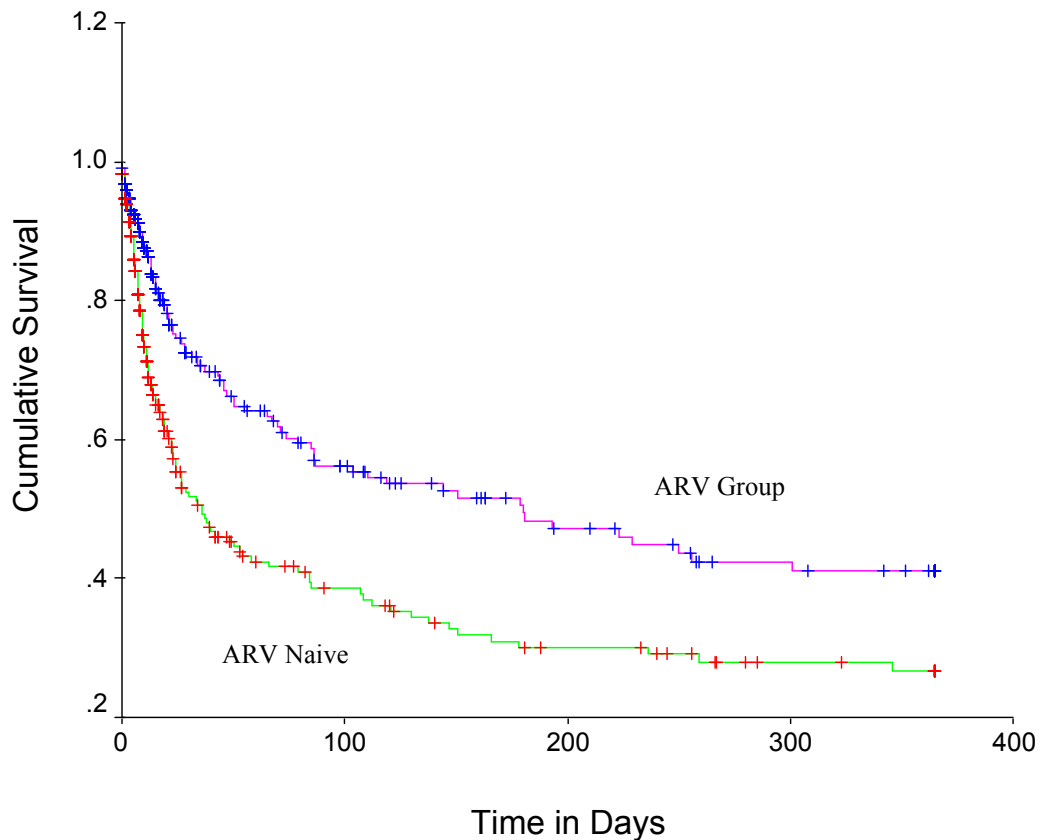


4.11.4 ARV use

The Kaplan-Meier product limit estimator was used to estimate the survival distributions of ARV-experienced and ARV-naïve patients by testing the null hypothesis of equality of the distributions. The length of stay in the ward was taken as the time variable. Observations for patients dying within the 1-year follow up period were taken as events of interest and those staying for more than 1 year were taken as censored observations. The factor of interest was ARV use.

The median survival among the ARV-naïve in-patients was 36 days while the median survival in the ARV group was 180 days. Further the Log Rank statistic was significant (log rank 22.35, 1, $p=0.000$) leading to conclusion that there is evidence that there is a difference in survival between ARV-experienced and ARV-naïve in-patients and indeed that the survival among ARV patients is better than that of ARV naïve patients.

Figure 4: Survival curves by ARV use



4.12 Prognostic factors in HIV/AIDS in-patients

A stratified analysis using Cox regression was fitted to identify prognostic factors associated with HIV/AIDS in-patients. The stratification variable chosen was disease staging (Stage 4 and Otherwise) and the length of time from first hospitalization to death was considered as the time variable. The status variable was taken as the survival status of the patient (dead or alive) in the follow up period.

The data shows that ARV use is a significant prognostic factor affecting survival among HIV/AIDS Stage 4 in-patients. Further ARV use is associated with a reduction in the risk of death by a factor of about 0.5. The Cox regression also shows that, age did not significantly affect survival of Stage 4 in-patients. Being in the older or lower age stratum was not a factor affecting survival among Stage 4 patients.

It was concluded that ARV use is a prognostic factor in HIV/AIDS and it increases the survival of HIV/AIDS Stage 4 in-patients.

Fitting the model for in-patients in other stages of disease, the model shows that only age group was a significant prognostic factor affecting survival of in-patients in other stages of disease. Table 5 gives the details of the fit.

Table 5: Cox Regression analysis for HIV/AIDS In-Patients in WHO Stage 4

Variable	B	S.E.	Chisq.	df	p	R	Exp(B)
ARV use	-.661	.141	22.003	1	.000	-.092	.516
AGE group	.097	.140	.478	1	.489	.000	1.102

Being in the upper age stratum increased the risk of in-patients dying by a factor of 2.72 ($p=0.001$) compared to patients in the lower age stratum. It was concluded that the age group had an effect on the survival of in-patients in disease stages other than 4.

It was also found that ARV use was not a significant factor in survival of patients in their lower stages of HIV disease.

Summary

About 29 % of ward admissions were readmissions and of these 41.4% had at least 3 readmissions over the follow up period. Tuberculosis was the common cause for readmission with a prevalence of 16.6%. Other diseases included PCP, toxoplasmosis, cryptococcal meningitis and encephalitis.

Other conditions diagnosed at hospitalization were candidiasis and anaemia with prevalence of 6.5% and 6.9% respectively. Gastroenteritis had a prevalence of 4.2% while malaria had 4.0%. Other significant conditions included community-acquired pneumonias (4.3%), kaposi's sarcoma (1.8%), upper respiratory tract infections (1.7%), urinary tract infections (1.6%) and peripheral neuropathy (1.3%). Candidiasis had a prevalence of 6.5%.

The prevalence of Gastro intestinal infections was 32.3% and of Respiratory infections was 20.5%. Diseases of the Nervous System contributed 16.9% and fevers (12.4%). Patients also suffered from diseases of other systems like genital urinary, skin, and cardiovascular but were prevalent (2%).

Respiratory infections included cough with 7.7%, tuberculosis with 5.9%, dyspnoea (2.5%), chest pain (1.4%), PCP (1%). Other respiratory infections like bronchopneumonia contributed less than 1% .

Diseases of the central nervous system included headaches with 5.3%, cryptococcal meningitis (4.5%), dizziness (1.3%), convulsions (2%). Others included encephalopathy, CMV, autonomic nervous dysfunction, and dysarthria with less than 1%. Cardiovascular diseases included heart failure and diseases of the lymph nodes included lymphadenopathy. Skin infections were herpes zoster and mucocutaneous kaposi's sarcoma (KS).

About 32% of admitted patients had been on or started ART while on ward. Many patients were reported to be inconsistent in taking their drugs and some stopped for extended periods of time.

About 30% of admitted patients died in the study period. Cryptococcal meningitis was the leading cause of death accounting for 27.3%. PCP was responsible for death in 21.4% and tuberculosis (18.1%). Other causes of death were encephalitis, toxoplasmosis, anaemia and enteritis.

The median survival time was 115.57 and high frequency of death occurred within the first 1 month with a hazard rate of 0.012. The hazard rate showed a decreasing trend, reaching 0.001 by the 6th month. Out of 271 patients who died during the follow up period, about 75% were in the first month and about 92% in the first 3 months of hospitalization.

5.3 Conclusion

There exists a disparity in the extent of access to admission by female and male AIDS patients because only about 44% of AIDS admissions in paying wards were female patients.

Tuberculosis is the most prevalent OI among AIDS in-patients admissions. Cryptococcal meningitis is the second most prevalent opportunistic illness and PCP is the third most prevalent illness in HIV/AIDS in-patients prevalent. Other major prevalent illnesses are toxoplasmosis, gastroenteritis, candidiasis and anaemia. Patient readmissions accounted for 29.1% of the total admissions in the ward.

Only 32.4% of admitted patients are on or started ART while on ward.

Though the male patient admissions are more, the males and the females have similar risk of dying from any of the opportunistic infections.

The leading causes of death in the ward were cryptococcal meningitis, PCP and tuberculosis. Other causes of death included encephalitis, toxoplasmosis, anaemia and enteritis.

Toxoplasmosis had the greatest maximum number of days to death of more than 365 days after first admission proving that if managed well life can be prolonged even in conditions of advanced HIV disease. Patients infected with PCP and cryptococcal meningitis however did not live long compared to those with toxoplasmosis.

ARV use prolonged the survival of in-patients. The median survival for ARV in-patients was 180 days while that of ARV naïve ones was 36 days.

ARV use is a prognostic factor for HIV/AIDS in-patients in Stage 4 of HIV disease and reduces the risk of death by a factor of 0.5. At this stage of disease age of the patient does not matter. For patients in other stages of disease however, ARV use has no significant effect but age is a prognostic factor with those greater than 39 years of age having a risk of dying 2.7 times than of their younger counterparts.

9. Recommendations

Governments should continue to emphasis programmes that improve the socioeconomic status of the females. They should also create awareness of the availability of HIV/AIDS health facilities and ART.

Government should support programs to cut down prices for ARVs, provide drugs for diseases like cryptococcal meningitis and toxoplasmosis for which patients require life-long support.

Health facilities should be equipped with capabilities to diagnose tuberculosis and PCP.

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