Nigerian Journal of Clinical & Biomedical Research June 2017 Vol. 7 No. 8 43 - 52

Original Article

# Trend in HIV associated mortality and risk factors in Lagos Nigeria

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**Summary**

The trend in HIV associated mortality and risk factors for morality in a large HIV treatment centre in Lagos are reported. Programmatic data of treatment outcome in HIV infected adult Nigerians receiving comprehensive HIV care, treatment and support services over a period of five years were reviewed. A total of 4792 patients were included in the analysis, out of which 2596(62%) were females and 38% males. The mean age ± standard deviation (SD) at start of drugs was 36.7±9.1 years. More than half of the patients were married (58.4%) and had at least secondary school education (70.0%). Thirty six deaths were recorded during the period; with slightly higher deaths (1.0%) among the males compared to the females (0.6%). More deaths were recorded among the patients less than 21 years (1.7%). The median CD4 Count of those that died was 79 cell/mm$^3$, compared to 139 cell/mm$^3$ among those that survived (p=0.002). Kaplan Meier estimates of death by the end of 60 months was (98.6%) and also the KM estimates at 6, 12, 24, 36 and 48 months were 99.9%, 99.7%, 99.5%, 99.3%, 98.9 and 98.6% respectively. Only ARV adherence less than 95% and low CD count less than 100 was found to be associated with Deaths.

**Keywords**: HIV, Deaths, Risk factors, Mortality, Adherence, antiretroviral drugs

## Introduction

As of 2013, an estimate of 35 million people are living with HIV compared with 26.2 million in 1999—a 33.6% increase. Since the start of the epidemic, around 78 million people have become infected with HIV and 39 million people have died of AIDS-related illnesses. The estimated 1.3 million people who died of HIV related illnesses in sub-Saharan Africa in 2009 comprised 72% of the global total of 1.8 million deaths attributable to the epidemic.[1]

Now with the advent and roll-out of effective treatment for case management, the situation is improving.[2] Highly active antiretroviral therapy (HAART) has transformed HIV from a disease associated with high rates of mortality and short life span to one characterized by much lower rates of mortality where people can live for a much longer period of time and the

infection can be treated as a manageable chronic condition.

With this increase in the use of HAART, it is important to evaluate whether the improved survival observed, associated with use of potent antiretroviral have reduced HIV related deaths and what factors are still observed associated with risk for mortality among a cohort of HIV infected patients on anti-retroviral treatment followed for five years.

## Method

A retrospective review of programmatic data of adult HIV positive patients enrolled between January 2006 and December 2010 and on drugs at the Clinical Research Centre of the Nigerian Institute of Medical Research (NIMR), Lagos all from an on-going ART programme. The patients enrolled in December 2010 were followed up to December 2011. The site , a federal ART site provides out- patient HIV Care and Treatment according to the Nigerian national guidelines. Before commencement of treatment all patients are confirmed HIV positive using Western Blot. Study population were adult male and female patients with HIV-1 infection aged ≥ 15 years of age.

Data on demographics, behavioral, clinical and laboratory data on patients were abstracted from the patient's database. The data collected on demographic characteristics (at baseline) includes: Enrollment date and year, Age at enrollment, Age at start of drugs, Sex, Marital status, Education, Baseline laboratory assessment (Hemoglobin, CD4 Count, Viral load, HBV, HBC), Behavioural ( HIV risk factor), Opportunistic infections, WHO disease stage. Clinical data collected were clinical evaluation, vital signs. Laboratory parameters ( CD4 Count, viral load, Hemoglobin and ALT).

The primary end point was death. And the death was either reported by relative or by contact tracing. The death date was reported as either the date the patient died as reported by the relative or contact tracing if known or otherwise if not know the day the patient was last seen at the clinic. The time of death was defined as the time of start of drugs to the time of occurrence of death.

**Statistical Methods**.

Univariate analysis was used to present, the demographic and baseline clinical characteristics of all the patients and also by the death profile, These characteristics were compared for patients surviving and those who had experienced death and significance differences were investigated at the 95% confidence level. Continuous variables were compared using the Wilcoxon rank-sum test; while categorical and dichotomous variables were compared using the chi-square test and Fishers exact test where appropriate. Kaplan-Meier method was used to estimate the time from the initiation of ART to the occurrence of death. For patients who did not reach the endpoint, the data were censored on 31$^{st}$ December 2011. The survival of one group of study subjects were compared with another using the survival curves. The log-

rank test was used to compare more than two survival curves. Cox proportional hazard regression model was used to determine the relationship between the survival of an individual and several explanatory variables which were right-censored, and showed statistically significant difference at P<0.1 using Log-rank test.

The proportional Hazard Model was: H (t) = Exp ($\beta_1$Sex **+** $\beta_2$Year $\beta_3$CD4 + $\beta_4$ADH) $H_0(t)$

Where H (t), the hazard of death at time t, and $H_0(t)$, the hazard function for individual for whom the values of all independent variables are zero.

The sex of the patient (Sex), year of start of drugs (Year), range of CD4 at start drugs (CD4) and adherence (ADH) were all significant at 0.1 from the univariate analysis.

Ethical approval was obtained from NIMR Institutional Review Board and also only data of subjects that consented that their information be used for HIV/AIDs research at enrollment into the treatment program were included in the study. Data retrieved for analysis were de-identified before analysis for confidentiality.

## Results

A total of 4792 patients were included in the analysis, out of which 2596(62%) were females and 38% males. The mean age ± standard deviation (SD) at start of drugs was 36.7±9.1 years. More than half of the patients were married (58.4%) and singles were about one third (26.3%). About 70% of the patients had at least secondary school education and looking across the educational status, secondary level was their highest educational attainment. (43.7%)

**Baseline socio-demographics**

For the entire 5 years follow up only about 1% of the total patients died. Male deaths was slightly higher than the female 0.6%. Mean age 38±10.8 of those subjects that died was higher than those that didn't die 36.4 ±9. Also age group < 21 years had the highest percentage of deaths (1.7%). The single patients recorded the highest deaths (1.1%) closely followed by the married (1.1%). (p=0.339). Although patients with no form of education had the highest percentage of deaths (1%), there was no statistically significant difference across the educational level. Patients that reported blood transfusion as route of HIV transmission had the highest death rate (1.3%) compared with others.(Table 1)

**Baseline Clinical Characteristics**

The median CD4 Count of those that died was 79 cell/$mm^3$, as compared with still alive 139 cell/$mm^3$ (p=0.002). The median RNA viral load of those patients that died was 4.7 $Log_{10}$ Copies and non deaths 5.0 $Log_{10}$ (p=0.370) . Although the percentage of patients that died was highest (1.1%) among the WHO staging IV group, this difference was not statistically significant.(p=0.239) Also there were higher deaths among the patients positive for Hepatitis B (0.6%) and C (1.8%) respectively as compared with the negative patients at start of drugs, (p=0.605 and

0.193 respectively) About 1.4%of the dead patients had less than 95% adherence to ARVS. (Table 2)

**Table 1 Baseline Demographic Characteristics of Patients at start of drugs by death**

| | Non Deaths N (%) | Deaths N (%) | Total N (%) | P-Value |
|---|---|---|---|---|
| **Sex** | | | | |
| Male | 1812(99) | 19(1) | 1831(38.2) | |
| Female | 2944(99.4) | 17(0.6) | 2961(61.8) | 0.102 |
| **Mean Age ± SD** | 36.4 ±9 | 38±10.8 | | |
| **Age group at start of drugs** | | | | |
| < 21 years | 57(98.3) | 1(107) | 58(1.2) | |
| 21-30 years | 1219(99.4) | 7(0.6) | 1226(25.6) | |
| 31-40 years | 2058(99.2) | 16(0.8) | 2074(43.3) | 0.774 |
| 41-50 years | 1052(99.2) | 8(0.8) | 1060(22.1) | |
| > 50 years | 370(98.9) | 4(1.1) | 374(7.8) | |
| **Marital Status** | | | | |
| Married | 2780(99.3) | 20(0.7) | 2800(58.4) | |
| Single | 1248(98.9) | 14(1.1) | 1262(26.3) | 0.339 |
| Divorced | 256(99.6) | 1(0.4) | 257(54) | |
| Separated | 455(99.8) | 1(0.2) | 456(9.5) | |
| Widowed | 17(1000) | 0(0) | 17(0.4) | |
| **Education** | | | | |
| None | 196(99) | 2(1) | 198(4.3) | |
| Primary | 956(99.6) | 4(0.4) | 960(20.7) | 0.526 |
| Secondary | 2079(99.2) | 16(0.8) | 2094(45.1) | |
| Tertiary | 1382(29.7) | 13(0.9) | 1395(30) | |
| **Route of Transmission** | | | | |
| Heterosexual | 3603(99.3) | 27(0.7) | 3630(75.8) | |
| IVDU | 4(100) | 0(0) | 4(0.1) | |
| MSM | 35(0.7) | 0 | 35(0.7) | |
| PMTCT | 216(100) | 0 | 216(4.5) | 0.701 |
| Transfusion | 231(98.7) | 3(1.3) | 234(4.9) | |
| Unknown | 667(99.1) | 6(0.9) | 673(14) | |
| **Total** | 4756(99.2) | 36(0.8) | 4792 | |

**Table 2 Baseline Clinical Characteristics of Patients at start of drugs by death**

| | Non Deaths (%) | Deaths N (%) | Total N (%) | P-Value |
|---|---|---|---|---|
| **Median CD4 Count (cells/µL)(IQR)** | 139(73-201) | 79(40-143) | 138(73-201) | 0.002 |
| **CD4Count (cells/µL) at start drugs** | | | | 0.021 |
| < 101 | 1571(98.6) | 11(1.4) | 1593(34.9) | |
| 101 – 200 | 1808(99.4) | 10(0.6) | 1818(39.9) | |
| 201 – 350 | 1010(99.6) | 4(0.4) | 1014(22.2) | |
| 351 – 500 | 96(100) | 0 | 96(2.1) | |
| > 500 | 41(100) | 0 | 41(0.9) | |
| **Median RNA Viral load (IQR)($Log_{10}$ Copies)** | 5.0(4.3-5.4) | 4.7(4.2-5.5) | 5(4.3-5.4) | 0.695 |
| **Range of RNA Viral load** | | | | 0.370 |
| ≤ 1000 | 99(100) | 0(0) | 99(2.2) | |
| 1001 - 10,000 | 579(99.5) | 3(0.5) | 582(12.7) | |
| 10,001 - 100,000 | 1619(99) | 17(1) | 1636(35.8) | |
| > 100,000 | 2237(99.3) | 15(0.7) | 2252(49.3) | |
| **WHO Staging** | | | | 0.239 |
| I | 828(99.8) | 2(0.2) | 830(20.1) | |
| II | 1441(99.1) | 13(0.9) | 1454(35.2) | |
| III | 1657(99) | 16(1) | 1673(40.5) | |
| IV | 173(98.9) | 2(1.1) | 175(4.2) | |
| **TB at Start Drugs** | | | | 0.174 |
| No | 3859(99.3) | 26(0.7) | 3885(81.1) | |
| Yes | 897(98.9) | 10(1.1) | 907(18.9) | |
| **Hepatitis C** | | | | 0.193 |
| Negative | 3706(99.3) | 261(0.7) | 3732(97.1) | |
| Positive | 109(98.2) | 2(1.8) | 111(2.9) | |
| **Hepatitis B** | | | | 0.605 |
| Negative | 3590(99.3) | 26(0.7) | 3732(97.1) | |
| Positive | 315(99.4) | 2(1.8) | 317(8.1) | |
| **Hepatitis B and C Co Infection** | | | | |
| Positive | 0 | 0 | 0 | |
| **Adherence** | | | | |
| < 95% adherence | 637(98.6) | 9(1.4) | 646(13.5) | 0.042 |
| ≥ 95% adherence | 4117(99.3) | 27(0.7) | 4144(86.5) | |
| **Total** | | | | |

**Kaplan Meier estimates**

Kaplan Meier estimates of death by the end of 60 months was (98.6%) and also the KM estimates at 6, 12, 24, 36 and 48 months were 99.9%, 99.7%, 99.5%, 99.3%, 98.9 and 98.6% respectively.

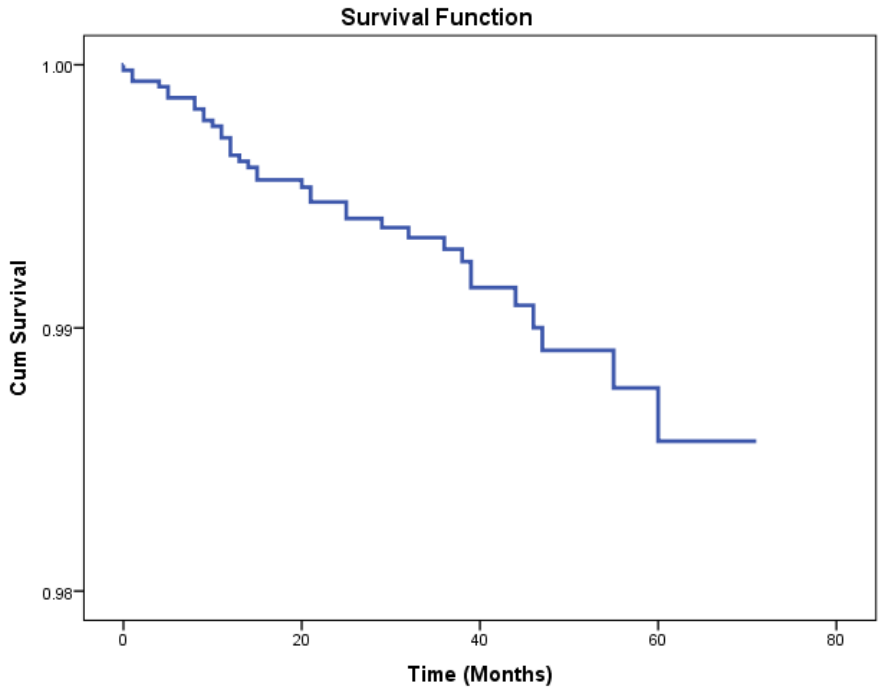


**Figure 1** Kaplan-Meier plots of death from start of ART

The KM survival estimates of death was slightly higher among the females (98.9%) was compared with that of males 98% by the end of 60 months p= 0.073. These also varied across the different CD4 Count groups P-Value = 0.034. Average adherence of ≥ 95% adherence (98.7%) survived better than those that had < 95 % adherence (97.2%) p =0.027. There were no significant difference in the KM curves of the other variables; Marital status, Education, Mode of HIV transmission, Age group, Viral load, HIV/HBC, HIV/HBV, HIV/TB, year of start drugs and WHO staging by log-rank test.

For the Cox hazard regression model being male (AHR 1.70; 95% CI, 0.88–3.29) and average adherence of < 95% (AHR 2.38; 95% CI, 1.10–5.16) were the predictors of death.

**Table 3A: Effects of selected factors associated with the different ARV treatment outcomes**

| Variable | B | UHR(95%CI) | β | AHR(95%CI) | β |
|---|---|---|---|---|---|
| **Sex** | | | | | |
| Male | 0.59 | 1.80(0.94-3.5) | 0.53 | 1.70(0.88-3.29) | 1.174 |
| Female (ref) | | 1.00 | | 1.00 | |
| **Age group at start of drugs** | | | | | |
| < 21 years | -1.135 | 0.32(0.04-2.61) | | | 0.620 |
| 21-30 years | -0.844 | 0.43(0.06-3.24) | | | 0.097 |
| 31-40 years | -0.884 | 0.41(0.05-3.30) | | | -0.147 |
| 41-50 years | -0.489 | 0.61(0.07-5.49) | | | -0.078 |
| > 50 years(ref) | | | | | |
| **Marital Status** | | | | | |
| Married | 0.14 | 1.15(0.60-2.22) | | | 0.15 |
| Single(ref) | | 1.00 | | | |
| **Education** | | | | | |
| None | 0.123 | 1.13(0.25-50) | | | 0.535 |
| Primary | -0.783 | 0.45(0.15-1.40) | | | 0.265 |
| Secondary | -0.158 | 0.85(0.41-1.78) | | | 0.229 |
| Tertiary(ref) | | 1.00 | | | |
| **Route of Transmission** | | | | | |
| Transfusion(ref) | | 1.00 | | | |
| IVDU | -12.63 | 0(0-0) | | | -0.029 |
| MSM | -12.63 | 0(0-0) | | | -0.331 |
| MTCT | -12.36 | 0(0-0) | | | -0.217 |
| Heterosexual | -0574 | 0.56(0.17-1.86) | | | -0.096 |
| Unknown | -0.423 | 0.65(0.16-2.62) | | | -0.055 |
| **Year of start drugs** | | | | | |
| 2006 | -0.271 | 0.76(0.24-2.43) | -0.62 | 0.54(0.17-1.74) | 0.501 |
| 2007 | -0.687 | 0.50(0.15-1.70) | -0.99 | 0.37(0.11-1.26) | 0.184 |
| 2008 | -0.290 | 0.75(0.26-2.13) | -0.43 | 0.64(0.22-1.83) | 0.161 |
| 2009 | -0.716 | 0.49(0.14-1.76) | -0.82 | 0.44(0.12-1.6) | 0.352 |
| 2010(ref) | | 1.00 | | | |

**Table 3B: Effects of selected factors associated with the different ARV treatment outcomes**

| Variables | B | UHR(95%CI) | β | AHR(95%CI) |
|---|---|---|---|---|
| **CD4Count(cells/µL) at start drugs** | | | | |
| < 50 | 9.711 | 1.14(0.76-∞) | | |
| 50-200 | | 0 | | |
| 201 – 350 | | 0 | | |
| >350(ref) | | | | |
| **RNA Viral load (Copies)** | | | | |
| ≤ 1000 | | 1.00 | | |
| 1001 - 10,000 | 7.618 | 2033(0-∞) | | |
| 10,001 - 100,000 | 8.362 | 4281(0-∞) | | |
| > 100,000 (ref) | 7.911 | 2728(0-∞) | | |
| **WHO Staging** | | | | |
| I(ref) | | 1.00 | | |
| II | 1.30 | 3.65(0.82-16.2) | | |
| III | 1.41 | 4.08(0.94-17.63) | | |
| IV | 1.81 | 6.13(0.86-43.6) | | |
| **TB at Start Drugs** | | | | |
| Negative(ref) | | 1.00 | | |
| Positive | -0.443 | 0.64(0.31-1.33) | | |
| **Hepatitis C** | | | | |
| Negative(ref) | | | | |
| Positive | -1.011 | 0.36(0.09-1.54) | | |
| **Hepatitis B** | | | | |
| Negative(ref) | | 1.00 | | |
| Positive | 1.102 | 1.11(0.26-4.67) | | |
| **Adherence** | | | | |
| < 95% adherence | 0.827 | 2.29(31-1.33) | 0.869 | 2.38(1.1-5.16) |
| ≥ 95% adherence(ref) | | 1.00 | | |

## Discussion

This study showed a considerable decrease in death rate when compared with results from other African countries.[7-9] However in Nigeria these rates were similar to previous studies, 1.4% compared with the 2.8% and 4%, reported by Odafe[3] and Idigbe[10] respectively from Nigeria. The wide range in death rate compared with other African countries maybe because death have been masked in patients that are lost to follow up, cultural beliefs of people not reporting

deaths or stigmatization (relatives don't want to be associated with HIV) or our poor vital registration system. Associated factors of death were low CD4 Count, earlier year of start drugs and < 95% average adherence. These predictors are similar to findings by. As expected, lower CD4 cell count was found to be an independent predictor of death, which is similar to findings described in other reports.[3-6] This may be due to diagnosis at an advanced stage of HIV infection.

One of the limitations of the study is that NIMR runs out-patient clinic only, hence it was a challenge knowing if patients that stopped coming are either dead or loss to follow up. Hence the number of deaths may have been underestimated.

**Conclusion**

The increased availability of highly active antiretroviral therapy (HAART) treatment in Nigeria has brought benefits to PLWHA. This increased availability has lowered morbidity and mortality rates.

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