Cause-Specific Mortality amongst Retroviral Disease Patients Admitted in a Tertiary Health Facility in Northeastern Nigeria- a Retrospective Analysis

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ABSTRACT

Background: *Compared with the general population, HIV infected patients are at an additional risk of death from direct effects of HIV virus and/or consequence of immune dysfunction.*

Aim: *To establish the cause(s) of death among persons with HIV and AIDS admitted into the Infectious Diseases Unit (IDU), in University of Maiduguri Teaching Hospital (UMTH).*

Methods: *Retrospective cohort study of causes of deaths among patients admitted with AIDS related complex (ARC), WHO III and/or AIDS defining illnesses (ADI), WHO IV in IDU between January 2004 and December 2014. Medical records including death certificates of 115 cases that fulfilled the criteria was retrieved and analyzed.*

Results: *Of the 115 total deaths, 45 (39.1%), 64 (55.7%) and 6 (5.2%) were due to AIDS, HIV related and non-AIDS or HIV related diseases respectively. Majority of patients were aged 16 - 49 years 87(87.9%). HIV associated wasting syndrome was the most common cause of AIDS related deaths. It was responsible for (46.8%), it was followed by oesophageal candidiasis (19.4%) and Pneumocystis jiroveci (13.0%). Severe sepsis was the most common cause of HIV related deaths, it was responsible for 27.9% of cases. Other HIV related clinical condition included TB 25% (Disseminated 13.6%, Tuberculoma 10% and Multi Drug Resistant (MDR) form 1.4%) and HIV associated nephropathy (HIVAN), 12.3%.*

Conclusion: *Patients admitted with advanced HIV disease in WHO clinical stages III and IV are at risk of death from HIV related diseases or AIDS defining illness. HIV associated wasting syndrome, sepsis and tuberculosis are common causes of death in patients with advanced HIV disease in our setting. The finding from this study suggests missed opportunities for early diagnosis and treatment of HIV infected patients exist in our environment.*

Keywords: *HIV/AIDS, Cause of death, Northeastern Nigeria.*

INTRODUCTION

Mortality due to HIV infection is among the leading cause of death from single infectious agent especially in middle and low-income countries.[1,2] Of the 3.1 million annual global HIV/AIDS related deaths, sub Saharan Africa contribute most cases (2.4 million), with an estimated 215,000 cases from Nigeria.[3] The introduction of antiretroviral therapy (ART) has ameliorated morbidities and mortalities due to HIV infection in both developed and developing countries.[4] The use of ART has also resulted in corresponding increase in non-AIDS deaths.[5] It has also led to reduction in risk of new infections to partners, increase longevity and improvement in quality of life among HIV patients.[5] However, despite several efforts to provide universal access to ART, almost 90% of ART eligible but has no access are found in no fewer than thirty low and middle-income countries (LMIC).[6] To address the huge unmet need for ART, the UNAIDS through its 2015 ART initiative targeted to include 15 million persons in need of ART have access by 2015.[7] In Nigeria, a progressive decline in the prevalence of HIV has been reported from peak 5.8% in 2001 to 3.0% in 2014.[8] The HIV prevalence in Nigeria is geographically heterogeneous, with significant variations across the six geopolitical region. It ranges from 5.8% in Northcentral to 1.9% Northwestern region, with 2.3% in Northeastern region.[8,9] Reports from Nigeria have described the critical role of HIV/acquired immunodeficiency syndrome (AIDS) as a cause of morbidity and mortality in both hospitalized and clinic-based adult patients.[9,10] Although studies have shown reductions in mortality from AIDS after the introduction of ART[7-10], little is known about cause-specific mortality in developing countries in the ART era. To the best of our knowledge, there is dearth of report on causes of death due to HIV infection or its complications in Nigeria. This study was conducted to document the causes of death among HIV patients admitted in a tertiary health facility in northeastern Nigeria.

METHODS

Study Design

Information from records of HIV – infected patients who died on admission in the infectious diseases unit during the study period (January 2004 to December 2014), were reviewed. Data retrieved was sourced from medical records, death certificates and electronic data capture from the database. Causes of death (COD) were collated from the death certificates and matched with information in the medical folder. Cause of death was coded according to the International Classification of Diseases, 10th Revision (ICD-10). Variables studied included age, gender, duration of admission at the time of death, ART use, and morbidity. "Morbidity" represented the number of concurrent illnesses present at the time of death. Primary causes of death were classified as "AIDS-related death" (WHO clinical stage IV), "HIV-associated death" (WHO clinical stage III)[11], or "Other". A death was considered "AIDS-related" when the primary COD was an AIDS-defining event as described in Category 3 of the CDC definition of AIDS[12], or WHO stage 4. "HIV-associated deaths" included those conditions that were HIV related but not CDC category 3 or WHO stage 4.

A cause of death not directly attributable to either of the foregoing was characterized as "Other", i.e. non-HIV associated. This

category included conditions such as hepatic disease or non-communicable diseases such as cardiovascular disease from hypertension.

Ethical consideration

Permission to conduct this study was obtained from the ethics and research committee of the institution.

Data management

Data was entered into an excel workbook and cleaned. Missing data were filled in where available and duplications removed. Records with incomplete information on the cause of deaths were excluded. The data was then exported into SPSS version 16 and variables coded for analysis.

Statistical Analysis

Statistical comparisons were made using the chi-squared test of hypothesis or Fisher's exact test, where appropriate. P values were two-tailed, and values of <0.05 were considered statistically significant. All analyses were done using SPSS version 16.

RESULTS

Demographic Characteristics

Record of 115 deaths recorded among HIV patients admitted into Infectious diseases unit between January 2004 and December 2015 were reviewed in this retrospective observational study. The mean age was 35.91±10.04 (37.43±9.76 in AIDS related and 34.84±10.17 in HIV related deaths, p = 0. 07). Overall, patients in the reproductive age group (16 -49) constituted 87(87.9%). The proportion of death within the reproductive group of 38(87.5%) in AIDS related was similar to 49(89.1%) in HIV related death, p =0.76. Of the available records, 12(17.4%) died within 24 hours of admission, 22(31.9%) spent between one and six days, while 35(50.7%) spent at least one week on admission before death. A total of 52 (68.4%) of patients were yet to commence HAART despite presentation with advanced HIV disease necessitating admission. On presentation, 67(74.4%) patients were admitted with ≥ 2 comorbidities. The mean BMI (kg/m2) was 18.36±3.55 (12.1 – 31) with 29(53.7%) of the patients within the underweight category. The characteristics of patients at time of mortality is as presented in Table 1.

Table 1: Characteristic of patients at time of mortality.

Factor (at the time of death)	AIDS related death, no (45)	HIV associated death, no (64)
Mean ±Std dev	37.43±9.76(16 -58)	34.86±10.17(16-62)
Proportion, no (%)		
15 – 49 years, no (%)	38(87.5)	49(89.1)
>49 years, no (%)	06(12.5)	06(10.9)
Sex		
Mean ±Std dev		
Females	19(33.72±11.2)	25(32.68±10.26)
Males	26(40.0±8.04)	39(36.26±9.89)
Duration on admission (at time of death)		
<24 hours	08(24.2)	04(11.1)
1 – 6 days	12(36.40	10(27.8)
≥7 days	13(39.4)	22(61.1)
ART use		
yes	14(35.0)	10(27.8)
no	26(65.0)	26(72.2)
Morbidity		
No concurrent illness	00	00
1 concurrent illness	12(26.1)	11(24.8)
2 concurrent illness	1123.9)	17(38.6)
≥3 concurrent illness	23(50.0)	16(36.4)
Mean BMI	17.93±3.86	18.76±3.25
Obese	01(3.9)	00
Overweight	00	00
Normal weight	09(34.6)	15(53.6
Under weight	16((61.5)	13(46.4)

Laboratory parameters

The mean haemoglobin of the patients at death was 9.20±1.9 (5.8 – 14.5) g/dl, the hemoglobin concentration of 9.51±2.09 in HIV related death was higher than 8.81±1.52 in AIDS related deaths (p = 0.04). Stratification of anaemia based on WHO grading of anaemia indicates that 17(17.3%) had moderate to severe anaemia (WHO

grades III&IV), The median CD4 cell count of all patients was 115.67±96.15 (3 - 458), most patients, 80(857%) had CD4 cell count < 200 cell/ul. The median log HIV-RNA viral load was 5.33±5.61. Patients that died from AIDS related illnesses had median log HIV-RNA viral load of 5.12±5.58; it was significantly higher than 3.69 ±5.63 in HIV related death, p = 0.03. Laboratory parameters of patients dying from AIDS defining and HIV associated illnesses is as depicted in Table 2.

Table 2: Laboratory parameters of patients dying from AIDS defining and HIV associated Mortality.

Factor (at the time of death)	AIDS related death, no(45)	HIV associated death, (64)	P -value
Mean Haemoglobin Concentration	8.81±1.52(6.2 – 1.52)	9.51±2.09(5.8 – 14.50)	0.041
WHO grading			
I(9.5 – 10.5)	11(29.7)	20(45.5)	0.444
II(8.0 – 9.4)	16(43.2)	17(38.6)	
III(6.5 -7.9)	09(24.3)	06(13.6)	
IV (<6.5)	01(2.7)	01(2.3)	
CD4 cell counts	99.13±94.73	109.6±90.3	
Median CD4 count	79.5±99.2(3- 458)	89.0±94.3 (13 – 438)	0.447
Proportion			
>350	02(4.8)	01(1.9)	
200 - 350	03(7.1)	08(15.4)	
<200	37(88.1)	43(82.7)	
Median viral load(Log)	5.12±5.58(3.34 – 5.16)	3.69±5.63 (2.3 – 6.36)	0.03
< 200	-	2(5.3)	0.04
200 - 4,999	-	8(21.1)	
5,000 – 49,999	7(29.2)	9(23.7)	
50,000 – 99,999	2(8.3)	6(15.8)	
≥100,000	15(62.5)	13(34.2)	
Urea			
normal	37	50	0.600
high	08	14	
Creatinine			
normal	39	54	0.739
High	06	10	

Causes of Death

Of the total deaths, 45 (39.1%), 64 (55.7%) and 6 (5.2%) were due to AIDS related, HIV related and Non AIDS or HIV related diseases. As shown in Figure 1, HIV associated wasting syndrome was the most common cause of death responsible for 29 (46.8%) of AIDS related deaths, it was followed by oesophageal candidiasis 12 (19.4%) and Pneumocystis jiroveci 8(13.0%).

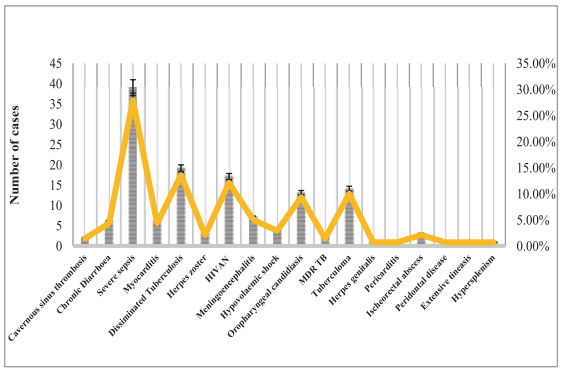

Figure 1: HIV associated diseases

The spectrum of diseases responsible for HIV related deaths (Figure 2), indicates that severe sepsis caused more deaths, it was responsible for 27.9% of cases, it was followed by TB 25% (Disseminated 13.6%, Tuberculoma 10% and Multi Drug Resistant form 1.4%) and HIV associated nephropathy (HIVAN), 12.3%.

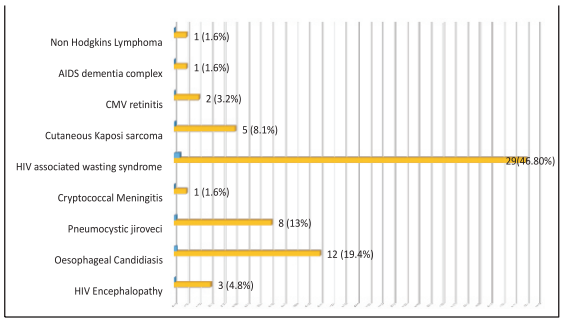

Figure 2: AIDS Defining illness

Acute liver injury was the most common co-morbidity, it was observed in 27.3% of cases. Others includes congestive cardiac failure, chronic renal failure and hemorrhagic stroke. Most patients, 67(74.4%) had with ≥ 2 associated non –HIV, non AIDS comorbidities (Figure 3).

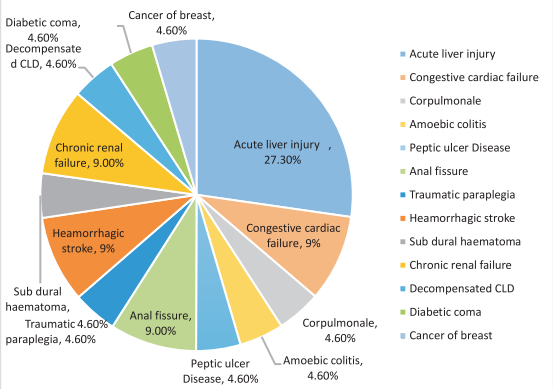

Figure 3: Spectrum of non –HIV, non AIDS associated co-morbidities

DISCUSSION

Knowledge of causes of death in HIV-positive persons enables appropriate targeting of interventions to improve the quality of patient care and reduce avoidable mortality.[13-15] In this study, HIV associated fatalities were seen among those with advanced disease, in those admitted with HIV related diseases (WHO stage III) and AIDS defining illness (WHO stage IV). The observation of mortality due to HIV among patients with advanced HIV disease has been reported in previous studies conducted in resource limited setting, and often portends late presentation or delay in initiation of HAART.[10,16,17] Several studies conducted in Nigeria have also corroborated that most HIV patients present late for care often in advanced stages.[18-20] In spite of global effort to provide universal access for HIV services such as HIV counseling and testing (HCT), free ART and management of other associated conditions such as tuberculosis (TB) and other opportunistic infections, several patients accessing HIV care in sub Saharan Africa including Nigeria still present late, often with advanced HIV disease.[19,20]

In this study, HIV associated wasting syndrome was the commonest AIDS defining illness constituting 46.8% of cases. It was followed by oesophageal candidiasis in 19.4%, *Pneumocystis jureveci*, 13% and Kaposi sarcoma in 8.1% of cases. Of the HIV related diseases, severe sepsis was responsible for death in 27.9% of cases, TB was responsible for 25% of mortality (Disseminated 13.6%, Tuberculoma 10% and Multi Drug Resistant 1.4%). Mortality due to HIV associated nephropathy was 12.1%. The characteristic late presentation and spectrum of clinical features observed in our study is similar to earlier reports on hospitalized HIV/AIDS patients in Nigeria in both pre-HAART era[21], post-HAART era[22] as well as other resource limited settings[16,23] in the HAART era. The high mortality due to advanced HIV diseases in this study and other reports underscores the urgent need for healthcare providers, policy makers, program funders alike to determine resource allocation and to optimize care and treatment strategies for HIV in low and middle-income countries (LMIC).

In this study, most HIV/AIDS related death occurred in patients aged 15 - 49 years, our finding agrees with several studies from LMIC that reported both higher mortality and incidence of HIV among young, productive and sexually active population.[23]

The high proportion of death of 68.4% recorded among HAART naïve despite presenting with advanced disease in this study indicate that mortality can be reduced if measures aimed at universal HIV counseling and testing (HCT) at strategic service delivery point in health institutions are fully implemented. Awareness campaign

and advocacy visit to community leaders also need to be intensified and sustained. Of those that commenced HAART, deaths occurred within 12 months of therapy. All the deaths in those that were on HAART ≥ one year had detectable viral load implying either poor adherence or resistance to HAART. The median CD4 counts of 79.5 cells/ul and 89.0cells/ul in AIDS defining illness and HIV related death respectively, in this study suggest severe immunosuppression notwithstanding the WHO clinical staging of III and IV. Several published studies have clearly shown that starting ART at a higher CD4 cell count will reduce morbidity and avert the high mortality rates seen among patients with advanced HIV disease.[25,26]

Mortality among males was higher than females in this study; it is in tandem with earlier study that reported higher HIV/AIDS associated deaths among males than females.[27] Conversely, other studies returned higher female preponderance.[3,28]

The record of more death among males in this study may be due to influence of socioeconomic factors on accessing health care. In our environment, the family economic power rest with the men and it is possible that females are under represented due to inability to fund hospital bills. It is also possible that females requiring hospitalization either never get to the hospital or die before decisions are made to take them to the hospital. Higher hospitalization of males than females has been reported in hospital-based studies of both HIV-infected and non-HIV infected populations from northern Nigeria.[9,29,30] The finding of more early mortality in males than females could be due to differences in healthcare seeking behavior between the sexes or poorer adherence in men or due to biological differences in ART response, but these differences need to be further examined as prior studies have found mixed evidence for sex differences in HIV disease progression, adherence and HIV treatment outcomes.[28,31,32] Our finding of older males than females has also been corroborated by other workers. Workers attributed finding of younger ages in females to earlier sexual maturity and, therefore, earlier risk of acquisition of HIV infection in females than males.[33]

Mortality due to non-HIV/AIDS related causes such as hemorrhagic stroke, Diabetic coma and congestive cardiac failure was exclusively seen among those that were in WHO clinical stage I and II. Mortality due to acute liver injury was observed among HIV – TB co infected patients that were commenced on anti-Tubercular medication. The combined affliction of HIV and/or Hepatitis B and TB poses multiple management challenges including high risk of anti TB drug induced liver injury and subsequent liver failure. The proportion of Hepatitis B or C virus was not significant for analysis in this study.

Limitations to our study

This study was limited by its retrospective design, as detailed clinical and laboratory variables were not available for all patients. Patients records with incomplete records or documentation of the cause of were excluded from the analysis. However, we believe the missing data did not significantly affect the major outcomes of the study since our findings were comparable to those within and outside Nigeria. Autopsy reports was not

available to validate or refute the causes of death. Autopsy is not performed in our setting due to sociocultural and religious belief except in litigation cases. Furthermore, etiology of sepsis was presumptuous as there were very few records of available blood culture results.

CONCLUSION

Patients admitted with advanced HIV disease in WHO clinical stages III and IV are at risk of death from HIV related diseases or AIDS defining illness. HIV associated wasting syndrome, sepsis and tuberculosis are common cause of death in our setting. The finding from this study suggests missed opportunities for early diagnosis and treatment of HIV infected patients exist in our environment.

RECOMMENDATION

Appraisal of current HIV management guidelines and protocol through strategic and rubout interventions directed at late presenters with advanced HIV are urgently needed in Nigeria and other HIV endemic nations. This can be achieved through universal access to HAART and adoption of novel approaches such as HIV test-and-treat strategies.

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