ORIGINAL ARTICLE

Factors Associated with Early Mortality in HIV Patients That Presented for Care in a Tertiary Health Facility in Northeastern Nigeria

Ballah Akawu Denue, Wadzani Gashau

ABSTRACT

Background: Despite huge success achieved in HIV management through early detection of cases and use of potent antiretroviral therapy (ART), human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) remains amongst the leading causes of death in sub-Saharan Africa.
Aim: To identify factors associated with death within one year of initiating ART in HIV/AIDS patients that presented for care with advanced disease (in WHO clinical stages III/IV).
Methods: This study analysed the records of patients admitted with advanced HIV disease, between January 2009 and December 2013. Information needed was sourced from patients' medical records and death certificates. During the study period, 273 patients were admitted, out of whom 119 satisfied the inclusion criteria. Of the 119 patients, 108 with complete data were analysed giving a retention rate of 90.1%. Among the participants, 51 cases died within one year of initial evaluation and 57 were alive after one year (survivors).
Results: Males were older than females in both the mortality cohort (p = 001) and survivor cohort (p = 0.01). Male gender (Crude odds ratio [COR] 2.27, 95% confidence interval [CI]: 1.08 – 5.21); HIV RNA viral load ≥ 100,000 copies/ml (COR 2.69, 95% CI: 1.20 – 6.03) and anaemia (haemoglobin concentration < 10.5g/dl) (COR 6.66, 95%CI: 2.74 – 16.17) were predictors of mortality in univariate analysis. After adjusting for confounding variables on multivariate analysis, anaemia (Adjusted odds ratio [AOR] 4.33, 95%CI: 1.27 – 14.83) remained the only predictor of death
Conclusion: Anaemia is an independent predictor of early mortality in patients that present with advanced HIV disease in our environment.

Keywords: Mortality, HIV/AIDS, northeastern Nigeria

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Introduction

The massive global effort towards providing universal access to highly active antiretroviral therapy (HAART) has resulted in significant reduction of HIV/AIDS-related morbidity and mortality worldwide.[1] However, a >3-fold increased rate of mortality within the first 12 months post-ART initiation has been reported in low and middle- income countries (LMIC) compared to high-income countries .[2] Report from adults accessing antiretroviral programs in sub-Saharan Africa identified a mortality estimate of 8-26% at 12 months post-ART initiation .[2,3] The national estimated annual death of 215,000 out of 3.1 million global HIV/AIDS related deaths reiterate that Nigeria continues to bear a large portion of global HIV burden.[4] The high HIV/AIDS associated mortality has been attributed to late initiation of ART .[5] Patients with advanced disease are at increased risk of opportunistic infections and immune reconstitution inflammatory syndrome .[5,6]Reports from Nigeria indicate that most HIV patients

present late for care often in advanced stage.[6,8] This is despite global effort to provide universal access for HIV services such as HIV counselling and testing (HCT), free HAART and management of other associated conditions such as tuberculosis (TB) and other opportunistic infections. Despite high loss of lives due to complications of HIV/AIDS, there is paucity of data on the predictors of mortality in patients that present with advanced disease in Nigeria. The few available studies reported heterogeneous predictors.[3,8]More studies are needed on predictors of early mortality in our environment as reports obtained elsewhere may not reflect what is obtainable in our setting due to our peculiar socio-demographic characteristics. Northeastern Nigeria is the least developed of the six geo-political region of Nigeria with high illiteracy level.Against this background, we evaluated the predictors of death within 12 months post-ART among clients that presented with advanced disease (in WHO Clinical Stages III or IV). Result obtained will assist in formulating protocol directed at late presenters with advanced HIV infection.

Methods

Study Design

This retrospective observational study analysed records of HIV infected patients with advanced disease (in WHO Clinical Stages III or IV) ,[9] that presented between January 2009 to December 2013. During the study period, 273 patients were admitted, out of which 119 satisfied the inclusion criteria. Records considered were from patients admitted with advanced disease that died of clinical conditions directly related to HIV/AIDS complications within one year of commencing ART. Of the 119 patients, 108 patients with complete data were analysed, with retention rate of 90.1%. The participants included 51 cases that died (mortality cohort) within one year of initial evaluation and 57 that were alive after one year (survivor cohort). Information needed was sourced from patient's medical records and death certificates. The two groups (Mortality versus Survivor) were compared to identify risk factors associated with death among HIV/AIDS presenting in late stages of HIV infection. Variables compared included age, gender, duration between initial evaluation and time of death, body mass index (BMI), baseline haemoglobin concentration, CD4 cell count, HIV RNA viral load, urea and creatinine and morbidity. "Morbidity" represented the number of concurrent HIV/AIDS related illnesses present at the time of death. Primary causes of death were classified as "AIDS-related death" (WHO clinical stage IV) or "HIV-associated death" (WHO clinical stage III). A death was considered "AIDS-related" when the primary cause of death (COD) was an AIDS-defining event as described in Category 3 of the CDC definition of AIDS [10], or WHO stage 4. "HIV-associated deaths" included those conditions that were HIV related but not CDC category 3 or WHO stage 4.

Deaths from other disease conditions not directly linked to HIV infection were excluded. Other exclusion criteria included patients that were already on ART before presentation or patients with incomplete documentation of clinicalevaluation and baseline laboratory parameters.

Operational definitions

Anaemia defined as haemoglobin concentration < 10.5 g/dl in both males and females

Advanced HIV disease is defined as clinical features consistent with WHO clinical stages III /or IV.

Early mortality is defined as death within one year of initiating ART

AIDS-related death is defined as death due to AIDS defining illness (consistent with WHO clinical stage IV).

HIV-related death is defined as death due to HIV related deaths (consistent with WHO clinical stage III) within one year of initiating ART.

Mortality cohort are HIV infected patients with advanced HIV disease that died due to AIDS or HIV related causes within one year of initiating ART

Survivor cohort are HIV infected patients with advanced HIV disease that were censored to be alive after one year on initiating ART

Ethical consideration

Permission to conduct this study was obtained from the ethics and research committee of University of Maiduguri Teaching Hospital.

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 (SPSS, Chicago, Illinois, USA) and analysed.

Statistical Analysis

Statistical comparisons of categorical variables were made using the chi-squared test or Fisher's exact test, where appropriate. Continuous variables were analysed using Student t-testMann Whitney U test was used to compare median where appropriate. P values of <0.05 were considered statistically significant.

Results

Clinical characteristics

A total of 108 cases were evaluated in this retrospective observational cohort study. They consisted of 51 cases of advanced HIV/AIDS that died within one year of initiating ART (mortality cohort) and 57 that survived (survivor cohort). The participants were matched with respect to WHO clinical stages (p = 0.569) and gender (p = 0.602). Males were older than females in both mortality cohort (p = 001) and survivor cohort (p = 0.01). The proportion of participants in both groups within the underweight and normal weight was significantly higher than those in overweight and obese category (p = 0.001). the HIV related illnesses, tuberculosis (37.3%), meningoencephalitis 13.7%), HIV associated nephropathy (HIVAN), 13.7%, severe sepsis 11.8%, chronic diarrhoea (11.8%) and ischiorectal abscess (7.8%) were the common presentation in death cases. Chronic dermatitis (31.5%), generalized adenopathy (27.8%), chronic diarrhoea (25.9%) and herpes zoster (7.4%) were amongst the common presentation in survivor cohort.

Laboratory parameters

The mortality and the survivor cohort had similar CD4 T cell counts, 114.7 ± 97.1 and 129.9 ± 66.4, p = 0.33 respectively. The proportion of cases in defined CD4 T cell (< 200, 200 – 349 and ≥ 350) was also similar (p = 0.056). The haemoglobin concentration of survivors of 11.0 ± 2.1 was significantly higher than 9.3 ± 1.9 in death cases (p = 0.01). However, the distribution of cases across the defined WHO grading was comparable (p = 0.57). The median HIV RNA viral load, 95,581 copies/ml (Interquartile range [IQR] 78,094.7) in death cases was higher than 65,094 copies/ml (IQR 59,820.6), respectively (p = 0.001),in survivors. All participants had detectable HIV RNA viral load (≥ 200 copies/ml). The proportion of detectable viral load within the stratified group was similar (p = 0.10). The laboratory parameters of the studied participants are as shown in Table 2.

Participants that presented with 2 or more concurrent illness were more than those that had none or single concurrent illness, but failed to reach statistical significance as presented in Table 1. The distribution of AIDS-Defining illness and HIV related diseases in mortality cohort indicates that 11 (21.6%) presented with AIDS defining illness, 17(33.3%) presented with both AIDS defining illness and HIV related diseases and 23(45.1%) presented with only HIV related diseases. Of the 57-survival cohort evaluated, none presented with only AIDS defining illnesses, 22(38.6%) presented with both AIDS defining illnesses and HIV-related diseases, and 35(61.4%) presented with only HIV related diseases as presented in Figure 1. The distribution of diseases responsible for HIV related deaths and AIDS related deaths is as depicted in Figure 2. HIV associated wasting syndrome was the commonest form of presentation in both death cases and survivors. Pneumocystis jiroveci (3.9%), HIV encephalopathy (5.9%) and cutaneous Kaposi sarcoma (3.9%) were commoner among death cases. Conversely, oesophageal candidiasis (5.6%) was commoner among survivors. Of

Determination of factors associated with early mortality as indicated in Table 3 shows that male gender (Crude odd ratio [COR] 2.27, 95% confidence interval [CI]: 1.08 – 5.21); HIV RNA viral load ≥ 100,000 copies/ml (COR 2.69, 95%CI: 1.20 – 6.03) and anaemia (haemoglobin concentration < 10.5g/dl) (COR 6.66, 95%CI: 2.74 – 16.17) were predictors of mortality in univariate analysis. After adjusting for cofounding variables (age, Sex, CD4 cell count, Viral load and number of comorbidities) on multivariate analysis, anaemia (Adjusted odds ratio[AOR] 4.33, 95%CI: 1.27 – 14.83) remained the only predictor of death

Table 1. Baseline characteristics of the study population

Factor (at the time of initial evaluation)	Mortality cohort (n=51)	Survivor cohort (n=57)	P value
Age range, n (%)			
15 – 49years	41 (80.4)	49 (86.0)	0.602
>49years	10 (19.6)	08 (14.0)	
Sex, mean±SD* (range), years			
Females	31.79±9.65	37.61±8.18	
Males	38.59±9.58	45.36±7.14	
Morbidity, n			
No concurrent illness	10	24	0.055
1 concurrent illness	12	07	
2 concurrent illness	12	08	
≥3 concurrent illness	17	18	
BMI, mean±SD	18.59±2.49	21.07±4.43	
BMI classes, n			
Obese	00	03	0.001
Overweight	00	08	
Normal weight	12	28	
Under weight	13	18	
WHO Clinical stage, n			
Stage III	37	31	0.569
Stage IV	20	21	

*SD – Standard deviation, BMI –Body mass index(Kg/m^2)

Table 2. Laboratory parameters of death cases and survivors

Factor (at the time of death)	AIDS-related death	HIV-associated death	P value
MHC[α] (g/dl)	9.27±1.89	11.0±2.12	0.00*
WHO grading, n			
I (9.5 – 10.5)	07	04	0.651
II (8.0 – 9.4)	21	12	
III (6.5 -7.9)	06	02	
IV (<6.5)	01	02	
CD4 T cell counts (cells/µl)			
Mean ± SD	114.7±95.05	129.9±66.36	0.334
Defined CD4 class, n			
>350	01	00	0.557
200 – 350	08	08	
<200	42	48	
HIV viral load, (copies/ml)			
Median[IQR]	95581[78,095]	65094[59,821]	0.001*
Defined viral load class, n			
< 200	00	00	0.101
200 – 4,999	08	16	
5,000 – 49,999	11	05	
50,000 – 99,999	07	05	
≥100,000	25	36	
Urea, n			
Normal	42	47	0.832
High	08	10	
Creatinine, n			
Normal	49	50	0.117
High	02	07	

*Statistically significant at $p < 0.05$ [α] MCH = Mean Haemoglobin Concentration

Table 3. Determinants of early mortality

Factor	N	Mortality n (%)	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age (years)						
< 50	88	41(46.6)	1.40(0.42 – 4.60)	0.584		
≥ 50	13	05(38.5)	**Reference**			
Sex						
Female	52	19(36.5)	**Reference**			
Male	52	30(57.7)	2.27(1.08 -5.21)	0.032*	1.86(0.58 – 5.94)	0.296
No of comorbidity						
< 3	73	34(46.6)	**Reference**			
≥ 3	35	17(48.6)	1.08(0.48 – 2.43)	0.846		
BMI						
Underweight	31	13(41.9)	2.35(0.90 – 6.15)	0.082	2.81(0.87 – 9.13)	0.085
Normal/Overweight	51	12(23.5)	**Reference**			
WHO Clinical Stage						
III	68	30(44.1)	**Reference**			
IV	40	21(52.5)	1.40(0.64 – 3.07)	0.400	1.74(0.54 – 5.62)	0.355
Anaemia status						
Anaemia	56	36(64.3)	6.66(2.74-16.17)	0.001*	4.33(1.27 –14.83)	0.020*
No anaemia	47	10(21.3)	**Reference**			
CD4 Cell count						
< 200 cells/µl	89	40(44.9)	1.38(0.49 – 3.90)	0.546		
≥ 200cells/µl	17	09(52.9)	**Reference**			
Viral load						
< 100,000 copies/ml	68	26(38.2)	**Reference**			
≥ 100.000 copies/ml	40	25(62.5)	2.69(1.20 – 6.03)	0.016*	1.74(0.51 – 5.96)	0.386

*Statistically significant at p < 0.05, Anaemia = haemoglobin concentration < 10.5g/dl

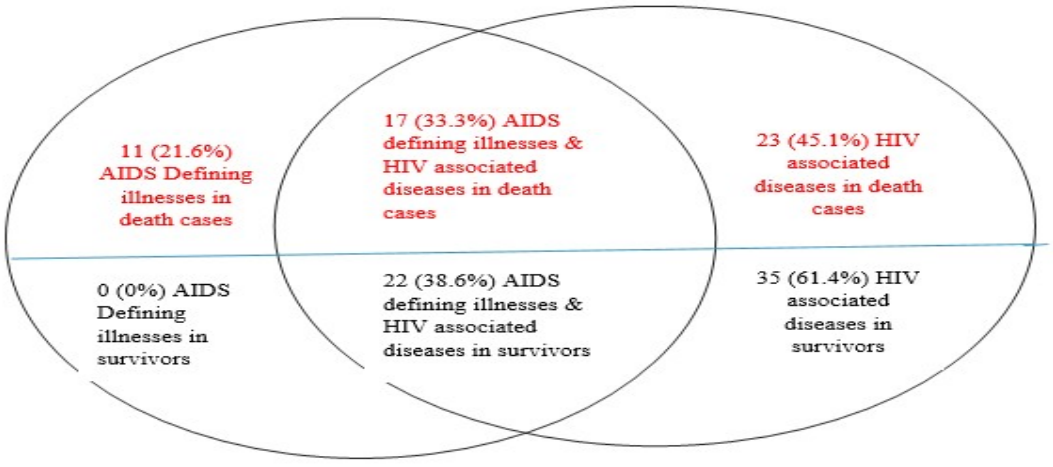

Figure 1. Distribution of AIDS-Defining illnesses and HIV-associated diseases

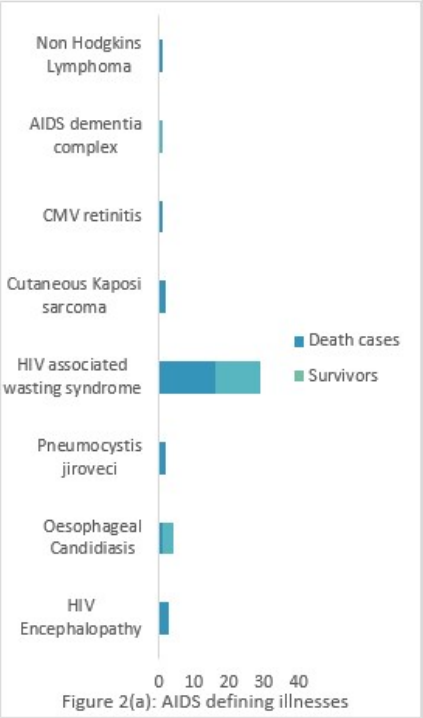

Figure 2(a): AIDS defining illnesses

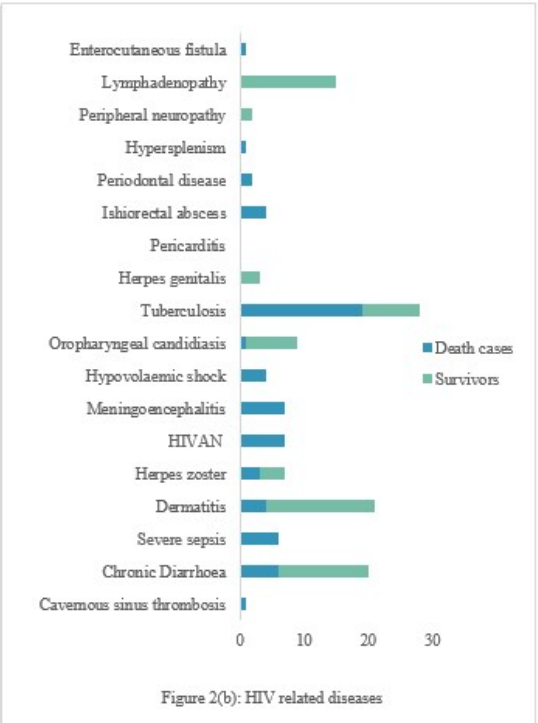

Figure 2(b): HIV related diseases

Discussion

The introduction of highly active antiretroviral therapy (HAART) has significantly improved survival and quality of life for persons living with immunodeficiency virus (HIV), ameliorating the devastating effect of fatal disease to manageable chronic condition .[12]Along with increased chance of survival, the causes of death in resource rich setting has undergone transition from HIV/AIDS related to non-HIV/AIDS.[13] In developed nations, the probability of survival in HIV infected patients without other risk factors on successful HAART is approaching closer to that in the general population of similar age.[13,14] The shift in causes of death toward non-HIV/AIDS-related in HAART era observed in studies in Western countries has not been observed in previous studies from developing countries as the proportion of HIV/AIDS-related death remained higher than non-HIV/AIDS-related deaths.[13-15] As observed in this study, despite widespread use of HAART, the risk of HIV/AIDS related death is high often at early time points in patients presenting with advanced HIV disease. Our finding of overwhelming AIDS-related death among patients presenting late often in WHO clinical stages III or IV has been corroborated by similar studies conducted previously in Nigeria and other low and middle-income countries (LMIC) .[2,3,15]

In this study, we sought to identify specific risk factor(s) related to death in HIV infected patients that presented late for care among patients in WHO clinical stages III or IV. We compared the clinical and laboratory parameters of cohorts that died within 12 months of initiating HAART and those that survived 12 months post-HAART. Most deaths occurred within 3 months of initial evaluation and initiation of ART, our finding agrees with previous African studies that estimated 8 -26% risk of death within 12 months of initiating HAART, often within the first three months. Mortality is attributed to late initiation of HAART when patients have advanced diseases with increased risk of opportunistic infections and immune reconstitution inflammatory syndrome (IRIS).

Patients aged (16-49) years were at risk of death in this report, similar to a previous study; [16] our observation is, however, contrast with studies that identified higher risk among older HIV patients .[17] Aging and HIV are thought to cause additive depletion of naïve T-cells as well as replicating senescence of T-lymphocyte, and

consequent poor treatment outcome in patient with advanced age.[17,18] However, the finding of preponderance of death in younger age group in this study need to be interpreted with caution as our finding may reflect the reported high incidence of HIV in patients within reproductive group in Nigeria.

The median CD4 cell count in both mortality and survivor cohorts beyond 12 months in this study indicates both arms presented with severe immunosuppression and therefore at an increased risk of opportunistic infections and IRIS. Studies have validated the immense benefit of initiating HAART at higher CD4 cell count to reduce morbidity and avert death rates seen in HIV patients with advanced disease. Given the reported late presenters in most LMICs, a more robust and aggressive testing and treating of HIV-infected persons irrespective of their CD4 cell level is desirable .[19] HIV-1 RNA viral load didn't predict mortality in this study, this may be explained by the fact that our participants were those with advanced diseases i.e. with already high viral load. HIV viraemia is associated with advanced HIV disease and is also implicated in aetio-pathogenesis of some AIDS defining illnesses in addition to depleting CD4 cells and causing distortion of the arms of immunity.[20]

Despite being an easily recognized feature and common presentation of HIV infection, the prognostic value of weight loss as a risk factor for mortality has not been validated in Nigeria. In this study, body mass index (BMI) as a possible surrogate of nutritional status didn't predict mortality. Our finding is in contrast with previous reports by workers that documented the association between weight loss and risk of death in developing countries.[21] Several factors such as poor nutritional intake, malabsorption, malignancies, wasting syndrome, increased basal metabolic rate due to HIV viraemia and opportunistic infections including tuberculosis could be possible causes of significant weight loss in patients with HIV infection .[21-24]

Anaemia as evidenced by low haemoglobin concentration (<10g/dl) was associated with risk of death. Anaemia is a common feature in HIV infected persons in developing countries, consequences of HIV-related anaemia such as fatigue, decrease quality of life and fatalities is enormous and of great concern in resource limited setting such as sub -Saharan Africa. As observed in this report, evidence from previous reports has shown HIV related anaemia as a predictor of morbidity and mortality irrespective of CD4 cell count and viral load.[25] Low haemoglobin in the setting of HIV infection except if it is due to acute loss or from identifiable non-HIV/AIDS related causes is a marker of progressive disease and a prominent feature of most opportunistic infections complicating HIV-disease including TB. Some studies demonstrated a six-fold risk of mortality in patients with severe anaemia[13,26] In the setting of HIV/AIDS, anaemia often result due to micronutrients deficiency, immunological myelosuppression, impaired erythropoietin production, and blood loss from intestinal opportunistic diseases, among other causes.[25-27]

Conclusion: Anaemia is an independent predictor of early mortality in patients that present with advanced HIV disease in our environment. The observation of HIV/AIDS related death in patients with advanced HIV disease implies the need for starting treatment earlier. This requires early diagnosis of HIV infection through improved counselling and testing practices.

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