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ORIGINAL ARTICLE

Early Versus Delayed Mortality among HIV Infected Patients Initiating Highly Active Antiretroviral Therapy in Tanzania

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Abstract: Development of HAART in the mid-1990's and its continued scale up has revolutionized the treatment of HIV-infected patients and led to remarkable reductions in HIV associated morbidity and mortality. However, recent studies have suggested a higher risk for early mortality in adults receiving ART in low-income countries as compared to those in high-income countries. There is dearth of data from developing countries where the burden of disease is high. The objective is to describe the burden and correlation between early vs. delayed mortality associated with HIV/AIDS in resource poor settings using data from Tanzania in East Africa. We performed a cross-sectional evaluation of routinely collected program data for 991 HIV-positive deceased adult patients who were placed on ART treatment, and died between January 1, 2007 and December 31, 2012. Data used were abstracted from records of patients who were treated at six health facilities in the Lake-zone Region of Tanzania in the timeframe. Bivariate and multivariate regression models were used to identify independent predictors of mortality and to calculate odds ratios. From the population, early deaths (within 3 months of ART initiation) occurred in 359 of the 991 cases, which represented 36.2%; while delayed deaths (after 3 months of ART initiation) occurred in 632 of 991 (63.8%). The average time to death for those who died within 3 months was 1 month compared to 22 months among those who died at > 3 months since initiation of ARV. In multivariate analysis, patients who were on WHO stage IV, had fever and cough symptoms at 6 months prior to death and patients with 0-1, 2-3, and 4-6 clinic visits had a higher risk of death in the first 3 months. Mortality among patients started on ART seems to be high. Where possible, healthcare providers should do more to vigorously monitor patients before starting them on ART for better outcomes. Additionally, public health efforts to encourage early testing and entry into treatment must be scaled up in resource poor countries to gain some lead-time and to keep the virus under control, sustain immune function, and delay the onset of opportunistic infections.

Keywords: Early, Mortality, Delayed, HAART, HIV.

Introduction

Highly active antiretroviral therapy (HAART) has improved the survival of people living with the human immunodeficiency virus (PLHIV) (Cockerham et al., 2010). Although human immunodeficiency virus and AIDS/HIV related mortality in low-income settings remains high in the first months of therapy (Falster et al., 2009). Despite improvements in access to HAART, between 8%-26% of PLHIV on highly active anti-retroviral therapy (HAART) in sub-Saharan Africa die within a few months of the first year of antiretroviral treatment initiation largely due to the fact that some PLHIV only access HAART when they have advanced symptomatic disease (Lawn et al., 2008). There is an increased rate of mortality occurring within the first 12 months post-HAART initiation observed in low-to-middle income countries (LMIC) compared to high-income countries (Braitstein et al., 2006). One of the four targets for the World Health Organization's Global Health Sector Strategy on HIV/AIDS 2011-2015 is to reduce HIV-related mortality by 25% from the 2009 baseline (WHO, 2011).

There are several factors illustrated to be associated with premature HIV/AIDS related mortality across different studies. In one observational clinical cohort study, 215 (5.1%) of the 4252 patients died during follow-up. AIDS related causes accounted for 41.4% of the mortality while CD4 cell count and HIV viral load were associated with AIDS mortality (Falster et al., 2009). According to Modrich et al. (2010), low baseline CD4 count, smoking, and older age were associated with HIV mortality (Cockerham et al., 2010). The major cause of early mortality was found to be tuberculosis (TB), which accounts for 21% of HIV related deaths (Lawn et al., 2008). Other studies have consistently shown TB to be a leading cause of mortality (Grant et al., 1998). In contrast, a study in Nepal found TB (30%) to be most common OI followed by candidiasis (14%) (Dhungel et al., 2008). The study showed a 32% mortality rate within 2 months of follow-up. A substantial proportion (about 70%) of these deaths occur very early (within the first 3 months) after starting ART (Zachariah et al., 2006). Routine program data indicates that patients starting HAART in resource-poor settings have increased mortality rates in the first months of therapy, compared with those in developed countries (Braitstein et al., 2006). Early HAART initiation could lead to improved outcomes (Kyeyune et al., 2010).

Despite increased access to HAART, people living with HIV continue to die; deaths that we believe could be averted. Appropriate diagnoses of opportunistic infections in people living with HIV in resource-limited settings are essential for the success of HIV care and treatment as well as the elimination of early mortality. There is dearth of data from developing countries where the burden of disease is high. The objective of this study is to describe the burden and correlate of early versus delayed mortality associated with HIV/AIDS in resource poor settings using data from Tanzania in East Africa.

Materials and Methods

Study Design

This was a cross-sectional evaluation examining mortality among HIV/AIDS patients who received treatment between January 1st 2007- December 31st 2012 from select hospitals in rural Tanzania. The data was collected as part of a routine quality improvement exercise involving a review of medical records for 991 deceased patients who were on ART within the defined time period. Data on socio-demographic and clinical variables were collected and entered into a Microsoft excel spreadsheet.

Study Population

Currently, many African countries are receiving ART support through the President's Emergency Plan for AIDS Relief in Africa (PEPFAR), the Global Fund, and other private donors. These funds have made ART available to thousands of people who are now receiving life-sustaining medications. The government of Tanzania implemented a regionalization approach leading stakeholders to direct attention to specific areas in an attempt to bring cohesive therapy and management to an entire geographical region across the entire country. This was directed first at reference-level hospitals followed by Regional and District Hospitals and later extending to health centers and dispensaries. In this paper, we specifically elaborate the characteristics of all mortality patients in six hospitals: 1 referral, 2 regional, 2 district hospitals, and 1 faith-based.

Analytical Methods and Statistical Analysis

Quality Improvement teams from the six hospitals were trained in data ethics and data abstraction procedures before they started the review of patients files. The data were cleaned and recoded by senior level program staff who also performed exploratory data analysis to identify any anomalies during the entry into the spreadsheet and potential outliers in the data.

Statistical analysis was carried out using STATA 12 (StataCorp LP, College Station, TX, USA for Windows). Descriptive statistics (mean, standard deviation) were used to examine the distribution of demographic characteristics of the study population, and other clinical characteristics such as patient symptoms, WHO staging and CD4 Cell count. At the bivariate, level we performed Chi-square (X^2) test of independence for categorical variables and Student T-test for continuous variables. Unadjusted odds ratios (OR), as well as 95% confidence intervals, were generated to identify factors directly associated with early mortality. Variables found to be statistically significant ($p < 0.05$) on unadjusted analysis were included in the adjusted logistic regression model.

Ethical Considerations

The current study is part of a routine quality improvement exercise for patient care. Permission for the use of the data was also obtained from the respective Hospital Management teams before embarking on this quality improvement exercise. This exercise was a highly participatory approach with the hospital administration and quality improvement teams taking a lead. There were no patient identifiers, data was kept confidential and remained anonymous. Results of this exercise were jointly summarized and communicated with the respective hospitals in the region.

Result

From the deceased population, mortality or death occurring within the first three months after ART Initiation (defined as Early Death) occurred in 359 (36.2%) cases while Delayed deaths (after 3 months of ART initiation) occurred in 632 (63.8%) of the samples. The average time to death for those who died within 3 months vs. less than 3 months was 35.9 days (SD:33.3-38) and 656 days (SD: 611.2-700.3), respectively. The mean age for the deceased patients was 39.1 years with a standard deviation (SD: 37.9 – 40.3) for early death and 41.2 years (SD of 40.3 – 42.1) for delayed deaths (Table 1).

Table 1. Distribution of baseline socio demographic, clinical and laboratory characteristics of deceased ART patients in Tanzania.

Characteristics	Early mortality (N= 359)	Delayed mortality (N=632)	P-value
Age (Mean, SD)	39.1 (37.9 – 40.3)	41.2 (40.3 – 42.1)	0.003
Gender (n=991)			
Male	190 (52.9%)	290 (45.9%)	0.033
Female	169 (47.1%)	342 (54.1%)	
Time in days to death (Mean, SD)	35.9 (33.3 – 38.5)	656.1 (611.2 – 700.3)	<0.001
Deaths per each site (n=991)			<0.001
Referal Hospital	98 (27.3%)	179 (28.3%)	
Regional Hospital 1	64 (17.8%)	130 (20.57%)	
District Hospital	33 (9.2%)	47 (7.4%)	
Regional Hospital 2	55 (15.3%)	133 (21.0%)	
District Hospital 2	65 (18.1%)	115 (18.2%)	
Faith Based District Hospital	44 (12.3%)	28 (4.4%)	
Baseline WHO staging (n=980)			0.030
Stage 1	6 (1.7%)	41 (6.6%)	
Stage 2	42 (11.7%)	142 (22.8%)	
Stage 3	148 (41.3%)	295 (47.4%)	
Stage 4	162 (45.3%)	144 (23.2%)	
Baseline CD4 (n=859) Mean (SD)	112 (98.5 – 127.2)	171 (158.5 – 184.4)	<0.001
0 – 200 /mm3	228 (80.0%)	387 (67.4%)	
201 – 350 /mm3	43 (15.1%)	120 (20.9%)	
>350 /mm3	14 (4.9%)	67 (11.7%)	
Baseline Weight (in Kgs) (n=921)			<0.001
<45	123 (41.6%)	173 (28.7%)	
45-54	120 (37.6%)	167 (27.7%)	
55+	76 (23.8%)	262 (43.5%)	

Last Weight Recorded (in Kgs) (n=966)			<0.001
<45	118 (33.6)	175 (28.4%)	
45-54	141 (40.2%)	182 (29.6)%)	
55+	92 (26.2%)	258 (41)%)	
No of Clinic visits Recorded(n=983)			<0.001
0-1	138 (38.6%)	49 (7.8%)	
2-3	193 (53.9%)	143 (22.9%)	
4-6	17 (4.7%)	80 (12.8%)	
7+	10 (2.8%)	353 (56.5%)	
Symptoms 6 months prior to death			
Fever and cough (n=977)	197 (56.3%)	288 (45.9%)	0.002
Shortness of breath (n=987)	79 (22.2%)	101 (16.0%)	0.016
OIs 6 months prior to death			
Tuberculosis (n=989)	111 (31.0%)	140 (22.2%)	0.002
Cryptococcal Meningitis (n=988)	32 (8.9%)	31 (4.9%)	0.013
Pneumocystic Jiroveci Pneumonia (n=975)	28 (8.0%)	34 (5.5%)	0.125
CD4 level 6 months prior to death (n=196)			0.446
0 – 200 /mm3	2 (25.0%)	88 (46.8%)	
201 – 350 /mm3	4 (50.0%)	60 (31.9%)	
>350 /mm3	2 (25.0%)	40 (21.3%)	
WHO staging at last visit (n=972)			0.030
Stage 1	3 (0.9%)	9 (1.4%)	
Stage 2	16 (4.6%)	60 (9.6%)	
Stage 3	144 (41.3%)	252 (40.5%)	
Stage 4	186 (53.3%)	302 (23.2%)	
Laboratory testing during illness			
Biochemistry (n=991)	158 (44.0%)	325 (51.4%)	0.077
Haematology (n=991)	210 (58.5%)	394 (62.3%)	0.490

Clinical characteristics

In regards to the Baseline WHO staging (n=980), 162 (45.3%) Early death cases and 144 (48.5%) late death cases were in stage IV. The mean baseline CD4 cell count (n=859) were 112 (SD: 98.5 – 127.2) and 171 (SD: 158.5 – 184.4) for early and delayed mortality cases. While 228 (80.0%) and 387 (67.4%) of the early and delayed cases had a baseline CD4 count of between 0 – 200 /mm^3. The presence of fever and cough as symptoms at 6 months prior to death were 197 (56.3%) and 288 (45.9%) for early and delayed deceased cases (Table 2).

Table 2. Risk factors associated with early mortality among HAART patients in Tanzania.

Characteristics	Unadjusted OR		Adjusted OR	
	OR (95%CI)	P value	OR (95%CI)	P value
Gender				
Female	1		1	
Male	1.3 (1.02-1.71)	0.033	1.3 (0.95-1.77)	0.08
CD4 level 6 months prior to death (n=196)				
0 – 200 /mm3	2.8 (1.54,5.13)	<0.001	2.6 (0.96-1.80)	0.084
201 – 350 /mm3	1.7 (0.87,3.36)	0.116	60 (0.84-3.58)	0.136
>350 /mm3	1		1	
WHO staging at last visit (n=972)				
Stage 1	1		1	
Stage 2	2 (0.80-5.0)	0.135	1.2 (0.44-3.17)	0.733
Stage 3	3.4 (1.4-8.25)	0.006	2.11 (0.84-5.33)	0.113

Stage 4	7 (3.17-18.64)	<0.001	5.5 (2.13-14.06)	<0.001
Symptoms 6 months prior to death				
Fever and cough (n=977)				
Yes	1.5 (1.16-1.97)	0.02	1.8 (1.23-2.57)	0.002
No	1		1	
Shortness of breath (n=987)				
Yes	1.5 (1.07-2.07)	0.016	1.2 (0.79-1.91)	0.355
No	1		1	
OIs 6 months prior to death				
Tuberculosis (n=989)				
Yes	1.6 (1.17-2.11)	0.002	1.4 (0.97-2.09)	0.069
No	1		1	
Cryptococcal Meningitis (n=988)				
Yes	1.9 (1.13-3.16)	0.014	1.4(0.74-2.70)	0.297
No	1		1	
Pneumocystic Jiroveci Pneumonia (n=975)				
Yes	1.55 (0.93-2.59)	0.092	1.1 (0.59-2.22)	0.689
No	1		1	
Baseline Weight (in Kgs) (n=921)				
<45	1.8 (1.35-2.63)	<0.001	1.3 (0.50-3.10)	0.62
45-54	2.2 (1.57-3.00)	<0.001	1.5 (0.74-2.97)	0.25
55+	1		1	
Last Weight Recorded (in Kgs) (n=966)				
<45	2.5 (1.73,3.46)	<0.001	1.8 (0.90-3.49)	0.09
45-54	2.4 (1.75,3.50)	<0.001	1.9 (0.81-4.82	0.13
55+	1		1	
No of Clinic visits Recorded(n=983)				
0-1	99 (48.97-201.81)	<0.001	112 (48.16-62.33)	<0.001
2-3	47 (24.51-92.61)	<0.001	52 (24.50-112.66)	<0.001
4-6	7 (3.31-16.99)	<0.001	6 (2.32-15.71)	<0.001
7+	1		1	

Factors associated with early mortality

At the bivariate analysis, gender; CD4 cell count level at 6 months prior to death; WHO staging at last visit; the hematological test; the presence of fever and cough and shortness of breath symptoms at 6 months prior to death; the presence of Tuberculosis; Cryptococcal Meningitis; Pneumocystic Jirovecii Pneumonia (PJP) at 6 months prior to death; baseline weight (in kg); last visit weight (in kg); and number of clinic visits attended were statistically and significantly associated with early mortality ($p<0.05$).

At the multivariate analysis level (Table 2), patients who were on WHO stage IV were 5 times likely to have an early death as compared to those on WHO stage I [OR = 5.5, 95% CI: 2.13-14.06). Patients who had fever and cough symptoms at 6 months prior to death were more likely to have an early death as compared to those who didn't experience the symptoms (OR = 1.8; 95% CI: 1.23-2.57). We observed a gradient relationship in which patients with less clinic visits were more likely to die in three month ($p <0.001$).

Discussion and Conclusion

In our findings, it is demonstrated that 359 (36.2%) of the cases have early mortality with the time duration of less than three months after the start of treatment. Several variables were significantly associated with early mortality including WHO staging at last visit, patients who had fever and cough symptoms at 6 months prior to death, and number of clinic visits/consultation.

Several studies in low- and middle-income countries have reported that patients who undergo treatment have early mortality after initiating HAART. Empirical evidence in Malawi showed that 61%) (n=116) of the death occurred within the first 3 months and 150 (79%) within the first 6 months (Zachariah et al., 2006). Along with this, in the same country, 206 (74%) people died within 3 months of initiating HAART at a primary health center

(Zachariah et al., 2009). In a Tanzania study, from 95 patients who died, 59 of the patients died within 3 months of starting HAART (Johannessen et al., 2008). These studies from Malawi, Tanzania, and Ethiopia (Tadesse & Hiruy, 2014) demonstrated that majority of the patients were in WHO stage 3 and 4 and had a CD4 count of less than 200 mm^3 at the baseline; and concurred that most of our study participants who presented to the health facilities for HAART had advanced diseases. It may be necessary to improve HIV testing strategies so that those found HIV-positive may be initiated on HAART early before the immune system is severely weakened and susceptible to opportunistic disease. Similarly, it might also be an indication that there is need for improved monitoring and increased access to HAART for patients awaiting HIV treatment to obtain better outcomes. More qualitative research needs to be done to better understand the reasons for delayed access to HAART among patients initiated late to improve both treatment strategies and disease management. Early testing should be encouraged at the facility and community level.

In our findings, advanced disease progression with WHO stage 4 were independent predictors of early mortality. Similar findings have been reported elsewhere. In a Nepal study, HIV-infected patients with WHO clinical stage III had a 3-fold increased risk of death compared to patients with stage I or II and the risk of death among WHO clinical stage 4 patients was even higher- compared to stage I or II patients (Bhatta et al., 2013). Another study found that patients in stage 3 and 4 were two to four times more likely to die than patients in stage 1 and 2 (Sieleunou et al., 2009). In the same way, mortality has also been found to be strongly associated with WHO stage 3 & stage 4 disease (Stringer et al., 2006). Even in a sub-Saharan Africa study, excess mortality was lower in women as compared to men, and higher in patients starting ART with advanced stage of disease (Brinkhof et al., 2009). High mortality during the first months of treatment was strongly associated with the advanced clinical stage in Ethiopia (Jerene et al., 2006). Among ART patients, WHO stages were strong predictors of mortality in ART patients. There was an eight fold higher hazard of death for WHO stage 4 vs. stage 1 (Mugisha et al., 2014) and in a Tanzanian study, WHO stage 4 at the start of ART was associated with four times higher death rate compared to WHO stage 1–3 combined (Mageda et al., 2012). In a Burkina Faso study, clinical staging (WHO stages) were significantly associated with death (Kouanda et al., 2012).

Another finding was that missing a clinic visit was associated with mortality. Mortality rates were more than 2 times higher for patients with missed visits, compared to mortality rates of patients who attended all scheduled appointments during the first year of care (2.3 vs. 1.0 deaths per 100 patient-years of follow-up (HR =2.90; p = 0.02) (Mugavero et al., 2009) and with persons with visits in all 4 quarters during the first year. The adjusted hazard ratio of death was 1.42, 1.67, and 1.95 for persons with visits in 3 quarters, 2 quarters, and 1 quarter, respectively (Giordano et al., 2007) and had a higher risk of hospital admissions (OR: 2.4) and mortality (OR: 6.7) (Colubi et al., 2012). Similarly, advanced clinical stage and longer total elapsed time without clinical visits for 1 year after HAART were all significant risk factors for the occurrence of new AIDS-defining illnesses or death (Park et al., 2007) and adherence to visits (Gupta et al., 2011).

There was missing data (undocumented) and this limited the richness of the findings; this is a concern in terms of patient management without adequate documented data. The cause of death was also not ascertained by verbal biopsy or other modality. As a subsequent to our quality improvement exercise, it was important to train and advocate for improvements in medical records documentation for improved care by health workers. However, the retrieval and abstraction of a large number of patient's medical records across different types of facilities could still represent a real reflection of a program setting data; therefore, this enables the enforcement of policy-making and can be taken as a major strength of this quality improvement exercise.

Mortality among ART patients is a cause for concern, especially since a significant proportion of patients die without a confirmed diagnosis. Healthcare providers need to do more vigorous monitoring of patients before starting them on ARTs for better outcomes. Simple tools should be developed for assessing opportunistic infections among high-risk patients. There is a need to do more systematic studies in order to explore early mortality in detail.

Conflict of Interests

All authors declare that they have no conflict of interests associated with the publication of this paper.

Authors' Contribution

PK, AM, and ET assisted in the collection of data and technical aspects of the paper. PM and PK conceived and designed the study, collected data in the field, performed analysis, interpreted data, and gave a critical review of the paper. SB, PM, CS, and SM participated in design and helped draft the paper. JM assisted with the design, interpretation of data, draft, and critical review of the paper. AP, CS and AH

worked on the edits. All authors approved and read the final paper. All authors participated in critical appraisal of the paper.

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