ORIGINAL ARTICLE

Predictors of Survival among Adult Ethiopian Patients in the National ART Program at Seven University Teaching Hospitals: A Prospective Cohort Study

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OPEN ACCESS

Citation: Daniel Fekade, Teklu Weldegebreal, Alula M. Teklu, et al. Predictors of Survival among Adult Ethiopian Patients in the National ART Program at Seven University Teaching Hospitals: A Prospective Cohort Study. Ethiop J Health Sci 2017;27(si1):63-71. doi: http://dx.doi.org/10.4314/ejhs.v27i1.7S.
Received: February 1, 2016
Accepted: August 12, 2016
Published: March 15, 2017

Funding: President's Emergency Plan for AIDS Relief (PEPFAR) through the US Centers for Disease Control and Prevention- Ethiopia)
Competing Interests: The authors declare that this manuscript was approved by all authors in its form and that no competing interest exists.
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ABSTRACT

Background: ***In Ethiopia, the publicly funded antiretroviral treatment (ART) program was started in 2005. Two hundred seventy-five thousand patients were enrolled in the national ART program by 2012. However, there is limited data on mortality and predictors of death among adult patients in the ART program. The study aimed to estimate mortality and risk factors for death among adult, ART-naïve patients, started in the national ART program from January 2009 to July 2013.***

Methods: ***Multi-site, prospective, observational cohort study of adult, age > 18 years, ART-naïve patients, started in the national ART program at seven university-affiliated hospitals from January 2009 - July 2013. Kaplan-Meier and Cox regression analyses were used to estimate survival and determine risk factors for death.***

Results: ***A total of 976 patients, 594 females (60.9 %), were enrolled into the study. Median age of the cohort was 33years. The median CD4 count at start of ART was 144 cells/µl (interquartile range (IQR) 78-205), and 34.2% (330/965) had CD4 < 100. Sixty-three percent (536/851) had viral load greater than 5 log copies/ml (IQR 4.7-5.7) at base line. One hundred and one deaths were recorded during follow-up period, all-cause mortality rate 10.3%; 5.4 deaths/100 person years of observation, 95% confidence interval 4.4-6.5. Seventy percent of the deaths occurred within six months of starting ART. Cox regression analyses showed that the following measures independently predicted mortality: age ≥51 years, (Adjusted Hazard Ratio (AHR) 4.01, P=0.003), WHO stages III&IV, (AHR 1.76, p = 0.025), CD4 count, <100, (AHR 2.36, p =0.006), and viral load >5 log copies /ml (CHR 1.71, p = 0.037).***

Conclusion: ***There is high early on- ART mortality in patients presenting with advanced immunodeficiency. Detecting cases and initiating ART before onset of advanced immunodeficiency might improve survival.***

Key Words: ***Ethiopia, HIV clinical cohort, Antiretroviral therapy, Survival***

DOI: http://dx.doi.org/10.4314/ejhs.v27i1.7S

INTRODUCTION

Several studies from both developed and low-income countries have demonstrated the survival benefits of anti-retroviral therapy, ART, (1-10). Although treatment effectiveness as measured by CD4 increase or viral suppression is similar between developed and low-income countries, there is greater than threefold increase in early mortality in resource-poor settings (3-7). In a meta-analysis of survival from 18 ART programs in sub-Saharan Africa, early mortality, within 12 months after start of ART, of 8% to 26% has been reported(8). Male sex, older age, advanced World Health Organization (WHO) clinical stages, low hemoglobin, and low CD4 counts, at baseline were independent risk factors for death (8). A meta-analysis that compared mortality among low- and middle-income countries reported that sub-Saharan Africa had the highest 12-month mortality probability of 17%, compared to 11% for Asia, and 7% for the Americas (10).

The publicly funded ART program in Ethiopia was started in 2005. By 2012, 275,000 people living with human immunodeficiency virus (PLHIV), 65% of whom were eligible for treatment, were in the national ART program. However, there are few studies that reported mortality rate of patients in the national ART program (11-14). Furthermore, the available studies were conducted at the beginning of the ART roll-out, estimates were based on small numbers of patients and short follow-up time (12), and were from single or two treatment sites (13, 14); thus limiting their generalizability.

The present study overcame these limitations by recruiting large number of patients from seven country-wide sites, and followed them for up to three years. The aim was to estimate mortality and risk factors for death among adult ART-naïve patients in the national ART program, and to inform policy on HIV care and treatment.

METHODS

Study design: Prospective, multi-site, observational cohort of previously untreated adult HIV-infected patients older than 18 years of age who started on ART in the national ART program from January 2009 - July 2013 as a sub-set of the advanced clinical monitoring cohort.

Setting: Seven university-affiliated hospitals in country-wide urban settings. Treatment sites were the Armed Forces and Tikur Anbessa Teaching Hospitals in Addis Ababa; Hiwot Fana Specialized Hospital in Harar, Harari Region; Gondar University Hospital in Gondar, Amhara Region; Jimma Specialized Referral Hospital in Jimma, Oromia Region; Hawassa Univerisry Referral Hospital in Hawassa, Southern Nations and Nationality People Region; and Mekelle Referral Hospital in Mekelle, Tigray Region.

Measurements: Socio-demographic characteristics including age, sex, marital status, type of health facility and level of education; and clinical parameters such as WHO clinical stage, functional status, diagnosis and treatment for tuberculosis (TB), cotrimoxazole prophylaxis (CPT) status, isoniazid preventive therapy (INH) and laboratory tests, including blood samples for pre-treatment CD4 count and viral load determination were collected, and results recorded in standardized national ART intake and follow-up forms.

Viral load (VL) determination was done in a reference laboratory at the Ethiopian Public Health Institute (EPHI). NucliSENS easyQ® HIV-1 Nucleic Acid Sequence-Based-Amplification (NASBA) assay (BioMérieux Diagnostics) was employed to determine VL in patients' plasm samples. CD4 count was determined using BD FACSCalibur machines (Becton Dickinson, San Jose, USA). The CD4 tests were done at laboratories within the participating health facilities using patients' uncoagulated whole blood. Quality of tests were ensured through employing internal quality control and external quality assurance systems.

Interventions: Eligibility for ART was according to the 2007 Ethiopian Guideline on ART (15). Indications for treatment were WHO clinical stages III/IV or CD4 < 200 cells/µl. Treatment consisted of two nucleoside analogues, azidothymidine (AZT), lamivudine (3TC), stavudine (d4T) and/or tenofovir (TDF) combined with either efavirenz (EFV) or nevirapine (NVP). Patients also received cotrimoxazole prophylaxis as per national guideline. Patients were followed up every month for the first three or more months until they are clinically stable and adherent to their medications, and every three month thereafter, or as clinically required. In addition, adherence assessment and support, nutritional assessment and counseling, risk reduction and safe-sex counseling services were provided as a routine standard of care during every visit and encounter.

DOI: http://dx.doi.org/10.4314/ejhs.v27i1.7S

Patients' follow-up status was tracked using a standard HIV chronic care follow-up form and patient appointment calendar. Lost to follow-up was defined if patient did not have follow-up visit at least 30 days after the last date of the next clinic appointment. Lost to follow-up patients tracing was done through telephone call or home visit using case managers who reported on the status of each patient to the data clerks. Transferred out (TO) define: if patient moved to another health facility with confirmed written documentation of transfer out.

Outcome measure: All-cause mortality was the outcome variable; ascertainment of death was from death certificates when patients died in hospital, or, if patient died in the community, information was obtained from participants' contacts using a structured data collection form.

Statistical analyses: Descriptive analyses of patients' socio-demographic and clinical parameters were made. The survival time was calculated in months using the time interval between the date of ART initiation and date of death, date of lost to follow-up, transferred out and completion of 36 months follow-up. Kaplan-Meier survival analyses employed to determine survival probability from the time of ART initiation. Participants who terminated their follow-up for a reason other than death and those who completed their follow-up until December 2013 were right-censored. Survival curve plotted to estimate survival time to event after ART initiation at 6, 12, 18, 24, 30 and 36 months of follow-up. A log rank test with p-value < 0.05 level of significance was used to compare survival time.

The Cox proportional hazard regression model was used to measure association of baseline predictor variables with mortality. Univariate associations of each predictor with mortality tested. Those predictor variables with significant association on univariate analysis ($p < 0.05$) included in the multivariate analysis. However, baseline hemoglobin measurement which showed significant association on univariate analysis was not included in the multivariate analysis for the missing data rate for the variable was 31.7%. Shared frailty with gamma distribution term fitted to the multivariate model to check for homogeneity within site clusters. Predictor variables with P-value < 0.05 used for the final model. Results reported in terms of the hazard ratios with their 95% confidence intervals and P-values. STATA version 12 and SPSS version 21 were used for the analyses.

Ethical considerations: Ethical approval was obtained from the Ethiopian Public Health Institute, the Ethiopian National Ethical Review Committee, Johns Hopkins University Institutional Review Board (IRB) as well as the Centers for Disease Control and Prevention IRB-Atlanta. Patients were enrolled after written informed consent. All patients were compensated for the time they spent for the study and for the inconvenience during blood draw for those included in the repository cohort.

RESULTS

Baseline socio-demographic and clinical characteristics: A total of 976 newly ART initiating PLHIV were included in the analysis. The cohort contributed a total of 1,825 person-years of follow-up. The median age of the cohort at ART initiation was 33 years (range 18-80 years). All study subjects were followed for a median of 25 months (IQR 12-34) on ART.

Table 1. Socio-demographic characteristics of the study participants on initiation of ART.

Characteristics	Number (%)
Participants from Hospital	
Armed forces	139 (14.2)
Tikur Anbessa	133 (13.6)
Gondar University	141 (14.4)
Jimma Univristy	128 (13.1)
Mekelle	135 (13.8)
Hiwot Fana	154 (15.8)
Hawassa University	146 (15.0)
Total	976 (100.0)
Sex	
Male	382 (39.1)
Female	594 (60.9)
Total	976 (100.0)
Age group	
18 -25	144 (14.8)
26 -30	272 (27.9)
31-35	183 (18.8)
36-40	184 (18.9)
41-45	83 (8.5)
46-50	65 (6.7)
>51	45 (4.6)
Total	976 (100.0)
Marital status	
Never married	172 (17.7)
Married	483 (49.7)
Divorced/Separated	198 (20.4)
Widow/widower	118 (12.2)
Total	971 (100.0)
Education	
No education	177 (18.4)
Primary	346 (36.0)
Secondary	312 (32.5)
Tertiary	125 (13.0)
Total	960 (100.0)

As seen in Table 1, we found that of 976 patients, 594 (60.9%) were females, 483 (49.7%) were married, and 177 (18.4%) had no formal education. The median CD4 count at the start of ART was 144 cells/µl (interquartile range (IQR) 78-205). Thirty-four percent of patients had CD4 < 100 cells/µl, and 63% had viral load greater than 5 log copies/ml. Patients ART regimen was efavirenz-based for 59.8% and nevirapine-based for 40.0% of patients.% on therapy. Ninty-three percent of patients received cotrimoxazole prophylaxis and 12.8% were on anti-tuberculosis treatment. Summary of clinical parameters of patients on initiation of ART is shown in table 2.

Table 2: Clinical characteristics of study participants at initiation of ART

Characteristics	Number examined
WHO Stage	
I & II	434 (45.0)
III & IV	530 (55.0)
Total	964 (100.0)
Hemoglobin	
<10 gm/dl	77 (11.5)
>10 gm/dl	590 (88.5)
Total	667 (100.0)
CD4 count	
<100	330 (34.2)
100-199	363 (37.6)
>200	272 (28.2)
Total	965 (100.0)
Viral load	
<100,000	315 (37.0)
>100,000	536 (63.0)
Total	851 (100.0)
ART regimen	
Efavirenz	584 (59.8)
Nevirapine	390 (40.0)
Other	2 (0.2)
Total	976 (100.0)
Cotrimoxazole prophylaxis	
Yes	909 (93.1)
No	67 (6.9)
Total	976 (100.0)
TB treatment at initiation	
Yes	125 (12.8)
No	851 (87.2)
Total	976 (100.0)
Isoniazid prophylaxis	
Yes	14 (1.4)
No	962 (98.6)
Total	976 (100.0)

Survival analyses: A total of 101 (10.3%) deaths were recorded during the observation period;all-cause mortality rate 5.4 /100 person-years of observation (PYO), 95% confidence interval 4.4-6.5. Fifty-three and Seventy percent of the deaths occurred during the first three and six months after start of ART, respectively. Of the 875 censored cases, 46 (5.2%) were lost to follow-up, and 100 (11.4%) moved from study areas and transferred-out to other health facilities to continue their treatment. Figure 1A shows overall survival of the cohort. Figure 1B show survival by baseline CD4 strata and 1C by WHO clinical stage

DOI: http://dx.doi.org/10.4314/ejhs.v27i1.7S

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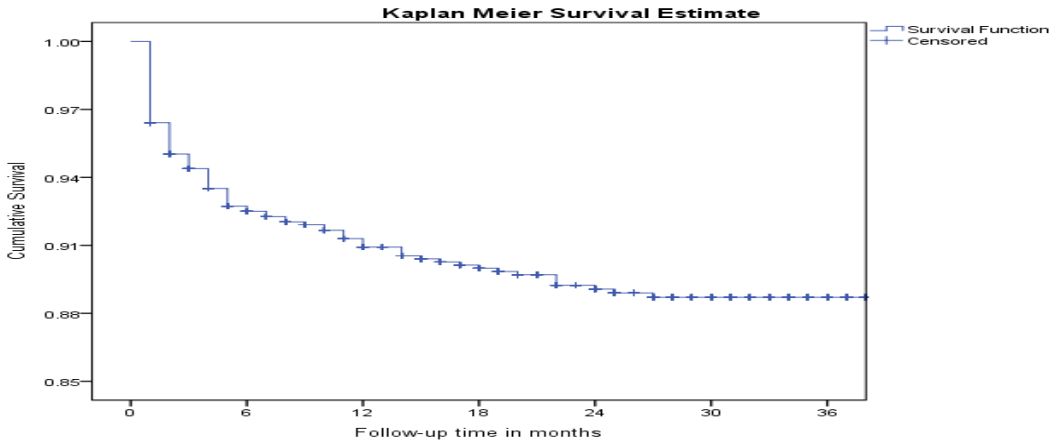

Figure 1 - A. Kaplan-Meier survival estimates of the cohort

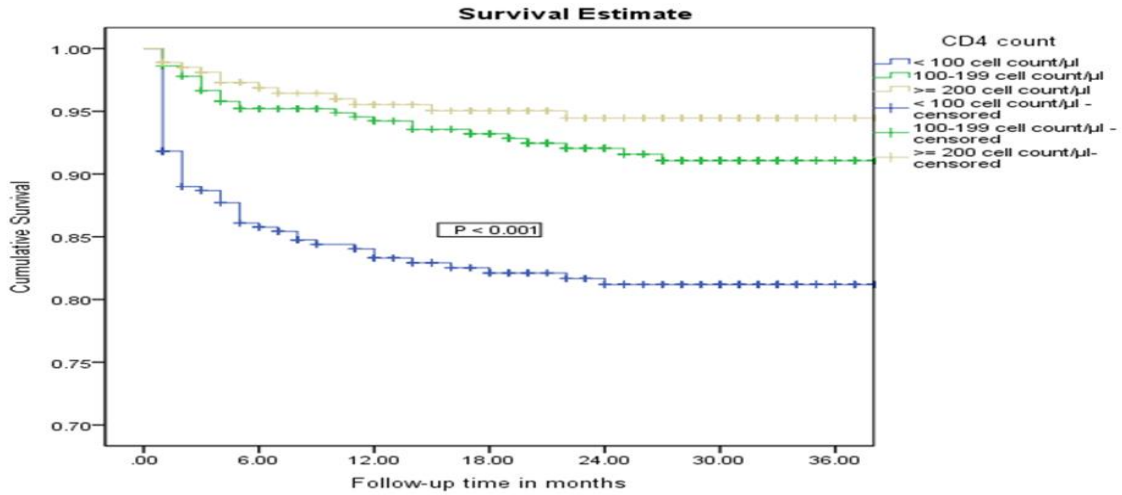

Figure 1B. Survival estimate of the Cohort by CD4

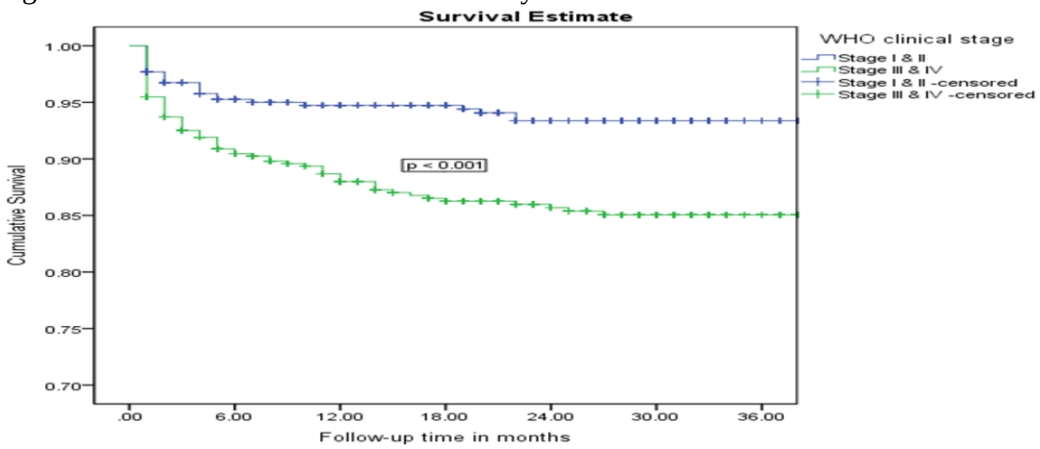

Figure 1C. Survival estimates by WHO clinical stages

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Risk factors for mortality: The crude and adjusted hazard ratios for death are shown in Table 2. Age ≥ 51 years, baseline WHO stages III/IV, CD4 count < 100 cells/µl, and viral load > 5 log copies/ml were significant predictors for death in both univariate and multivariate analysis.

Table 3. Crude and Adjusted Hazard Ratios for mortality among the cohort

Patient characteristics	Crude HR (95% CI	P- Value	Adjusted HR (95% CI)	P-Value
Sex				
Male	1	0.071	0.99 (0.64 – 1.53)	0.969
Female	1.54		1	
Age group				
18-25	1		1	
26-30	1.11 (0.50 - 2.45)	0.797	0.97 (0.43 – 2.17)	0.939
31-35	1.97 (0.91 - 4.27)	0.087	2.09 (0.95 – 4.60)	0.065
36-40	1.74 (0.79 - 3.82)	0.168	1.57 (0.70 – 3.54)	0.273
41-45	1.79 (0.71 - 4.50)	0.218	1.47 (0.55 – 3.91)	0.443
46-50	2.53 (1.03 – 6.22)	0.044	1.93 (0.67 – 5.50)	0.217
≥51	4.27 (1.79 – 10.14)	0.001	4.01 (1.58 – 10.15)	0.003
WHO Stage				
I & II	1	0.000	1	0.025
III & IV	2.35 (1.50 – 3.68)		1.76 (1.07 -2.87)	
Hemoglobin				
<10 mg /dl	2.26 (1.25-4.08)	0.007		
>10 mg /dl	1			
CD4 count				
<100	3.35 (1.90– 5.91)	0.000	2.36 (1.28 – 4.36)	0.006
100-199	1.37 (0.73- 2.57)	0.321	1.24 (0.64 – 2.38)	0.526
>200	1		1	
Viral load				
<100,000	1		1	
>100,000	2.21 (1.36 – 3.59)	0.001	1.71 (1.03 – 2.83)	0.037
Shared frailty				
Theta			0.085	0.05

DISCUSSIUON

In recent years, access to ART services for PLHIV in Ethiopia is improving; number of health facilities which provide ART service has increased. However, data from this prospective cohort study shows patients were presenting with advances clinical stages following infection with HIV: 530 (55.3%) of patients with WHO clinical III & IV, and 693 (71.8%) with CD4 count < 200 cells/µl; emphasizing the need to early diagnose, link and engage patient into the comprehensive ART care program.

This study showed that age >51 years was an independent risk factor for mortality among the cohort, similar to several reports from industrialized countries (19); but only one study from sub-Saharan Africa found such an association (20). This may be due to the predominantly young age of patients and shorter duration of follow-up in resource-limited settings.

Advanced WHO clinical stages have been consistently reported as risk factors for mortality in several studies from sub-Saharan Africa (6, 8, 12, 15, 21-23) as well as the current study, reflecting the advanced immunodeficiency at the time patients present for treatment.

Similar to many studies from sub-Saharan Africa, low hemoglobin level < 10 gm/dl was a risk factor for increased mortality (7, 16, 20, 24, and 25). This may be a marker for nutritional deficiency, opportunistic infections, cancers, or the effect of advanced HIV disease on the hematopoietic system.

Low CD4 count < 100 cells/µl at initiation of treatment was strongly associated with increased

DOI: http://dx.doi.org/10.4314/ejhs.v27i1.7S

mortality, similar to many studies from sub-Saharan Africa (2, 4-6, 8, 16, 21, 26). Wider availability of HIV testing and starting ART at higher CD4 counts will prevent many of the early on-ART mortality (27, 28).

In contrast to the current study, viral load was not found to be an independent predictor of mortality in a meta-analysis of 18 African treatment programs (8), probably a reflection of the small numbers of patients that had pre-treatment viral load measurement in resource-limited settings.

There was no significant difference in survival rate between male and female sexes, unlike other studies from resource-poor settings which had reported male sex as a risk factor for increased mortality (2, 6, 8, 16 -18). However, this finding is similar with another study report from Ethiopia, (13).

In Ethiopia, there are few studies that reported on-ART mortality of HIV-infected adults. At the beginning of the ART roll-out in 2006, mortality of 16.7/100 PYO was reported from a district hospital in South Ethiopia. Most deaths occurred within a month of starting treatment, and WHO clinical stage IV was a strong predictor of mortality (12). The reported mortality was three times higher than the current study; this may be due to differences in treatment facilities, or to improvement of the ART program in later years.

In an observational study from two district hospitals in Oromiya Region that followed 290 patients for 24 months on ART, an overall mortality of 10.3% was reported. However, estimates were based on only 28 deaths, and there was an 18% loss to follow-up, which underestimate the true mortality (13).

Comparable to the present study, a mortality rate of 6.9% was reported among adult patients on ART at a tertiary hospital in Addis Ababa; 57% of the deaths occurred in the first six months after start of ART (14). WHO stage III/IV, CD4 < 50 cells/µl, and tuberculosis after ART initiation were independent risk factors for death

In the present study, cause-specific mortality was not reported because of unavailability of data on cause of death. Therefore, the relative contributions of advanced immunodeficiency and opportunistic infections and cancers to the high early on-ART mortality could not be determined. Another limitation was that the setting was urban, and facilities were university affiliated hospitals which may limit generalization to more rural settings and lower-level health care facilities.

The study demonstrated that there was high early on-ART mortality which could be reduced by wider availability of HIV testing, improved package of care services for patients with advanced disease and starting treatment before advanced immuno-deficiency.

Disclaimer

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

Attribution/ Acknowledgement

This Research has been supported by the President's Emergency Plan for AIDS Relief (PEPFAR) through the US Centers for Disease Control and Prevention (CDC) under the terms of Cooperative Agreement with Johns Hopkins School of Public Health number PS000858.

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