Research Article
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AIDS-duration predictors of HIV/AIDS patients on antiretroviral therapy at Debre Berhan referral hospital, north-central Ethiopia

Abstract

Background: Receiving ART treatment prolongs the life of HIV/AIDS patients by increasing substantially their CD4 count, even though the level is different from one individual patient to the other. The aim of this study was to identify the potential predictors of death of HIV-infected patients attending ART treatment.

Methods: A hospital-based retrospective cohort chart review study design was conducted on 647 HIV-infected patients at a public hospital in North-Central Ethiopia from July 2012-January 2017. Kaplan-Meier plots, Log-rank and Wilcoxon tests, and Cox-proportional hazard model were employed. Data analysis was done with the help of statistical software (R version 3.2.2). 95% confidence interval for hazard ratio (HR) and p-value ≤ 0.05 was used to statistically associate with time till event occurred.

Results: Among the total of 647 patients on 192(29.68%) event were occurred; while 455(70.32%) were censored. HIV-infected patients were followed for a total of 54 months, with a mean of 22.13(13.16) and a median of 21.47months. The prevalence of event was about 30 out of 100 HIV patients. According to the present study, the median CD4 count at the initial time of ART was 247 (IQR:120-375) cells/μl, whereas the median CD4 count at the time of event was 362 (IQR:225-532)cells/μl. Patients with higher baselineCD4 count,>200*cells/*μl were 32.10% lower in risk of death than patients with lower baselineCD4 count, < 200*cells/*μl (HR:0.679; 95%*CI*:0.537-0.857; p-value=0.001).

Conclusions: ART treatment is effective enough in slowing down the progression of HIV-infection to AIDS and decreasing the mortality rate of patients significantly. Being Widowed/ divorced, bedridden, ambulatory began with lower baseline CD4 count and being on TDF-3TC-EFV regimen were the predictors of mortality in HIV-infected patients on ART. It is recommended that HIV patients start antiretroviral treatment early, track the progression of HIV to AIDS.

Keywords: AIDS, art, cox-ph, Ethiopia, HIV

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Abbreviations: AIDS, acquired immune deficiency syndrome; ART, antiretroviral therapy; BMI, body mass index CI, confidence interval; DBRH, Debre Berhan referral hospital; HR, hazard ratio; HIV, human immune deficiency virus; IQR, inter quartile range; LMICs, low-and middle income countries; PH, proportional hazard; WHO, world health organization

Introduction

In recent times, more people than ever are living with HIV. HIV is the leading cause of death in low and middle-income countries (LMICs). In Africa, 64% [48% 76%] of people living with HIV were able to access antiretroviral therapy (ART) in 2018.[1] Different access-related barriers to ART make a challenge.[2] Despite there has been a continued success in scale-up and access to HIV/AIDS treatment in Sub-Saharan Africa over the past few decades,[3–5] it is still the major cause of death and home of about 71% of people living with HIV.[6] In Ethiopia, since 2008 the HIV incidence rate has begun to rise by 10% and the number of new infections diagnosed each year increased by 36% among all age groups.[7]

The availability and administration of ART have been significantly reduced the mortality and morbidity associated with HIV/AIDS.[8–10] ART track the progression of HIV to AIDS, and it attacks an immune cell called the CD4+ cell, which is accountable for the body's immune response to infectious agents. HIV attacks CD4 cell count primarily; though during HIV-infection CD4 count decreases. A rapid decline of CD4 cell counts leads to the development of HIV to AIDS.[11] Since CD4 count is the strongest predictor of subsequent disease progression and survival,[12] the lower in CD4 count leads to a higher mortality rate.[13] ART is associated with higher survival rate. Different studies find out that the prognosis of peoples living with HIV/AIDS is substantially improved due to ART.[9,14–19]

Free ART treatment was initiated in developing countries, including Ethiopia, for the improvement of the survival of peoples living with the HIV/AIDS. A free ART program was launched in Ethiopia in early 2005, while it was nationally started in 2003.[20] The country has been observed remarkable progress over the past two decades, reducing HIV prevalence rate from 3.3% in 2000 to 0.9% in 2017[21] due to the availability of free ART. Based on WHO adopted guidelines of using ART for treating and preventing HIV-infection;[22] ART needs a strong management support system.[23] Failure to use of antiretroviral treatment and toxicity are feared complication of long-term ART users.[24]

A study conducted in Ethiopia recommends that it is very important if early initiation of patients on ART is taken seriously;[25] to prolong the life of the patients. Even if, taking ART treatment prolongs the life of HIV/AIDS patients by increasing substantially their CD4 count, it is varied from one individual patient to the other. This might happen due to different factors like socio-demographic, laboratory and clinical implications. This study was conducted to explore the socio-demographic, laboratory and clinical implication of mortality among HIV-infected patients attending antiretroviral treatment.

Methods

Study design and population

A hospital-based retrospective cohort chart review study design was conducted at a public hospital in North-Central Ethiopia. The hospital has an ART clinic for HIV/AIDS patients to undertake Antiretroviral Therapy (ART). Medical records and other basic information sheets of HIV/AIDS patients who were on the followed-up from July 2012 to July 2015, and were followed-up through the ART routine registered records up to January 2017 were considered.

Inclusion and exclusion criteria

All HIV/AIDS-patients aged 18 years and above were included. Those patients who started ART before July 2012 or after July 2015 were excluded. Only 647 patients, who fulfilled the inclusion criteria, were included in the study.

Data collection

Data extractions were applied from the patients' medical chart by the ART clinic staff experts. The patient's medical chart has been adopted by the Federal Ministry of Health (FMoH) of Ethiopia, to be uniformly used by ART clinics to early identify and document laboratory, clinical and epidemiological variables.

Variables

The dependent variable was time-to-event and the event can be death or all causes of mortality, measured in months. Censored implies alive and death is due to HIV.

The predictor variables included in this study were baseline age, BaselineCD4 count, Sex, Marital status, Body Mass Index (BMI)(kg/m^2), Functional status, current CD4 count, WHO clinical stages and ART Regimen class.

Statistical analysis

The collected data were coded and stored in MS-excel and exported to R 3.2.2 and SPSS version 20 for analysis. Kaplan-Meier (K-M) plot was applied to assess the survival experience among the different categorical predictor variables.[26] Log-rank and Wilcoxon tests were used to assess the significance difference between survival status of categorical variables for quality tests.

Univariate analysis was performed to screen out the potentially significant predictor variables at 25% significance level. The association between the significant variables and time-to-event were conducted using Cox-Proportional Hazard (Cox-PH) model.[27] The 95%CI for hazard ratio (HR) was considered, and p-value ≤ 0.05 was used to statistically associate with time till the first event in months.

Results

Socio-demographic variables statistics

The study included 647 HIV-infected patients, 423(65.38%) of them were females and 224(34.62%) of them were males. Patients were followed for a total of 54 months, with a mean of 22.13(13.16) and a median of 21.47 months; for a minimum of 0.03 months and a maximum of 53.1 months. The median age, weight, height, baselineCD4 count and BMI of patients at baseline were 30years(IQR:25-38years), 52kg(IQR:45-59kg), 1.60meters(IQR:1.55-1.67meters), 247cells/μl(IQR:120-375cells/μl) and 19.75kg/m^2 (IQR:17.5-22kg/m^2); respectively. Of the total subjects 269(41.58%) were single, 217(33.54%) were married and 161(24.88%) were divorced/ widowed marital status. Regarding functional status 303(46.83%) were able to do their day-to-day activities (working), 142(21.95%) were ambulatory and 202(31.22%) were bedridden. The majority of the study participants had normal weight 359(55.49%), 227(35.08%) had underweight and 61(9.43%) had overweight (Table 1).

Baseline clinical and laboratory related variables

From the total 647 HIV patients, 224(34.63%) had started ART treatment with an initial WHO- clinical stage of stage-I and 126(19.47%) of stage-II, 176(27.20%) of stage-III, and 121(18.70%) of IV. At baseline the ART regimen class of patients were AZT-3TC-EFV, 165(25.50%); AZT-3TC-NVP, 137(21.18%); TDF-3TC-NVP, 88(13.60%); d4t-3TC-NVP, 114(17.62%) and TDF-3TC-EFV, 143(22.10%) (Table 1).

Censoring status

Of the total 647 patients, 192(29.68%) were event occurred, while 455(70.32%) were censored (Table 1).

Comparison of survival experience

The association between each single covariate and time-to-event of HIV patients on ART are presented using Log-rank and Wilcoxon tests (Table 2). Time to event was significantly associated with marital status, functional status, CD4 counts and ART regimen class subgroups (p-value=0.0001), but not sex (p-value=0.4587) and BMI (p-value=0.3356). The overall survival and hazard function on ART at 54 months follow-up using K-M plots were shown (Figure 1).

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Table 1 Baseline Socio-demographic, Clinical and Laboratory information of HIV/AIDS patients initiated ART at Debre Berhan Referral Hospital, North-Central Ethiopia; 2012-2017(N=647)

Variables	Category	Total(%)	Censored(%)	Event(%)
Gender	Male	224(34.62)	156(69.64)	68(30.36)
	Female	423(65.38)	299(70.69)	124(29.31)
Marital Status	Single	269(41.58)	180(66.82)	89(33.18)
	Married	217(33.54)	137(63.20)	80(36.80)
	Widowed/Divorced	161(24.88)	140(86.96)	21(13.04)
Functional Status	Working	249(82.18)	54(17.82)	
	Ambulatory	142(21.92)	105(73.94)	37(26.06)
	Bedridden	202(31.22)	101(50.00)	101(50.00)
WHO-clinical stages	Stage-I	224(34.63)	127(56.70)	97(43.30)
	Stage-II	126(19.47)	111(88.10)	15(11.90)
	Stage-III	176(27.20)	117(66.48)	59(33.52)
	Stage-IV	121(18.70)	100(82.64)	21(17.36)
ART Regimen class	AZT-3TC-EFV	165(25.50)	131(79.39)	34(20.61)
	AZT-3TC-NVP	137(21.18)	101(73.72)	36(26.28)
	TDF-3TC-NVP	88(13.60)	74(84.09)	14(15.91)
	d4t-3TC-NVP	114(17.62)	59(51.57)	55(48.43)
	TDF-3TC-EFV	143(22.10)	90(62.94)	53(37.06)
BMI(Body Mass Index) (kg/m^2)	underweight(<18.50)	227(35.08)	161(70.90)	66(29.10)
	Normal weight(18.50-24.99)	359(55.49)	245(68.20)	114(31.80)
	Overweight(> 25)	61(9.43)	49(80.30)	12(19.70)
Baseline CD4 count	> 200cells/µl	392(60.60)	298(76.02)	94(23.98)
	< 200cells/µl	255(39.40)	157(61.57)	98(38.43)
Current CD4 count	> 200cells/µl	511(78.98)	390(76.32)	121(23.68)
	< 200cells/µl	136(21.02)	65(47.79)	71(52.21)

∗**CD4 count recorded at the time of event**

Table 2 Log-rank and Wilcoxon tests of Survival Differences for Categorical Variables

Variable	Log-rank Test			Wilcoxon Test		
	Test Statistics	df	p-value	Test Statistics	df	p-value
Sex	0.5491	1	0.4587	0.8750	1	0.7706
BMI	2.5230	2	0.2310	2.8901	2	0.3356
Marital Status	6.5319	2	0.0001	5.6506	2	0.0001
WHO Clinical Stage	3.0687	3	0.1301	4.5145	3	0.0901
ART Regimen Class	8.1095	4	0.0001	8.4725	4	0.0001
Functional Status	23.9239	2	<.0001	20.2649	2	<.0001
Baseline CD4 count	5.1270	1	0.000	5.3250	1	0.000
Current CD4 count	4.1330	1	0.0001	4.3250	1	0.0001

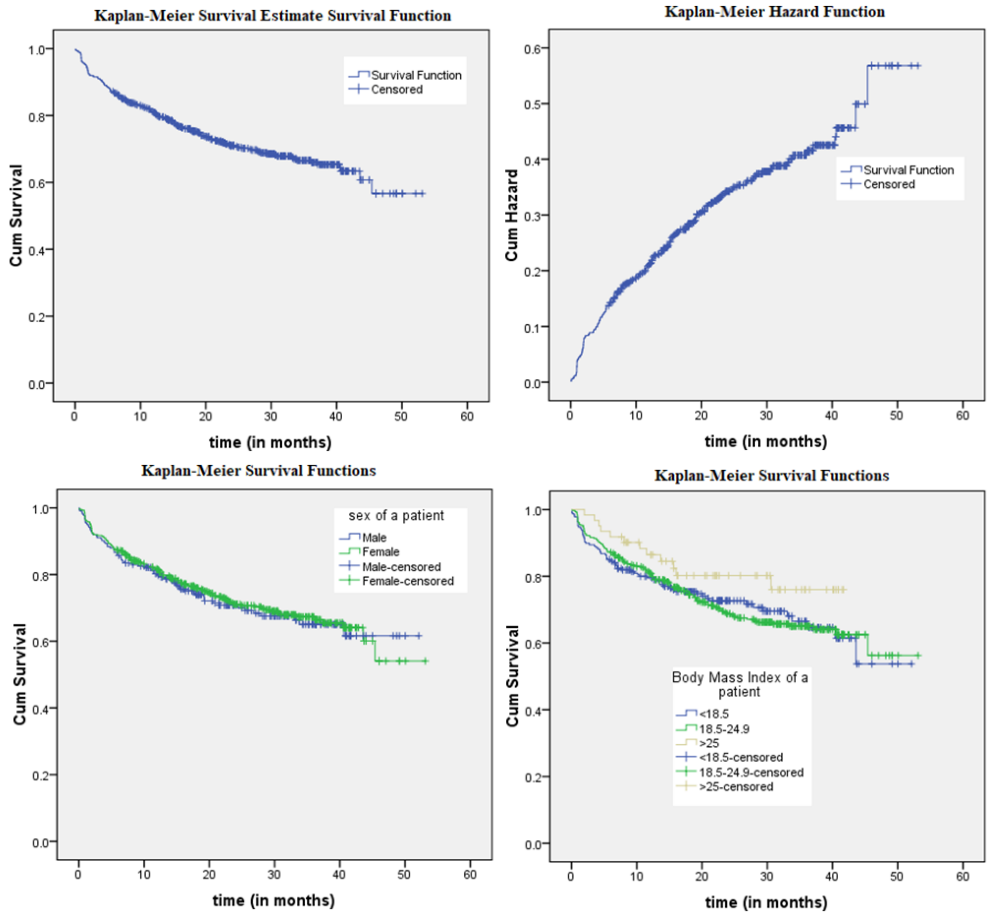

Figure 1 K-M plots of HIV/AIDS patients starting ART in DBRH, from July 2012-January 2017.

Cox-PH regression results

The predictors of death were widowed/divorced marital status, bedridden and ambulatory functional status, lower baseline CD4 count, and lower current CD4 count and regimen class of patients. The probability of death among HIV patients of married was 65.30% lower in risk than patients who were widowed/ divorced [HR:0.347,95%*CI*:0.238-0.505], and single was 50% lower in risk than widowed/divorced [HR:0.500, 95%*CI*: 0.341-0.731]. Bedridden and ambulatory were 3.3 times and 1.21 times higher in risk than working functional status HIV patients; respectively. Patients with baseline CD4 count of >200 cells/μl were 32.10% lower in risk than patients with an initial CD4 count of <200cells/μl [HR: 0.679, 95%CI: 0.537-0.857] (Table 3).

Table 3 Cox-Proportional hazard (Cox-PH) model parameter estimates

Variable	Category	HR(exp(β))	95%CI for HR	Chi-sq	P-value
Gender	Female	1.065	(0.868,1.306)	0.132	0.547
	Male (Ref)	-	-	-	
Age	Age	1.005	(0.993,1.018)	0.491	0.381
BMI (kg/m^2)	Over weight((>25))	0.738	(0.536,1.017)	9.16	0.063
	Normal (18.50-24.99)	0.97	(0.686,1.373)	0.004	0.865
	Underweight ((<18.50))(Ref)	-	-	-	
Marital Status	Single	0.5	(0.341,0.731)	12.764	0.000*
	Married	0.347	(0.238,0.505)	30.304	0.000*
	Widowed/Divorced(Ref)	-	-	-	

Table Continued...

Variable	Category	HR(exp(β))	95%CI for HR	Chi-sq	P-value
Functional Status	Ambulatory	1.21	(1.021,1.760)	4.019	0.042*
	Bedridden	3.279	(1.261,8.530)	5.92	0.015*
	Working (Ref)	-	-	-	
WHO-clinical stages	Stage-I	0.758	(0.435,1.321)	0.815	0.328
	Stage-II	0.92	(0.514,1.644)	0.064	0.777
	Stage-III	1.151	(0.655,2.023)	0.469	0.625
	Stage-IV (Ref)	-	-	-	
ART Regimen class	AZT-3TC-EFV	1.073	(0.763,1.510)	0.165	0.685
	AZT-3TC-NVP	0.564	(0.371,0.855)	7.26	0.007*
	TDF-3TC-NVP	0.598	(0.388,0.924)	5.369	0.020*
	d4t-3TC-NVP	0.387	(0.187,0.802)	6.508	0.011*
	TDF-3TC-EFV(Ref)	-	-	-	
Baseline CD4 count	> 200cells/μl	0.679	(0.537,0.857)	10.625	0.001*
	< 200cells/μl (Ref)	-	-	-	
Current CD4 count	< 200cells/μl	1.169	(1.129,1.193)	4.41	0.035*
	> 200cells/μl (Ref)	-	-	-	

Ref: Reference category; significant at 0.05 level of significance; HR: Hazard Ratio

Discussion

For these study 647 HIV-infected patients enrolled for care and treatment in the ART clinic of DBRH were considered. The time-frame of the study was from July 2012 to January 2017, for 54 months. The median follow up time was 21.47 months. The prevalence of event was about 30 out of 100 HIV patients. Even if, the follow-up time of the cohort is different, the probability of death was 16% in Malawi[28] and Southwest Ethiopia.[29]

The majority of patients, 392(60.60%) were initiated ART with a higher level of immunity indicator (> 200*cells/μ*l); while about 255(39.40%) were with lower CD4 count (< 200*cells/μ*l). The median CD4 count at the initial time of ART was 247[IQR: 120-375] cells/*μ*l, whereas the median CD4 count at the time of the event was 362[IQR: 225-532] cells/*μ*l. It shows an improvement in the immunity indicator.

About 255(39.40%) of HIV patients at baseline had a CD4 count of < 200*cells/μ*l. Of those 157(61.57%) were censored and 98(38.43%) event occurred. But, from 392(60.60%) HIV patients with higher baseline CD4 count (>200*cells/μ*l) only 23.98% of events were recorded. In this study patients with higher baseline CD4 count were 0.679 times (32.10%) lower in risk than patients with baseline CD4 count of <200*cells/μ*l [HR:0.679;95%CI:0.537-0.857; p-value:0.001]. Our finding was in agreement with the results of previous reports in which patients initiating ART with lower CD4 counts were at higher risk of death than patients initiated with higher CD4 counts[29–33] The lower CD4 count is a marker of advanced immunodeficiency, and it increases the risk of death,[34] but other reports such as[35–39] showed that there are other associated factors other than CD4 count.

In the current cohort study, event occurred in 30.36% male and 29.31% female HIV patients. It didn't show a statistically significance difference between gender groups (p-value=0.547). And also, it didn't show any difference in age and BMI on the occurrence of event. According to previous Studies being male;[40,41] under-nutrition[40,42] and older age[43,44] were the significant predictors of mortality.

Being married 65.30% and being single 50% reduced in risk of mortality than widowed/divorced HIV patients [HR:0.347; 95%*CI*: 0.238-0.505; p-value=0.000] and [HR:0.500; 95%*CI*:0.341-0.731; p-value=0.000]; respectively. Ambulatory and bedridden functional status HIV patients were 1.210 times [HR: 1.210; 95%CI: 1.021-1.760; p-value=0.042] and 3.279 times [HR: 3.279; 95%CI: 1.261-8.530; p-value=0.015] the probability of event of working HIV patients. This finding coincides with the study undergone in Ethiopia,[35] in which HIV patients, who had actively participated in daily activities, were lower in probability of death than the others.

Baseline WHO clinical stages didn't show any significant difference among HIV patients. But, clinical stages had showed significant difference in the probability of death of patients on studies conducted in Ethiopia,[42] Sub-Sahara Africa,[40] Cameroon,[41,45] Tanzania[46] and Uganda.[47]

The ART regimen class of AZT-3TC-NVP, 0.564 times (95%CI: 0.371-0.855; p-value=0.007); TDF-3TC- NVP, 0.598times (95%CI: 0.388-0.924; p-value=0.020) and d4t-3TC-NVP, 0.387times (95%CI: 0.187-0.802; p-value=0.011) of the probability of death of the regimen class of TDF-3TC-EFV HIV patients. It may show other clinical implication. The current study didn't further investigate the cause and effect of clinical implications.

At the time of the event, the last followed-up CD4 count of HIV patients was recorded. We called it the current CD4 count in this study. The current CD4 count below 200cells/μl, lower CD4 count were 16.90% more to risk than above 200cells/μl or higher CD4 count [HR: 1.169; 95%CI: 1.129-1.193, p-value=0.035]. This result was in agreement with the previously discussed baseline CD4 count in which patients with lower CD4 count were at risk of death of HIV than higher CD4 count HIV patients. About 39.40% of HIV patients were with lower CD4 count (<200*cells/*μl) at baseline, but it was reduced to 21.02% at the time of the event. The median CD4 count also indicated at baseline 247cells/μl, whereas it was increased to 362cellsμl at the time of the event. Providing free antiretroviral treatment by the government is the right decision, as it does change the quality of life of patients, by improving their immunity indicator. Hence, Health care providers should undertake a detailed discussion with HIV/AIDS patients about their willingness and readiness to start ART.[48] The study also found out that more events has been occurred among the lower CD4 count HIV patients. According to previous studies, HIV patients attending ART treatment were improved their CD4 count.[49–50] The study would like to recommend HIV patients to start antiretroviral treatment early before their immunity level becomes lower and the concerned health care providers gives attention to those patients.

Conclusion

Being widowed/ divorced, bedridden, ambulatory began with lower baseline CD4 count and lower current CD4 count, and being on TDF-3TC-EFV regimen class of patients were the predictors of mortality in HIV-infected patients attending ART. To conclude, ART is effective enough in slowing down the progression of HIV-infection to AIDS and decreasing the mortality rate of patients significantly.

Limitations

Patients with incomplete records (dropouts) were excluded from the study; this may affect the conclusion of the study.

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Conflicts of interest

The authors declare that there was no conflict of interest.

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