

Survival Analysis of HIV/AIDS Patients Under ART Follow up in Attat Referral Hospital

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Abstract: Background: The non-curable HIV/AIDS epidemic has become a serious health and development problem especially for developing country like Ethiopia despite using ART treatment. The antiretroviral treatment (ART) scale-up service has been a recent development in Ethiopia, but its impact on mortality has not been well investigated. This study aimed to analyze the survival time of HIV-positive patients under antiretroviral therapy (ART) and identifies associated risk factors in Attat Referral Hospital. Methods: A retrospective study was conducted to examine the survival of HIV/AIDS patients under ART at Attat Referral Hospitals. Total of 408 HIV/AIDS patients in ART from April 30, 2010 up to March 30, 2017 were included in the study. Cox proportional hazard model was employed to assess the survival of HIV/AIDS patients and the associated factors. Results: A total of 408 patients were followed for a survival mean time of 46 months. In the followed-up period, 121 (29.7%) patients dead and 287 (70.3%) patients were censored. Based on functional status of patients, higher mortality was significantly associated with bedridden (HR: 3.934) and Ambulatory (HR: 1.790). According to WHO stages the patients under ART follow up with stage- IV (HR: 7.277), stage-III (HR: 4.536) and stage-II (HR: 2.213) were high risk of dying than patients in stages-I and male patients are at high risk of death than females. Conclusions: This study found that the survival time of the HIV patient under ART follow-ups in Attat Referral Hospital of Guraghe zone was significantly associated with factors: functional status, Weight, Original Regimen, CD4 count and WHO stage.

Keywords: Survival, Cox Proportional Hazard Model, Antiretroviral Therapy

1. Background

HIV/AIDS (Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome) epidemic has become a serious health and development problem in many countries around the world having claimed more than 38.0 million lives so far [1]. In 2019, and 32.7 million people died from HIV-related cases globally since the start of the epidemic. 25.4 million people were accessing antiretroviral therapy in 2019. 1.7 million people became newly infected with HIV in 2019 [1].

The world health organization (WHO) African region is the affected region, with 25.6 million people living with 2016. The African region also accounts for almost two thirds of the global total of new HIV infection [2]. In Sub-Saharan Africa remains the most heavily affected region, accounting for 71% of all new HIV infections and AIDS related deaths

globally (1).

It is the fact that Ethiopia is one of the countries hit by the HIV/AIDS epidemic. The epidemic has claimed the lives of the country's adult that would have contributed immensely to the country's development in many respects. Adult HIV prevalence in Ethiopia in 2016 was estimated to be 1.1%. The HIV epidemic in Ethiopia is primarily associated with areas of urban concentration (5.1% in cities above 50 thousand compared to 3.1% in smaller cities and 0.6% in rural areas) and proximity to major transport corridors. Those living within five kilometers of a major road have HIV prevalence rates that are four-times higher than those who live further away [3].

Even though no cure for HIV/AIDS infection effective antiretroviral (ARV) drugs can control the virus and enables to enjoy healthy, long life and productive lives. It is estimated that currently only 70% of people with HIV know their

status. Between 2000 and 2016, new HIV infections fell by 39%, and HIV-related death fell by one third with 13.1 million lives saved due to ART in the same period. This achievement was the result of great efforts by national HIV programs supported by civil society and a range of development partners [2].

Studies conducted in different parts of the world showed a decline of death due to HIV/AIDS epidemic but now days in Ethiopia existing facts shows that an increasing prevalence death due to HIV/AIDS epidemic. Little attention seems to have been given to study the situation of those living with the virus. Therefore, the aim of this study was to determine the associated factors of survival time to death of HIV positive patients under ART follow up in Attat Referral Hospital of Gurage Zone, Southern Ethiopia.

2. Methods

2.1. Source of Data and Study Design

This retrospective study used secondary data on HIV patients who enrolled in Attat hospital, which is located 175 km south west of Addis Ababa, Ethiopia. The hospital is managed and run by Medical Mission Sisters under the Eparchy of Emdibir since its establishment back in 1969 G. C. A total of 408 patients who started ART from April 30, 2010 were included for the study and were followed up until March 30, 2017. The study was based on a review of the intake forms and follow-up cards of HIV patients on ART. Patients' intake and follow up cards were cross examined for inconsistencies so that data quality issue could be ensured.

2.2. Variables Included in the Study

The response variable was survival time of HIV patients taking ART defined as the length of time from ART start date until the date of death, measured in months. The predictors variables considered in this study were: gender (male, female), Age (in years), Baseline Weight (in kg), Patient Original Regimen (AZT-based, D4T-based and others), Functional status (Bedridden, Ambulatory, Work), Baseline

CD4, and WHO stage (I, II, III, IV).

2.3. Method of Data Analysis

Cross tabulation, Kaplan-Meier (KM) method and a semi-parametric method known as Cox-proportional hazards (Cox-PH) regression model were used. The KM method is employed to estimate survival, and the associated log-rank is used for comparing estimated survival curves. The parameters in Cox PH model were estimated by the partial maximum likelihood technique. The PH assumption, which asserts that the hazard ratios (HR) should remain constant overtime, is vital to the interpretation and use of a fitted PH model. Graphical method and adding time-dependent covariates were used for the purpose of verifying the proportionality assumption. The likelihood ratio and Wald tests were used to test the goodness of fit of a Cox regression model [4, 5].

Data cleaning, management and analysis were carried out using STATA, Version 12. Variables were re-coded to meet the desired classification. All hypotheses testing to determine differences, associations and relationships were judged significant at $p < 0.05$.

3. Results

The Summary result of Table 1 shows that, about 408 HIV/AIDS patients under ART from April 30, 2010 to March 30, 2017 at Attat Referral Hospital were considered in this study. About 30% of them were died while the remaining 70% were censored. About 179 (43.9%) of them were female and 229 (56.1%) of them were male. The mean survival time of patient was 46 months. According to functional status of the patients, 302 (74.0%) of them were working, 87 (21.3%) were ambulatory and 19 (4.7%) were bedridden. Based on patients initiating ART original regimen suggested that 148 (36.3%), 72 (17.6%) and 188 (46.1%) of them were AZT-based, D4T-based and other respectively. According to WHO Stage, 57 (14.0%), 139 (34.1%), 135 (33.1%), 77 (18.9%) were Stage-I, Stage-II, Stage-III and Stage-IV respectively.

Table 1. Summary result on the study participants.

Variables	Category	Status		Total
		Dead	Censored	
Sex	Male	77 (33.6%)	152 (66.4%)	229 (56.1%)
	Female	44 (24.6%)	135 (75.4%)	179 (43.9%)
	Bedridden	11 (57.9%)	8 (42.1%)	19 (4.7%)
Functional Status	Ambulatory	31 (35.6%)	56 (64.4%)	87 (21.3%)
	Working	79 (26.2%)	223 (73.8%)	302 (74.0%)
	AZT-based	72 (48.6%)	76 (51.4%)	148 (36.3%)
Original Regimen	D4T-based	18 (25%)	54 (75%)	72 (17.6%)
	Other	31 (16.5%)	157 (83.5%)	188 (46.1%)
	Stage-IV	49 (63.6%)	28 (36.4%)	77 (18.9%)
WHO Stage	Stage-III	35 (25.9%)	100 (74.1%)	135 (33.1%)
	Stage-II	25 (18%)	114 (82%)	139 (34.1%)
	Stage-I	12 (21.1%)	45 (78.9%)	57 (14.0%)
Total		121 (29.7%)	287 (70.3%)	408 (100%)

3.1. The KM Estimate of Time-to- Death for Different Group of Patients

The survival plots for time-to-death by sex, WHO stage and functional status are displayed in Figure 1 – Figure 3. The graphs showed that the survival time of male is less than female and according to original regimen D4T-based patients has lower survive than AZT-based and other patients. The functional status of working patients has better survive than the bedridden and ambulatory patients, and the ambulatory patients longer survive than bedridden patients. Based WHO stages, Stage I have longer survival than stage II, stage III and stage IV. While we compare the remaining, patients WHO Stage II has longer survival than stage III and stage IV, and WHO Stage III is lower risk of death than Stage IV. The corresponding log-rank test is given in Table 2 below and the survival difference is statistically significant at 5%.

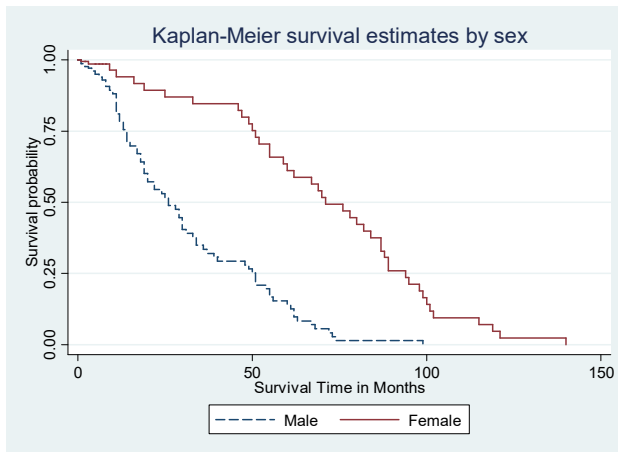


Figure 1. Kaplan-Meier estimate of time to death of HIV patients under ART by sex.

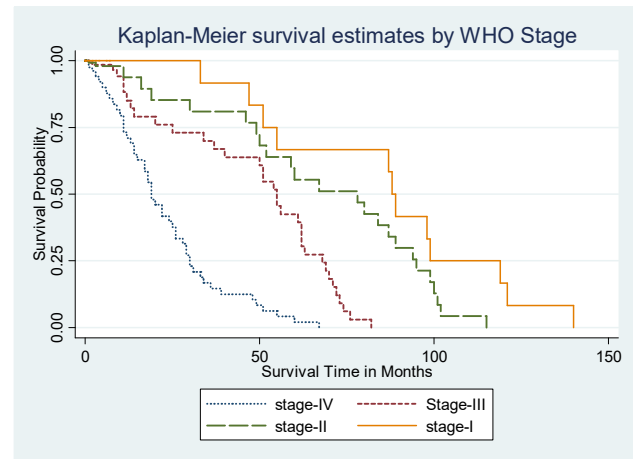


Figure 2. Kaplan-Meier estimate of time to death of HIV patients under ART by WHO stage.

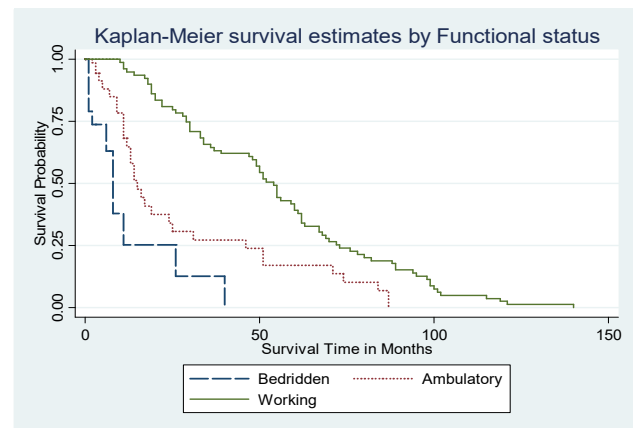


Figure 3. Kaplan-Meier estimate of time to death of HIV patients under ART by functional status.

Table 2. Long-rank test for categorical variable.

Variable	Category	Observed	expected	d.f	P-value
Sex	Male	77	45.25	1	<0.0001
	Female	44	75.75		
Functional Status	Bedridden	11	1.71	2	<0.0001
	Ambulatory	31	16.62		
	Working	79	102.67		
Original regimen	Other	31	62.97	2	<0.0001
	AZT-based	72	52.50		
	D4T-based	18	5.53		
WHO stage	Stage-IV	49	18.83	3	<0.0001
	Stage-III	35	33.85		
	Stage-II	25	39.36		
	Stage-I	12	28.96		

d.f= degree of freedom

3.2. Analysis Method of Cox PH Model

The result of final Cox PH model is presented in Table 3. The risk of death in bedridden and ambulatory functional status was 3.934 and 1.790 times greater than working functional status respectively.

The estimated hazard ratio for the Weight of a patient were 0.890 (95% CI: 0.857 0.924) implied that the risk of death decreases by 10% for 1kg increase in weight. The estimated HR and CIs of HRs for Other and ATZ-based patients were 0.269 (95% CI: 0.126-0.576) and 0.492 (95% CI: 0.269-0.900), respectively. The implication is that other and ATZ-based patients were 0.269 and 0.492 times at lower risks of

death than patients who were using in D4T-based respectively.

According to WHO stages, the estimated HR and CIs for WHO stage-IV, WHO stage-III and WHO stage-II were 7.277 (95% CI: 3.031-17.467, $p < 0.001$), 4.536 (95% CI: 1.964-10.476, $p < 0.0001$), 2.213 (95% CI: 1.007-4.860,

$p = 0.048$) respectively. This implied that patients with stage-IV, stage-III and stage-II were 7.277, 4.536 and 2.213 times at risk of dying than patients in stages I respectively. The satisfaction of PH assumption was assessed for each factor by using log-log survival curves and adding time-dependent covariates in the model.

Table 3. Cox Proportional Hazard Model to HIV Positive Patients.

Variable	Category	B	HR	95% CI for HR	p-value
Functional Status	Working	Ref.			
	Bedridden	1.370	3.934	(1.958, 7.905)	0.000
	Ambulatory	.582	1.790	(1.105, 2.901)	0.018
Weight		-.117	0.890	(0.857, 0.924)	0.000
Original Regimen	D4T-based	Ref.			
	Other	-1.311	0.269	(0.126, 0.576)	0.001
	ATZ-based	-.710	0.492	(0.269, 0.900)	0.021
CD4 Count		-.006	0.994	(0.991, 0.998)	0.001
WHO Stage	Stage-I	Ref.			
	Stage-IV	1.985	7.277	(3.031, 17.467)	0.000
	Stage-III	1.512	4.536	(1.964, 10.476)	0.000
	Stage-II	.794	2.213	(1.007, 4.860)	0.048

B = Estimated parameter value, HR = Hazard Ratio, CI = Confidence Interval

Table 4. Statistical Test for PH Assumption of the Covariates and Their Interaction with Time.

Interaction	Coef.	P>z	(95% Conf. Interval)	
Functional status*ln(time)	.204483	0.158	(-0.0793545	0.4883204)
weight*ln(time)	.0000761	0.865	(-0.0770664	0.0772185)
Original regimen*ln(time)	.1404749	0.379	(-0.1724341	0.4533838)
cd4*ln(time) count*ln(time)	-.0020928	0.157	(-0.0049883	0.0008026)
Who stage*ln(time)	.1552373	0.138	(-0.0498581	0.3603326)

4. Discussion

The main objective of this study is to analysis the survival time of HIV-positive patients under ART and identifies associated risk factors in Attat Hospital.

The study was conducted based on retrospective cohort study, from a total of 408 HIV/AIDS patients under ART from April 30, 2010 to March 30, 2017 at Attat Referral Hospital.

This study also showed that the mean of survival time of patients at Attat Referral Hospital were 46 months with 95% confidence interval (30-51). This result was approximately equal when it was comparing with finding done in Sudan with mean of survival time of patients (47.7 weeks) [6].

The results of this study suggested patients functional Status, WHO stage and weight was significant predictor factor for time-to-death of patients under ART in Attat Referral Hospital. Higher mortality was significantly associated with bedridden and Ambulatory performance status, WHO Stage-IV& Stage-III and low body weight. The finding was consistence with different studies [7-10].

According to WHO stages the patients under ART follow up with stage- IV, stage-III and stage-II were high risk of dying than patients in stages I. The risk of death in bedridden and ambulatory was greater than working functional status. Both findings were consistent with previous studies [6-11].

In this study the survival time of male is less than female and according to original regimen D4T-based patients has

lower survive than AZT-based and other patients it was in line with research done in Debre-Markos Referral Hospital, Northwest Ethiopia and others study [6, 12, 13].

The other predictor of the hazard of death in HIV/AIDS patients who are taking antiretroviral therapy is CD4 count. CD4 cell count measures the concentration of a particular type of lymphocyte, the T-helper cell, in a specified volume of the patient's blood and enables professionals to decide the initiation of antiretroviral therapy (ART). Often, CD4 count is significant predictor of the hazard of death in HIV/AIDS patients. CD4 count is significant predictor of mortality, this have been documented in previous study in Ethiopia the research findings of five studies showed that CD4 cell count would have an impact on the survival longevity of HIV-positive person; higher CD4 count is associated with longer survival experience. Our result agrees with the findings of the above documented sources [14-18].

5. Conclusions

In this study, Cox proportional hazard regression model was applied to determine factors under ART that were most predictive of survival time in HIV/AIDS patients under ART in Attat Referral Hospital, Ethiopia. In the study, patients functional Status, Weight, Original regimen, CD4 Count and WHO Stage are statistically significantly related to survival time of HIV/AIDS patients.

HIV/AIDS patients in work functional status had prolonged survival time than others. Bedridden patients are at high risk of

death than ambulatory patients. CD4 cell count was also a significant predictor of survival time in HIV/AIDS patients. The increment of patient CD4 cell count and weight had a significant effect on favorable survival time. WHO stage IV patients had low survival experience than others.

The primary goal of ART is to improve the health, prolong the life of the HIV-infected patient and reduction in HIV-related mortality even though mortality related to HIV is continued in ART. Higher mortality was significantly associated with bedridden and Ambulatory performance status, WHO Stage-IV& Stage-III and low body weight. Higher risks of death of patients were significantly associated with using D4T-based. Therefore, all patients should be treated by other than D4T-based.

List of Abbreviations

AIDS: Acquired Immune Deficiency Syndrome; ART: Antiretroviral Treatment; ARV: Anti-Retroviral; COP/ROP: Country/Regional Operational Plan; D4T: Stavudine; FMOH: Federal Ministry of Health; HAART: Highly Active Antiretroviral Treatment; HIV: Human Immunodeficiency Virus; HR: Hazard Ratio; NASA: National Aeronautics and Space Administration; PEPFAR: Presidents Emergency Plan for AIDS Relief PH: Cox proportional hazards; PLWHA: People Living with HIV/AIDS; UNAIDS: United Nations Program on HIV/AIDS; USAID: United States Agency for International Development; WHO: World Health Organization; ZDV: Zidovudine; PH: Proportional Hazard

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

Ayele Gebeyehu wrote the proposal, participated in data collection, analyzed the data and drafted the paper. Mohammed Derese approved the proposal with some revisions, participated in data collection, entry and revised subsequent drafts of the paper. All authors read and approved the final manuscript.

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