



Determinants of Survival in HIV Patients: A Retrospective Study of Dilla University Hospital HIV Cohort

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Abstract

Introduction: Highly Active Antiretroviral Therapy (HAART) has remarkably improved the survival of Human Immunodeficiency Virus (HIV) patients though it is not sufficient alone to achieve better HIV related clinical outcomes. There are many other modifiable factors that might have an impact on survival of HIV-infected patients. So far, few studies with small sample size have tried to assess the survival experience of HIV positive patients who are on treatment in Ethiopia. This study assessed the determinants of survival among HIV infected persons.

Methods: Retrospective cohort study design was used including HIV infected patients, who were enrolled in to Dilla University Hospital HIV/AIDS chronic care unit between September 2005 and September 2013. Data was extracted from Antiretro Viral Therapy (ART) database and clinical charts. Time dependent Cox proportional hazard regression models was fitted to identify factors associated with survival. Data was analyzed using SPSS-windows version 20 and R-software version 3.0.1. Kaplan Meier plots, and log rank tests was used to illustrate survival probability in ART and pre-ART groups.

Results: A total of 2579 adult patients with HIV were included in the analysis. Reasons for the exclusion were age (n = 308) and availability of complete data (n = 2579). Of these, 243 patients (9.4%) died giving a crude death rate of 3.4 per 100 person-years (95% CI; 2.6 - 4.2), 1562 (60.6%) censored alive, while total of 774 (30%) were lost to follow up. The 8 years survival probability was significantly different between the groups with and without ART, (P < 0.001). In adjusted Cox regression model, age, baseline line functional status, baseline weight, baseline World Health Organization Acquired Immunodeficiency Syndrome (AIDS) staging, Isoniazid prophylactic therapy (IPT), and ART were significantly associated factors with mortality.

Conclusion: The study has shown a relatively low mortality rate as compared to other African countries. By identifying those high risk groups during routine clinical care the survival status of the HIV/AIDS patients can be improved.

Keywords

Survival, Chronic HIV/AIDS care and support, Hospital, HIV infected

ciency Virus (HIV) associated mortality both in developed [1-5] and developing countries [6,7], prolonged Acquired Immunodeficiency Syndrome (AIDS) free survival [5] and clinical benefits by viral suppression [8]. HAART reduces morbidity and mortality by suppression of viral replication, restoration and preservation of immune function, and prevention of drug resistance [9].

Mortality was higher in low-income settings than in high-income settings. Patients starting HAART in resource-poor settings had an increased mortality rates in the first months on therapy, compared with those in developed countries [10].

Finding from previous studies on HIV-infected person's mortality showed that baseline CD4 cell count [9,11-13], baseline hemoglobin level [11,14,15], World Health Organization (WHO) AIDS staging [14,16,17], body mass index [18], age [18-21], gender [12,14,16,18], and adherence to ART [11,22] were important influencing factors for HIV survival differentials.

The prevalence of HIV among adult Ethiopian in 2011 was 1.5% [23]. There are nearly 789,900 people currently living with HIV/AIDS (607,700 adults and 182,200 children aged 0-14 years); and 952,700 AIDS orphans [24]. Few studies conducted so far reported that mortality rate in Ethiopia among HIV-infected adults on HAART ranged from 7.2% to 14.8% [25-28]. These studies' findings are based on few sample size. So that this study aimed at assessing the mortality and factors contributing to it using a data of large cohort of HIV/AIDS patients in southern Ethiopia.

Materials and Methods

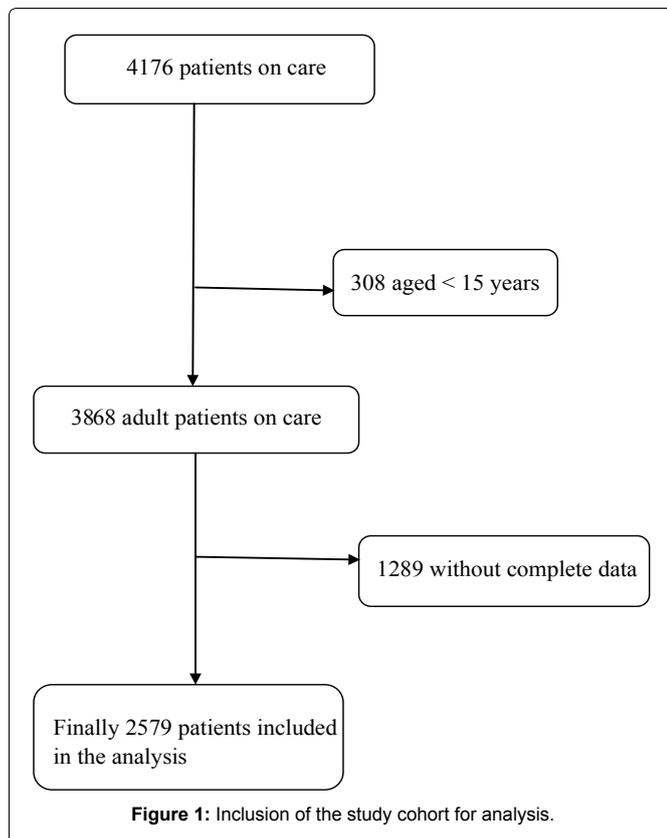
This retrospective cohort study was conducted in Dilla University hospital, Gedio zone, South Ethiopia. The hospital has been providing free Antiretro Viral Therapy (ART) to eligible HIV positive people since September, 2005 according to the national ART guideline. The eligibility of the patients determined by WHO AIDS disease staging and CD4 counts (if WHO clinical stage is above II or CD4 cell count is ≤ 200 cell/mm³). Patients who are aged 15 years and above and whose record is completely available, and who entered in HIV/AIDS care and support program from September 2005 to September 2013 were eligible for analysis.

Outcome

All cause mortality was the outcome and those patients alive in September, 2013 and lost to follow up were censored in the analysis.

Introduction

The introduction of Highly Active Antiretroviral Therapy (HAART) has led to substantial reduction of Human Immunodeficiency



The death of patients was ascertained by death report from the clinical charts, ART database or interview of relatives.

Determinants

The primary exposure was ART including other important determinants such as Isoniazid prophylactic therapy (IPT) and cotrimoxazole prophylaxis. The potential base line confounders were WHO AIDS disease stage, WHO functional status, CD4 count, haemoglobin body weight, age, gender, marital status, and educational status. All determinants data were retrieved from patients' electronic ART data base.

Statistical Analysis

Data was cleaned and coded using SPSS-20. Baseline covariates including, functional status, WHO AIDS staging, marital status, educational level, hemoglobin, and weight had less than 5% missing observations and data was imputed with multiple imputation. The estimates of five imputed data were pooled using Rubin's rule. Chi square test was used to compare baseline characteristics between pre-ART and ART initiated patients for categorical variables and t-test for continuous variables. Kaplan Meier plot used to illustrate survival experience of the cohort. Incidence rates (IRs) for mortality and 95% confidence intervals was calculated for the periods. An unadjusted and adjusted HR was computed with a time dependent Cox proportional hazard regression model. A corresponding two-sided 95% confidence intervals and associated p-values < 0.05 considered as statistically significant. The effects of co-trimoxazole and Isoniazid prophylaxis therapy on mortality were determined in subset analysis restricted to patients who were receiving ART.

Ethical Clearance

The study protocol was reviewed and approved by Dilla

Table 1: Baseline socio-demographic and clinical characteristics of study participants by ART.

Variables	All subjects (2579)	ART (n = 2178)		Pre-ART (n = 401)		P-value
		Number	Percentage	Number	Percentage	
Sex						
Male	1148 (44.5)	995	45.7	153	38.2	0.006
Female	1431 (55.5)	1183	54.3	248	61.8	
Age in Years (Mean ± sd)	32.5 ± 9.10	32.89 ± 9.01		30.78 ± 9.32		0.001
Marital Status						
Married	1558 (60.4)	1286	59.0	272	67.8	0.001
Never Married	223 (8.6)	219	10.1	4	1.0	
Divorced /Separated	591 (22.9)	467	21.4	124	30.9	
Widowed	207 (8.0)	206	9.5	1	0.2	
Literacy Status						
Illiterate	414 (16.1)	396	18.2	18	4.5	0.001
Primary	1700 (65.9)	1346	61.8	354	88.3	
Secondary and above	465 (18.0)	436	20.0	29	7.2	
Baseline functional Status						
Ambulatory	847 (32.8)	815	37.4	32	8.0	0.001
Bedridden	379 (14.7)	119	5.5	260	64.8	
Working	1353 (52.5)	1244	57.1	109	27.2	
Baseline Weight (Mean ± sd)	52.22 ± 9.13	52.22 ± 9.92		52.25 ± 1.48		0.949
WHO stage						
Stage I	200 (7.8)	199	9.1	1	0.2	0.001
Stage II	415 (16.1)	334	15.3	81	20.2	
Stage III	1749 (67.8)	1431	65.7	318	79.3	
Stage IV	215 (8.3)	214	9.8	1	0.2	
CD4 count at baseline (cells/μL) Mean ± sd	164.02 ± 117.84	163.99 ± 128.23		164.18 ± 5.27		0.976
Hemoglobin (g/dl) Mean ± sd	12.32 ± 1.84	12.32 ± 1.97		12.31 ± 0.69		0.875
CPT initiation						
Before	230 (8.9)	230	10.6	0	0	0.001
With ART	2349 (91.1)	1948	89.4	401	100	
INH initiation						
NO	2128 (82.5)	1727	79.3	401	100	0.001
Before ART	65 (2.5)	65	3.0	0	0.0	
After ART	386 (15.0)	386	17.7	0	0.0	

ART: Antiretroviral Therapy; WHO: World Health Organization; CPT: Cotrimoxazole Prophylaxis Treatment; IPT: Isoniazid Preventive Therapy

University ethical clearance committee. Letter of permission to access data was obtained from Dilla referral hospital clinical director. Before importing the data to SPSS for analysis, and analysis was performed in anonymized data.

Results

Base line characteristics of patients

A total of 4176 patients were ever enrolled on Chronic HIV care and support program in Dilla hospital between 15 September, 2005 and 10 September, 2013. A total of 1597 subjects were excluded from analysis criteria due to age < 15 years (n = 308) and lack of information (n = 1289) leaving a total of 2579 study participants for final analysis (Figure 1).

Table 1 compares the baseline socio-demographic and clinical characteristics of the ART initiated and pre-ART groups. Pre-ART study subjects were more likely to be female (61.8% Vs. 54.3%, $P = 0.006$), were younger (Mean, 30.78 Vs. 32.89 years, $P < 0.001$), married (67.8% Vs. 59.0%, $P < 0.001$), had primary education (88.3% Vs. 61.8, $P < 0.001$), and bedridden (64.8% Vs. 5.5%, $P < 0.001$) than those participants on ART at baseline. There was no statistical difference between the two treatment group with respect to mean weight ($P = 0.949$), mean CD4 cell count ($P = 0.976$) and mean hemoglobin level ($P = 0.875$) at baseline.

Mortality

The cohort contributed a total of 7151 person-years of follow up with 532 person-years for pre-ART and 6619 person-years for ART groups. The overall median follow-up was 34 months (inter quartile range, 9-64 months). The exposure specific median follow up was 12 months (inter quartile range, 2-32 months) and 39 months (inter quartile range, 12-67 months), respectively, for subjects in pre-ART and ART groups ($P < 0.001$).

During the study period, a total of 243 patients (9.4%) died giving a crude death rate of 3.4 per 100 person-years (95% CI; 2.6-4.2), 1562 (60.6%) were censored alive, while total of 774 (30%) were lost to follow up. Of this, the majority 443 (57.2%) were those who started

ART. For ART groups, 196 deaths (9.0%) were reported, giving an overall mortality rate of 3.0 per 100 person-years (95% CI; 2.3-4.0), while in a pre-ART group 47 (11.7%) deaths were reported giving a mortality rate of 8.8 per 100 person-years (95% CI; 6.1-11.5). The 8 years survival probability was significantly different between the groups with and without ART, $P < 0.001$ (Figure 2).

Table 2 shows the results of unadjusted and adjusted Cox regression models fitting factors associated with mortality. Age, baseline functional status, baseline weight, baseline WHO stage, IPT initiation, and ART initiation were independent predictor of mortality in adjusted Cox regression model. However, marital status, education background, cotrimoxazole prophylaxis baseline CD4 cell count, and baseline hemoglobin level were not associated with mortality. A 1 year increase in age increase the risk of death by 2%, similarly, a 1kg increase at baseline weight led to 3% reduction in mortality, which were statistically significant. The hazard of death for patients who were bedridden was 2.6 times than risk for ambulatory patients. Patients at WHO stage IV were at increased risk of death as compared to their counterparts (AHR = 2.77, 95% CI 1.14-7.26). Taking IPT prophylaxis after initiation of ART decreased the risk of death by 87%. There was 2.2 times risk of death for patients not taking ART as compared to patients taking ART.

Discussion

This 8-year retrospective cohort study of HIV infected patients on ART gives an insight in survival and its determinants in a semi-urban hospital setting in Ethiopia. The overall 8 years mortality was 3.4 per 100 person-years. Which is lower than the mortality rate from previous studies from Ethiopia [25], African countries [9,14-17,29-31], and findings from other areas [19,21,32]. However there were also studies which reported similar findings with ours [13,33-36]. Factor contributed to low mortality in our study might be continuity of care and follow up at home by adherence supporter and free of charge ART services. There are different reasons for the discrepancy of results which has been seen among studies in low income countries that mortality were higher within the first month of HAART start than in later months [35]. Longer follow up period is required in

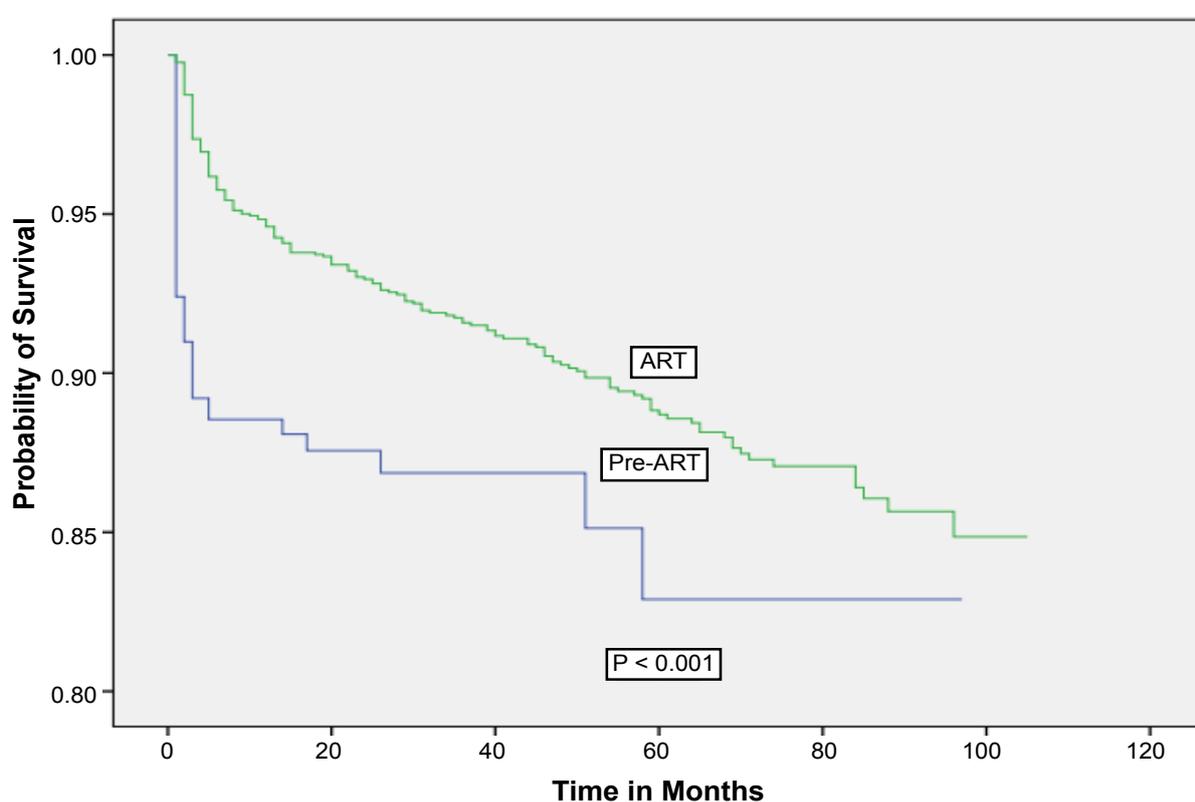


Figure 2: Kaplan meier estimates of the survival rates between ART and pre-ART groups Dilla referral Hospital, Ethiopia; 2014.

Table 2: Unadjusted and adjusted analysis mortality with different risk factors Dilla Ethiopia, 2014.

Variables	UHR**	95% CI***	AHR****	95% CI
Gender				
Male	1	1	1	1
Female	0.84	0.66-1.08	0.85	0.64-1.14
Age (per 1 year increase)	1.02	1.01-1.03	1.02	1.01-1.03
Marital Status				
Married	0.95	0.64-1.41	1.02	0.68-1.53
Never Married	1	1	1	1
Divorced /Separated	0.79	0.39-1.61	0.78	0.41-1.49
Widowed	0.84	0.47-1.49	0.93	0.51-1.70
Literacy Status				
Illiterate	1	1	1	1
Primary	1.18	0.73-1.64	1.07	0.72-1.60
Secondary and above	1.25	0.78-1.74	1.01	0.76-1.49
Baseline functional Status				
Ambulatory	1	1	1	1
Bedridden	3.06	2.08-4.49	2.60	1.73-3.92
Working	0.50	0.37-0.67	0.74	0.53-1.02
Baseline Weight (per 1 kg increase)	0.97	0.95-0.98	0.97	0.96-0.99
WHO stage				
Stage I	1	1	1	1
Stage II	2.08	0.76-5.71	1.76	0.63-4.89
Stage III	3.38	1.35-8.45	2.17	0.82-5.31
Stage IV	7.11	2.77-18.25	2.77	1.14-7.26
CD4 count at baseline (per 1 unit increase)	0.99	0.99-1.10	0.99	0.92-1.00
Hemoglobin (per 1g/dl increase)	0.93	0.97-1.09	0.98	0.96-1.09
CPT initiation				
Before	1	1	1	1
With ART	1.85	1.15-3.19	1.13	0.65-1.98
INH initiation				
NO	1	1	1	1
Before ART	0.11	0.04-0.68	0.18	0.03-1.34
After ART	0.14	0.07-0.27	0.13	0.06-0.26
ART				
NO	2.59	1.83-3.66	2.21	1.55-3.17
Yes	1	1	1	1

UHR: Unadjusted Hazard ratio; CI: Confidence Interval; AHR: Adjusted Hazard Ratio; WHO: World Health Organization; CPT: Cotrimoxazole Prophylaxis Treatment; IPT: Isoniazid Preventive Therapy ART: Antiretroviral Therapy

order to assess the true reduction of mortality after ART initiation, most of the findings from African countries has estimated mortality of maximum 2 years follow up which might have estimated high death rate than the present finding. Another very important reason that makes our result different from previous studies might be that ART was treated as time varying covariates.

Unlike previous finding from Ethiopia [25], age is important predictor of death in our study. Multiple studies have demonstrated that an increase in age at the time of HIV infection was associated with more rapid progression to AIDS [5,16,19-21,32,35]. Old age is associated with immunologic vulnerability, exposure to infectious diseases, psychosocial comorbidities and the other factors of disease progression [37] having had an AIDS diagnosis could more severely impair subsequent immune function in older individuals than in young people, preserving an overall age effect on mortality. Gender of the patient may be an important biological prognostic factor in AIDS, but the results of various studies are conflicting. Several authors described gender differences in ART outcome, where men had a higher mortality rate than women [12,14,16,19,21,30,31,38], but others found none [5,9,13,15,17,20,25,29,33,35,36,39]. In our

study, although females had a slightly better survival than males, this was not statistically significant. Female patients experienced lower risk of death during follow-up compared with males [40]. This may be explained by differences in treatment adherence, health seeking behaviour and women's more timely access to ART through antenatal care.

WHO AIDS staging, which is a well known predictor of mortality in most studies, [14,16,17,19,30,34-36,38] was significantly associated with mortality. Finding from Uganda [16], established that a 5 kg increase in baseline weight led to a 23% reduction in the risk of death. Similarly, in present study baseline weight had a significant effect on survival of patients. Several studies [16,21,29,30] found that increasing CD4 count resulted in lower hazard of mortality among HIV/AIDS patients. Our result showed that for a 1 unit increase in CD4 count, the hazard of death lower by 1%, yet this was not statistically significant. Unlike Previous studies [9,36,41] haemoglobin was not a significant predictor of mortality in our study despite observational studies conducted in Botswana and Uganda are in agreement with current study [12,16]. The low level of hemoglobin in HIV positive patients could be due to an advanced clinical stage, especially secondary to latent opportunistic infections. The cause of anemia in HIV patients is likely to be multifactorial factors such as bleeding, nutritional deficiency, hemolytic anemia, bone marrow suppression, etc.). This inconsistency compels further research to see the effect of hemoglobin on mortality among HIV/AIDS patients.

IPT initiation after HAART was an important predictor of mortality. Since such an effect has not been reported previously in other African cohort studies, this unmeasured confound could also have biased the estimates. This finding need to be replicated in similar settings elsewhere. Most studies found it difficult to analyze the effect of cotrimoxazole prophylaxis on survival independent of ART. However, we were able to see the effect of cotrimoxazole prophylaxis given before and with ART. Even though, those patients who took cotrimoxazole prophylaxis with ART had a higher mortality than those who took before starting ART, the difference was not statistically significant. But some studies found that taking cotrimoxazole prophylaxis had a significant effect on reduction of mortality as compared to not taking the prophylaxis [16,25,32].

The independent effect of being bed ridden on survival of patients could be explained by advanced clinical stage of the HIV/AIDS and low CD4 count. Such type of patients need special attention, by health care providers, in daily clinical care.

Our study cohort had a long observation period (8 years) and reflects the operational realities of the hospital. The large number of patients and events analyzed was an important strength of this study. Also, because all patients were treatment naive, our results are not confounded by previous antiretroviral therapy. To avoid time dependent bias we estimated hazard rates by fitting ART as time varying covariate. This avoids the so called time dependent (immortal time) bias [42-45].

This study has some limitations. First, we were not able to determine the exact cause of the deaths, and to attribute them all to HIV, over estimates the AIDS-related mortality rate. Second, the data were collected retrospectively from patient files in a context of routine care and hence there might be a certain degree of underreporting of events. Lack of data on adherence prevented us from analyzing the role of adherence on survival time, though several studies report this as an important determinant [9], and similarly, we were not able to see the effect of Body mass index on survival. Third, underestimation of mortality could have occurred because of significant proportions (30%) of the participants were lost to follow up, which was higher than studies conducted in other African countries. Patient tracing significantly increased the number of reported deaths as there may be substantial death among lost to follow up [12]. Death rates after HAART initiation within antiretroviral therapy clinics may be systematically underestimated if losses to follow-up were large and patients with very low pre-treatment CD4 counts were presenting

for care, however in our study there was no statistically significant difference in CD4 count and WHO clinical staging between the lost to follow up and those in the followed up, so it is unlikely for the mortality to be underestimated. However readers need to be caution while reading the low mortality rate reported in this study, that it could still be explained by the high proportion of lost to follow up. It needs further research to address the possible reasons for large proportion of lost to follow up and the outcome of those lost to follow up.

Conclusion

The study has shown a relatively low mortality rate as compared to other African countries. Age, low baseline body weight, bedridden functional status, stage IV AIDS disease, and isoniazid prophylaxis were found to be independent predictors of mortality in HIV/AIDS patients.

This mortality and its determinants need to be addressed by assessing patients for those risk factors and improving the quality of existing services like nutritional evaluation for identifying those with low body weight. Health worker need to give more emphasis during clinical care for patients like bedridden, advanced WHO HIV disease stage and those who are older. The high lost to follow up should be addressed by initiating a tracing mechanism through house visits.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

SH contributed in the generation of the topic, preparation of proposal, data collection, analyses and development of the manuscript. GT contributed in reviewing the proposal, assisted in data collection, and critical review of final manuscript. HT contributed in data analyses, and critically reviewing the manuscript. PK contributed in reviewing the manuscript. All authors read and approved the final manuscript.

Acknowledgments

The authors acknowledge Dilla University research and dissemination office and Dilla referral hospital HIV/AIDS care and support program team.

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