Heliyon 9 (2023) e12840

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Survival analysis and predictors of mortality among adult HIV/AIDS patients initiated antiretroviral therapy from 2010 to 2015 in Dubti General Hospital, Afar, Ethiopia: A retrospective cohort study

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ARTICLE INFO

Keywords:
Survival
Mortality rate
Predictors
HIV/AIDS
ART
Afar
Ethiopia

ABSTRACT

Background: Although antiretroviral therapy (ART) is well accepted to increase survival of patients with HIV/AIDS, AIDS related deaths continue to be a major problem in sub-Saharan Africa like Ethiopia. Studies have showed variable findings in the survival status of patients with HIV/AIDS initiating ART, and there was no such study in the study area. Therefore, purpose of this study was to determine the survival and predictors of mortality among HIV/AIDS patients starting taking ART in Dubti General Hospital, Afar, Ethiopia.

Methods: A 5 year retrospective cohort study was performed among 702 HIV/AIDS patients aged ≥15 years that started ART between December 31, 2010, and December 31, 2015 in Dubti General Hospital, Afar, Ethiopia. A simple random sampling technique was used to select the study subjects from each WHO stage based stratum. Socio-demographic, clinical and survival status data were extracted by reviewing patients' records. Data were analyzed by using SPSS Version 21. Kaplan-Meier and Cox-regression models were used to estimate survival, and explore predictors of mortality. Variables with a p value of <0.05 in multivariate Cox regression analysis were considered statistically significant.

Results: Among 702 study participants, 82 (11.7%) died during follow up, and the overall incidence rate of mortality was 5.81 per 100 person-years. Identified predictors of mortality were being not married (AHR = 3.71, 95% CI: 1.97–6.99), had no formal education (AHR = 2.33, 95% CI: 1.33–4.38), bedridden functional status (AHR = 5.91, 95% CI: 2.71–12.88), advanced WHO stage III and IV (AHR = 4.36, 95% CI: 2.20–8.64), BMI 16–18.4 kg/m^2 (AHR = 3.03, 95% CI: 1.50–6.13), and BMI<16.0 kg/m^2 (AHR = 5.47; 95% CI: 2.85–10.50), CD4 count ≤50 cells/mm^3 (AHR = 6.62, 95% CI: 4.73–8.52), hemoglobin <8 g/dl (AHR = 5.21; 95% CI: 2.64–10.26), not used cotrimoxazole prophylaxis therapy (AHR = 2.78, 95% CI: 1.61–4.73), stavudine based regimen (AHR = 2.34, 95% CI: 1.32–4.13), and zidovudine based regimen (AHR = 2.49, 95% CI: 1.41–4.39).

Abbreviations: ALHIV, Adults living with HIV; AHR, Adjusted hazard ratio; ART, Antiretroviral therapy; BMI, Body mass index; CI, Confidence Interval; DGH, Dubti General Hospital; OIs, Opportunistic infections; WHO, World Health Organization.

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https://doi.org/10.1016/j.heliyon.2023.e12840
Received 27 August 2021; Received in revised form 31 December 2022; Accepted 3 January 2023
Available online 5 January 2023

Conclusion: High mortality was observed in this cohort, and participants with stage III and IV, low CD4 count, low hemoglobin level, bed ridden functional status, low BMI should be closely monitored even with the scarce resources. In addition, the use of cotrimoxazole prophylaxis therapy should be more encouraged to increase survival.

1. Introduction

The pandemic of Human Immunodeficiency Virus (HIV) creates a big challenge to the survival of humankind [1]. HIV/Acquired Immunodeficiency Syndrome (AIDS) is a devastating chronic disease that affects the world's health, social, economic, and political systems both in the past, and the present. In 2019, more than 36 million adult people were living with HIV worldwide. In the same year, the prevalence of HIV, new infection, and AIDS related deaths were the highest in Eastern and Southern Africa region [1].

Based on HIV related estimates and projections for Ethiopia in 2021, 717,153 adults were living with HIV/AIDS (ALHIV) and 7437 died. From this estimation, Afar region had 9,783ALHIV, and 109 adult deaths [2]. Although Anti-Retroviral Therapy (ART) plays a crucial role in terms of improving quality of life, reducing morbidity, and mortality of people living with HIV/AIDS, higher rates of AIDS related deaths were noticed in African countries compared to high income countries [3]. In addition, regional variation in survival status after ART initiation of people living with HIV/AIDS was observed in Ethiopia [4].

According to several studies done in Ethiopia, the mortality rate was estimated to be 4.2%–43%, with the majority of deaths occurring within six months of starting ART [5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20]. Almost all of these studies were conducted before the adoption of "Test and Treat" policy in Ethiopia. Ethiopia has implemented the "Test and Treat" policy in 2016 by putting all people living with HIV/AIDS on ART irrespective of their World Health Organization (WHO) clinical stage or CD4 cell count level [21]. Low baseline CD4 count, advanced stage disease (stage III and stage IV), nonworking functional status (bedridden and ambulatory), low baseline hemoglobin level, tuberculosis co-infection, lower baseline weight, and poor treatment adherence were commonly identified as predictors of death in HIV patients [22]. Despite the fact that there have been numerous studies about the mortality of HIV/AIDS patients in Ethiopia, the results are inconsistent. . In addition, little is known about the survival status, and predicting factor of early mortality in HIV/AIDS patients after the initiation of ART in the pastoralists like Afar. Therefore, this study aimed to elaborate survival status, and predictors of mortality among HIV infected patients after the initiation of ART at Dubti Hospital.

2. Methods

2.1. Study setting, period, and study design

Afar region is located in the north-eastern part of Ethiopia. It borders Eritrea to the north-east and Djibouti to the east. The production system of the Afar Region is dominated by pastoralism (90%) and agro-pastoralism (10%). The region has a total population of about 1.4 million (55% male) [23]. Dubti General Hospital is one of the General Hospitals in the region which provides a variety of clinical services including comprehensive HIV care since 2005. A retrospective cohort study design was employed among adults with HIV/AIDS starting ART from December 31, 2010 to December 31, 2015.

2.2. Eligibility criteria

All adult patients with HIV/AIDS aged $\geq$15 years old, and who were initiated on ART at Dubti General Hospital from December 31, 2010 to December 31, 2015 were eligible for inclusion. However, patients who initiated treatment outside Dubti General Hospital (Transfer in), HIV-positive patients $\geq$15 years old who enrolled in to the treatment in Dubti General Hospital before December 31, 2010, and after December 31, 2015, those with incomplete medical records (when one of the independent variable is not registered in medical cards namely, $CD4^+$ cells, hemoglobin, WHO stage, functional status and TB status), and HIV-positive patients $<$15 years old during ART initiation were excluded from the study.

2.3. Sample size determination

As it was a cohort study, the required sample size to achieve statistically significant results was calculated by using double proportion formula. The major exposure variables were taken into account to determine the sample size by using open epi version 3.01 statistical packages [24]. From the exposure variables, World Health Organization (WHO) staging was selected as a major exposure variable of non-accidental mortality during the 5 years of follow up since it was considered to give the optimal sample size and most significant result. Two sided 5% level of significance, a power of 80%, a ratio of unexposed to exposed of 1:1, and estimated proportion of mortality in Ethiopia was taken as 4.1% for non-exposed group (WHO stage I and II), and 10.1% for exposed group (WHO stage III and IV) [25]. Based on these assumptions, the calculated sample size was 638 (319 for each exposed and non exposed group). After adding 10% as a contingency modifier, the total sample size became 702 (351 for exposed subjects and 351 for non-exposed subjects).

2.4. Sampling technique and sampling procedure

First the eligible individuals were stratified into WHO clinical stage I + II as non-exposed group and WHO clinical stage III + IV as exposed group. Then, a simple random sampling was applied to each group eligible patients' records with ART in Dubti General Hospital to select study participants. By extracting the ART unique numbers from ART smart care database in to single Excel spreadsheet for each group, random selection of records was made for all eligible records until the predetermined sample size was achieved for each group (Fig. 1).

2.5. Study variables

Time to an event in years was the dependent variable. Age, sex, marital status, educational level, body mass index, functional status, hemoglobin level, WHO clinical stage, CD4 count, initial ART regimen, adherence, opportunistic infections, tuberculosis treatment, cotrimoxazole prophylaxis therapy (CPT), and isoniazid preventive therapy (IPT) and substance use were baseline predictors. Baseline variables are variables for which the measurement taken nearest to the date of ART initiation. For variables which were available pre-ART initiation, the most recent one was taken as baseline variable. For most of opportunistic infections, CPT, IPT, and tuberculosis treatment, data were available before ART initiation but for some of them data were available post-ART initiation only. Variables of post-ART initiation including ART adherence were considered as baseline variable if measured or recorded within 30 days of ART initiation. In addition, ART regimen changes during the course of follow up was taken as the independent variable.

2.6. Data collection procedures and data quality control

All necessary socio-demographic, clinical, and laboratory data were collected by reviewing pre-ART register, ART intake form, laboratory request form, monthly cohort form, and follow up form. This work was done using specifically developed data collection instrument by thoroughly trained ART nurses who worked in ART clinic at Dubti General Hospital. They were supervised by a thoroughly trained supervisor, and occasionally by the principal investigator. Any errors found during the training process were corrected. All completed data collection forms were examined for completeness, consistency, and clarity during data management,

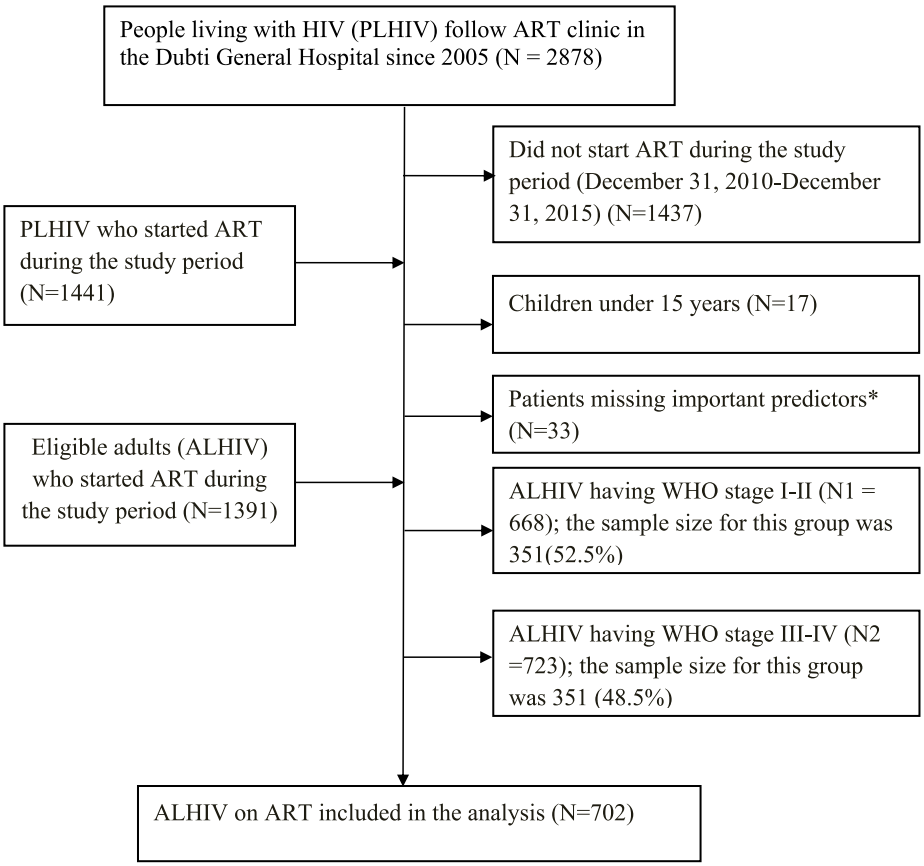

Fig. 1. Sampling procedure of the study cohort used in analysis at Dubti General Hospital, Afar, Ethiopia. *Important predictors namely $CD4^{+}$ cells, hemoglobin, WHO stage, functional status and TB status.

storage, and analysis.

2.7. Data management, analysis and interpretation

The collected data from all the questionnaires were coded, entered, and cleaned to check for completeness. Then, it was analyzed using SPSS version 21. Descriptive statistics such as median, quartile bounds (QB), mean, and standard deviation (SD) were used to summarize the characteristics of the cohort. Multiple imputations were done to manage missing data, and there were few missing data (<5%). Incidence of deaths with respect to person time at risk was calculated, and reported as number of deaths per 100 person-years of follow up by assessing the date of enrolment for ART, and death or censoring. Life table was used to estimate the cumulative survival, and Kaplan-Meier survival curve together with log rank test was used to compare survival between different categories of independent variables. The following steps were followed to determine estimated mean survival time: running Kaplan-Meier, sort data in ascending order and sort cases by time, removing duplicate event times, computing the duration for each step in the survival function, computing contribution to mean value, and finally, computing sum of contributions [26,27]. The necessary assumption for the model was checked by using log-log plot and time dependent Cox model having a follow up time cut off point. The assumption of models was not violated. The results of cox model were reported as hazard ratio (HR) with 95% confidence interval (CI). Variables with $p < 0.25$ in bivariate analysis were included in multivariate analysis. We did a sensitivity analysis using only baseline predictors. A p-value of <0.05 was considered as statistically significant.

2.8. Ethical consideration

Ethical clearance was obtained from the Ethical Review Committee (ERC) of Samara University (ERC 0062/2018), and an official letter from College of Medical and Health Sciences, Samara University was given to Dubti General Hospital to facilitate the study process. All information collected from clients' medical record cards were kept anonymous and confidential.

2.9. Operational definitions

Survival: When the patient is known to be alive as evidenced by his/her clinical follow up till the end of the study period.

Survival time: The period that a patient stays in life after starting ART.

Death: is defined as confirmed HIV/AIDS-related death with the certification of death by a medical practitioner, or a verbal or telephone confirmation of death from a relative or friend.

Censoring: Means when loss to follow-up, drop out, stop treatment, transferred out, or on follow up/end of study.

Lost to follow up: Means missed his or her next clinic or pharmacy refill appointment for at least 1 month, but at most 3 consecutive months.

Drop out: Patient defined as "dropped out" had missed his or her planned clinic or pharmacy refill appointment for more than 3

Table 1
Baseline socio-demographic characteristics of ALHIV who initiated ART from 2010 to 2015 at Dubti General Hospital, Afar, Ethiopia (n = 702).

Variables	Category	Total (%)	Died (%)
Age (years)	15–24	93 (13.2)	5 (5.4)
	25–34	287 (40.9)	40 (13.9)
	35–44	206 (29.3)	23 (11.2)
	≥45	116 (16.5)	14 (12.1)
Sex	Male	293 (41.7)	43 (14.7)
	Female	409 (58.3)	39 (9.5)
Religion	Muslim	453 (64.5)	65 (14.4)
	Orthodox	239 (34.1)	17 (7.1)
	Others*	10 (1.4)	0 (0)
Marital Status	Married	291 (41.5)	25 (8.6)
	Never married	104 (14.8)	23 (22.1)
	Divorced	228 (32.5)	25 (11)
	Widowed	79 (11.3)	9 (11.4)
Employment Status	Employed	236 (33.6)	22 (9.3)
	Not employed	466 (66.4)	60 (12.9)
Educational Level	No formal edu.	259 (36.9)	46 (17.8)
	Primary	198 (28.2)	26 (13.1)
	Secondary	189 (26.9)	9 (4.8)
	College/Above	56 (8)	1 (1.8)
Residence of the participant	Urban	317 (45.2)	48 (15.1)
	Rural	385 (54.8)	34 (8.8)
Dependent Children at home	Yes	411 (58.5)	49 (11.9)
	No	291 (41.5)	33 (11.3)

Others*, protestant and catholic; edu., education; ALHIV, Adults living with HIV; ART, Anti-retroviral therapy; the percentage in total column = total number of each category divided by the sample size whereas the percentage in died column = number of deaths in each category divided by total number of each category.

consecutive months.

3. Results

3.1. Socio-demographic characteristics of patients

Among 1391 ALHIV (age ≥15 years old) who started ART from December 31, 2010 to December 31, 2015, 702 patients were included in the study. Among 702 participants, 409 (58.3%) were females, 385 (54.8%) were from rural area. The mean and median age of the participants at ART initiation was 34 years with SD of ±9.54, and 32 years (quartile bounds = 27, 40 years), respectively (Table 1).

From the total participants, 694 (96.0%) did not drink alcohol, 99 (14.1%) smoked cigarette, and 389 (55.4%) engaged in practice of substance abuse, mostly khat. Regarding to sexual partner, 205 (29.2%) had regular sexual partner while 278 (39.6%) had casual sexual partner (Table 2).

3.2. Baseline clinical, and laboratory characteristics

At the time of ART initiation, greater than 50% of participants had working functional status. Among the study participants, 344 (49.0%) had a body mass index (BMI of equal and above 18.5 kg/m^2, 217 (30.9%) had history of tuberculosis (TB) treatment, and 138 (19.6%) opportunistic co-infection (OI). Regarding to chemoprophylaxis, 569 (81.1%), and 51 (7.3%) participants received CPT, and IPT, respectively. The baseline median (with quartile bounds) CD4 count, BMI, and hemoglobin of the cohort were 142 (94,198) cells/μl, 18.2 (15.6, 20.5), and 11.5 g/dl (10, 13), respectively. At ART initiation, tenofovir, zidovudine, and stavudine based regimen were used almost in equal proportion (Table 3).

3.3. Overall survival of patients on ART

In the present study, 702 patients on ART were followed up for up to 5 years. The estimated mean survival time of the patient was 4.39 years (95% CI: 4.27–4.52). The median follow-up time of all the patients was 1.34 years. The overall mortality rate in the cohort during the 1411 person-years of observation (PYO) was 5.81 per 100 person-years follow-up. The cumulative incidence of death for this study was 82 (11.7%) of patients up to 5 years. However, 620 (88.3%) of participants were censored, including 310 (44.2%) were still being followed on ART, 160 (22.8%) were lost to follow up, 11 (1.6%) were drop outs, and 139 (19.8%) transferred out to other health facilities. The Kaplan–Meier survival estimation depicted that the overall estimated survival rate after the initiation of ART was 85.4% at 5 years of follow-up. The estimated cumulative survival was 91.9%, 90.8%, 89.9%, and 89.2% at 0.25, 0.5, 1, and 2 years, respectively (Fig. 2). The study showed that the highest mortality rate occurred during the first year of initiation of ART, especially in the first half of the first year.

3.4. Survival function among different groups of patients on ART

The existence of any significant difference in survival among various categorical variables in the study was checked by applying the log rank test. The test statistics in Kaplan–Meier analysis indicated significant evidence of differences in baseline marital status, functional status, educational level, ART adherence level, BMI, WHO clinical staging, baseline hemoglobin, CPT use, and baseline CD4 count. The Kaplan–Meier survival analysis depicted that those who had WHO clinical stage I, and II at baseline had a longer estimated mean survival time than those with WHO clinical stage III, and IV (4.96 & 4.74 versus 4.43 & 2.71 years, respectively, $P < 0.0001$)

Table 2
Baseline risk behavior characteristics of ALHIV who initiated ART from 2010 to 2015 at Dubti General Hospital, Afar, Ethiopia (n = 702).

Variables	Category	Total (%)	Died (%)
Alcohol consumption	Yes	28 (4)	2 (7.1)
	No	674 (96)	80 (11.9)
Sexual partner	Regular	205 (29.2)	26 (12.7)
	Casual	278 (39.6)	34 (12.2)
	None	219 (31.2)	22 (10.1)
Substance use	Yes	389 (55.4)	37 (9.5)
	No	313 (44.6)	45 (14.4)
Condom use	Never	205 (29.2)	26 (12.7)
	Sometimes	278 (39.6)	34 (12.2)
	Mostly	219 (31.2)	22 (10.1)
Smoking	Yes	99 (14.1)	20 (20.2)
	No	603 (85.9)	62 (10.3)
Disclosed HIV sero-status to relatives &/or friends	Yes	247 (35.2)	26 (10.5)
	No	455 (64.8)	56 (12.3)

ALHIV, Adults living with HIV; ART, Anti-retroviral therapy; The percentage in total column = total number of each category divided by the sample size whereas the percentage in died column = number of death in each category divided by total number of each category.

Table 3
Baseline clinical, and laboratory characteristics of ALHIV initiated on ART from 2010 to 2015 at Dubti General Hospital, Afar, Ethiopia (n = 702).

Variables	Category	Total (%)	Died (%)
Functional status	Working	385 (54.8)	10 (2.6)
	Ambulatory	217 (30.9)	34 (15.7)
	Bed ridden	100 (14.2)	38 (38.0)
CD4 Count	≥200	171 (24.4)	2 (2.3)
	101–199	340 (48.4)	14 (4.1)
	51–100	118 (16.8)	20 (16.9)
	≤50	73 (10.4)	46 (63.0)
WHO Staging	Stage I	225 (32.1)	5 (2.2)
	Stage II	126 (17.9)	6 (4.8)
	Stage III	231 (32.9)	31 (13.4)
	Stage IV	120 (17.1)	40 (33.3)
BMI (Kg/m^2)	≥18.5	344 (49.0)	16 (4.7)
	16–18.4	156 (22.2)	19 (12.2)
	<16	202 (28.8)	47 (23.3
ART Regimen	Tenofovir based	215 (30.6)	25 (11.6)
	Stavudine based	268 (38.2)	29 (10.8)
	Zidovudine based	219 (31.2)	28 (12.8)
Hemoglobin Level (g/dl)	≥12	283 (40.3)	14 (4.9)
	10–11.9	193 (27.5)	11 (5.7)
	8–9.9	116 (16.5)	18 (15.5)
	<8	110 (15.7)	39 (35.5)
TB treatment	Yes	217 (30.9)	36 (16.6)
	No	485 (69.1)	46 (9.5)
OIs Co-infection	Yes	138 (19.7)	23 (16.4)
	No	564 (80.3)	59 (10.5)
CPT	Given	569 (81.1)	58 (10.2)
	Not given	133 (18.9)	24 (18.1)
INH Prophylaxis	Given	51 (7.3)	16 (31.4)
	Not given	651 (92.7)	66 (10.1)
Treatment Support	Available	20 (2.8)	2 (10.0)
	Not available	682 (97.2)	80 (11.7)
ART Adherence	Good	382 (54.4)	32 (8.4)
	Fair	144 (20.5)	19 (13.2)
	Poor	176 (25.1)	31 (17.6)

Note: ART adherence assessed based on Giordano et al. [28]. Abbreviations: ALHIV, Adults living with HIV; WHO, World Health Organization; BMI, Body mass index; TB,Tuberculosis; OIs, Opportunistic infections; CPT, Cotrimoxazole prophylaxis therapy; INH, Isoniazid; ART, Antiretroviral therapy; the percentage in total column = total number of each category divided by the sample size whereas the percentage in died column = number of death in each category divided by total number of each category.

(Fig. 3). The estimated mean survival time for those who had a baseline CD4 count of at least 200 cells/mm^3 (4.98 years, 95% CI: 4.95–5.01, P < 0.0001) was longer than those who had a CD4 count of under 50, 51–100, and 101–199 cells/mm^3 (Fig. 4).

The lowest survival probabilities were observed for patients with baseline hemoglobin <8 g/dl (63.1%), bed ridden (57.5%), CD4 count ≤50 cells/mm^3 (0%), WHO stage III & IV (70.1%), and BMI (<16 kg/m^2 (73.3%). The estimated mean survival time of patients with bedridden functional status (3.06 years, 95% CI: 2.54–3.53, P < 0.0001) was shorter than those with ambulatory, and working functional status (Fig. 5). Regarding to marital status, being never married had a shorter estimated mean survival time (3.81 years, 95% CI: 3.42–4.21, P < 0.0001) compared to being married, divorced, and widowed. In addition, patients who did not have formal education had a shorter estimated mean survival time (4.09 years, 95% CI: 3.85–4.33, P < 0.0001) than those who had primary education, secondary education, and college and above education level. Concerning to cotrimoxazole prophylaxis therapy (CPT) use, patients who took CPT had longer estimated mean survival time (4.47 years, 95% CI: 4.35–4.60, P = 0.012) than those who did not take CPT.

Regarding to baseline hemoglobin status, patients with a hemoglobin of less than 8 g/dl had a shorter estimated mean survival time (3.07 years, 95% CI: 2.67–3.48, P < 0.0001) compared to those patients with a hemoglobin level of 8–9.9, 10–11.9, and ≥12 g/dl (Fig. 6). Patients with normal and above baseline BMI (≥18.5 kg/m^2) had longer estimated mean survival time (4.86 years, 95% CI: 4.78–4.95, P < 0.0001) than those with BMI of <16, and 16–18.4 (Fig. 7).

The Kaplan–Meier graph along with the Log rank test showed that the estimated mean survival time for those who had poor adherence to ART was shorter (2.43 years, 95% CI: 2.22–2.65) than those who had fair, and good adherence (3.86 years, 95% CI: 3.56–4.16; 4.6 years, 95% CI: 4.48–4.74, respectively). This difference was statistically significant at $P < 0.0001$ (Fig. 8). Furthermore, participants with baseline zidovudine based regimen had significantly shorter estimated mean estimated survival time ($P < 0.001$) compared to tenofovir based regimen (Fig. 9).

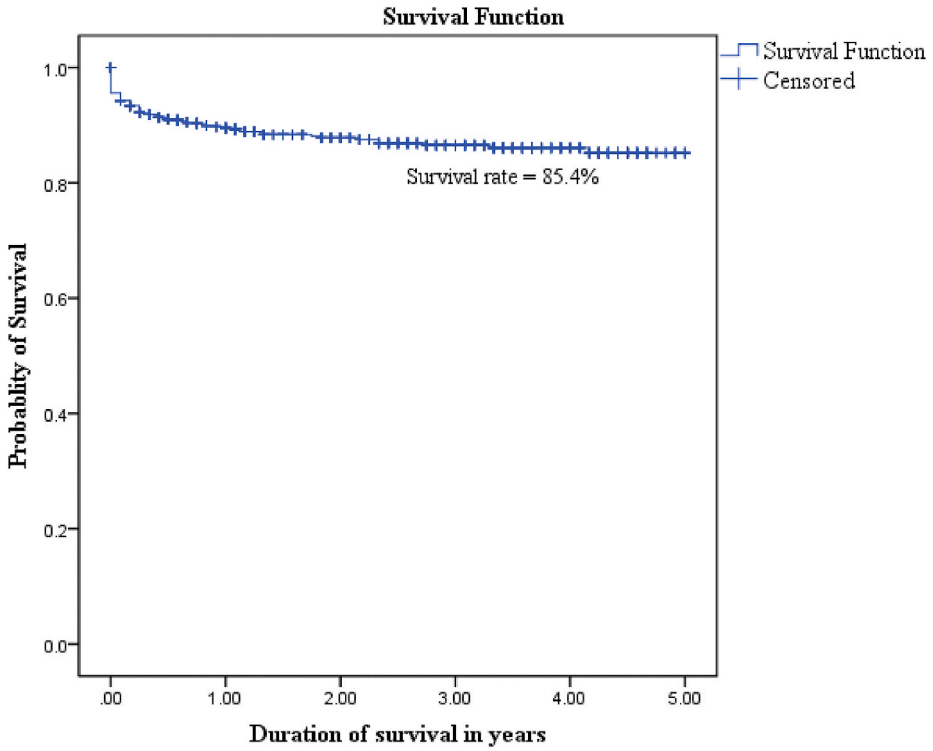

Fig. 2. The five year survival rate of the study population was 85.4% for starting ART in Dubti General Hospital, Afar, Ethiopia from December 31, 2010 to December 31, 2015.

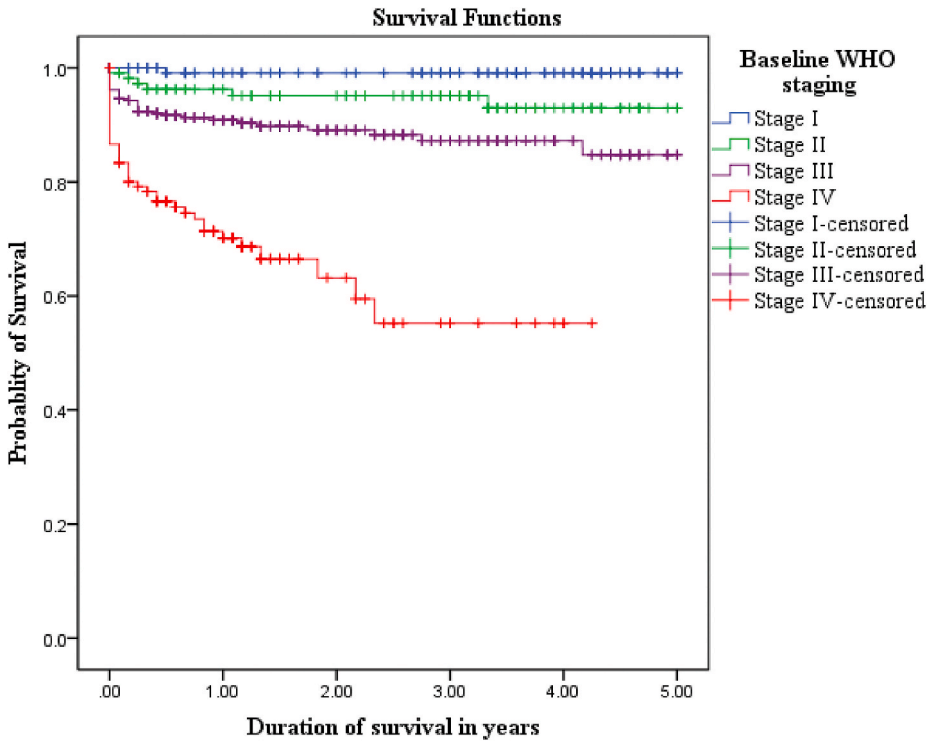

Fig. 3. The Kaplan–Meier Survival Curves Compare Survival Time of Patients Starting ART by Baseline WHO Clinical Stage in Dubti General Hospital, Afar, Ethiopia from December 31, 2010 to December 31, 2015 (Log rank test $p < 0.0001$).

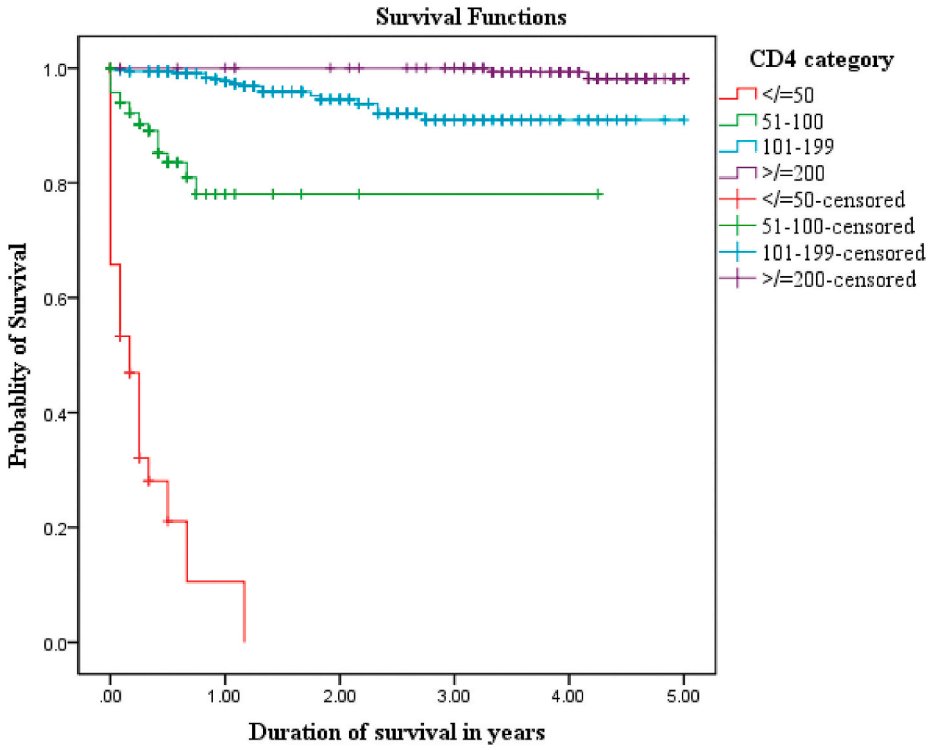

Fig. 4. The Kaplan–Meier survival curves compare survival time of patients starting ART by baseline CD4 Count in Dubti General Hospital, Afar, Ethiopia from December 31, 2010 to December 31, 2015 (Log rank test $p < 0.0001$).

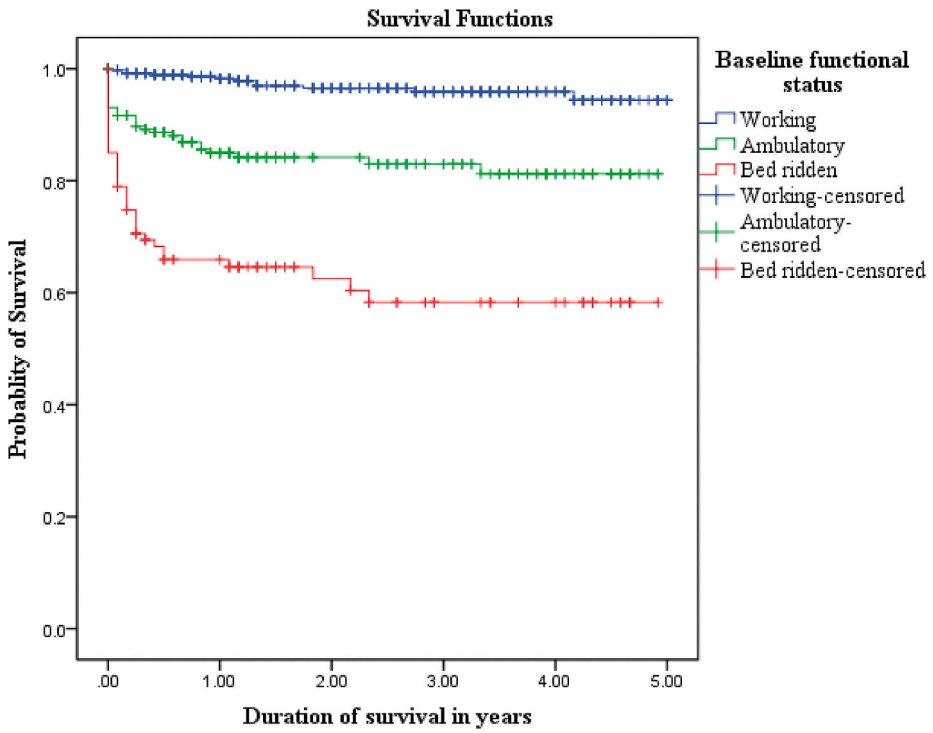

Fig. 5. The Kaplan–Meier survival curves compare survival time of patients starting ART by baseline functional status in Dubti General Hospital, Afar, Ethiopia from December 31, 2010 to December 31, 2015 (Log rank test $p < 0.0001$).

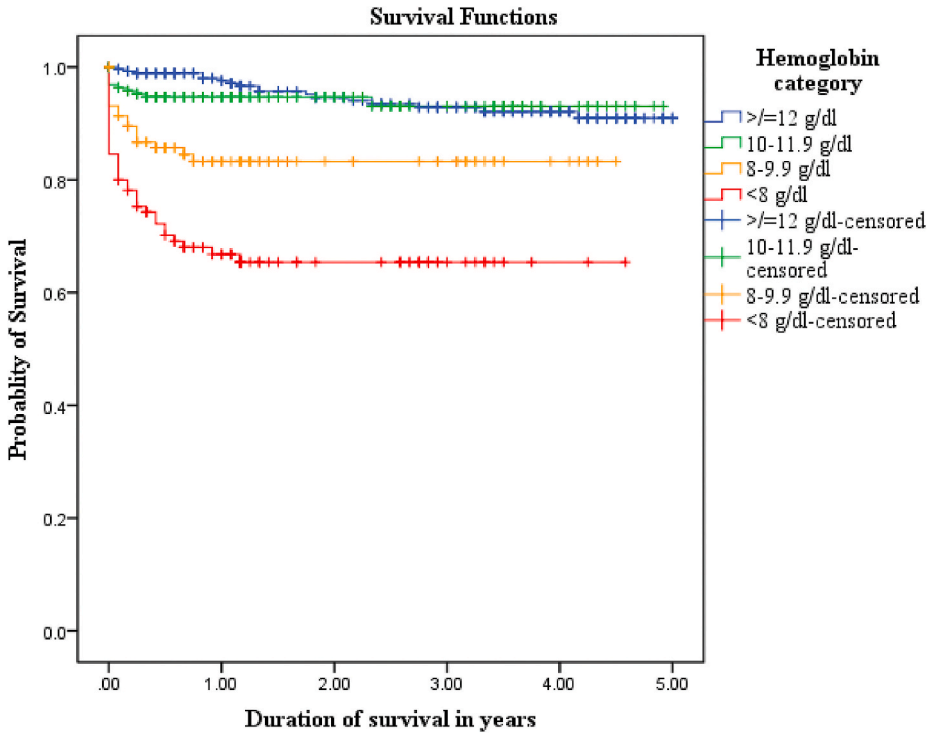

Fig. 6. The Kaplan–Meier survival curves compare survival time of patients starting ART by baseline hemoglobin in Dubti General Hospital, Afar, Ethiopia from December 31, 2010 to December 31, 2015 (Log rank test $p < 0.0001$).

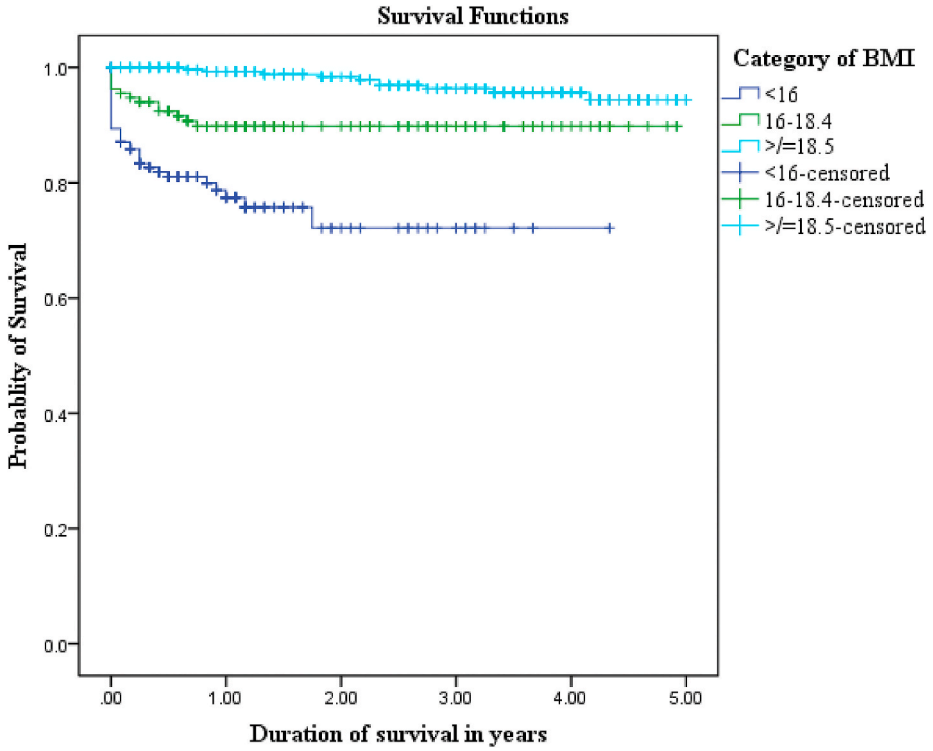

Fig. 7. The Kaplan–Meier Survival curves compare survival time of patients starting ART by baseline body mass index in Dubti General Hospital, Afar, Ethiopia from December 31, 2010 to December 31, 2015 (Log rank test $p < 0.0001$).

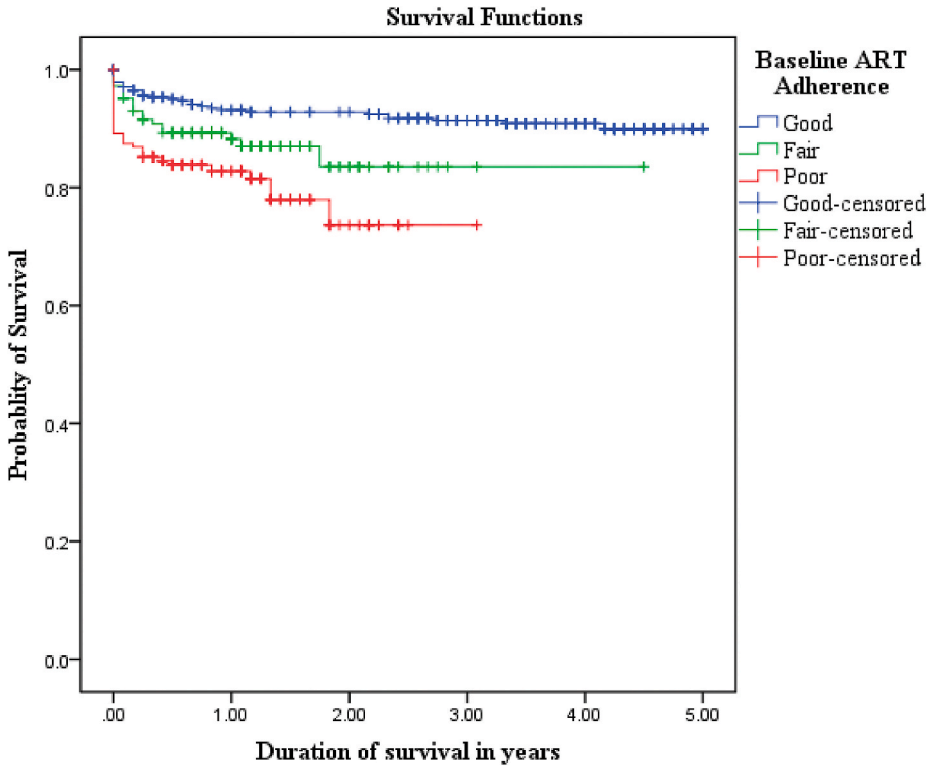

Fig. 8. The Kaplan–Meier survival curves compare survival time of patients starting ART by baseline ART adherence in Dubti General Hospital, Afar, Ethiopia from December 31, 2010 to December 31, 2015 (Log rank test $p < 0.0001$).

3.5. Predictors of mortality

In the bivariable Cox Proportional Hazard regression model, sex, marital status, educational level, employment status, residence, WHO clinical stage, functional status, hemoglobin level, CD4 count, body mass index, cotrimoxazole prophylactic therapy, isoniazid preventive therapy, tobacco smoke, substance use, opportunistic infections, ART regimen, Tuberculosis treatment, and ART adherence were associated with survival status ($P < 0.25$). Using the multivariate Cox proportional hazard adjusted model, significant predictors of mortality in ALHIV on ART were never married status (AHR = 3.71; 95%CI: 1.97–6.99) compared to married status, having no formal education (AHR = 2.33, 95% CI: 1.33–4.38) compared to having at least college education, bedridden functional status (AHR = 5.91; 95% CI: 2.71–12.88) compared to working functional status, advanced WHO stage III & IV (AHR = 8; 95%CI: 3.6–80.5, AHR = 30.4; 95%CI: 6.5–221.3, respectively) compared to WHO stage I, BMI<16.0 kg/m^2 (AHR = 11.52; 95% CI: 5.52–24.06) & BMI 16–18.4 kg/m^2 (AHR = 3.69, 95% CI: 1.61–8.46) compared to having BMI of at least 18.5 kg/m^2, CD4 count ≤50 cells/mm^3 (AHR = 6.62, 95% CI: 4.73–8.52) compared to having CD4 count of at least 200 cells/mm^3, hemoglobin <8 g/dl (AHR = 5.21; 95% CI: 2.64–10.26) compared to having hemoglobin level of at least 12 g/dl, stavudine based regimen (AHR = 2.34, 95% CI: 1.32–4.13), & zidovudine based regimen (AHR = 2.49, 95% CI: 1.41–4.39) compared to tenofovir based regimen, and not taking CPT (AHR = 2.78, 95% CI:1.61–4.73) (Table 4). The analysis using only baseline values yielded similar results.

4. Discussion

Knowing the magnitude of survival and predictor of mortality is crucial to take corrective measures in routine clinical services, and health policy makers. Therefore, the present retrospective cohort study aimed to determine survival status, and predictors of mortality among HIV/AIDS patients initiating antiretroviral therapy. From a total of 702 study participants, 620 were censored, and 82 died by 5 years follow up. In this cohort, a cumulative incidence of death was 11.7% up to 5 years. This finding is similar with the result of the studies done at the Armed Forces General Teaching Hospital in Addis Ababa, which found 11.7% [5], in the Somali Region, which reported 11.1% [10], at Jinka Hospital, South Omo, that showed 10% [12], at Debre Berhan Referral Hospital, which reported 12.1% [20] and in Burkina Faso which found 12.3% [29]. However, the finding of the present study was higher than findings of other studies conducted in Northwest Ethiopia (4.2%) [17] and Southern Ethiopia (7.5%) [18]. On the other hand, the result of the present study was lower than the findings of some studies in ART center of Maharaja Krishna Chandra Gajapati (MKCG) *Medical College,* Berhampur, Ganjam, and Odisha (21.33%) [30], Nigeria (31.9%) [31], Debre Markos Referral Hospital (39.4%) [7] and Attat Referral Hospital (29.7%) [19].

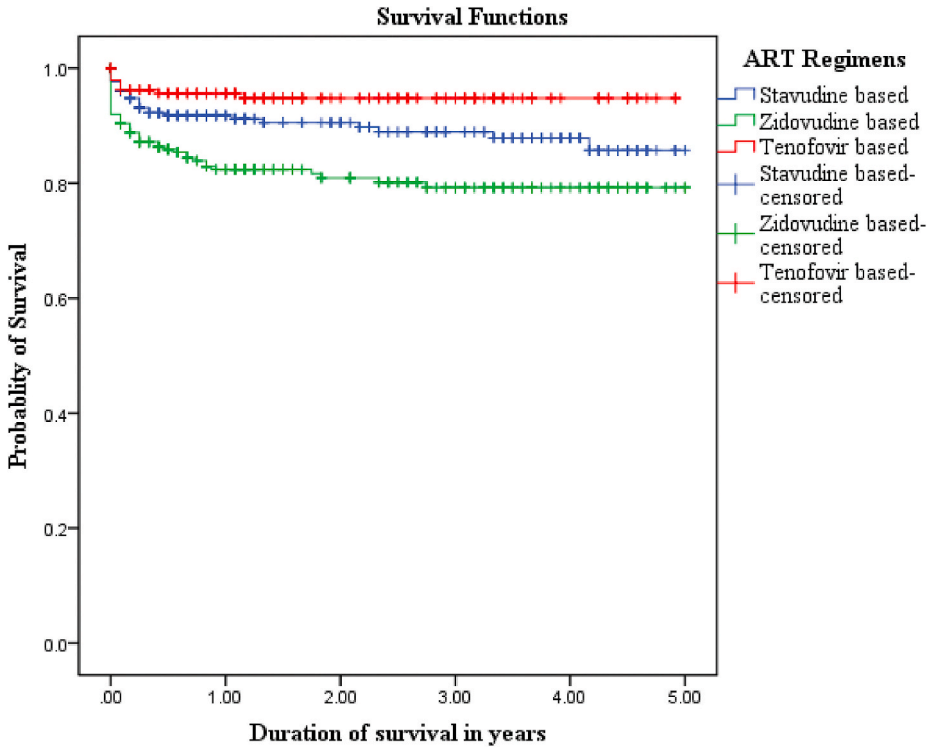

Fig. 9. The Kaplan–Meier survival curves compare survival time of patients starting ART by baseline ART regimen in Dubti General Hospital, Afar, Ethiopia from December 31, 2010 to December 31, 2015 (Log rank test $p < 0.001$).

The overall mortality rate of patients on ART in the current study was 5.81 per 100 person-years during 5 years of follow up. This result is similar with the findings of the studies done in Ethiopia at Dilla University Hospital, and seven university teaching hospitals, and in Burkina Faso [29], where the incidence rates per person-year were 3.4,5.4 and 6, respectively [13,14]. However, the result of the current study is higher than the findings of the studies at Jinka Hospital, South Omo Zone, Ethiopia [12], Botswana [32], and Aksum Hospital, Northern Ethiopia [9], to which the mortality rates were reported as 1.75, 2.71 and 3.2 per 100 person-years, respectively. Overall mortality rate in our study was lower than the finding (22.9 per 100 person-years) of the study at Debre Markos Referral Hospital, North West, Ethiopia [7]. The disagreement of findings among studies might be explained by the differences in the time duration each cohort contributed, sociodemographic and clinical features of the population studied.

In the current study, patients with baseline WHO clinical stage III and IV were 8.0 and 30.4 times more likely to die compared to patients with WHO clinical stage I, respectively. This finding is supported by previous studies [20,33]. This might be explained by late initiation of ART which result in worse health condition, and more deaths. Initiation of ART as soon as confirmation of HIV diagnosis and prior to the disease advancement helps reduce morbidity, and mortality of patients with HIV/AIDS.

Patients with CD4 count of less than and equal to 50, 51–100, and 101–199 cells/mm^3 were more likely to die compared to patients with CD4 count of 200 cells/mm^3 (6.62, 4.5, and 1.88 times respectively). This finding is supported by a study done in Aksum Hospital where patients with a CD4 count of less than and equal to 50 cells/mm^3 2 times more likely to die compared to patients who had a CD4 count of greater than 200 cells/mm^3 [9]. Patients with lower CD4 count have more compromised immunity, and risk of developing various opportunistic infections that result in deaths.

In the present study, patients who never married, had no formal education, and had only primary education were more likely to die compared to other marital status, and educational status, respectively. This finding is supported by previous studies [9,34]. This might be explained by the reason that never married patients may have more sexual contact with multiple sexual partners who may cause advancement of disease, and death. In addition, patients who had no, and lower education level may not understand the importance of ART, and may have poor ART adherence that lead to disease advancement as well as death.

The current study showed that patients with baseline functional status of bed ridden and ambulatory were 5.91, and 2.35 times more likely to die compared to working functional status. This finding is supported by studies done in Jinka Hospital (4.67, and 2.97 more likely to die) and Attat Referral Hospital (3.93, and 1.79 times more likely to die) where patients with bed ridden, and ambulatory functional status had more risk to die compared to patients with working functional status [12,19].

Having BMI of less than 16, and 16–18.4 kg/m^2 were 11.5, and 3.69 times more likely to die compared to patients having at least normal BMI in the present study. Similarly, studies at Kharamara Hospital, and South Africa showed that patients having lower BMI had 2.2–2.9 times higher risk of dying than those with a higher BMI [10,35]. In addition, increased BMI was found to be associated with increased CD4 counts, and improved survival [36,37].

Table 4
Multivariate Cox-proportional hazard regression model of predictors of mortality among ALHIV initiated on ART from 2010 to 2015 at Dubti General Hospital, Afar, Ethiopia (n = 702).

Variables	Category	Total (%)	Died (%)	Bivariate	Multivariate	
				CHR (95% CI)	AHR (95% CI)	P-Value
Marital status	Married	291 (41.5)	25 (8.6)	1	1	
	Never married	104 (14.8)	23 (22.1)	4.82 (2.41–9.62)*	3.71 (1.97–6.99)	0.0001
	Divorced	228 (32.5)	25 (11)	1.39 (.78–2.47)	1.39 (.781–2.52)	0.26
	Widowed	79 (11.3)	9 (11.4)	1.07 (.49–2.31)	0.82 (.369–1.82)	0.63
Educational level	College/Above	56 (8)	1 (1.8)	1	1	
	Secondary	189 (26.9)	9 (4.8)	0.99 (.541–9.59)	1.56 (.580–3.61)	0.15
	Primary	198 (28.2)	26 (13.1)	2.07 (1.08–10.50)*	2.26 (1.23–4.31)	0.025
	No formal edu.	259 (36.9)	46 (17.8)	2.41 (1.54–10.81)*	2.33 (1.33–4.38)	0.019
Functional status	Working	385 (54.8)	10 (2.6)	1	1	
	Ambulatory	217 (30.9)	34 (15.7)	1.90 (1.26–2.71)*	2.35 (1.10–5.11)	0.001
	Bed ridden	100 (14.2)	38 (38)	2.88 (2.25–3.7)*	5.91 (2.71–12.88)	0.001
CD4 count (cells/mm^3)	≥200	171 (24.4)	2 (1.2)	1	1	
	101–199	340 (48.4)	14 (4.1)	2.06 (.540–3.59)*	1.88 (.189–3.57	0.03
	51–100	118 (16.8)	20 (16.9)	4.56 (2.97–6.15)*	4.50 (2.67–6.34)	0.0001
	≤50	73 (10.4)	46 (63)	6.83 (5.22–8.43)*	6.62 (4.73–8.52)	0.0001
WHO clinical staging	Stage I	225 (32.1)	5 (2.2)	1	1	1
	Stage II	126 (17.9)	6 (4.8)	7.14 (0.86–59.3)*	5.3 (2.6–40.7)	0.07
	Stage III	231 (32.9)	31 (13.4)	16.5 (2.26–120.4)*	8.0 (3.6–80.5)	0.0001
	Stage IV	120 (17.1)	40 (33.3)	60.54 (8.33–446.3)*	30.4 (6.5–221.3)	0.006
BMI (kg/m^2)	18.5–24.9	344 (49.0)	16 (4.7)	1	1	
	16–18.4	156 (22.2)	19 (12.2)	2.87 (1.45–5.68)*	3.69 (1.6–8.46)	0.002
	<16	202 (28.8)	47 (23.3)	7.40 (4.04–13.55)*	11.5 (5.5–24.06)	0.0001
Hemoglobin level (g/dl)	≥12	283 (40.3)	14 (4.9)	1	1	
	10–11.9	193 (27.5)	11 (5.6)	1.19 (0.56–2.56)	1.12 (.497–2.53)	0.781
	8–9.9	116 (16.5)	18 (15.5)	2.53 (1.18–5.4)*	2.18 (1.02–4.67)	0.04
	<8	110 (15.7)	39 (35.5)	5.54 (2.69–10.6)*	5.2 (2.64–10.26)	0.0001
ART Regimen	Tenofovir	215 (30.6)	25 (11.6)	1	1	
	Stavudine	268 (38.2)	29 (10.8)	2.68 (1.44–4.97)*	2.34 (1.32–4.13)	0.001
	Zidovudine	219 (31.2)	28 (12.8)	3.09 (1.66–5.77)*	2.49 (1.41–4.39)	0.0001
CPT	Received	569 (81.1)	58 (10.2)	1	1	
	Not received	133 (18.9)	24 (18.1)	1.8 (1.13–2.92)*	2.78 (1.61–4.73)	0.0001

Note: * stands for $p < 0.25$; Analysis based on two category of WHO) staging (WHO stage I & II versus stage III & IV) yielded significantly different result, including mean survival analysis. Abbreviations: ALHIV, Adults living with HIV; ART, Antiretroviral therapy, WHO, World Health Organization; BMI, Body mass index; CPT, Cotrimoxazole prophylaxis therapy.

Having baseline hemoglobin of less than 8, and 8–9.9 g/dl were 5.21, and 2.18 times more risky of dying compared to patients having baseline hemoglobin of at least 12 g/dl in the present study. This result is supported by the findings of other studies at Zewuditu Memorial Hospital, and Debre Berhan Referral Hospital [8,20]. This might be explained by the fact that anemia is the result of advanced disease, which in turn increases mortality.

The current study revealed that patients taking stavudine, or zidovudine based regimen have more risk of dying than patients taking tenofovir based regimen. A study in China revealed that zidovudine, and tenofovir based regimen had a lower risk of death compared to stavudine based regimen [38]. The discrepancy between the results of the studies might be due to the difference in duration of follow up, socio-demographic, and clinical characteristics of participants.

Regarding to cotrimoxazole prophylaxis therapy use, patients not taking cotrimoxazole prophylaxis therapy were 2.78 times more likely to die compared to patients taking cotrimoxazole prophylaxis therapy in the current study, which is supported by other studies [39,40]. This may be the fact that reduction of opportunistic infections by using cotrimoxazole prophylaxis therapy result in reduction of morbidity, and mortality. As far as we know, this is the first study which assessed mortality and its predictors among ALHIV in Afar region. In addition, it is the first to report that patients taking stavudine or zidovudine based regimen had more risk of death compared to those taking tenofovir based regimen in Ethiopia.

5. Limitations of the study

Exclusion of patients with incomplete information during data collection might introduce selection bias. Mortality might be underestimated by the fact that lost to follow up, and drop out patients that might have died at home without being reported. Moreover, the fact that subgroups of some variables did not have the full follow-up time, these might affect results of the analysis.

6. Conclusion

In the present study, 82 (11.7%) patients were died over 5 years. The overall estimated mean survival time of the cohort was 4.34 years with an overall mortality incidence rate of 5.81 per 100 person-years. Survival distributions were significantly different by WHO

clinical stage, BMI, CD4 count, functional status, hemoglobin, and ART adherence level. Patients with baseline WHO clinical stage III and IV, BMI <18.5 kg/m^2, CD4 count <200 cells/mm^3, zidovudine based regimen, functional status of bed ridden, and ambulatory, and hemoglobin <10 g/dl should be given close follow up, and monitoring as they were significant predictors of mortality. In addition, the use of contrimoxazole prophylaxis therapy should be encouraged with optimized drug adherence. More predictors of mortality need to be identified in prospective cohort study design.

Ethical approval and consent to participate

Ethical clearance was obtained from Ethical Review Board of College of Medical and Health sciences, Samara University (ERC 0062/2018). This study was done by applying the principles of Declaration of Helsinki. Data regarding personal information were coded and kept confidential.

Data sharing statement

All relevant data are included in the manuscript.

Funding

The author received no specific funding for this work.

Disclosure

The authors have no any competing interests.

Acknowledgments

The authors are glad to thank, College of Medical and Health Sciences, Samara University, and Dubti General Hospital for their support to complete this study. The authors are also extending their great thanks to the data collectors.

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