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Predictors of mortality among HIV positive adults on highly active antiretroviral therapy in Attat primary hospital, Southern Ethiopia: A retrospective cohort study

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Abstract

Background: Over the last decade, Ethiopia has made significant progress in combating the HIV epidemic. Even though there have been improvements in service delivery and utilization since the introduction of Antiretroviral Treatment services in Ethiopia, mortality among Human Immunodeficiency Virus (HIV) infected patients on Highly Active Antiretroviral Treatment (HAART) remains high, with mortality rates varying from place to place. Therefore, this study intends to explore the predictors of mortality among adult HIV-positive patients on active anti-retroviral therapy in Attat primary hospital. **Methods:** Retrospective cohort study was conducted from May 15 to June 15, 2021. Records of 422 HIV-positive adults, who had been taking antiretroviral treatment between January 2016 to January 2021, were included in the study. The data were collected and entered by an Open Data Kit (ODK) and exported to STATA version 14.1 for analysis. Kaplan-Meier and a log-rank test were used to compare survival probability. Cox proportional hazards regression was used to predict the risk of death. **Results:** Of the total of 422 participants 239(56.6%) were female. The median age was 34.5 years with an interquartile range of 26 to 40.25 years. The median follow-up time was 33 months with an IQR of 18 to 48 months. The overall mortality rate was 4.71/100 person-years at risk. Bedridden functional status (AHR: 2.658; 95% CI: 1.177-6.328), hemoglobin level <10 g/dl (AHR: 3.525; 95% CI: 1.387-8.954), clinical-stage IV (AHR: 3.294; 95% CI: 1.290-8.411) and active TB during treatment (AHR: 3.108; 95% CI: 1.478-6.534) were the main factors associated with mortality. **Conclusion:** Bedridden, functional status, low hemoglobin level, advanced clinical stage, and Tuberculosis co-infection were significant predictors of mortality for patients under ART. The mortality rate needs to be reduced by emphasizing individuals with advanced clinical stage, anemia, bedridden functional status, and Tuberculosis co-infection.

Keywords: *HIV, ART, Mortality, Ethiopia*

1. Introduction

Acquired Immune Deficiency Syndrome (AIDS), caused by the Human Immunodeficiency Virus (HIV) continues

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to impact millions of people around the world (UNAIDS, 2000). Globally, an estimated 38 million persons (31.6 million-44.5 million) were living with HIV in 2019. In the same year, 1.7 million people (1.2 million-2.2 million) became HIV-positive for the first time. Since the beginning of the epidemic, 32.7 million people have died from AIDS-related illnesses. AIDS-related diseases claimed the lives of 690,000 people worldwide in 2019 (UNAIDS, 2019). The vast majority of HIV-positive people live in low- and middle-income countries, with 25.5 million in Sub-Saharan Africa alone (UNAIDS, 2017). In the era before Antiretroviral Therapy (ART), survival trends after HIV infection in African populations formed a clear demarcation for gauging future treatment program effectiveness (Isingo *et al.*, 2007).

ART is a substantial public health success story that has improved HIV-infected people's survival rates. The global scale-up of ART is attributed to a decrease in AIDS-related deaths (Astuti and Maggiolo, 2014). Since 2010, the number of people receiving care in the world's most affected countries, Eastern and Southern Africa, has more than doubled, reaching nearly 15 million people. Since then, AIDS-related deaths in the area have decreased by 36%. Antiretroviral medication was available to 26 million HIV-positive patients worldwide at the end of June 2019 (UNAIDS, 2019). Antiretroviral therapy can help prevent people living with HIV from dying from AIDS and from developing tuberculosis, becoming ill and transmitting tuberculosis and HIV. Emerging science indicates that people should start HIV treatment earlier to realize these benefits (Case *et al.*, 2019).

The first evidence of an HIV infection was detected in Ethiopia in 1984. Since then, AIDS has killed millions of people and left hundreds of thousands of orphans. Ethiopia's government, on the other hand, took several steps to stop the disease from spreading further and to enhance HIV care, treatment, and support for those living with HIV (FMOH, 2017). ART was introduced in Ethiopia in 2003, and it was made free in 2005. Ethiopia has made great progress in tackling the HIV / AIDS epidemic during the previous decade. Ethiopia is on the verge of taming the HIV epidemic, according to recent reports (Ethiopia Update Sheet on HIV / AIDS, 2015). However, the incidence remains very high in urban areas, where estimates show a prevalence rate of 3%, compared to less than 1% nationally. Only 426,000 Ethiopians are now on ART out of an estimated 669,236 people living with HIV who require treatment (Ethiopia Update Sheet on HIV / AIDS, 2015; FMOH, 2017; EPHI, 2017).

Despite the fact that current HIV / AIDS monitoring estimates reveal some positive signals that the epidemic is stabilizing, the observed improvements fall short of the epidemic response's projected targets. Several factors, including economic, demographic, behavioral risk, and health factors, are thought to influence the survival of AIDS patients treated with ART in resource-poor countries like Ethiopia (FMOH, 2017). Studies conducted in developed and low and middle-income countries indicates age, sex, educational level, marital status, religion, active TB during ART, weight, World Health Organization (WHO) clinical stage, CD4 count, ART regimen, drug allergy, ART regimen update, and functional status all affect the survival of HIV-infected patients on ART were significantly affect the survival status of PLWHA (Ferradini *et al.*, 2006; Johannessen *et al.*, 2008; Assefa *et al.*, 2011).

Even though, there have been improvements in service delivery and utilization, since the introduction of ART services. Mortality rates and their determinants among HIV patients on ART in different studies across the globe demonstrate differences in important determinants. There are also regional variations of clinical benefits of ART for AIDS patients in terms of mortality reduction and improved quality of life. A systematic research report done before a test and treat strategy had been begun showed mortality rate variation from place to place ranging from 1.75 to 10.74 deaths per 100 person-years (Tachbele and Amenim 2016; Abebe *et al.*, 2014). To illustrate the context in Ethiopia for instance, the mortality rate at the University of Gondar Hospital, in North-western Ethiopia was 3.4 per 100 person per year (Wubshet *et al.*, 2012), whereas 9.1 per 100 person per year at Arbaminch Hospital in Southern Ethiopia (Mulissa *et al.*, 2010).

To identify this variation it is necessary to identify significant determinants of mortality in HIV-infected patients to target those who are at a higher risk of death. In addition, there is a paucity of information on the recent rate of death and its determinants since the universal test and treat strategy was implemented in 2016 (World Health Organization, 2015). Therefore, this study intends to estimate the mortality rate and identify predictors of HIV-infected adults on ART at Attat primary hospital Gurage zone, Southern Ethiopia. Furthermore, the findings of this study can contribute to the existing knowledge on the predictors of mortality

of HIV-infected patients on ART and may provide information for program evaluators and policymakers about the current mortality rate and its predictors. The study also included variables that haven't been tested in other studies.

2. Methods and materials

2.1. Study design, area, and period

A retrospective cohort study was conducted at Attat Primary Hospital Gurage Zone**,** Southern Nations, Nationalities and People Region (SNNPR). It is one of the early established non-governmental hospitals during the Derge era (1969), and is located 187 km Southwest of Addis Ababa along the Jimma road in the Southern region of Ethiopia. The hospital renders comprehensive HIV/AIDS-related services including Voluntary Counseling Test (VCT), Provider-Initiated Counseling and Testing (PICT), Prevention of Mother-to-Child Transmission, and ART program. There were 3215 clients enrolled in the hospital since it started ART service. Currently, there were about 428 HIV/AIDS adult patients attending HAART in the hospital. The study was employed from May 15 to June 15, 2021

2.2. Study population and sampling

All HIV-positive adults ever enrolled in antiretroviral treatment at Attat Primary Hospital were the source population. All HIV-positive adults enrolled in antiretroviral treatment at Attat primary hospital from January 2016 to January 2021 were examined in this study.

All HIV-positive adults who had been registered and initiate antiretroviral treatment in the hospital with at least one follow-up visit and whose age was above 14 years were included in this study. HIV-infected adults with missed baseline characteristics (patients without date of ART initiation) and date of occurrence of events (i.e., death, loss to follow up, and transferred out) were excluded from the study.

2.3. Data collection tool and procedure

A data collection tool was prepared by reviewing relevant literature and ART registration books and patient follow-up charts. Data were collected from the ART clinic registration book and electronic database and patient clinical chart by using (ODK). The ODK cloud or server was prepared critically and pre-tested before the actual data collection was started.

Data were collected on both the outcome and independent variables. The outcome variable was the time gap, in a month, between the beginning of ART treatment and the date of death or censoring. The independent variables consist of demographic characteristics (age, sex, educational level, marital status, occupation, residence), Clinical characteristics (active Tuberculosis (TB), baseline weight, baseline Body Mass Index (BMI), baseline WHO clinical stage, baseline CD4 count, functional status, baseline Haemoglobin (Hgb) and Co-trimoxazole prophylaxis's, Opportunistic Infections (OIs), Isoniazid (INH) prophylaxis's, treatment adherence, and History of drug side effect) and behavioral factors (substance abuses, chat, smoking, and alcohol drinking).

A pre-test was conducted in Gunchiera primary hospital to clear any ambiguity on the tool. Intensive orientation was given to data collectors about, the purpose of the study, ethical aspects, and the Open Data Kit (ODK) application. The principal investigators and supervisors made day-to-day on-site supervision during the whole period of data collection. Completeness of the information on all variables as recorded in the registers and legibility of each filled data collection tool was audited at the end of each day to ensure accuracy. To keep confidentiality, the data was collected with the principal investigator's personal tablet computer, and the data were sent to the server after being checked by the principal investigator and supervisor daily and nobody knew the server password other than the principal investigator. Two data collectors who have health background working in the hospital ART clinics and one health informatics who working on the ART database and one public health master was recruited as supervisors respectively.

2.4. Operational definitions

Event: Time to the occurrence of mortality, which was recorded as the death of the patient in the follow-up chart.

Adult: Age greater than 14 years and People Living with HIV (PLHIV) who started ART between the study periods.

Censored: A patient does not develop event (transferred out, alive and lost to follow up).

Functional status: This is defined based on the national ART guideline as; working (able to perform ordinary work inside or outside the home), ambulatory (capable of performing daily routine activities), and bedridden (unable to perform daily living activities) (FMOH, 2018).

Adherence: This means adherence to ART drugs and is estimated using three levels; good when patient adherence level is as high as 95% (of 30 doses missed as low as 2 doses), fair when patient adherence level is 85-94% (of 30 doses missed as low as 3-4 doses), and poor when patient adherence level is as low as 84% (of 30 doses missed as low as 6 doses) (FMOH, 2018).

Incomplete card: When one of the independent variables is not registered namely, CD4+ cells, WHO stage, functional status and TB status, date of ART start.

Death: Death was recorded for those who died from all causes related to HIV / AIDS during the study period while on ART.

Loss to follow-up: Patients missing their follow-up visits for more than 3 months, and the date of the last registered follow-up visit were recorded as the date of loss to follow-up.

Transferred out: ART using HIV-infected patients, who were transferred to another ART facility.

Alive: HIV-infected patients who were still alive and using the treatment on June15, 2021 were assessed.

Time: Is the time gap, in a month, between the beginning of ART treatment and the date of last observation.

2.5. Data processing and analysis

The electronic data collection software (ODK Collect) was synchronized with Google Drive (server) and, data was uploaded directly to Google Sheets at the time of data collection. After the data collection was accomplished, the data is downloaded from Google Drive in excel format and exported to SPSS version 20 and STATA version 14.1 for analysis. Descriptive statics such as percent and median and interquartile range (IQR) were used to summarize the characteristics of the cohort. Kaplan-Meier (KM) model was used to estimate survival probability after ART initiation. A log-rank test was used to compare survival curves among the categories of each variable. Person-years of follow-up in a month were calculated by assessing the date of enrolment for ART and death or censoring. The Cox-proportional hazard model was used to assess the relationship between the independent variables and mortality where the Hazard Ratio (HR) indicates the strength of the relationship.

The bivariate Cox-regression analysis was used to estimate the unadjusted Hazard Ratios (HRs), and variables with a p-value < 0.25 were considered as candidate variables for multivariate Cox-regression analysis. Multivariable Cox-regression was performed to estimate adjusted hazard ratios with 95% CI and a p-value of less than 0.05 was considered statically significant. Proportional Hazard Assumption (PHA) was assessed using a global test (Schoenfeld residuals) and graphically and thus, a post estimation test was conducted to check the assumption of proportionality after fitting the multivariable Cox regression model. The covariates were not violated the proportional hazard assumption (p-value >0.05).

3. Results

3.1. Socio-demographic characteristics of the participants

During the follow-up period, of 438 people registered, 422 patients' charts were eligible for analysis. The remaining 16 records were excluded due to incomplete information (missing data). Of the total 422 records analyzed, 56(13.3%) were lost to follow-up, 19(4.5%) were transferred out to other ART centers, and 293(69.4%) were alive at the end of the study

Regarding the socio-demographic characteristics of the respondents, more than half of the participants 239(56.6%) were females. The median age was 34.5 years with an Interquartile Range (IQR) of 26 to 40.25 years. More than half 244(57.8%) were married. Concerning educational status, 175(41.5%) attended primary (grade

1 up to 8) school and 82(19.4%) secondary (9-12) school. More than half of the participants 237(56.2%) were from rural areas (Table 1).

Table 1: Socio-demographic characteristics of HIV-positive adults in Attat Primary Hospital, Gurage Zone, Southern Ethiopia, 2021

Variables	Died No (%)	Censored No (%)	Total No (422)
Sex			
Male	32(17.5%)	151(82.5%)	183(43.4 %)
Female	22(9.2%)	217(90.8%)	239(56.6%)
Age (years)			
15-24	6(9.5%)	57(90.5%)	63(14.9%)
25-34	17(11.5%)	131(88.5%	148(35.1%)
35-44	16(12.2%)	115(87.8%)	131(31.0%)
≥45	15(18.8%)	65(81.2%)	80(19.0%)
Residence			
Urban	19(10.3%)	166(89.7%)	185(43.8%)
Rural	35(14.8%)	202(85.2%)	237(56.2%)
Educational level			
No formal education	30(19.6%)	123(80.4%)	153(36.3%)
Primary education	15(8.6%)	160(91.4%)	175(41.5%)
Secondary education	8(9.8%)	74(90.2%)	82(19.4%)
Above secondary	1(8.3%)	11(91.7%)	12(2.8%)
Marital status			
Single	15(19.7%)	61(80.3%)	76(18.1%)
Married	25(10.2%)	219(89.8%)	244(57.8%)
Divorced	4(6.9%)	54(93.1%)	58(13.7%)
Widow / widower	10(22.7%)	34(77.3%)	44(10.4%)
Occupation			
Merchant	15(16.7%)	75(83.3%)	90(21.3%)
NGO employee	2(33.3%)	4(66.7%)	6(1.4%)
Gov't employee	3(8.3%)	33(91.7%)	36(8.6%)
Jobless	22(22%)	78(78.0%)	100(23.7%)
Daily laborer	1(1.9%)	51(98.1%)	52(12.3%)
Farmer	10(11.9%)	74(88.1%)	84(19.9)
Housewife	1(1.9%)	53(98.9.1%)	54(12.8)

3.2. Clinical characteristics

The median BMI was 19.41 kg / m^2 with Interquartile Range (IQR) of 17.44 to 22.10 kg / m^2. The median baseline haemoglobin of the participants was 10 g / dl (IQR 8-11 g / dl). Of the participants, 40(9.5%) had active TB during the follow-up. The median weight at the baseline was 53 kg (45-60 kg). The baseline median CD4 count was 221.5 (cells / μl) (IQR = 106.50-377.25 cells / dl). Of the total participant, 163(38.6%) of them were at WHO

Table 2: Clinical characteristics of HIV-positive adult at Attat Primary Hospital, Gurage Zone, Southern Ethiopia, 2021

Variables	Died No (%)	Censored No (%)	Total (N = 422)
Active TB			
Yes	24(60%)	16(40%)	40(9.5%)
No	30(7.9%)	352(92.1%)	382(90.5%)
WHO clinical stages			
Stage I / II	16(5.8%)	258(94.2%)	274(64.9%)
Stage III	21(19.6%)	86(80.4%)	107(25.4%)
Stage IV	17(41.5%)	24(58.5%)	41(9.7%)
Base line CD4+ (cells/μl)			
<50	8(19.5%)	33(80.5%)	41(9.7%)
50-199	25(17.0%)	122(83.0%)	147(34.8%)
≥200	21(9.0%)	213(91.0%)	234(55.5%)
Substance use			
Yes	9(15.8%)	48(84.2%)	57(13.5%)
No	45(12.3%)	320(87.7%)	365(86.5%)
Body mass index (kg/m²)			
<18.5	26(16.3%)	134(83.7%)	160(37.9%)
≥18.5	28(10.7%)	234(89.3%)	262(62.1%)
OI			
Yes	27(17.3%)	129(82.7%)	156(37%)
No	27(10.2%)	239(89.8%)	266(63%)
Adherence			
Good	39(11.6%)	296(88.4%)	335(79.4%)
Fair	5(15.6%)	27(84.4%)	32(7.6%)
Poor	10(18.2%)	45(81.8%)	55(13.0 %)
Drug side effect			
Yes	8(12.3%)	57(87.7%)	65(15.4%)
No	46(12.9%)	311(87.1%)	357(84.6%)

clinical stage I and 41(9.7%) at WHO clinical stage IV. Concerning functional status, more than half 228(54%) of the participants were in working functional status, and 138(32.7%) were ambulatory during ART initiation. Concerning Co-trimoxazole therapy (91.7%) of the participant was given Co-trimoxazole therapy and 95.5% of participants took INH prophylaxis (Table 2).

3.3. Mortality rate

There was 54 (12.8%; 95% CI: (9.7-16)) death during the follow-up period of whom 18(33.3%) died within 12 months after the start of treatment. The median survival duration was 33 with an IQR of 18 to 48 months. Kaplan-Meier survival estimation showed that the overall estimated survival duration after ART initiation was 57.494 (95% CI: 55.648-59.339) months. The study participants contributed 1146.41 person-years of observation. Over the study period, the total mortality rate was 4.71 per 100 person-years at risk (Figure 1).

3.4. Kaplan–Meier survival curve and log-rank test (comparison of the survival probability)

Kaplan-Meier and log-rank test for different groups of patients showed that the difference in survival curves such as sex of participant, active TB, WHO clinical staging and baseline haemoglobin during treatment were variables that showed significant association in the Log-rank test (Figures 2-5).

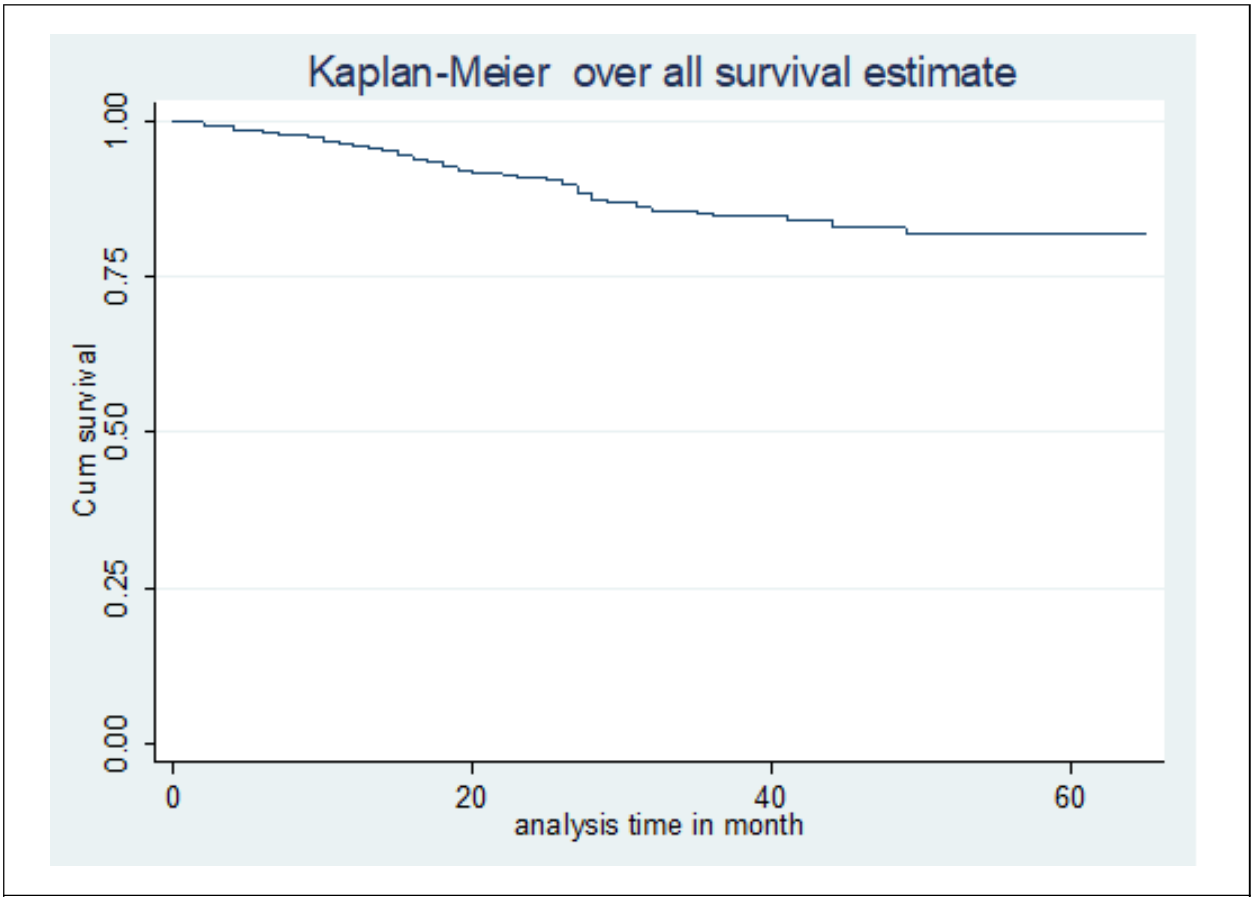

Figure 1: Kaplan-Meier analyses of overall survival status for patients on HAART at Attat Primary Hospital Gurage Zone Southern Ethiopia, January 2016 to January 2021

Kaplan-Meier analysis of survival status revealed that females show better survival than males; estimated survival was 59.586 months (95% CI: 57.448-61.725) vs. 53.246 months (95% CI: 50.236-56.257). From baseline clinical characteristics of patients, those in WHO clinical stage I survived better, 60.737 months (95% CI: 58.442-63.032) than those in WHO clinical stage IV (51.281 estimated months, 95% CI: 43.080-59.482). Patients with Hgb < 10 g / dl showed lesser survival (53.197 estimated months, 95% CI: 50.269-56.125) than those with higher Hgb $\geq$ 10 g / dl (62.642 estimated months, 95% CI: 60.908-63.620) and educational status, marital status**,** occupation**,** functional status, baseline CD4+ (cells / μl) and adherence shows significant difference in log-rank test p-value <0.05 (Table 4).

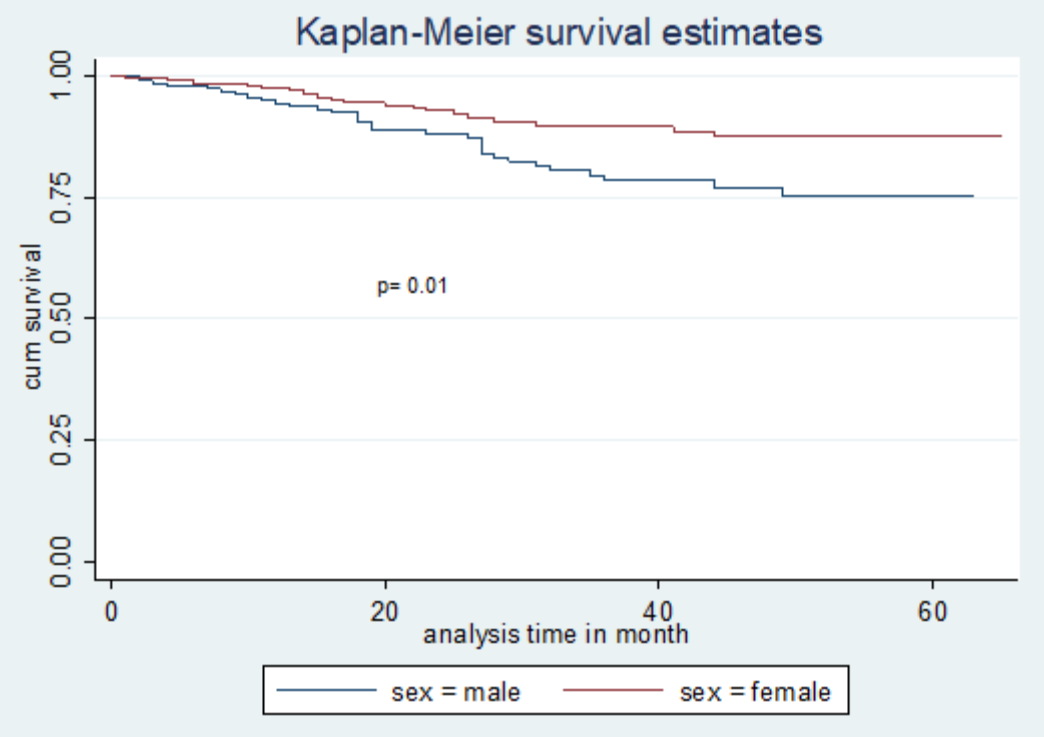

Figure 2: Kaplan-Meier analyses and log-rank test of patients on HAART by sex at Attat Primary Hospital, Gurage Zone, Southern Ethiopia, January 2016 to January 2021

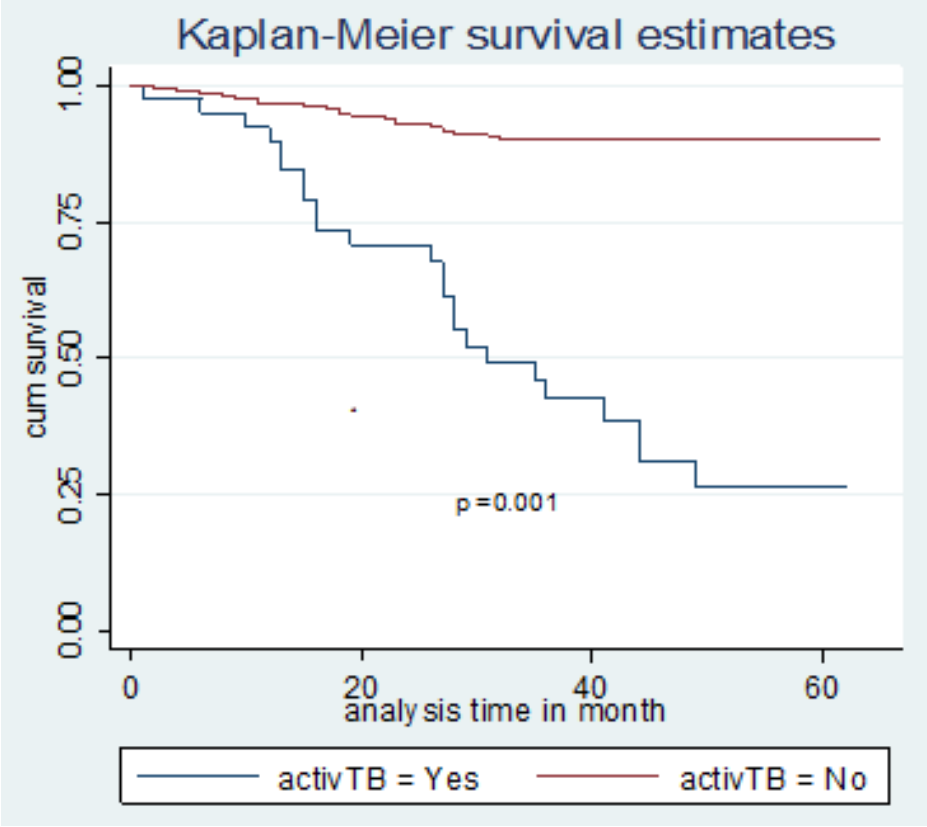

Figure 3: Kaplan-Meier analyses and log-rank test of patients on HAART by TB status at Attat Primary Hospital, Gurage Zone, Southern Ethiopia, January 2016 to January 2021

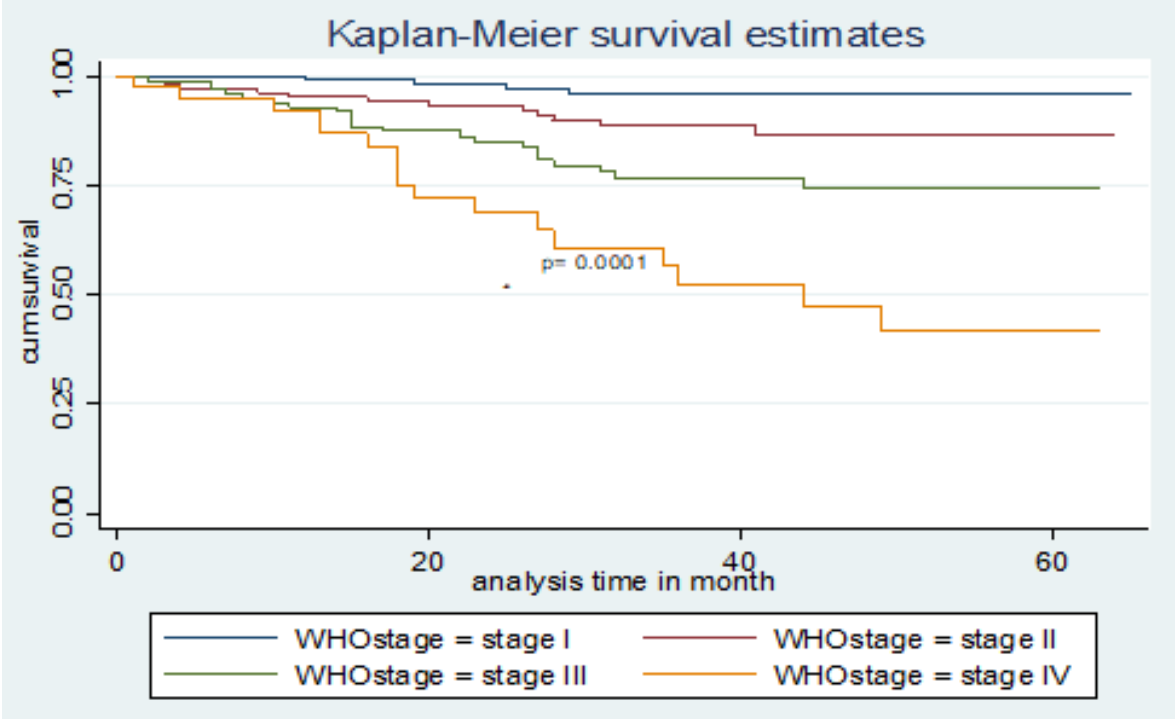

Figure 4: Kaplan-Meier analyses and log-rank test of patients on HAART by WHO clinical staging at Attat Primary Hospital, Gurage Zone, Southern Ethiopia, January 2016 to January 2021

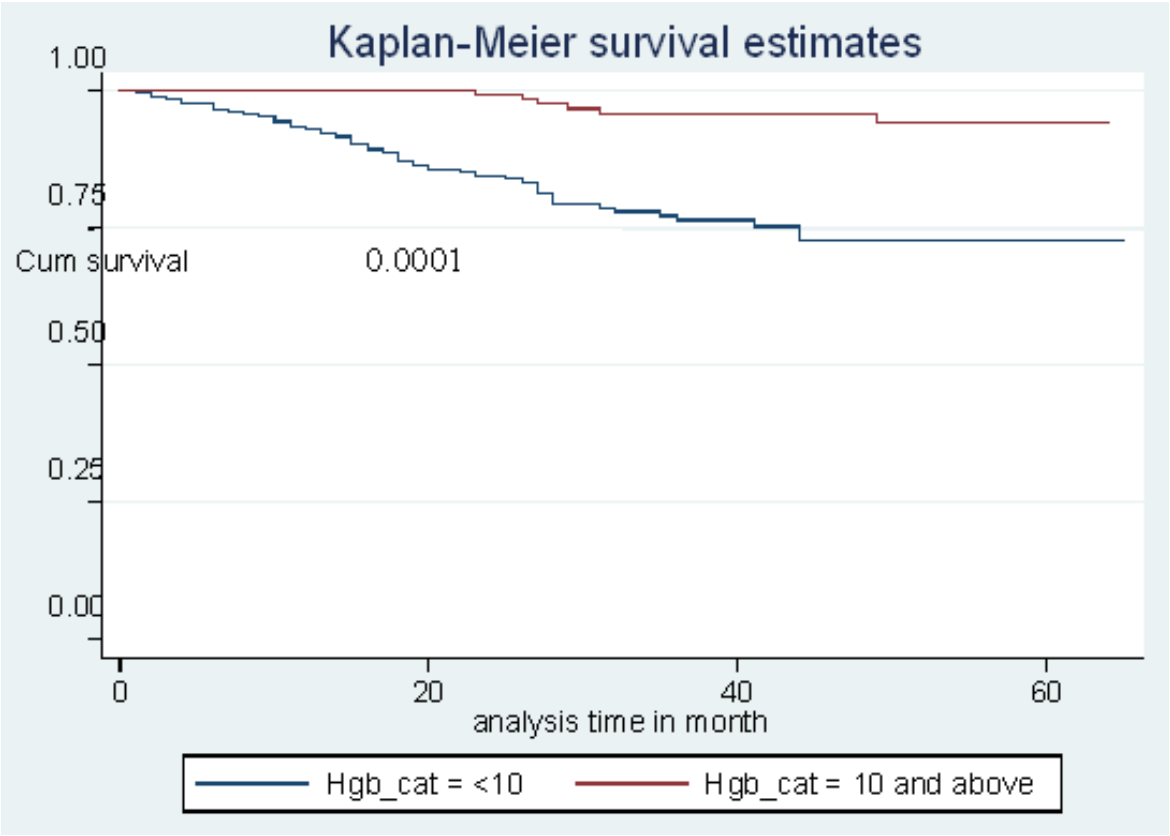

Figure 5: Kaplan-Meier Analyses and log-rank test of patients on HAART by baseline haemoglobin at Attat Primary Hospital, Gurage Zone, Southern Ethiopia, January 2016 to January 2021

Table 3: Kaplan-Meier Analyses and Log-rank test of HIV positive adult in Attat Primary Hospital, Gurage Zone, Southern Ethiopia, January 2016 to January 2021

Variables	Estimated survival in months	Confidence interval (CI 95%)	Log-rank test (P-value)
Age			0.16
15-24	59.02	54.54-63.49	
25-34	56.42	53.51-59.33	
35-44	57.22	54.14-60.30	
≥45	53.67	49.06-58.29	
Residence			0.12
Urban	58.58	56.02-61.14	
Rural	55.80	53.25-58.35	
Educational status			0.01
No formal education	53.04	49.57-56.51	
Primary education	59.76	57.27-62.26	
Secondary education	57.94	54.61-61.27	
Above Secondary	56.57	44.90-68.23	
Marital status			0.01
Single	51.41	46.07-56.74	
Married	57.38	55.13-5 9.62	
Divorced	59.18	54.40-63.96	
Widowed	56.80	52.04-61.57	
Occupation			0.003
Merchant	53.48	49.17-57.78	
NGO employee	47.00	33.22-60.77	
Govt. employee	58.89	53.37-64.41	
Daily laborer	56.51	56.88-60.98	
Farmer	58.93	52.75-60.26	
House wife	61.90	59.76-64.03	
Jobless	52.93	48.58-57.29	
Functional status			0.0001
Working	58.47	56.60-60.35	
Ambulatory	57.46	54.05-60.88	
Bedridden	43.40	36.66-50.14	
Base line CD4+ (cells/µl)			0.014
<50	51.45	44.39-58.51	

Table 3 (Cont.)			
Body mass index (kg/m²)			0.09
<18.5	53.98	50.87-57.09	
≥18.5	58.71	56.54-60.89	
Adherence			0.02
Good	58.58	58.78-62.16	
Fair	53.0634	39.11-59.81	
Poor	49.70	41.90-52.41	
Drug side effect			0.91
Yes	56.31	51.43-61.19	
No	57. 53	55.53-59.52	
Substance use			0.5
Yes	55.38	50.35-60 .41	
No	57.725	55.75-59.69	

3.5. Bi-variable and multivariable cox-proportional hazard model for predictors of mortality

Selected variables that were significantly associated in the bivariate analysis were further included in the multivariable analysis to see their relative effects. Variables comprising sex, age, active TB during treatment, functional status, WHO clinical stages, baseline CD4, baseline haemoglobin, BMI, Co-trimoxazole, adherence, occupation, marital status, educational status, residence, and OI were candidates for multivariate analysis at p-value (<0.25). In multivariable Proportional Hazards Cox Regression Analysis; functional status, baseline haemoglobin level, active TB during treatment, and advanced WHO stage IV were significant predictors of mortality.

The risk of death was about two and half times higher among patients with baseline bedridden functional status (AHR: 2.65; 95% CI: 1.11-6.32) as compared to patients with working functional status. The hazard of death was 3.5 times higher in HIV patients with baseline haemoglobin levels <10 g/dl (AHR: 3.52; 95% CI: 1.38-8.95) as compared to those patients with baseline haemoglobin levels ≥10 g/dl. Those clients with advanced WHO clinical staging stage IV had a high hazard of death as compared to stages I and II, (AHR:

Table 4: Predictors of mortality among HIV-positive adults at Attat Primary Hospital, Gurage Zone, Southern Ethiopia, January 2016 to January 2021

Variable	Died	Censored	CHR (95% CI)	AHR (95% CI)	p-value
Sex					
Male	32	151	1.99(1.16-3.43)	1.26(0.63-2.51)	0.57
Female	22	217	1		
Age					
15-24	6	57	1		
25-34	17	131	1.18(0.46-3.01)	1.92(0.53-6.91)	0.36
35-44	16	115	1.20(0.47-3.07)	1.53(0.38-6.15)	0.67
≥45	15	65	1.87(0.72-4.84)	2.29(0.52-8.0)	0.80

Table 4 (Cont.)					
Marital status					
Single	15	61	1		
Married	25	219	0.02(0.25-91)	0.71(0.27-1.82)	0.47
Divorced	4	54	0.05(0.11-1.03)	0.29(0.07-1.13)	0.07
Widowed	10	34	0.09(0.51-2.53)	0.84(0.31-2.28)	0.74
Educational status					
No education	30	123	1		
Primary	15	160	0.43(0.23-0.81)	0.65(0.28-1.49)	0.14
Secondary	8	74	0.45(0.20-0.98)	0.63(0.19-2.11)	0.28
Above secondary	1	11	0.48(0.06-3.58)	0.40(0.04-3.98)	0.72
Occupation					
Merchant	15	75	0.81(0.42-1.57)	1.93(0.77-4.84)	0.12
NGO$	2	4	1.35(0.31-5.75)	1.27(0.15-10.37)	0.95
Government	3	33	0.40(0.12-1.33)	0.61(0.13-2.95)	0.35
Daily laborer	22	78	0.09(0.01-0.66)	0.27(0.03-2.27)	0.18
Farmer	1	51	0.53(0.25-1.13)	0.96(0.34-2.71)	0.96
House wife	10	74	0.08(0.01-0.62)	0.34(0.04-2.94)	0.28
Jobless	1	53	1		
Residence					
Urban	19	166	0.65(0.37- 1.13)	0.97(0.46-2.05)	0.97
Rural	35	202	1		
BMI (kg/m^2)					
<18.5	26	134	1.57(0.92-2.68)	0.93(0.48-1.80)	1
≥18.5	28	234	1		
Active TB					
Yes	24	16	8.45(4.94-14.47)	3.10 (1.47-6.53)	0.003*
No	30	352	1		
Functional status					
Working	15	213	1		
Ambulatory	17	121	2.12(1.05-4.25)	1.22(0.55-2.77)	0.06
Bed ridden	22	34	7.21(0.73-13.25)	2.65(1.11-6.32)	0.02*
Opportunistic infection					
Yes	27	129	1.68(0.98-2.86)	0.94(0.50-1.76)	0.89
No	27	239	1		

Table 4 (Cont.)

Cotrimoxazole					
Yes	53	334	1		
No	1	34	0.25(0.03-1.85)	0.36(0.04-2.89)	0.39
Adherence					
Good	39	296	1		
Fair	5	27	3.87(0.77-5.02)	0.94(0.33-2.61)	0.90
Poor	10	45	4.29(1.15-4.65)	2.23(0.89-5.55)	0.08
CD4 (cells/µl)					
<50	8	33	2.58(1.14-5.83)	0.67(0.23-1.96)	0.47
50-199	25	122	2.05(1.14-3.67)	1.22(0.58-2.56)	0.75
≥200	21	213	1		
WHO staging					
I and II	16	258	1		
III	21	86	3.57(1.8-6.84)	2.05(0.97-4.33)	0.07
IV	17	24	8.5(4.31-16.94)	3.29(1.29-8.41)	0.01*
Hgb g/dl					
<10	40	195	6.8(2.91-16.07)	3.52(1.38-8.95)	0.008*
≥10	14	173	1		

Note: *: Significant association, 1: Means reference category, $: Non-Government Organization.

3.29; 95% CI: 1.29-8.41), and the hazard of death was three times more likely among those with active TB as compared to their counterparts (AHR: 3.10; 95% CI: 1.47-6.53) (Table 4).

The Proportional Hazard Assumption was also tested statically for each covariate using a global test (Schoenfeld Residuals) that fit the model with a p-value greater than 0.05 and graphically.

4. Discussion

The mortality of HIV patients on ART remains a major public health problem and needs great attention. This study aimed to identify predictors of mortality in HIV patients who are on ART at Attat Primary Hospital, Gurage Zone, Southern Ethiopia. This study identified a high rate of mortality with a total of 54 deaths (4.7 per 100 PYR) among HIV patients on ART. Bedridden functional status haemoglobin level <10 g / dl, WHO clinical stage IV, and active TB during treatment were the main factors associated with mortality.

The death rate in this study is approximately similar to the rates reported in the Somali region of Ethiopia (11.1%) and Suhul Hospital, Tigrai, Northern Ethiopia (12.5%) (Misgina *et al.*, 2019; Damtew *et al.*, 2015). The total mortality rate of 4.71 per 100 person-years at risk in this study closely agrees with the findings of a study conducted at the University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia which showed a mortality rate of 5.3 per 100 person-year observation (Teshale *et al.*, 2021). However, the finding is contrary to a study conducted in Nepal which revealed an overall mortality rate of 6.33 per 100 person-years at risk (Bhatta, 2012). This high mortality in Nepal might be due to factors like lack of prior access to ART services, stigma and discrimination related to HIV / AIDS, and limited availability of quality Voluntary Counseling and Testing that might have played a role in delayed diagnosis. The difference might also be due to the shortage of diagnostic facilities and proper screening of opportunistic infections, limited

availability of prophylaxis, and also may be due to the time gap between the two studies. The current study found a much lower mortality incidence rate than early studies carried out in Ethiopia that reported mor-tality rates of 15.4 and 16.7 per 100 person-years in ART tak-ing patients (Etemad-Moghadam *et al.*, 2000; Milazzo *et al.*, 2012). This indicates that ART is significantly re-ducing deaths among AIDS patients in Ethiopia and proves that the ART program is functioning well.

In this study, the overall estimated survival duration after ART initiation was 57.49 (95% CI: 55.64-59.33) months. This finding is in line with a study conducted in Debre Markos referral hospital in Northwest Ethiopia where the average survival of patients after ART was 65.22 months (Abebe *et al.*, 2014) and very concordant with the study conducted in Cameroon, where the mean survival probabilities were 57% (95% CI, 53 to 60%) (Sieleunou *et al.*, 2009). Contrary to this study, the survival of patients after ART initiation was 48 months in the study conducted in South Wollo, Ethiopia. This might be due to the short study period, 4 years, in which death is very high in early periods of treatment and more than 1000 subjects were in WHO stage IV as compared to the current study (Ayalew *et al.*, 2014). There is also a survival difference between the current study and the study conducted at the Armed Forces General Teaching Hospital, Addis Ababa, Ethiopia where the survival of patients after ART initiation was 72 months (Kebebew, 2012). This difference might be due to patients having better information on HIV/AIDS, better clinical care and nutrition, and socio-demographic differences as compared to the current study setting.

Patients with bedridden functional status were about two and half times more likely to die as compared to patients with working functional status. The findings were supported by the study conducted in Zambia, Cameroun, and Ethiopia which revealed that bedridden patients were at nearly three-and-half times, higher risk of death than working patients (Sieleunou *et al.*, 2009; Kebebew, 2012; Stringer *et al.*, 2006). Other studies also showed similar findings that bedridden patients were more likely to die compared to those engaged in active working (Tachbele and Ameni, 2016).

Another variable showing association with death is baseline haemoglobin level in which the hazard of death was 3 times higher in HIV/AIDS patients with baseline haemoglobin level <10 g/dl (AHR: 3.52, 95% CI: (1.38, 8.95)) as compared to those patients with baseline haemoglobin level ≥10 g/dl. This finding was similar to studies in Ethiopia that showed patients with anemia were at high risk of death after ART initiation (Biset, 2017; Teshale *et al.*, 2020; Benu *et al.*, 2016). This may be due to the incidence of anemia being increased in advanced HIV states indicating the highest immune suppression in clients with anemia which makes them susceptible to opportunistic infections and finally death (Obirikorang *et al.*, 2016; Masaisa *et al.*, 2011).

In this study, we found that patients with advanced baseline WHO stage IV had higher hazards of death as compared with their counterparts. This finding is in agreement with the studies done in Nepal, Cameroon, Zambia, South Africa, and Ethiopia (Misgina *et al.*, 2019; Bhatta, 2012; Sieleunou *et al.*, 2009; Stringer *et al.*, 2006; Mutevedzi *et al.*, 2010; Tadesse *et al.*, 2014). This might be because infections are the leading causes of death, like opportunistic infections such as tuberculosis is the main cause of death in HIV patients (Tachbele and Ameni, 2016; Sieleunou *et al.*, 2009; Nigussie *et al.*, 2020). The other plausible explanation might be, because having an advanced WHO stage indicates a patient is in an immune-suppressed state, the virus is easily multiplied with increased HIV/AIDS-related severity and the patient will end up with death. Finally, active Tuberculosis during treatment was an independent predictor of mortality this result was supported by studies done in Illubabor and Buno Bedele Zones, Oromia Regional State, and in Sothern Ethiopia (Tadege, 2018; Setegn *et al.*, 2015). This may be because TB by itself is a deadly disease worldwide, and the virulence of the organism is high in patients that have a suppressed immune system and can establish infection easily (Khan *et al.*, 2010).

Due to the retrospective nature of the study, some of the patient records were incomplete; the gap was filled by collecting the data from both smart care and patient charts and the cross-checking for missing data, and exclude from data with a missing value. Since the study was done in a single facility this may underestimate the outcome and death was ascertained from records this also may hinder the true death rate because there were lost follow-ups and transferred out.

5. Conclusion

The incidence of mortality in the first year of ART initiation was relatively low in this study compared to other studies, but the overall mortality was still considerably high. Bedridden functional status, low baseline haemoglobin level, advanced WHO Clinical stage, and TB co-infection were significant predictors of survival for patients under ART.

Strengthening screening programs for early initiation of ART and rising awareness on early treatment-seeking should get due attention to decrease the mortality of patients on ART and governmental and non-governmental organizations should give emphasis to decrease the mortality of HIV positive patients on Highly Active Anti-Retroviral Therapy (HAART). Bedridden functional status patients should be assessed for other possible disease conditions and treated with closer follow-up to minimize the risk of death. Patients with lower haemoglobin levels should be closely followed. Need to conduct a prospective cohort to overcome the limitation of the retrospective cohort study.

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Declarations

Ethical considerations: Ethical clearance was obtained from the Institutional Review Board (IRB) of Hawassa University College of Medicine and Health Sciences (Ref No: IRB/133/13). Since it is secondary data that was taken retrospectively no need to take informed consent from study subjects instead of it is written support letter was given to the hospital and permission was obtained from the hospital administration to collect the data. To ensure confidentiality, patient records are coded and accessed only by personnel working in the ART clinic of the hospital.

Availability of data and materials

All the data used to strengthen the results of this study are fully available without restriction at the hand of the corresponding authors

Competing interest

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