Investigating Correlates of the Survival of HIV/AIDS Patients Treated Under ART Follow-up: The Case of University of Gondar Hospital, Northwest Ethiopia

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Abstract

Background: It is believed that, in resource poor countries like Ethiopia the survival of patients with AIDS treated with ART depends on a variety of factors, which may also vary greatly with economic, demographic, risk behavioral and clinical factors. Understanding the survival time and its patterns is the key for policy formulation in bringing improvements. The aim of this study was to compare the survival estimates of different subgroups, and investigating the predictors of survival of cohort of HIV/AIDS patients.

Methods: A retrospective cohort study of AIDS patients aged 15 years or more followed-up under ART at University of Gondar Hospital was conducted. We used survival analysis of Kaplan-Meier plots for survival curve comparisons. Finally, the Cox proportional hazards model was employed to investigate the determinant covariates of survival experience of AIDS patients.

Results: This study cohort comprised of 354 AIDS patients under ART follow-up. Of the patients, 5.91% were uncensored or death cases. Covariates or factors associated with lower survival were age (HR = 1.051) and no formal education (HR = 5.032) while covariates or factors associated with longer survival were family size of 1 to 2 (HR = 0.167), three to four (HR = 0.120), no alcoholic consumption (HR = 0.294), no tobacco and chat use (HR = 0.101), baseline weight (HR = 0.920), current weight (HR = 0.928), baseline CD4 cell count (HR = 0.990), baseline hemoglobin (HR = .800) and negative/no TB status (HR = 0.145).

Conclusions: As there was good adherence level of patients in the study area, fewer death cases were reported as compared to previous similar studies. The covariates age, educational status,

family size, alcohol consumption, tobacco and chat usage, baseline and current weight, baseline CD4 cell count, baseline hemoglobin and TB status were significant predictors of survival.

Keywords: HIV/AIDS, ART, Survival analysis, Cox proportional hazards model

1. Introduction

Acquired Immune Deficiency Syndrome (AIDS) which is believed to be caused by the Human Immunodeficiency Virus (HIV) has been the major problem for the past three decades worldwide. HIV infection is one of the most prevalent infectious diseases in the world, affecting more than 35 million people globally (1). During these years HIV infection has changed from a fatal condition to a manageable chronic illness mainly due to the development of antiretroviral therapy (ART). The goal of this therapy is to improve survival; to reduce HIV associated morbidity and mortality, to increase the quality of life, to restore immune function and to achieve maximal and sustained suppression of viral replication (2).

Knowledge of the survival times of patients with AIDS and variables that influence survival are important both for increasing understanding of the patho-physiology of the disease, clinical decision making and planning health service interventions (3). The main challenge here is the sustainability of providing ART and other medications at district hospitals.

About one million people were living with HIV in Ethiopia in the year 2008 (4**).** Survival patterns following HIV infection in African populations in the era before antiretroviral therapy (ART) form an important baseline for measuring future successes of treatment programs (5). Despite the availability of a large body of research evidence that addresses issues about AIDS in Ethiopia, the level of understanding about predictor variables associated with survival experience of HIV patients is low (6).

The study had discovered the mathematical model with a focus on survival models in predicting the probability of survival of patients and identifying the factors associated with survival time of AIDS patients.

Statement of the Problem

Although the current HIV/AIDS surveillance estimates indicate some encouraging signs in that the epidemic is stabilizing, the observed changes are not sufficient enough compared to the desired goals of the response against the epidemic. It is believed that, in resource poor countries like Ethiopia the survival of patients with AIDS treated with ART depends on a variety of factors, which may also vary greatly with economic, demographic, behavioral risk and health factors. In other words, even if ARV treatment has shown significant clinical importance by meeting the goal of therapy, we are still facing a number of deaths that can otherwise be avoided by appropriate interventions on certain socio-economic, demographic, behavioral risk and health factors.

The performance of ART programs can be improved if we can bring behavioral change among HIV patients under ART follow up, take appropriate clinical and non-clinical measures like providing medicine and support to patients. Therefore, this study is motivated to investigate the major factors of survival time of AIDS patients. The questions we want to address here are:

1. What is the mean survival time of HIV/AIDS patients?
2. Which factors have significant (major) effect on the survival of HIV/AIDS patients?

Objectives of the Study

General objective:

The general objective of this study was to model and identify the associated factors of survival time of HIV/AIDS patients.

Specific objectives:

- ✓ To pronounce the survival experience of HIV/AIDS patients
- ✓ To estimate and compare survival probabilities with a given time of AIDS patients groups.
- ✓ To identify the major factors that may affect survival of AIDS patients.
- ✓ To develop a statistical model that can predict the probability of survival of AIDS patients.
- ✓ To provide scientific information on the results obtained to policy makers and future researchers.

2. Methods

2.1. Study Design

A retrospective study design was employed on of people living with AIDS and followed-up under ART at University of Gondar Hospital, Gondar, Ethiopia. All patients under ART follow-up between September 2009 and March 2015 were considered as a target population. At ART follow-up database, a total of 3397 AIDS adult (greater than 14 years) patients were registered.

2.2. Sample Size Determination

We had applied the following simple rand sampling equation (7) to determine the size of the participants to be included in the study.

$$n = \frac{\frac{Z^2 p(1-p)}{d^2}}{1 + \frac{1}{N}\left(\frac{Z^2 p(1-p)}{d^2} - 1\right)} \qquad \ldots\ldots\ldots (1)$$

where Z is the upper α/2 points of standard normal distribution with significance level, which is Z = 1.96. *d = 3.36% is* the degree of precision that mostly selected by the investigator. The term *p* represents proportion of death among HIV/AIDS patients. The proportion of death *p* that was selected for this study was obtained from the previous comparable study done by (8) on data taken from Felege-Hiwot referral hospital which is 13.4%. Therefore, in this study, a sample of 354 adult patients' chart review was conducted using the above equation.

2.3. Variables

AIDS survival time was estimated from the date of AIDS diagnosis to the date of AIDS-related death or censoring date (in months). And we have used demographic, clinical and risk behavior factors to measure the survival experience of AIDS patients.

2.4. Data Analysis

We have used a number of data analysis techniques. Descriptive measures were conducted to explore the proportion of patients lay in different subgroups of each variable, and to know the mean survival time of patients in this subgroups. We used Kaplan-Meier survival estimates or curves to compare the survival time estimate of patients under different classifications. And

finally, the Cox proportional hazards model was employed to measure the estimated hazard of death of patients and to identify the factors associated with the survival experience of AIDS patients. Actually, the data was analyzed using SPSS and STATA software packages.

3. Ethical Issues

This study had already obtained ethical approval by the research Ethics Committee of University of Gondar, Ethiopia. In addition, the University of Gondar Hospital Medical director office permitted the use of patients' data for this study.

4. Results

4.1. HIV/AIDS Patients Demographic Information

Information on demographic characteristics, and clinical and risk behavior factors of HIV/AIDS patients under ART follow-up were collected in their follow-up charts. In this study, a sample total of 354 HIV/AIDS patients were considered. Out of which 5.93% (21) death cases occurred, and 94.07% (336) were censored. As we see from Table 1 below, most of the patients (211(59.6%)) were female while the remaining (40.4%) were male. Almost all of the study subjects live in urban areas but small patients (13.6%) reside in rural places. According to the patients' marital status information or figure, 162 (45.8%), 90(25.4), 76(21.5) and 26(7.3%) were married, separated/divorced, single and widowed, respectively.

From 354 patients under follow up, very large numbers of patients (320) were followers orthodox religion where as 29 and 5 patients were Muslim and other religion followers, respectively. Of the total study participants, 201(56.8) patients had a family size between one to two person/s. Patients without formal education took 26.3% of the total sample, while those whose educational status were primary, and secondary and above covered 28.5 and 45.2%, respectively.

Table 1: Summary Results for Socio-demographic Composition of HIV/AIDS Patients Treated under ART Follow-up (University of Gondar Hospital, 2009 - 2015)

Variables		Frequency	Percent
Sex	Female	211	59.6
	Male	143	40.4

Residence	Urban	306	86.4
	Rural	48	13.6
Marital Status	Single	76	21.5
	Married	162	45.8
	Separated/Divorced	90	25.4
	Widowed	26	7.3
Religion	Orthodox	320	90.4
	Muslim	29	8.2
	Other	5	1.4
Family Size	1-2	201	56.8
	3-4	91	25.7
	>=5	62	17.5
Educational Status	No formal education	93	26.3
	Primary	101	28.5
	Secondary and above	160	45.2

4.2. HIV/AIDS Patients Clinical and Risk Behavior Descriptive Information

The study revealed that 63.6% of HIV/AIDS patients under ART follow-up consumed alcohol, and the remaining (36.4) did not consumed (Table 2). As shown in Table 2, only few patients (10.7%) used tobacco and chat. Almost all of the patients (94.4) disclosed their HIV infectivity. Of the patients in the study, 86.4%, 11.3% and 2.3% were under working, ambulatory and bedridden status, respectively. 96.1% of the total patients in the study were with good ART adherence level while 2.8% and 1.1% of the patients' adherence level were poor and fair respectively. Patients TB history indicated that 332 (93.8%) had not faced TB infection where as few figures (22) infected with TB (Table 2.

Table 2: Summarized Information on HIV/AIDS Patients' Clinical and Risk Behavior Factors under ART (University of Gondar Hospital, 2009 - 2015)

Variables		Frequency	Percent
Alcohol Consumption	No	225	63.6
	Yes	129	36.4
Tobacco and chat use	No	316	89.3

	Yes	38	10.7
HIV disclosure Status	Not disclosed	20	5.6
	Disclosed	334	94.4
Functional Status	Bedridden	8	2.3
	Ambulatory	40	11.3
	Working	306	86.4
ART Adherence level	Poor	10	2.8
	Fair	4	1.1
	Good	340	96.1
TB_History	No	332	93.8
	Yes	22	6.2

The average age of 354 HIV/AIDS patients followed-up under ART was 34.8 years (Table 3). The patients in the study had an average baseline weight of 51.2 kg, and their mean current weight was about 54.8 kg. The average baseline CD4 cell count of HIV/AIDS patients in the study was around 183.6 cells/µl. The mean baseline lymphocyte count and baseline hemoglobin for the 354 patients were reported as 33.1 cells/mm^3 and 13.2 g/dl, respectively (Table 3).

Table 3: Description of Continuous Covariates/Measures of 354 HIV/AIDS Patients under the Study (University of Gondar Hospital, 2009 - 2015)

Variables	Minimum	Maximum	Mean	Std. Deviation
Age	16.00	70.00	34.7740	9.54665
Baseline weight	15.00	80.00	51.2062	9.81103
Current weight	28.00	92.00	54.7994	10.57320
Baseline CD4 cell count	11.30	1022.00	183.5800	118.58572
Baseline lymphocyte count	1.10	317.00	33.1274	19.42361
Baseline hemoglobin	5.00	36.40	13.2435	3.61894

4.3. Survival Time Comparison

Number of death cases in each covariate, mean and median survival times, and test of equality of survival distributions for the different levels of variables were all presented in Table 4. In the study subjects, 19 female and 2 male deaths were registered. The mean survival time of urban

and rural patients were 104.9 and 82.3 months, respectively. Patients having 1 to 2 family size had highest mean survival time as compared to those having three to four and more than five family size (Table 4). The median survival time of patient who used tobacco and chat was 73.8 months.

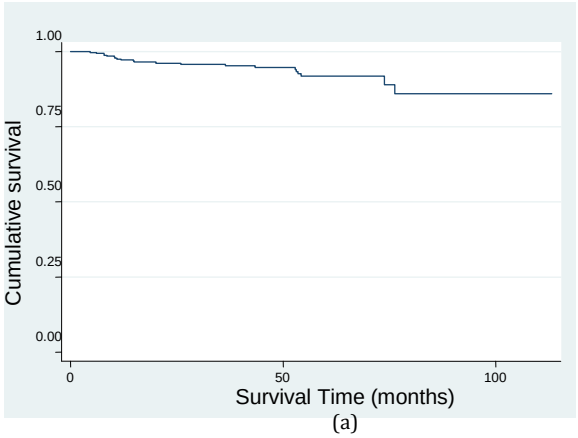
Survival functions among the subgroups of each covariate were compared by the log rank test. The subgroups/levels in the variables: sex, marital status, family size, educational status, alcohol consumption, tobacco and chat use, HIV disclosure status, functional status and TB history were different in their survival distribution (p-value < 0.05, Table 4). But there was no survival distribution difference between the levels on each of the covariates residence, religion and ART adherence level (p-value > 0.05).

Table 4: Survival Time by Potential Demographic, Clinical and Risk Variable for HIV/AIDS Patients Treated under ART (University of Gondar Hospital, 2009 - 2015)

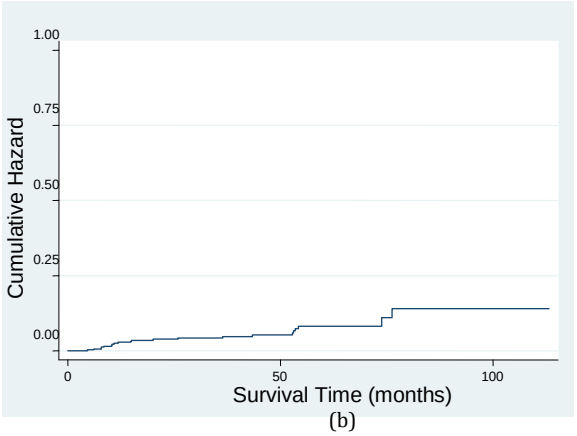
Variable		Number of Patients	Number of Deaths	Mean Survival Time	Median Survival Time	p-value
Sex	Female	211	19	99.893	-	0.004
	Male	143	2	104.548	-	
Residence	Urban	306	19	104.856	-	0.896
	Rural	48	2	82.279	-	
Marital Status	Single	76	11	86.732	-	0.000
	Married	162	4	101.391	-	
	Separated/Divorced	90	2	105.998	-	
	Widowed	26	4	86.761	-	
Religion	Orthodox	320	18	-	-	0.592
	Muslim	29	3	-	-	
	Other	5	0	-	-	
Family Size	1-2	201	8	108.070	-	0.001
	3-4	91	3	100.170	-	
	>=5	62	10	82.682	-	
Educational Status	No formal education	93	13	94.794	-	0.019
	Primary	101	5	96.924	-	

	Secondary and above	160	3	106.474	-	
Alcohol Consumption	No	225	9	107.231	-	0.018
	Yes	129	12	92.048	-	
Tobacco and chat use	No	316	14	106.865	-	0.000
	Yes	38	7	62.160	73.80	
HIV disclosure Status	Not disclosed	20	3	85.811	-	0.028
	Disclosed	334	18	104.747	-	
Functional Status	Bedridden	8	1	66.847	-	0.008
	Ambulatory	40	6	67.033	73.800	
	Working	306	14	106.592	-	
ART Adherence level	Poor	10	2	-	-	0.147
	Fair	4	0	-	-	
	Good	340	19	-	-	
TB_History	No	332	16	105.650	-	0.000
	Yes	22	5	52.348	-	

The survival and hazard functions of HIV/AIDS patients followed-up under ART were presented in Figure 1 (a) and (b), respectively. Patients followed up for more than 75 months had 0.85 probability of survival (Figure 1 (a)). The hazard of death for higher survival months was increased (Figure 1(b)). After 75 months of follow up, patients had a constant probability of death (0.15).



(a)



(b)

Figure 1: Estimated Survival Function (a) and Hazard Function (b) of HIV/AIDS Patients

Figure 2 presented the survival curve comparison of different subgroups/levels of covariates of HIV/AIDS patients under ART follow-up. The Kaplan-Meier survival function indicated that patients with five or more family members had lower survival experience than lower family sized patients as follow-up time increased (Figure 1(a)). Educational status determined the survival status of HIV patients. Patients having secondary and above educational status had slightly better survival chance for longer survival times (Figure 1(b)). The Kaplan-Meier survival plot also indicated that patients who consumed alcohol and used chat and tobacco had lower survival probability with increased survival time (Figure 1(a), (b)).

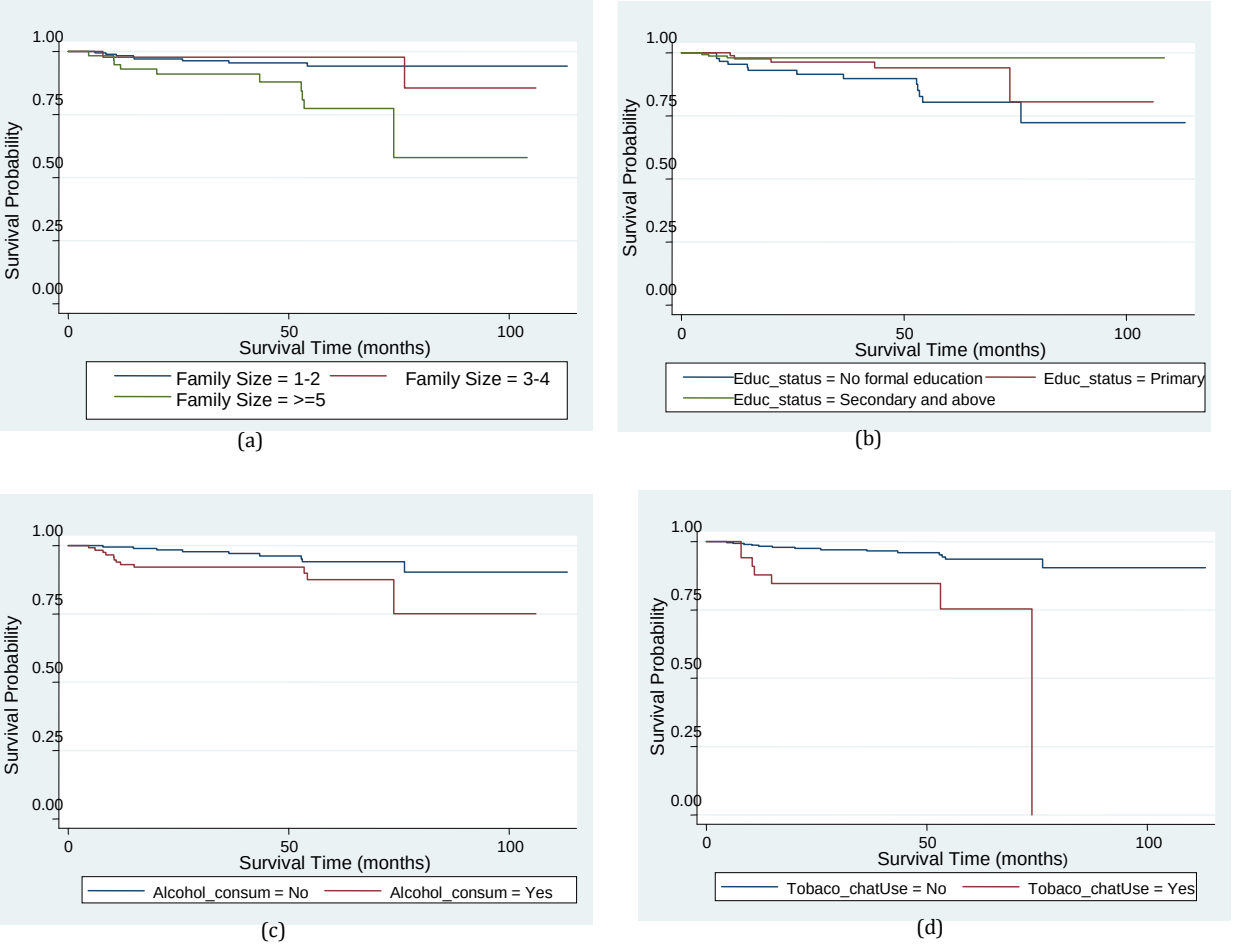


Figure 2: Comparison of Survival Curves for Different Subgroups of Each Covariate.

4.4. The Hazard of Death in HIV/AIDS Patients

Table 5 described all covariates which had significant association with the survival time of HIV patients, and their hazard of death. The variables age, family size, educational status, alcohol consumption, tobacco and chat usage, baseline weight, current weight, baseline CD4 cell count, baseline lymphocyte count, baseline hemoglobin and TB history were significantly associated with survival time of HIV patients under ART fellow-up (p-value < 0.05).

Thus, one can interpret the effects of each covariate using the estimated hazard ratio (HR) given in Table 5. Age had a significant effect on the survival time of HIV patients (HR =1.051, 95% CI: 1.002, 1.101). For a year increase, the hazard of death of HIV/AIDS patient was increased by 5.1%.

Table 5: The Hazard Estimates of Covariates Associated with the Survival Time of HIV/AIDS Patients under ART Follow-up (University of Gondar Hospital, 2009 - 2015)

Predictor Variables	B	SE	Wald	df	Sig.	AHR	95.0% CI for HR	
							Lower	Upper
Age	.049	.024	4.228	1	.040*	1.051	1.002	1.101
Family Size			9.854	2	.007*			
> = 5 (ref)								
1 - 2	-1.791	.604	8.785	1	.003*	.167	.051	.545
3 - 4	-2.120	.852	6.197	1	.013*	.120	.023	.637
Educational Status			6.612	2	.037*			
Secondary and above (ref)								
No formal Education	1.616	.762	4.491	1	.034*	5.032	1.129	22.423
Primary	.213	.858	.061	1	.804	1.237	.230	6.646
Alcohol consumption								
Yes (ref)								
No	-1.225	.623	3.873	1	.049*	.294	.087	.995
Tobaco and chat Use								
Yes (ref)								
No	-2.296	.646	12.633	1	.000*	.101	.028	.357
Baseline weight	-.084	.042	4.019	1	.045*	.920	.847	.998
Current weight	-.074	.034	4.900	1	.027*	.928	.869	.992
Baseline CD4 cell count	-.010	.003	7.895	1	.005*	.990	.984	.997
Baseline lymphocyte count	-.035	.023	2.296	1	.130	.966	.924	1.010

Baseline hemoglobin	-.224	.066	11.400	1	.001*	.800	.702	.910
TB_History								
Yes (ref)								
No	-1.932	.703	7.552	1	.006*	.145	.037	.575

Key: * Significant (p-value < 0.05), df: degree of freedom, ref: reference category, AHR: Adjusted Hazard Ratio

Family size was the other significant predictor of survival time of patients. The hazard of death of HIV/AIDS patient treated under ART whose family size was one to two was 0.165 times less likely as compared to a patient having five or more family size (HR = 0.165, 95% CI: 0.051, 0.545). The hazard of death was 88% less for patients having three to four families than those patients having five or more patients (HR = 0.120, 95% CI: 0.023, 0.637).

The probability of death for illiterate HIV/AIDS patients on ART follow-up was 5.032 times higher than patients whose educational status was secondary or above (HR = 5.032, 95% CI: 1.129, 22.423).

HIV/AIDS patient who did not consume alcohol was 0.294 times less likely to be at risk of death than those patients who drink alcohol (HR = 0.294, 95% CI: 0.087, 0.995). The hazard of death for patient who did not use tobacco and chat was 89.1% less than a patient who used tobacco and chat (HR = 0.101, 95% CI: 0.028, 0.357).

Baseline weight had also an association with the survival time of HIV patients. As baseline weight increased by one kilogram, the hazard of death of a patient decreased by 8% (HR = 0.920, 95% CI: 0.847, 0.998). The probability of death of a patient was also 7.2% less for one kilogram increase in current weight (HR = 0.928, 95% CI: 0.869, 0.992).

A 1cell/µl increase in baseline CD4 cell count can decrease the hazard of a patient by 1% (HR = 0.990, 95% CI: 0.984, 0.997). The risk of death of an HIV patient decreased by 20% as baseline hemoglobin increased by 1 g/dl (HR = 0.800, 95% CI: 0.702, 0.910).

Compared with TB history, HIV patients with negative TB history had 85.5% reduced risk of death than the patients with positive TB history (HR = 0.145, 95% CI: 0.037, 0.575).

5. Discussion

This study used the Classical techniques to analyze risk factors for the survival time of HIV/AIDS patients under ART follow-up. A number of variables were used to explain the variation in the survival time of HIV patients using the Cox Proportional Hazards Model.

This Study found that 5.91% of the patients were died. This death rate was very small as compared to other similar studies (6, 8, 9, 10). The reason for this low figure reported may be due to good adherence level of patients to ART in the study area.

Age of the patient was significantly associated with the survival time of HIV patient. Older aged patients had smaller survival probability as compared to younger age. This result also coincides with previous studied in Ethiopia by (6, 9), and in Brazil by (10). This may be due to that the immune recovery of older ages became decreased.

In this study, the association of gender with survival experience was found not to be significant. Past studies by (5, 11, 12) also found the same result. The number of family members within the patient had a contribution for the survival time of the patient. In this study, we found that one to two family sized patients survived for long time as compared to the patients with large family (specifically, five or more). If more dependents and non fertile aged people in a limited economy were in the household, then it may be difficult to provide balanced and timely diet for the patient. So, the result may be happened due to this clue.

Educational status was also a statistically significant predictor of the survival of patients. Illiterate patients had lower survival experience than the patients with primary or above educational level. This result was similar to the findings of (10, 13). This figure probably happened due to lack of the psychological, mental, healthcare and economic preparedness of less educated patients.

Alcohol consumption, chat and tobacco usage were another influential covariates for the survival of patients. Drinking alcohol, tobacco and chat usage or taking other drugs can affect your immune system and may speed up the progression of the disease. Drinking or taking drugs also can affect your HIV treatment adherence.

The variables baseline and current weights had a statistically significant effect on the chance of survival of AIDS patients. The result of this study was consistent with the finding of other studies (6, 9).

In this study, we found that baseline CD4 cell count determined the survival time of patients. Patients with lower CD4 cell count had lower survival experience. This study coincided with other similar studies (10, 13). CD4+ count is a major biological marker of immune status (14, 15 16) and an indicator of late diagnosis and untimely treatment. Currently international consensus recommendations for treatment initiation are based on CD4+ counts, viral loads and clinical data (17, 18).

This study also found that survival time was statistically associated with baseline hemoglobin. The study results indicated an association between positive TB status (patients with TB) and lower survival, which corroborates the finding of other study (13).

6. Conclusions

In this study we found very lower death cases as compared to many similar past studies. Results revealed that the variables age, family size, educational status, alcohol consumption, tobacco and chat usage, baseline weight, current weight, baseline CD4 cell count, baseline lymphocyte count, baseline hemoglobin and TB history were significantly associated with the survival experience of HIV patients under ART fellow-up.

7. Recommendation

We found that alcohol consumption had a significant effect on the survival time of HIV/AIDS patients. And we have seen that high number of patient were alcohol consumers. So, we recommend patients to abstain from choosing alcohol consumption. Clinicians and health workers must teach patient and create awareness on the terribleness of alcohol consumption to their survival.

Weight also plays a crucial role on the survival of patients. Therefore, patients need to eat balanced diets that help from weight loss. And balancing the size of the family would greatly reduce the hazard of death of patients.

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