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Analysis of Survival and Associated Risk Factors among HIV/AIDS Patients Who Started Antiretroviral Therapy (ART) in Central, Western and North Gondar Zones, North West Ethiopia

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Abstract

Background: The rate of spread of the HIV/AIDS and damages accompanying it have reached a level which shock economists, health workers, politicians etc that it has now become a worldwide issue in general and developing countries in particular. Unfortunately all our prevention programs will not realize their targets unless otherwise we give due consideration for people living with HIV/AIDS. **Objective:** The objective of this study was to determine the socio-economic, demographic and health factors that influence the survival/mortality status of HIV-Positive individuals under ART follow up. **Subjects and Methods:** A sample of 1066 ART follow-up HIV/AIDS patients card were reviewed in North Gondar Zone using secondary data. We used semi-parametric Cox proportional Hazard model to identify the factors that affect survival time of HIV/AIDS patients after ART analysis. **Results & Conclusion:** The death rate in the study area was 10.1% from the sample patients. The hazard of death of male HIV/AIDS patients treated under ART 18.87% higher than that of female. Patients their marital status was divorce 25.38% more likely to die as compared to the reference group single patients. The Cox Proportional Hazard model revealed that the factors that affect independently the survival/death time of HIV/AIDS patients who take ART include sex, age, residence, marital status, educational level, condom, clinical stage, CD4, previous counseling attendance about HIV/AIDS. In this study TB infection was not significant on the survival time of HIV. So we recommend other researchers in future to give more attention about this covariate using parametric survival model.

Keywords: ART, HIV/AIDS, Risk factors, Survival/Death, Cox Proportional Hazard model

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Introduction

The rate of spread of the HIV/AIDS and the damages accompanying it have reached a level which shock economists, health workers, politicians etc that it has now become a worldwide issue in general and developing countries in particular. The disease being one without any cure is still accountable for economic, social and health crises especially in developing countries. Its high prevalence and/or distribution among the youth made things even more complicated.[1]

As the immune system becomes increasingly damaged by HIV it becomes susceptible to opportunistic infections. Besides to other socioeconomic and environmental factors, TB is the most common opportunistic infection complicating HIV infection especially in developing countries, and may occur at any stage in the course of immunodeficiency. TB/HIV co-infection significantly changes the natural history of both diseases and it is recognized as a major setback of both HIV and tuberculosis infection control program.[2,3]

Knowledge of the survival times of patients with AIDS and variables that influence survivals are important both for increasing understanding of the patho-physiology of the disease, clinical decision making and planning health service interventions. 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. Pre-antiretroviral therapy includes guidelines that attempt to address factors which are important in the holistic approach to patient management which could also influence the progression and outcome of disease including natural history of HIV infection, primary prophylaxis and immunization, nutrition, support and counseling.[4,5] Although ART treatment has decreased HIV associated mortality and morbidity, a number of patients still die after the start of ART. This might be due to the effect of other related disease and factors. Thus, this study

was conducted to address the survival status of patients under ART and influencing factors associated.[6]

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. Given the size of the population and the magnitude of the damage inflicted, it will take us a number of years to see significant declines in HIV prevalence and incidence with concerted and sustained efforts. Unfortunately all our prevention programs will not realize their targets unless otherwise we give due consideration for people living with HIV/AIDS (PLWHA). 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. There was no comparative and inclusive study conducted in these zones. The previous study only focuses on prevalence and descriptive statistics about ART users among HIV/AIDS patients in the country. The rationale behind such a research is to improve the achievements of ART programs run by different health institutions of the country in order to minimize HIV related mortality. The question we addressed here was "Which social, demographic, economic, health etc factors/variables affect the chance of survival/death among HIV-positive people taking ART?"

Objectives of the study

- to determine the prevalence of mortality among HIV/AIDS patients under ART follow up in the study area
- to predict the median survival time of HIV patients after ART follow up

To assess risk factors associated with the death of HIV/AIDS patients under ART follow up

Subjects and Methods

Data Collection

The data used in this study was secondary data obtained from University of Gondar Referral Hospital and from other health centers that have ART clinic as described in the study area. The study period was from November 7 2016 to April 14 2017. The health facilities involved in this study were University of Gondar Referral Hospital, Metema Hospital, Aykel Health Center and Debark Hospital. Data for this study extracted from the available standard national medical registers, which have been adopted by the Federal Democratic Republic of Ethiopia Ministry of Health (FDRE, MOH). The registers include the Pre ART register (register of patients at their first visit), the ART register (registration after ART initiation), and the follow-up patient form. The patient charts include the patient intake forms and follow up cards, which were prepared by FDRE, MOH to be uniformly used by clinicians to early identify and document clinical and laboratory variables. A sample of 1066 ART follow-up charts was reviewed in these zones. The study considered only patients above 15years old.[7]

Variables Included in the Study

Dependent Variable

The response/dependant variable in this study was the length of time with a dichotomous random variable "survival/death status" (death=1 and alive=0) of an HIV positive individual under ART follow up.

Independent Variables

The independent variables in survival data analysis were called covariates. These are given below:

Age in years
Sex
Marital status
Baseline Weight
Baseline Height
Baseline Hemoglobin
Baseline Lymphocyte
Level of education
Baseline CD4 cell count
WHO clinical stage
Functional Status
Regimen type
Previous attendance of HIV counseling
Residence
Employment Status
ART Adherence
TB Status
Partners HIV status
Alcohol
Condom use
Tobacco

Data Analysis

Survival Analysis

Survival analysis is a collection of statistical procedures for data analysis for which the outcome variable of interest is time until an event occurs. By time, we mean years, months, weeks, or days from the beginning of follow-up of an individual until an event occurs; alternatively, time can refer to the age of an individual when an event occurs. By event, we mean death, disease incidence, relapse from remission, recovery (e.g., return to work) or any designated experience of interest that may happen to an individual. The problem of analyzing time-to-event data arises in several applied fields such as medicine, biology, public health, epidemiology, engineering, economics, sociology, demography and etc. The terms lifetime analysis, duration analysis, event-history analysis, failure-time analysis, reliability analysis, and transition analysis refer essentially to the same group of techniques although the emphases in certain modeling aspects could differ across disciplines.[8]

The use of survival analysis, as opposed to the use of other statistical method, is most important when some subjects are lost to follow up or when the period of observation is finite certain patients may not experience the event of interest over the study period. In this latter case one cannot

have complete information for such individuals. These incomplete observations are referred to as being censored. Most survival analyses consider a key analytical problem of censoring. In essence, censoring occurs when we have some information about individual survival time, but we do not know the survival time exactly.

The Cox Proportional Hazards Regression Model

The Cox Proportional Hazard (PH) Model is a multiple regression method and is used to evaluate the effect of multiple covariates on the survival.[9] Cox (1972) proposed a semi-parametric model for the hazard function that allows the addition of covariates, while keeping the baseline hazards unspecified and can take only positive values and it is defined as:

$h(t, X, \beta) = h_0(t)e^{\beta' \chi}$ where h (t, X, β) hazard function at time t with covariates X=(X1, X2,….XP), ho (t) is the arbitrary baseline hazard function that characterizes how the hazard function changes as a function of survival time, $\beta = (\beta_1, \beta_2, ..., \beta_p)^T$ is a column vector of p regression parameters associated with explanatory variables, $\exp(\beta' \chi)$ characterizes how the hazard function changes as a function of subject covariates and t is the failure time. Each individual has its own hazard function of survival time. Then, the above model becomes $h(t, x_i, \beta) = h_0(t) \times \exp(\beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + ... + \beta_p x_{ip}), i = 1,2,3 = n$

Where: n is total number of observations in the study, $x_i = (x_{i1}, x_{i2}, ..., x_{ip})$ are the values of the indicator variables of individual (patient) which are assumed to affect the survival probability.

Ethical Approval

Ethical approval was obtained from the Institutional Ethical Review Board of University of Gondar and supportive letter was found from Zonal administration health offices of the study areas. To build more trust and resolve related confidentiality issues we have employed record officers. We have used charts with pseudo identity markers which keeps the participants identity anonymous throughout the study courses. Besides, during report writing full considerations was made to protect the moral and confidence of the study population.

Results

Information on demographic characteristics, clinical and risk behavior factors of HIV/AIDS patients under ART follow-up were collected from their follow-up charts. The HAART data used in this study included 1066 patients who were ≥15 years old and who were under HAART treatment between 2005 and 2016 in Central, North and Western Gondar Zones. Patients who were bellow 15 years and thocsc paticnts who startcd ART bcforc 2005 or aftcr 2016 were excluded from the study. From these 108(10.1%) death occurred and 958(89.9%) were censored. Most of the patients 633(59.4%) were female while the remaining 433 (40.6%) were male. Most all the study subjects live in urban areas 762(71.5%). According to the patients' marital status 442(41.5%) of the patients were married. 206(19.3%), 303(28.4%) and 115(10.8%) of the patients were single, separated and widowed, respectively. Most of the patients were working 777(72.9%), the remaining 42(3.9%) and 247(23.2%) patients functional status were bedridden and ambulatory, respectively. From the total patients 93% are Orthodox followers; the remaining 7% are Muslim, Protestant and Catholic followers. Five hundred twenty five (49.2%) the patients were at clinical stages III, 249(23.4%) were at clinical stage II, 209(19.6%) were at clinical stage I, the rest at clinical stage IV. The average age of the sampled HIV patients was 33.49year. The average baseline weight of these 1066 ART follow-up patients was 48.787kg. The average CD4 for these HIV patients was 228. The survival distribution of female and male was statistically different (P-value<0.05). Table 1 below shows that; variable sex, HIV disclosure, functional status and adherence level of the patient have significant difference on the survival of the ART patients among groups.

Table 1: Log rank test for the comparison of survival difference for the different categorical variable, Central, Western and North Gondar, 2017.

Variable	Test Statistics	Df	P-value
Sex	4.561	1	0.033
Residence	3.732	1	0.053
Marital Status	3.294	3	0.349
Religion	0.6	4	0.96
Educational level	1.1	4	0.89
Occupation	0.8	4	0.93
Alcohol Consumption	0.83	1	0.362
Tobacco & Chat	0.037	1	0.84
Condom use	0.389	1	0.53
Partners HIV status	0.875	2	0.646
HIV disclosure	15.98	1	0.00
Functional status	9.508	2	0.009
Clinical stage	6.299	3	0.098
Adherence Level	16	2	0.000
TB status	1	1	0.32

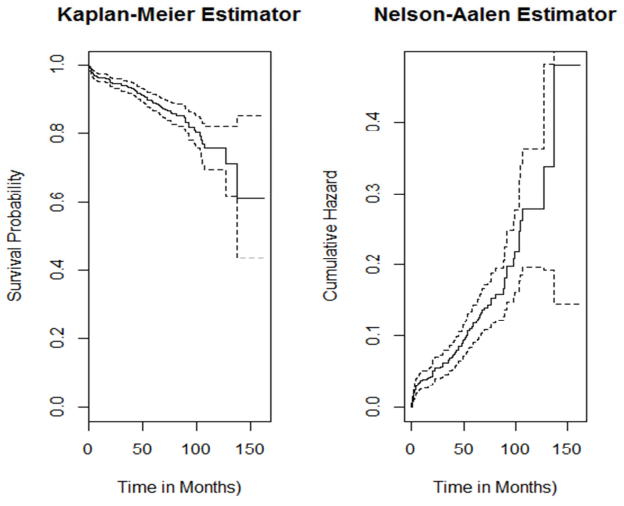

Figure 1: Estimated Survival Function and Hazard Function of HIV/AIDS Patients, Central, Western and North Gondar, 2017.

The survival and hazard functions of HIV/AIDS patients followed-up under ART were presented in figure 1 above. The survival of patients strictly decreased until 137 months and the cumulative hazard of the patient's strictly increased until 137 months. The survival and cumulative hazard function is constant after 137 months. Patients followed up for more than 137 months had a constant probability of o.61 survival [Figure 1].

The survival curve comparison of different subgroups/levels of covariates of HIV/AIDS patients under ART follow-up presented in figure 2 below. The Kaplan-Meier survival function indicates that female patients have a good survival experience than that of male. From the functional status group patients there functional status was bedridden have a good survival experience than that of patients there functional status was working. The Kaplan-Meier survival plot also indicated that patients who do not disclosed themselves have lower survival experience than that of disclose. As shown from the [Figure 2] below, the survival of patients under adherence level fair was good.

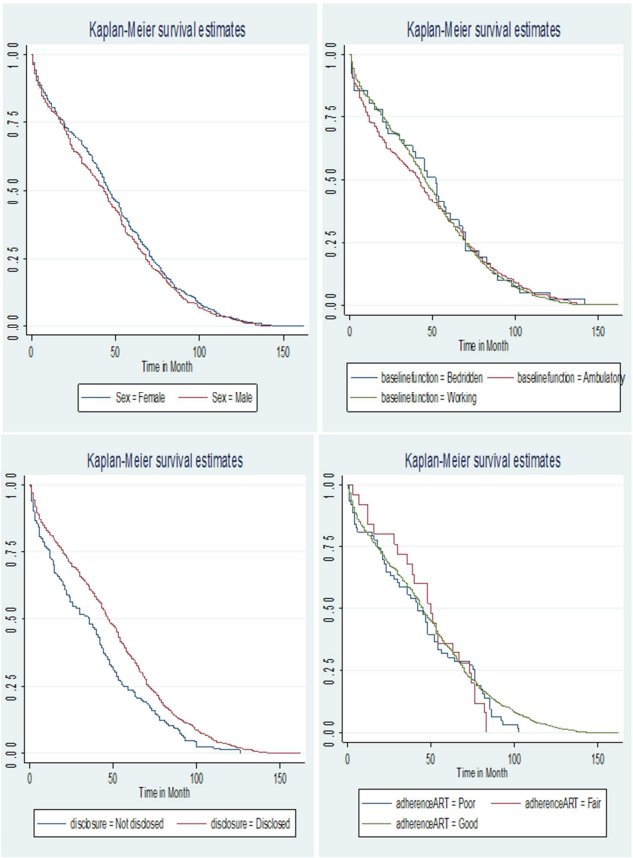

Figure 2: Comparison of Survival Curves for difference subgroups of each covariates, Central, Western and North Gondar, 2017

The Hazard of death in HIV/AIDS Patients due to potential Covariates

[Table 2] below describes all covariates which had significant association with the survival time of HIV patients and their hazard of death using semi-parametric Cox Proportional Hazard model. The variable sex, age, residence, marital status, education, condom use, WHO clinical stage, CD4 count, pervious HIV counseling attendance were significantly associated with survival time of HIV patients under ART fellow-up (P-value<0.05). Age had a significant effect on the survival time of HIV patients (HR=0.9819, 95% CI: 0.9744, 0.9894). Hazard ratio of a subject of age i (in years) compared to a subject of age i-1(in years) was 0.9819. As the age of the patient increased by 1year, the hazard of death of a patient decreased by 1.81%.

Table 2: The Hazard Estimates of Covariates Associated with the Survival Time of HIV/AIDS Patients under ART Follow-up, Central, Western and North Gondar, 2017.

Predictor Variables	B	SE	Z	P-value.	HR	95% CI for HR Lower Upper
Age	-0.0182	0.0039	-4.64	0.000	0.9819	0.9744-0.9895
Sex(Ref. Female)						
Male	0.1698	0.0741	2.33	0.020	1.1887	1.0279-1.3745
Residence (Ref. Urban)						
Rural	0.2792	0.0750	3.73	0.000	1.3228	1.1419-1.5323
Marital(Ref. Single)						
Married	0.1177	0.1006	1.19	0.236	1.1267	0.9251-1.3722
Divorced	0.2250	0.1056	2.14	0.032	1.2538	1.0193-1.5422
Widowed	0.0688	0.1318	0.54	0.592	1.0732	0.8289-1.3895
Education(Ref. no formal educ.)						
Primary	-0.2078	0.0799	-2.60	0.009	0.8123	0.6944-0.9502
Secondary	-.03096	0.0989	-3.13	0.002	0.7337	0.6044-0.8906
Tertiary	-0.2833	0.1607	-1.76	0.078	0.7532	0.5496-1.0322
Others	-0.3133	0.3675	-0.85	0.394	0.7309	0.3556-1.5022
2.Condom	-0.1402	0.0713	-1.97	0.049	0.8691	0.7557-0.9995
Clinical Stage(Ref. Stage I)						
Stage II	-0.1636	0.0963	-1.70	0.089	0.8490	0.7029-1.0254
Stage III	-0.2314	0.0891	-2.60	0.009	0.7933	0.6662-0.9446
Stage IV	-0.2460	0.1469	-1.67	0.094	0.7818	0.5862-1.0428
BaselineCD4	-0.002	0.001	2.60	0.019	0.998	0.997-0.999
Previous HIV Attend.(Ref. No)						
Yes	-0.3542	0.1028	-3.44	0.001	0.7016	0.5736-0.8583

Key: Ref: reference category, HR: Hazard Ratio

The hazard of death of male HIV/AIDS patients treated under ART is 18.87% higher than that of female HIV/AIDS patients treated under ART (HR=1.1887, 95% CI: 1.0279-1.3745). Patients who live in rural area are 1.3228 times more likely to die than patients that who live in urban area (HR: 1.3228, 95% CI: 1.1419-1.5323). Patients whose their marital status was divorced are 25.38% more likely to die as compared to the reference group single patients (HR: 1.2538, 95% CI: 1.0193-1.5422). The hazard of death of HIV patients whose educational level primary and secondary decreased by 18.77%, 26.63% as compared to the hazard of death of HIV patients whose educational level was no formal education(HR:0.8123, 95% CI:0.6944-0.9502, HR:0.7337, 95% CI: 0.6044-0.8906) respectively.

Covariate condom use statistically related with the hazard of death of HIV/AIDS patients. Patients who use condom during sexual intercourse are 13.09% less likely to die as compared to patients who do not use condom during their sexual intercourse (HR: 0.8691, 95% CI: 0.7557-0.9995). Baseline clinical stage III patients are 20.67% less likely to die as compared to the reference group clinical stage I patients (HR: 0.7933, 95% CI: 0.6662-0.9446).

Al cell/µ1 increase in baseline CD4 cell count can decreased the hazard of death of a patient by 0.2%(HR:0.998, 95% CI: 0.997-0.999). ART follow-up HIV/AIDS patients who got previous counseling about HIV/AIDS are 29.84% less likely to die as compare to patients who do not got pervious counseling about HIV/AIDS(HR: 0.7016, 95% CI: 0.5736-0.8583).

Discussion

This study covered 1066 ART follow-up HIV/AIDS patients in Central, Western and North Gondar Zones. The study used Cox Proportional Hazard model to identify the risk factors that affect the survival time of ART follow-up HIV/AIDS patients in the zone. Based on our study, 10.1% death occurred from the total participants in the study. The death rate that found in the study area was less as compared with the study in Somalia region of Ethiopia where 11.1% death rate is reported.[10]

Age of the patient was significantly associated with the survival time of HIV patients. From this young patients had smaller survival probability as compared to old age patients. This study may contradict with the previous study like.[11] This may due to the save of sexual interest at the old age.

The study indicates that male patients more likely to die than that of female patients. This result may be due to the exposure of male patients for so many things. Paste studies also found the same result.[4] [Figure 1] showed that the survival of male patients less as compared to female patients for these ART follow-up HIV/AIDS patients. The hazard of death of HIV/AIDS patients who live in rural area was 32.28% more likely to die as compared to patients live in urban area. This may occurred because patients who live in rural area couldn't attend the ART follow-up regularly and they do not got counseling about HIV/AIDS.

The mortality rate of patients whose marital status was divorced was higher than that of patients whose marital status was single. This might occurred due to partners HIV status, searching new partners, economic status and way of life, other study revealed the same result.[12] Patients whose educational level was no formal education had lower survival experience than the patients with primary or above educational level. This result was similar to the findings of previous study.[10] This figure probably happened due to lack of the psychological, mental, healthcare and economic preparedness of less educated patients.

The negative sign for the odds ratio of the variable condom use implies that death risk is lower for those patients who use condom during sexual intercourse. Its magnitude indicates that, the odds of being at risk of death for those patients who use condom during sexual intercourse is 13.09% less than for those who do not use. This is due to the scientific reason that, the condom prevents the transfer of stronger HIV virus to the patient. Patients who attend regular HIV counseling less likely to die as compared to patients did not attend counseling about HIV. This may be found due to lack of information, patient does not know their clinical stage and their progress regarding to ART.

The larger the number of CD4 counts, the lower the danger of being at risk of HIV death. The outcomes of this study revealed that the odds of death higher for those with lower CD4 counts. The study supported by other studys.[10,13-15]

Baseline clinical stage III patient 20.67% less likely to die as compared to the reference group clinical stage I patients (HR: 0.7933, 95% CI: 0.6662-0.9446). This may be due to carefully follow-up of ART and eradicating risk factors that affect the survival time of the patient.

Conclusion

The prevalence of death in the zone based on the sample ART follow-up HIV patients was 10.1% with a median survival time of 44.5month. The Cox Proportional Hazard model based on this study from the different Health centers of Central, Western and North Gondar Zones revealed that the factors that affect independently the survival/death time of HIV/AIDS patients who take ART include sex, age, residence, marital status, educational level, condom, clinical stage, CD4, previous counseling attendance about HIV/AIDS. In the case of univariate analysis using log rank test the variable that become significantly related with survival/death time of ART follow-up HIV patients were sex, HIV disclosure, adherence level and baseline functional status.

We found that young and male HIV patients more likely to die on the study area. It needs awareness creation and counseling about their day to day progress. The hazard ratio of patients live in rural area was high. So clinicians and health workers must create awareness for patients who live in rural area. Patients who use condoms during their sexual intercourse are less likely to die from HIV/AIDS. Health workers should guide those patients who do not use condom during sexual intercourse with their partners to wear condom in order to control virus transmission and other

infection. In this study TB infection was not significant on the survival time of HIV patients using Cox Proportional Hazard model. So we recommend other researchers in the future to give more emphasis about this covariate using parametric survival model.

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