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Detecting Predictors of Viral Load Count Change and Risk for Death of HIV Infected patients under HAART at Dile-Chora Referral Hospital: A Joint Modelling Data Analysis

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Abstract

Introduction: Viral Load is the number of HIV viral particles per milliliter of blood; determinations are important prognostic marker of disease progression than CD4 count and, when used appropriately, provide a valuable tool for the management of individual patient. This research was conducted with the objective to identify potential predictors for Viral Load change and time to death for HIV/AIDS infected patients under HAART at Dil-Chora Specialized Hospital from January 2016 up to December 2020.

Methods: A retrospective study design was conducted from 632 selected HIV infected patients in the ART clinic at Dile-Chora specialized Hospital under the follow-up period from January 2016 up to December 2020. The analysis consists of exploratory data analysis, the Kaplan-Meier survival estimate and Log-Rank test were used to compare the survival time and fitting three different models namely; a generalized linear mixed-effects model for the longitudinal data, a semi-parametric survival model for the time-to-event data and joint modeling of the two responses linked through their unobserved random effects.

Results: The log of expected Viral Load change of the educated HIV infected patients was significantly lower by 0.0429 copy/cells (p-value=0.008) compared to the non-educated HIV infected patients keeping all other variables constant. The estimated association parameter (θ_0) in the joint model is 0.269 and statistically significant (p-value =0.043). This providing evidence that there was a very high association between the two sub-models. The relationship between the longitudinal change of Viral Load and the risk of death was positively associated.

Conclusions: The predictor education level, Weight, functional status, and clinical stages were statistically significantly associated with the two responses of HIV/AIDS patients. When evaluating the overall performance of both the separate and joint models in terms of model parsimony, goodness of fit and the statistical significance of the association parameters, the joint model performs better.

Keywords: Viral Load change, HAART, generalized linear mixed model, Cox proportional hazard model, Joint Model

1. Introduction

Human immunodeficiency virus gradually attacks the immune system, which is our body's natural defense against illness [1]. AIDS is deadly infectious disease caused by HIV [2]. It is the final stage of HIV infection, where the body can no longer protect itself.

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HIV/AIDS infects peoples of all of age, sexes, races and income status, leading to poor health and socio-economic outcomes across the world [2]. HIV has no cure still now. However, with the right treatment and support, infected people can live longer and healthy lives with it. To do this, it is especially important to take treatment correctly and deal with any possible side-effects [1]. Determining viral load, the number of HIV virus particles per milliliter of blood, is a more important prognostic marker of disease progression than CD4 counts and, when used properly, is a valuable tool in the management of individual patients [3]. Routine viral load testing, which is the golden standard for the monitoring of HIV treatment, was recommended by WHO [4].

Globally, around 74.9 million people have been infected with HIV and 32.0 million people have died of AIDS-related illnesses since its emergence in 1981. By the end of 2018, about 37.9 million people globally were living with HIV of which 36.2 million are adults. Sub-Saharan Africa remains among the hardest hit regions by the pandemic, with nearly one in every 25 adults 4.2% living with HIV, accounting for nearly two-thirds of the global total HIV cases [8]. In 2018, about 690,000 people were infected with HIV in Ethiopia, and 23,000 were newly infected with HIV. According to EDHS 2016 report show Gambella region (4.8%) and Addis Ababa (3.4%) to have the highest HIV prevalence rates while Somali (<0.1%), and Southern Nations, Nationalities and peoples (SNNP, 0.4%) regional states have the lowest. The adult HIV prevalence in Ethiopia is 0.9%, with varying burdens by sex, age, and other demographic characteristics, across sub-regions and population groups.

ART was introduced in Ethiopia in 2003, and in 2005 the Ethiopian government launched free access in different health sectors to improve the quality of life of People Living with HIV/AIDS [10]. As of June 2017, 20.9 million people living with HIV were accessing ART globally. In eastern and southern Africa there were 11.7 million people were accessing ART in 2016 [8]. For the year 2013-14, FMOH reported that 1047 health facilities were providing ART 492, 649 PLWHA had started ART, and 344,344 people were using ART. The Amhara regional state in north-west Ethiopia comprises the highest proportion of ART users, with 102,088 individuals [10].

The absence of multidimensional and multispectral approaches in dealing with the HIV/AIDS-related problems and an inability of public managers to link the needs of those, whom they serve with good governance and administrative support, reduce the resilience of communities towards HIV/AIDs [13]. A few numbers of studies like [18], with their massive limitations attempted to determine the trend of viral load and its associated factors after patients started ART. Longitudinal data analysis should be used to analyze the change of Viral Load over time of HIV-infected patients under ART treatment as there is correlation among Viral Load of an individual

measured at different time points. Most researches conducted about HIV-infected patients were on the survival time of the patients after the initiation of ART [19, 20]. Even though the number of people living with HIV on antiretroviral treatment is increasing from year to year, there are a number of AIDS-related deaths registered every year. This indicates that there are other factors affecting the progression of the disease and the survival status of HIV positive patients as well. Therefore, it is important to asses' other factors those affect the effectiveness of the treatment over time by using Joint modeling analysis. Joint models for longitudinal and time-to-event data are models that bring these two data types together (simultaneously) into a single model so that one can infer the dependence and association between the longitudinal biomarker and time to event to better assess the effect of a treatment [21]. Available methods for the joint modeling of longitudinal and time to event outcomes have typically allowed for single longitudinal outcome and a solitary event time. This study was undertaken with the objective to identify some common socio-demographic, clinical variables and other variables that affect viral load change and deaths from ART treatment of HIV infected patients under ART at DCRH through joint model analysis and make recommendations so that guidelines can be provided in order to help combat the problem of viral load change and deaths from ART treatment for HIV/AIDS adult patients. The result of the study may enable clinicians to enhance the awareness of the society about factors that increase the probability of death by HIV/AIDS. It helps the government & non-governmental institutions to take evidence-based interventions to give awareness for factors and covariates that affect HIV/AIDS and related disease. It recommends different methods to control the disease progression.

2. MATERIALS AND METHODS

2.1. Study Area and Design:

A retrospective follows up study design was conducted at Dil Chora Referral Hospital, Dire Dawa, and Ethiopia.

2.2. Source of data and Study population

All HIV/AIDS infected patients in Dile Chora Referral Hospitals are used as source of population for this study. The study population consists of all HIV infected adult patients started the HAART treatment any time between 1st January 2016 to 30th December 2020 at Dil Chora Referral Hospital.

2.3. Inclusion Criteria

Patients whose age was above 18 years' old that were attended two and more than two follow up visit HAART treatment in ART clinic for refilling their prescription, and who were initiated

on ART during the period 1st January 2016 to 30th December 2020 at Dil-Chora referral Hospital would be included in the study.

2.4. Sample size determination

For current investigation, there were 2304 HIV positive patients whose follow ups were from January 2016 to December 2020. Among these patients, 632 were adult patients and considered as a sample by considering inclusion criteria. Hence, all patients under treatment whose follow ups were in the study period considered as sample size.

2.5. Variables under current investigation

The two response variables under current investigation were the longitudinal measure outcome, Viral Load count change, and the survival outcome, time to death of HIV positive patients: The longitudinal response variable was the number of Viral Load count change (copies/mL) in absolute value over the EAC session (3–6 months) and the survival endpoint of interest is death from HAART treatment.

In this study, expected covariates that may associate with Viral Load change and survival time from HAART among patients living with HIV/AIDS are: - Sex, Age, weight, religion, disclosure of the disease, Place of residence, marital status, Adherence level, Opportunistic infection, WHO clinical stage, Functional status and Baseline CD4.

2.6. Method of Data Analysis

Descriptive Statistics and Data Exploring

Data exploration is a very helpful tool in the selection of appropriate models. Thus, individual profiles plot, and the mean profile plot for the longitudinal and Kaplan Meier plot for survival data sets are considered. A frequency table for all datasets is used.

Inferential Statistics

In this study we use a generalized linear mixed model for longitudinal data, cox-proportional model for survival data and joint model of two outcomes for longitudinal and survival measurements. The joint longitudinal analyses are used to identify factors that affect the longitudinal measures of Viral Load change and survival status. In this study we use Poisson generalize mixed model and cox-regression model and joint analysis of Poisson generalized mixed model and cox- regression model. The data were analyzed using Stata and R statistical software packages. The statistical decision was made at a 5% level of significance.

Separate Longitudinal Models

Longitudinal responses may arise in two common situations. One is when the measurements are taken on the same subject at different times (i.e., when multiple observations are made on the same subject or unit of analysis over time) and the other is when the measurements are taken on related subjects. In both cases, the responses are likely to be correlated. In this study, we use

longitudinal count data, which is Viral Load data by using a generalized linear mixed model. In this study, a Poisson regression model with normal random effects and a model that accounts for both correlations between repeated measures and over dispersion simultaneously, combined (Poisson-Gamma-Normal) model was considered in line with [22].

Survival Data Analysis

Survival Data Analysis is used to analyze data in which the time until the event is of interest. The survival time response is usually continuous. The principal endpoint for modeling and analysis of survival data was the time until an event occurs (time to event data). In the study, we used the cox-proportional hazard model to identify factors that affect the time to death of HIV infected patients who are taking HAART. The survival distribution provides estimates of descriptive statistics such as the median survival time. The Kaplan-Meier, Nelson-Aalen, and life tables are the most widely used to estimate survival and hazard functions. In this study, we used the Kaplan-Meier estimator.

Joint Modeling for Longitudinal and Survival Data

In clinical trials often generate both longitudinal data and survival data. There are many ways to analyze the data separately [23]. However, when longitudinal data are correlated with survival data, fitting separate models for each kind of data may not give complete information. However, the joint model consists of two linked sub-models, the measurement model for the longitudinal Process and the time to event model for the survival process. This approach used to obtain less bias and more efficient inference [24].

The intuitive idea behind these models is to couple the survival model, which is of primary interest, with a suitable model for the repeated measurements of the endogenous covariate that was account for its special features. In this situation, we used a generalized linear mixed models (GLMM) sub-model for longitudinal measurements and a Cox proportional hazard sub-model for survival data.

Longitudinal sub model

In most joint models studied in the past decade, longitudinal data are delineated by a generalized linear mixed model assuming heterogeneous within-subject variance. Let us use the true unobserved value of the longitudinal covariate m_i (t). Taking into account that the longitudinal information y_{ij} is collected with possible measurement errors, the first step towards measuring the effect of the longitudinal covariate to the risk for an event is to estimate m_i (t), to reconstruct the complete true history m_i (t) to each subject. Therefore, the GLMM for the longitudinal outcome is given by,

$$g(\mu_i(t)) \quad = g(E(y_i(t)/\beta, b_i)) = x_i'(t)\beta + z_i'(t)b_i$$
$$m_i(t) = g(E(y_i(t)/\beta, b_i)) = x_i'(t)\beta + z_i'(t)b_i$$

$m_i(t)$= true and unobserved longitudinal outcome

For the case of Viral Load change which Poisson data is (i.e. $Y_i(t)$ ~Poisson ($\lambda_i(t)$)), then the longitudinal sub model becomes:

$$ln(\lambda_i(t)) = x_i'(t)\beta + z_i'(t)b_i = \lambda_i(t) = e^{x_i'(t)\beta + z_i'(t)b_i}$$

$$m_i(t) = \exp(x_i'(t)\beta + z_i'(t)b_i)$$

$m_i(t)$= true and unobserved longitudinal outcome

For the case of Viral Load Poisson data with over dispersion becomes

$$Y_i(t) \sim \text{Pois}\ (\lambda_i(\text{t}) = \theta_i(\text{t})\text{k}_\text{i}\ (\text{t})),\ \ \text{k}_\text{i}(\text{t}) = \ x_i'(t)\beta + z_i'(t)b_i$$

$$m_i(t) = \lambda_i(t) = \theta_i(\text{t})e^{x_i'(t)\beta + z_i'(t)b_i}$$

$m_i(t)$= true and unobserved longitudinal outcome

$$b_i \sim N(0, D),$$

Where $\theta_i(\text{t})$ is over dispertion parameter, $\boldsymbol{x_i(t)}$and $\boldsymbol{z_i(t)}$are the design vectors for fixed effects $\boldsymbol{\beta}$, and for the random effectes $\boldsymbol{b_i}$ respectively, D is a covariance matrix for random effects .

Survival sub model

We assume a Cox proportional hazards model for the survival data model. The goal used to associate the true and unobserved value of the longitudinal outcome at time t, denoted by $m_i(t)$, with the event outcome t_i. To know the effect of $m_i(t)$ on the hazard of death, a standard option is to use a relative risk model of the form [56] then the Cox proportional model formula is given by: $\lambda(\text{t}/x_{ij}, m_i(t)\ , \theta_o\ , \gamma) = \ \lambda_o(t)\exp(\gamma^T x_{ij} + \theta_o\ m_i(t))$

Where

x_{ij}=is a vector of fixed effect covariates in the Cox model

β = Denotes a vector of parameters for fixed effect covariates in the Cox model

θ_o =Quantifies the vector effect of the underlying longitudinal outcome (Viral Load change) to the risk for an event (death) $m_i(t)$=$g(\mu_i(t)) = x_i'(t)\beta + z_i'(t)b_i$ the true values of longitudinal covariates.

The two sub-models are linked by joint random effects in the two outcomes (longitudinal change of viral load and survival time to death). If the regression coefficient θ_o= 0, there is no association between two random effects in the two outcomes, and the joint model is reduced to a separate model. Thus, the association between longitudinal response and survival is determined by the regression coefficient (θ_o) of covariate $m_i(t)$ in the Cox model [25]. We assume that these two sub-models are independent given the covariates and random effects.

$$b_i = N(0, D)$$

Joint Model Diagnosis

Diagnostic checking is particularly important. A standard tool to perform model diagnostics was residuals plots and formal statistical tests

Goodness of Fit Tests for GLMM

In the presence of over dispersion, an alternative approach to model is an over dispersion Poisson regression model. For over dispersion Poisson regression model, the major assumption considered is the variance of the count data is larger than the mean. Here the diagnostic tests are concerned with checking for fitness of the model. The most well-known goodness of fit test of statistics used was the Deviance function and Pearson's chi-square [26]. The Wald test statistic is commonly used to test the significance of individual parameter regression coefficients for each independent variable.

Diagnosis of the Cox proportional Hazards Model

The hazard function of one individual is proportional to the hazard function of the other individual is Proportional hazard, i.e., the hazard ratio is constant over time. There are several methods for verifying that a model satisfies the assumption of proportionality, among those the Schoenfeld residuals were considered in this study to check the assumption of proportionality. The Cox-Snell residuals were considered residuals for the survival sub model [27]. It is the most common type of survival time residual.

Missing Data Treatment

Missing data (or missing values) is defined as the data value that is not stored for a variable in the observation of interest. There were different imputing missing values in the longitudinal study. The most popular imputation method for handling missing value is multiple imputations [28].

3. Results

Descriptive statistics were used to summarize the baseline characteristics of participants in the study area. The baseline characteristics of respondents were summarized as indicated in Table 1.

Table 1 indicates out of a sample of 364 female patients, 73.63 % were censored and the remaining 26.37% were died. Majority (78.73%) of the infected patients with censored status were with working functional status, (i.e., an individual able to perform usual work in and out of the house), followed by those with ambulatory type of functional status who accounted for 70.1% were censored, and 48.48 % of bedridden patients were died. Regarding the clinical stage of censored patients, 76.04% were at clinical stage I, 76.71% at clinical stage II, 80.75% at clinical stage III and the rest 71.88% were at clinical stage IV when they started HAART. The adherence statuses of censored patients 67.72% were poorly adhered, 68.31% were fairly adhered, and 80.8 % were good adhered. From urban area 26.05% of patients were died and 24.15 % of died patients were free from opportunistic infection disease (no OIs). Among a total

sample of 29.14 % of died patients were orthodox. At enrolment, the average (std.dev) baseline age in years, baseline weight per kilogram and baseline CD4 count per cells/mm3 were 34.81(6.91), 46.7(8.001) and 385.38(197.68) respectively.

Table 1. Baseline Characteristics of Potential Predictors for HIV/AIDS infected Patients

Characteristics	Categories	Survival status		
		Censored (%)	Event (%)	Total (%)
Sex	Female Male	268(73.63) 194(72.38)	96 (26.37) 74 (27.62)	364(100) 268(100)
Marital status	Living without partner Living with partner	151(65.65) 311(77.36)	79(34.35) 91(22.64)	230(100) 402(100)
Educational level	No -education Education	165(67.07) 297(76.94)	81(32.93) 89(23.06)	246(100) 386(100)
Religion	Muslim Orthodox Others	103(71.53) 197(70.86) 162(77.14)	41(28.47) 81(29.14) 48(22.86)	144(100) 278(100) 210(100)
Residence	Urban Rural	321(73.95) 141(73.44)	119(26.05) 51(26.56)	440(100) 192(100)
Disclosure	No Yes	140(74.07) 322(75.69)	49 (25.93) 121(24.31)	189(100) 443(100)
Clinical Stage	Stage I Stage II Stage III Stage IV	92(76.04) 168(76.71) 256(80.75) 46 (71.88)	29 (23.96) 51(23.29) 61(19.25) 18(28.12)	121(100) 219(100) 317(100) 64(100)
Functional status	Ambulatory Bedridden Working	143(70.10) 34(51.52) 285(78.73)	61(29.9) 32(48.48) 77(21.27)	204(100) 66(100) 362(100)
Adherence	Poor Fair Good	107(67.72) 153(68.31) 202(80.8)	51(32.28) 71(31.69) 48(19.2)	158(100) 224(100) 250(100)
Opportunistic infectious	No Yes	271(75.85) 191(73.46)	101(24.15) 69(26.54)	372(100) 260(100)
TB status	Yes No	161(67.08) 301(76.79)	79(32.02) 91(23.21)	240(100) 392(100)
	Characteristics of some continuous variables			
Mean Age (Std. dev) at baseline	34.81(6.91)			
Mean Weight (Std. dev) at baseline	46.7(8.001)			
Mean CD4cell count (Std. dev) at baseline	385.38(197.68)			

Exploring Individual Profiles

The result of Figure 1 shows that the individual profile plot of Viral Load Change of HIV infected patients included in this study. It is the plot of Viral Load Change of each patient over visit time. The individual profile plot was obtained to gain some insights into the data or to show the pattern of the data over time. Some individuals have erratic Viral Load Change and others have a slowly increasing and decreasing Viral Load Change over time.

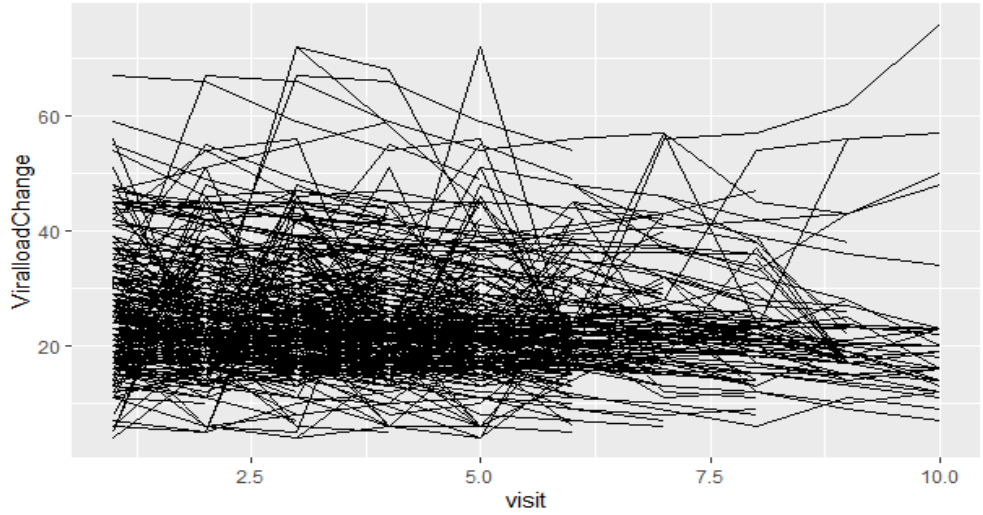

Figure 1. the individual profile plot of Viral Load Change of HIV infected patients

Exploring Mean Profiles

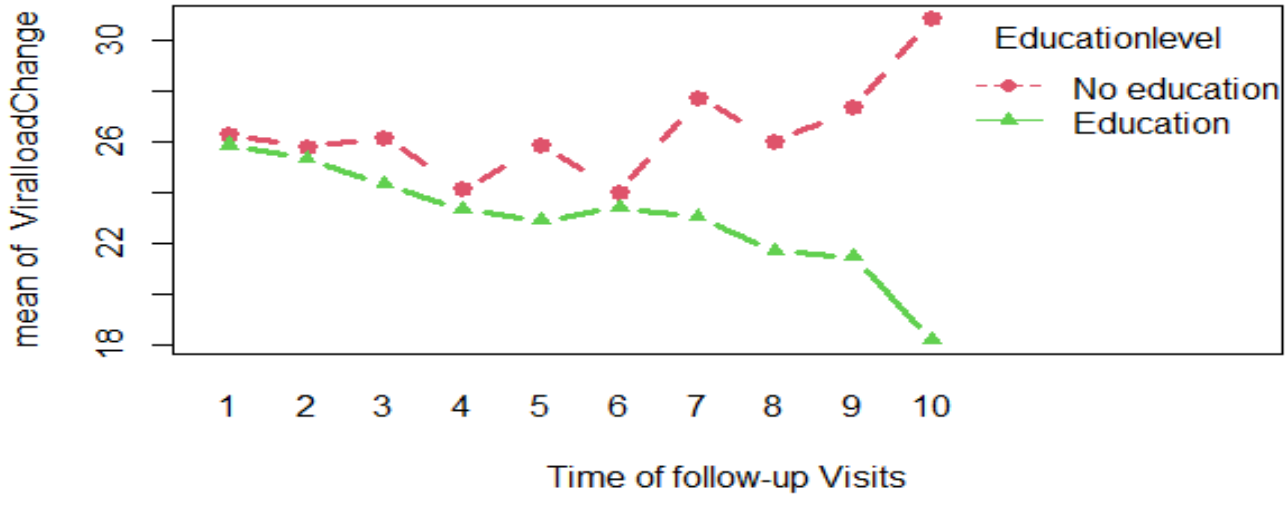

Figure 2. Mean profile plot of Viral load Change by Education level of respondents

The above figure displays the mean profile plot of Viral load Change by the education level of patients over the follow-up visit times, as we can see from the graph, educated patients were relatively lower average Viral load Change over the follow-up times than non-educated patients.

Kaplan- Meier Survival Curves

The Kaplan-Meier survival curves for each study predictor provide an initial insight into the shape of the survival function. The Kaplan-Meier survival curves to see whether there is a difference in time to death between different categories of the covariates.

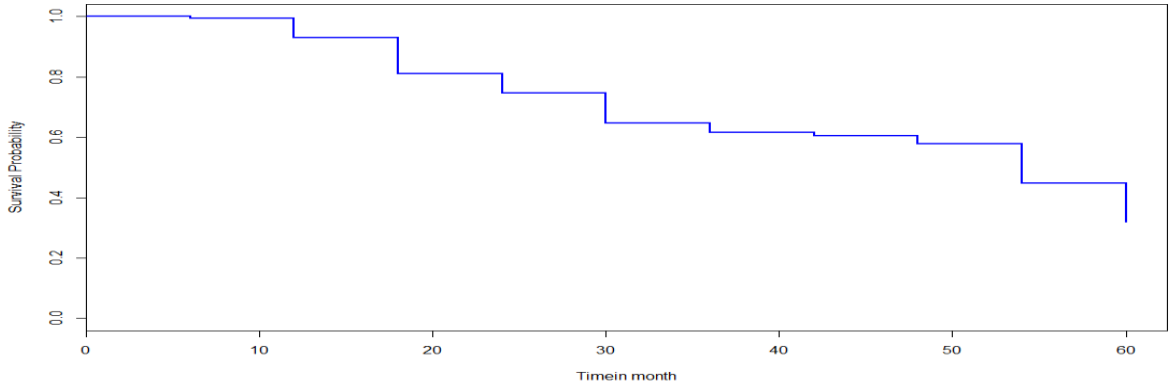

Figure 3. The overall estimate of Kaplan-Meier survivor function plot of HIV/AIDS infected patients

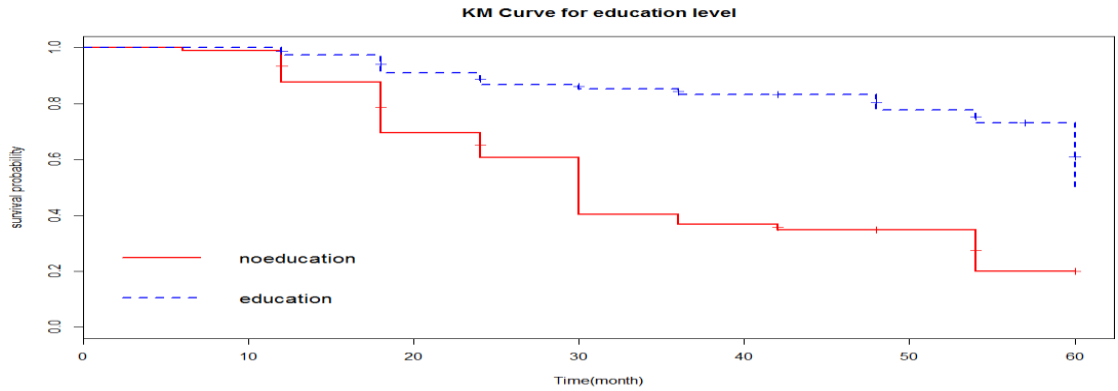

Figure 4. Kaplan-Meier survival plot for educational level for HIV infected patients

We observed a difference between the survival curves. The plots indicate that educated patients had better survival time than non-educated patients. The plots of other baseline covariates were presented

Joint Model Analysis and Interpretations

An unstructured covariance structure was applied for a longitudinal response as well as we did in separate model analysis to fit the joint model for the two responses viral load change and time to death. The estimate of the association parameter (θ_o) in the survival sub model under joint

analysis was significantly different from zero, providing that there is evidence on the association between the two outcomes. The amount of variability among patients due to the effect of observation time was 0.0483 and the correlation is -0.0223which indicates the negative correlation between intercept and slope.

Table 2. Parameter Estimates and Standard Errors (Std.Err) under the joint modelling analysis

Longitudinal process				Survival Process			
Parameters	$\hat{\beta}$	Se($\hat{\beta}$)	p-value	Parameters	$\hat{\beta}$	Se($\hat{\beta}$)	p-value
Intercepts	3.1743	0.0679	<0.001	Weight	-0.0426	0.0147	0.004
Obstime	-0.1087	0.0229	<0.001	Age	-0.3632	0.0585	<0.001
BaselineCD4	-0.0239	0.0111	0.031	Educ(ref=No_educ)			
Weight	-0.1077	0.0226	<0.001	Education	-0.1133	0.0228	<0.001
Educ(ref= No education)				Clinic stag (ref=stage Iv)			
Education	-0.0429	0.0161	0.008	Stage I	-0.0491	0.0241	0.042
Clinictg(ref=stage IV)				Stage II	-0.0752	0.0165	<0.001
Stage I	-0.0454	0.0148	0.002	Stage III	-0.402	0.097	<0.0001
Stage II	-0.0825	0.0374	0.027	Adherence (ref=Good)			
Stage III	-0.0141	0.0113	0.212	Fair	0.0192	0.0176	0.278
Functional status(ref=Ambulatory)				poor	0.3315	0.0972	0.001
Working	-0.1712	0.0131	<0.001	Functional status (ref =Ambulatory)			
Bedridden	0.0976	0.0323	0.0025	Working	-0.351	0.106	0.001
OIS (ref=No)				Bedridden	0.258	0.097	0.008
Yes	0.0599	0.0333	0.072	OIS (ref=No)			
Adherence (ref=Good)				yes	0.107	0.086	0.21716
Fair	0.0239	0.0147	0.104	Association parameter(θ_0)	0.269	0.133	0.043
poor	0.0753	0.0106	<0.001				

Random effects	Std.dev	95% CI	
		Lower	Upper
Intercept (b_{0i})	3.1743	3.0413	3.3073
Obstime(b_{1i})	0.0483	0.0305	0.0661
cor(b_{0i}, b_{1i})	-0.0223	-0.0517	0.0072

Note: - b_{0i} and b_{1i} are random effects

HR=hazard ratio

According to the joint result, we can interpret that the parameters of the longitudinal sub-model and survival sub-model.

In the longitudinal sub-model, the estimated coefficient of fixed effect intercept was 3.1743, indicates that the log of expected Viral load change of the HIV infected patient was 3.1743 copy/cells by excluding all covariates in the model (p-value<0.001).

For a one kilogram increased in the weight, the log of expected Viral Load change of HIV infected patients was significantly decreased by 0.1077 copy/cells (p-value <0.001) keeping all other variables constant. For a unit increased in the baseline CD4 cell count, the log of expected Viral Load change of HIV infected patients was significantly decreased by 0.0239 copy/cells

(p-value =0.031) keeping all other variables constant. The log of expected Viral Load change of the educated HIV infected patients was significantly lower by 0.0429 copy/cells (p-value=0.008) compared to the non-educated HIV infected patients keeping all other variables constant.

The log of expected Viral Load change for HIV infected patients who had clinical stage I were significantly lower by 0.0454 copy/cells (P_value=0.002) compared to the HIV infected patients who had clinical stage IV keeping all other variables constant and the log of expected Viral Load change for HIV infected patients who had clinical stage II were significantly lower by 0.0825copy/cells(P_value=0.027) compared to the HIV infected patients who had clinical stage IV keeping all other variables constant.

The log of expected Viral Load change of the HIV infected patients who had working functional status was significantly lower by 0.1712 copy/cells (p-value<0.001) compared to the HIV infected patients who had ambulatory functional status keeping all other variables constant and the log of expected Viral Load count change of the HIV infected patients who had bedridden functional status were significantly higher by 0.0976 copy/cells (p-value=0.0025) compared to the HIV infected patients who had ambulatory functional status keeping all other variables constant. For a unit increased in the observation time (follow-up time), the log of expected Viral Load change of HIV infected patients were significantly decreased by 0.1087 cells/ mm3 (p-value = <0.001) with a unit increment of time in month keeping all other variables constant.

In the survival sub model, the estimated hazard ratio of death for educated HIV infected patients relative to non-educated HIV infected patients were exp (-0.1133) = 0.8928), indicates that the risk of death of the educated HIV infected patients was 89.28% [P_value =0.000] lower than the risk of death of the non-educated HIV infected patients keeping all other variables constant.

The estimated hazard ratio of death for HIV infected patients who had clinical stage I, clinical stage II and clinical-stage III relative to HIV infected patients who had clinical stage IV were exp(-0.0491)= 0.9521,exp(-0.0752)=0.9276 and exp(-0.402)= 0.6689, indicates that the risk of death of the HIV infected patients who had clinical stage I, clinical stage II and clinical-stage III were 95.21% [P_value=0.042], 75.05%[P_value=0.000] and 64.49%[P_value=<0.001] lower than the risk of death of the HIV infected patients who had clinical stage IV respectively keeping all other variables constant.

The estimated hazard ratio of death for HIV infected patients who had poor adherent relative to HIV infected patients who had good adherent were exp (0.3315) =1.3931 indicates that the risk of death of HIV infected patients who had poor adherent were 39.31% [P_value =0.001] higher than the risk of death of HIV infected patients who had good adherent keeping all other variables constant.

The estimated hazard ratio of death for HIV infected patients who had working functional status relative to patients who had ambulatory functional status was exp(-0.351)= 0.7039, indicates that the risk of death of the HIV infected patients who had working functional status was 70.39% [P_value=0.001] lower than the risk of death of the HIV infected patients who had ambulatory functional status keeping all other variables constant and the estimated hazard ratio of death of HIV infected patients who had bedridden functional status relative to patients who had ambulatory functional status was exp(0.258)= 1.2943, indicates that the risk of death of the HIV infected patients who had bedridden functional status was 29.43 [P_value =0.008] higher than the risk of death of the HIV infected patients who had ambulatory functional status keeping all other variables constant.

The estimated association parameter was θ_0 = 0.269 (p-value=0.043), indicates that there is a positive association between the change of Viral Load over time and time to death of HIV/AIDS infected patients. The result indicates that the lower value of change of Viral Load over time was associated with a lower risk of deaths.

4. Discussion

The overall performance of the separate and joint models in terms of model parsimony and goodness of fit, the joint model was performed better based on its standard error. In our study, the association parameter was statistically significant in the joint model, indicates that the two responses were correlated and shows that the joint model is better fit to the data than the separate models. This finding was consistent with another study [25]; the result showed that the statistical significance of the association parameter is evidence that the joint model is a better fit than the separate models.

The log of expected Viral Load change was lower for educated patients compared to non-educated patients. This might occur because as patients become more educated, they may have better care of their health and they may have enough understanding about HAART for this reason, the Viral Load change may decrease. This result was consistent with another study [27]. For this study, the risk of deaths for the educated patient was lower than non-educated patients.

This might be the more non-educated patients the more being a higher risk of death, since they may not have enough understanding and knowledge about HAART, the patients have not to use ART properly then the patients were a higher risk of death. This result was consistent with another study [31, 32].

The log of expected Viral Load change was found evolving differently between patients with clinical stage I, stage II, and patients with clinical stage IV based on the result of separate and joint models. The log of expected Viral Load change was higher for patients who had clinical stage IV compared to patients who had clinical stage I and clinical stage II. Since, patients who are found in clinical stage I and II, indicates they are less likely affected by the disease relative to patients who are found in clinical stage IV, this might make them able to take the treatment properly due to less replication of the virus in their body and this leads to decreasing their viral load progression. This result was consistent with another study [30]. For this study that the risk of death of the patient who had clinical stage IV was higher than the hazard of death of the patient who had clinical stage I, stage II, and stage III. Since, patients who are found in clinical stage I, II and III indicate they are less likely affected by the disease relative to patients who are found in clinical stage IV, this might make them able to take the treatment properly due to less replication of the virus in their body and due to this death from HAART may be lower. This result was consistent with another study [17,31].

The log of expected Viral Load change was found evolving differently between patients with working functional status and patients with ambulatory functional status based on the result of separate and joint models. The log of expected Viral Load change was lower for patients who had a working functional status compared to patients who had ambulatory functional status and the log of expected Viral Load change was higher for patients who had bedridden functional status compared to patients who had ambulatory functional status. This might be due to the fact that the functional status of patients can be seen as an indicator of the severity of the progression of the disease. Those patients who are in working functional status have the strength to work and engage themselves usual work in or out of the house which may help them generate additional income and improve their quality of life, have to get the drug on time. This result was consistent with another study [30].

For this study, the risk of deaths of the patient who had a working functional status was lower than the patient who had ambulatory functional status and the risk of deaths of the patient who had ambulatory functional status was lower than the patient who had bedridden functional status. This might be due to the fact that the functional status of patients can be seen as an indicator of the severity of the progression of the disease. Those patients who are in working functional

status have the strength to work and engage themselves usual work in or out of the house which may help them generate additional income and improve their quality of life and ambulatory functional status have able to perform activities of daily living but cannot work out of the house. Even though patients who are staying in bed in hospitals are accessing medical care and support, cannot do anything on their own to create a stress-free environment for them. Thus, as expected, patients with ambulatory and bedridden status are at a higher risk of mortality than working patients. This result was consistent with another study [32, 17].

Weight is an important socio-demographic predictor of Viral Load change implies that the log of average Viral Load change decreases with an increase in Weight. This result shows consistent with other studies [29]. For this study, the risk of death for good adherent patients was lower than in poor adherent patients. This could happen because poor adherence to ART negatively affects the suppression of viral replication, increasing the risk of drug resistance and treatment failure. This result shows consistent with other studies [32].

4. Conclusion and Recommendation

4.1. Conclusion

The main goal of this study was to identify predictors that have strong association with the longitudinal change of Viral Load and the survival experience (time to deaths) of HIV/AIDS patients attending HAART at Dile-Chora General Hospital using joint model analysis.

From the result we conclude that log-rank tests showed that the survival experience of different groups of AIV/AIDS patients on functional status, education level, adherence, Clinical stage and OIS statistically significant.

From this specific study the joint model was the better fit than the separate survival and longitudinal models. The longitudinal sub model under the joint modeling analysis shows that the predictor observation time, weight, baseline CD4 cell count, education level, clinical stage, and functional status were significantly associated with Viral Load change. From the survival sub model under joint modeling analysis the predictor education level, clinical stage, weight, adherence, and functional status were significantly associated with time to death of HIV infected patients. Additionally, the association parameter (the effect of unobserved true longitudinal outcome) was statistically significant on time to the death of HIV infected patients. Based on the joint model analysis found that the education level, weight, functional status, and clinical stages were statistically significantly associated with the two responses (longitudinal change of

Viral Load and time to death) of HIV infected patients. Thus, authors concluded that the joint model was preferred for simultaneous analyses of repeated measurement and survival data.

4.2. Recommendation

It is recommended that further studies of this nature include other important covariates that were not included in this study. Such covariates include nutritional status and many others. Starting from our finding we recommended that concerned bodies should create awareness in the society about factors of increasing Viral Load change and increased risk of mortality. From the results of our final model, we observed that functional status with bedridden harms the suppression of Viral Load change. And also this study depicted those patients who were adherence with poor, functional status with bedridden were associated with higher risk/hazard of deaths. Therefore, such patients should be informed about the need for early diagnosis of HIV infection, and starting treatment early is very important. Finally, a fitting joint model is recommended when the two responses or outcomes are correlated.

5. Data Sharing Statement

Authors confirmed that the data used for this research are available from the corresponding author.

6. Acknowledgment

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7. Author Contributions

AA wrote the proposal, develop data collection format, supervise the data collection process, analyzed and interpreted the data. KB participated in design and data analysis and critically read the manuscript and gave constructive comments for betterment of the manuscript based on her field of specialization.

8. Disclosure

The authors report no financial and non-financial competing interests in this work.

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