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On Survival of Hiv Patients Using Share Frailty Model

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Abstract: *In a situation of terminal event of death happening during follow-up period to preclude further occurrence for recurrent event, the shared frailty model is used considering proportional hazard model for the recurrent and terminal process. Covariates effect taken into account are the ART status of entry, number of medication taken and CD4PepBase of the HIV patient and dependence modeled by the shared frailty model on survival. Human immunodeficiency virus has now reduced from a fatal disease to a chronic disease due to a high rate of antiretroviral treatment ART. ART helps in reducing the viral load and hence bringing mortality due to HIV/AIDS to the lowest minimum. Factors associated with mortality in HIV has significantly studied in the most literature, less attention given to the stages of HIV at which the ART began about the survival time. The awareness and risk factors for mortality at each stage of HIV on when the ART starts for a subject considered in this paper. The research aimed at constructing appropriate measures on stages at which the ART is started to the survival time is evaluated using a shared frailty model to account for heterogeneity within groups of stages of HIV subject.*

Keywords: *HIV, ART, shared frailty.*

I. Introduction

The human immunodeficiency virus HIV has now reduced from life-threatening illness to a chronic disease due to the high rate of antiretroviral treatment ART, which has helped in reducing or suppressing the viral load and hence restoring the immune system. ART has been very effective in reducing mortality and mortality related cases in HIV/AIDS.(.(Masenyetse, Manda, & Mwambi, 2015)(Otwombe, Petzold, Modisenyane, Martinson, & Chirwa, 2014) Africa has the highest number of people living with HIV and the highest ART globally by the need to achieve the millennium development goal MDG of making an increase in the number of people leaving with HIV access the ART HIV infection has significant emotional attachment especially to newly diagnosed patients, most of the patients choose to delay disclosure and treatment until the deal with the emotional shock associated with the diagnosis. This emotional instability is related to high level of stress, depression, anxiety, social stigma, loss of control, potential violence. '(Serovich, Craft, & Reed, 2012) Although the role of factors associated with mortality has significantly studied on HIV- infected persons, to date only a few literature give much attention to the stage at which the patient diagnosed and started the ART and about the survival time. The factor associated with mortality in HIV-infected patients is mostly reported(Protopopescu et al., 2015)mortality as a result of HIV is still high even with the ART, the awareness and the risk factors for mortality at each stage of HIV on when the ART starts need to be studied. Understanding and reporting the dynamics of mortality in ART on HIV stages in Nigeria needs to be investigated and reported as that will influence patient management care as well as awareness of the impact of ART on HIV.

II. Review Literature

Repeated events has a lot of challenges in estimation of effect of covariates of event history model. In recurrent events analysis within subject correlation due to heterogeneity within groups have either higher or lower event rate than other reasons which can be even dependent or measured with the frailty model. (Box-Steffensmeier, Linn, & Smidt, 2014; Mauguen et al., 2013; Mazroui, Mathoulin- Pélissier, MacGrogan, Brouste, & Rondeau, 2013) recurrent event and terminal event such as death can be considered separately or jointly using frailty model aimed at accounting for potential heterogeneity caused by prognostic factors, time dependent recurrent events.

Frailty models was introduced by (Vaupel, Manton, & Stallard, 1979) with universal data used to model heterogeneity among individuals. Improved to multivariate survival model were individuals are allowed to share the same frailty within group or clusters known as the shared frailty model.

Shared frailty model is the multivariate extension of the univariate used in modelling correlation between groups with similar characteristics, with unobserved frailty shared among groups of individual. It can also be regarded as the random effect model for survival data.

The shared frailty model in accounting homogeneity in groups or clusters were failure times has common characteristics which is individuals with common frailty. The subject i (i=1,2,…N),X_{ijk} with jth

recurrence time (j=1,2,…n_i) with cluster k (k=1,2,…n_i), c_i the censoring time of the event, the follow up time T_{ijk} =min (X_{ijk} , c_i) and δ_{ijk} is a binary indicatore for event recurrence is zero when observation is censored and 1 when X_{ijk} is observed. Let $Z_{ijk} = (Z_{1ij}, \dots Z_{nij})$ be a vector of n covariate which can be fix or time dependent for individual i at cluster k at time j. let ω_i a random effect normally distributed with mean 0 and variance θ^2. The standerd frailty assumes all individuals experiences the event of interest with different risk greater than zero, the shared frailty model extends the cox proportional hazard accounting for unobservable heterogeneity among individuals, the shared frailty accounts for the heterogeneity among group of clusters.

The hazard at t_{ijk} for individual with random effect and shared frailty is given by

$$\lambda_{ijk}(t_{ijk}/\omega_i) = \lambda_0(t_{ijk})\exp(\beta' z_{ijk} + \omega_i) \qquad \text{Equ 1.2}$$

λ_0 Is the baseline hazard function ω_i is the random effect that takes account for dependency between successive event within a patient in a specified cluster. The model corresponds to the survival function,

$$s(t_{ijk}/\omega_i) = \exp(-\Lambda_0(t_{ijk})\exp(\beta' z_{ijk} + \omega_i)), \qquad \text{Equ 1.3}$$

Where $\Lambda_0(.)$ is the cumulative hazard function,

When the population is a mixture of susceptible and non-susceptible individuals in different groupsthe shared frailty model can be used. Let $\pi(Z^*)$=P (U=1/Z^*) be the proportion of the more fragile individuals depending on covariate vector $Z^* = (Z_1^*, \dots Z_q^*)$ associated by logistic form with the incidence, $(Z^*) = \frac{\exp(b' z^*)}{1+\exp(b' z^*)}$. Let T be a time to event which is defined only when u=1 with conditional survival function s (t/u=1) =p (T>t/u=1) for the frail subject. Let Z be a covariate vectored associated with latency. Hence the marginal distribution is,

S (t) =1-$\pi(Z^*) + \pi(Z^*)S(t/u=1)$ there for the equation of shared frailty model is

$$\begin{cases} s(t_{ijk}/\omega_i) = 1 - \pi_{ik}(z_{ik}^*) + \pi_{ik}(z_{ik}^*)\exp(-\Lambda_0(t_{ijk}/U_{ik}=1)\exp(\beta' z_{ijk} + \omega_j)) \\ \pi_i(z_{ik}^*) = p(U_{ik} = 1/z_{ik}^*)\dfrac{\exp(\beta' z_{ik}^*)}{(1+\exp(\beta' z_{ik}^*))} \\ \omega_i i.i.dN(0;\theta^2) \end{cases} \qquad \text{Equ 1.4}$$

For one event for an individual. The model can be extended to having more than one event for an individual that is possibility of having a progression after each event ART.

$$\begin{cases} s(t_{ijk}/\omega_i) = 1 - \pi_{ij}(z_{ijk}^*/\omega_i)exp\left(-\Lambda_0(t_{ijk}/U_{ijk})exp(\beta' z_{ijk} + \omega_i)\right) \\ \pi_{ij}(z_{ijk}^*/\omega_i) = p(U_{ijk} = 1/z_{ijk}^*) = \dfrac{exp(b' z_{ijk}^* + \alpha\omega_i)}{\left(1+exp(b' z_{ijk}^* + \alpha\omega_i)\right)} \\ \omega_i \sim i.i.d.N(0;\theta^2) \end{cases} \qquad \text{Equ1.5}$$

Incorporating model with two random effects $\omega_{1ik}\ and\ \omega_{2ik}$ is assumed independent, $\omega_{1ik} + \omega_{2ik}\ and\ \omega_{2ik}$ are correlated. Variance of random effectω_{2ik}, θ_2^2 represent similar heterogeneity for both event, that is the maintained and progression rates. Hence we can assume that maintained and progression rate are correlated with the same random effectω_{2ik}. The other random effect ω_{1ik} is independent of ω_{2ik} accounting for heterogeneity between recurrent event times due to random effect not including the progressed fraction

$$\begin{cases} s(t_{ijk}/\omega_{1ki}\omega_{ik}) = 1 - \pi_{ijk}(z_{ijk}^*/\omega_{2ik})exp\left(-\Lambda_0(t_{ijk}/U_{ijk})exp(\beta' z_{ijk} + \omega_{1ik} + \omega_{2ik})\right) \\ \pi_{ij}(z_{ijk}^*/\omega_{2k}) = p(U_{ijk} = 1/z_{ijk}^*) = \dfrac{exp(b' z_{ijk}^* + \alpha\omega_{2ik})}{\left(1+exp(b' z_{ijk}^* + \alpha\omega_{2ik})\right)} \\ \omega_{1i} \sim N(0;\theta_1^2) \\ \omega_{2i} \sim N(0;\theta_2^2) \end{cases}$$

Through the application of cure shared frailty to model the maintained and progressed on HIV patients at different stages owing to the similarity in clusters, hence using the multiple approach through introduction of rank specific covariates and allowing stage of HIV patient to be different from each event as cluster. This model can simplify by using the traditional stepwise regression analysis on SPSS.

This research will aim at constructing an appropriate measure on stages at which the art is started to the survival time to evaluate this, measure and predict the increase in mortality risk in ART HIV patients. The association at the stage ART begins on survival time will be of great importance, the common frailty use does not address the issue, it used on survival analysis to account for unobserved heterogeneity in risk to disease or death of a subject. To report a family data shared frailty are mostly used. Hence, the shared frailty will be used to account for the stages of administration of ART about survival time.

III. Methods

This research will make use of data collected during the follow-up time from 2009 to 2014 at the University of Maiduguri Teaching Hospital (UMTH) from a population of HIV-patients taking antiretroviral therapy in the hospital at that period, data on 2021 patients will apply to this study. The study subjects will be HIV infected patient diagnosed at different stages as WHO clinical stages (stage 1, stage 2, stage 3, stage 4), at the age range from 15 to 75 years. The shared frailty model will apply at the four different stages.

The dependent variable will be "survival time" while the independent variables will be "social variables". Survival time is defined as the number of days from the date of enrollment of a patient in the HIV-care till one of the events occurs. These events are "death", "lost to follow-up", "and dropped out", "transferred out to other health centers or hospitals" occurred on the stage at diagnosis. However, the social variables will be defined by, the demography, the medical and clinical background of the patients. With classifications such as age, gender, marital status, religion, weight (kg), functional status, clinical stages as classified by WHO (1, 2, 3, 4), the number of ART taken, CD4 cell count (in mm3), and antiretroviral therapy (ART) (yes, no).

Ethics and Data Analysis

Approval for the use of hospital data approved by the University of Maiduguri Teaching Hospital UMTH, Borno state Nigeria.

The most convenient part on the shared frailty model is, it can be analyzed through regression analysis using hierarchy, with the most common and easy to use software SPSS the independent variables were inserted into the analysis in several steps. The control variables age, gender, weight, ART status, number of medications taken, CD4PepBase and CD4Resent.

Step One

The first step of the analysis with relevant independent measures about age. The result of ART status of entry with the value ($\beta - 0.33, p < 0.01, p < 0.05$) has significant influence towards the survival of patients at both 99% and 95% degree of significance.

Step Two

In the second step number of medication taken were considered, which shows that there is a non-significant difference with the value of (β 0.77 $p < 0.01, p < 0.05$). This implies that the number of medication taken those not influence the survival rate of the HIV patient at both 99% and 95% degree of significance.

Step Three

CD4PepBase with the value of (β 0.02, $p < 0.01, p < 0.05$) showing that the CD4PepBase is not significant at 99% but significant at 95% degree of significance influencing the survival rate of the patient at the 95% degree of freedom.

Step Four

CD4Recent with the value (β 0.04, $p < 0.01, p < 0.05$) also shows significance at 95% degree of freedom and not significant at 99%level of significance. This shows that the survival of a HIV patient CD4Recent significantly affect the survival of the patient and does not affect the survival of the patient at 99% degree of significance.

IV. Conclusions

This study demonstrate that the shared frailty model can be analyzed using SPSS software and the result/outcome of the analysis on the stages of HIV about ART status has a significant influence on the survival of HIV patient at both 99% and 95% level of significance. The number of medication taken has no significant difference or influence on the patient at both 99% and 95% level of significance. CD4PepBase and CD4Resent is not significant at 99% level of significance but has a significant influence at the 95% level of significance.

Table 1: Demographic profile of Respondents

Demographic profile of Respondents		
Demographics	**Frequency**	**Percentage (%)**
Gender		
Male	593	41.4
Female	839	58.6
Marital Status		
Single	211	14.7
Married	865	60.4
Widowed	148	10.3
Divorced	187	13.1
Separated	21	1.5

Functional Status		
Active	41	2.9
Died	685	47.8
Lost to follow-up	23	1.5
Lost to dropped out	15	1.0
Transferred	669	46.7
Clinical Stage		
Primary HIV Infection	250	17.5
Clinically Asymptomatic Stage	591	41.3
Symptomatic HIV Infection	382	26.7
Progression from HIV to AIDS	209	14.6
ART Status Entry		
Yes	1358	94.8
No	74	5.2
	Mean	**Std. Deviation**
Age	40.0	9.5
Weight	57.7	11.8

Table 2: Means Standard Deviations, and Intercorrelation for Study Variables,

Means Standard Deviations, and Intercorrelation for Study Variables,											
Variable		**Mean**	**SD**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	Age	40.0	9.5	1							
2	Gender	1.6	0.5	-.220**	1						
3	Wieght	57.7	11.8	.082**	-.027	1					
4	ART Status Entry	1.1	0.2	.013	.036	-.060*	1				
5	Number of Medication	27.5	21.2	.046*	.033	.094**	-.284**	1			
6	CD4PepBase	177.0	123.0	-.076**	.079**	.045*	.182**	-.033	1		
7	CD4 Recent	199.0	129.7	-.038	.064**	.033	.059*	.108**	.461**	1	
8	Survival time	899.3	685.7	.081**	-.021	.074**	-.230**	.775**	-.012	.121**	1
	Note: Gender was coded using dummy variable (I = male; 2 = female)										
	** p< 0.01; *p<0.01. All tests were based on one-tailed.										

Table 3: Hierarchical Regression Analysis Results for Survival time

Hierarchical Regression Analysis Results for Survival time								
Independent Variables	Step 1		Step 2		Step 3		Step 4	
	β	t	β	t	β	t	β	t
Age	0.08	3.06	0.04	2.16	0.04	2.25	0.04	2.26
Gender	0.01	0.24	-0.04	-2.25	-0.04	-2.32	-0.04	-2.37
Wieght	0.05	2.11	0.00	-0.16	0.00	-0.24	0.00	-0.25
ART Status Entry	-0.23	-8.87	-0.01	-0.55	-0.01	-0.78	-0.01	-0.80
Number of Medication			0.77	44.15	0.77	44.13	0.77	43.49
CD4PepBase					0.02	1.28	0.00	0.13
CD4Recent							0.04	2.21
R Square	0.06		0.60		0.60		0.61	
R Square Change	0.06		0.54		0.00		0.00	
F Change	23.89		1949.15		1.64		4.89	
Sig. F Change	0.00		0.00		0.20		0.03	
Note: Dependent Variable- Survival time; ** p< 0.01 * p<0.05 (one-tailed)								

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