

Longitudinal Analysis of CD4 Cell Counts Data on HIV Patients Initiated on Anti-retroviral Therapy: Case of Ayder Comprehensive Specialized Hospital, Tigray, Ethiopia

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Abstract: Human immune virus (HIV) attacks an immune cell called cluster of differentiation 4 (CD4) cells which are responsible for the body's immune response to infectious agents. Even if, HIV is treated through ART, the occurrence of event is still continued. The objective of this study was identifying risk factors of the change in CD4 cell counts on HIV positive patients initiated on Anti-Retroviral Therapy (ART). The study population of this study were consists of 632 HIV+ patients who were under ART follow up from September 2016 - August 2019 in Ayder Comprehensive Specialized Hospital, Ethiopia. Retrospective Longitudinal study was used with minimum three and maximum six times follow up time per individual. The CD4 cell count data were explored using basic descriptive statistics and also a profile of the mean CD4 cell count over the period of the study. Generalized Linear Mixed Model (GLMM) and Generalized Estimation Equation (GEE) models were used to modeling the change in CD4 cell counts over the time. The mean of CD4 cell count revealed that there is an improvement with duration of treatment in linear trend. From the Generalized Linear Mixed Model covariates time, sex, age, weight, hemoglobin level, functional status, regimen class, WHO stage, TB status, time by WHO stage and time by weight significantly determined a change in the CD4 cell count over time. Generalized Linear Mixed Model was the better fitted model compared to GEE as proven by the minimum standard error. Moreover, CD4 count increases in a linear trend over time after patients initiated to the ART program i.e. the immune system increases whereas the progression of the disease turn down due to the therapy. Therefore, patients should start ART treatment early to increase their CD4 cell count.

Keywords: ART, CD4 Cell Count, GEE, GLMM, Longitudinal Data Analysis

1. Introduction

An estimated 1.8 million individuals become newly infected with HIV from the worldwide these about 5,000 of them are new infections per day about 59% of them were accessing ART. This indicates that globally, since 2016 there is an increase of 2.3 million and up from 8 million in 2010 where majority of people who living with HIV are in low and middle income countries [1]. Ethiopia is one of the countries that have been affected by the epidemic with a prevalence of 1.5% [2]. Its burden has been also affected in the North Region, because the prevalence of TB/HIV co-infection at Ayder comprehensive specialized Hospital, Northern Ethiopia was high.

HIV is a virus that attacks an immune cell which is called

CD4 cell that is responsible for the body's immune response for the infectious agents [3]. A normal CD4 cell count contains from 500 to 1400 cells per cubic millimeter of blood. For some people, CD4 counts can drop dramatically, even going down to zero. But it is more important to pay attention to the pattern of CD4 counts than to any one test. Since, HIV infection can getting worse as CD4 count is going down and immune system is getting weaker and the patient is more likely to get sick [4]. In untreated patient, CD4 cells subsequently decline over several years. Significant depletion of CD4 cells can be lead to opportunistic infections and mortality in untreated patient [5].

Longitudinal study considers both the between-subject and within-subject time-related variations, and provides more

efficient estimators than the cross-sectional designs with same number and patterns of observations [6]. But modeling this data using linear regression models might give us inefficient in estimates and measuring the change of CD4 cell count in a longitudinal study is that individuals are measured repeatedly through time. So, the researcher got better to use the natural and most appropriate longitudinal count models in order to find efficient and unbiased estimates in modeling on CD4 count of HIV infected patients who are under the treatment of antiretroviral therapy.

Some researchers like [7] were used a longitudinal approach and suggested that the pattern of growth in CD4 cell count was not linear. But the researchers didn't included the patient that less than 18 years old and didn't explain their justification why they did excluded those patient and also they didn't included most clinical value like TB status at baseline and ART regimen class. Therefore in this study, CD4 counts of HIV infected patients undergoing ART treatment in Ayder comprehensive referral Hospital were used to evaluate the disease response to the treatment over time and to determine the risk factors that affect CD4 count of HIV infected people who are on under ART.

2. Methodology

In this study the latest data were recorded from all HIV/AIDS positive patients initiated to follow up ART from September 2016 to August 2019 in Ayder comprehensive referral Hospital. Ayder comprehensive referral Hospital is located in Tigray region in Mekelle city, Ethiopia. Mekelle is the capital town of Tigray region and it is found about 781kms distance from Addis Ababa. It serves as a teaching and referral center for its catchment areas of the Tigray, Afar and North-eastern parts of the Amhara Regional States including the Eritrean refugees. The Hospital is now emerging as a shining hot-spot for advanced medical care and treatment in the Northern part of Ethiopia. The data used for this study was extracted from the follow up patients chart.

The target populations of this study were HIV positive patients who are followed under ART from September 2016 to August 2019 in Ayder referral Hospital. The total patients in the study period were 814, but due the patients who have less information, dead and lost from the follow up were excluded from the study and then the data consisted of 632 individuals measured their CD4 cell counts with minimum of three and maximum of six measurements per individual, including the baseline and those who started first line ART regimen class were also included in the study population. The CD4 cell counts per mm³ of blood were taken approximately in every 6 months regardless of their visit to ART clinic. The data were consisted missing values, and in this study applied random hot-deck imputation of circumcised and non-circumcised respondents separately. Random hot-deck on a single vector can be applied with the impute function of the Hmisc package in R.

The dependent variable of this study was the CD4 cell count per cubic millimeter of blood of HIV-infected patients who are under ART treatment. Since it is measured

approximately every 6 months (recorded at the ART entry and at 0-6, 6-12, 12-18, 18-24, 24-30 and 30-36 visits), a common measuring (observation) time was used for all patients. The covariates that was used for this study was selected from different literatures and those were: Sex, Age, Weight (kg), Time, Place of resident, Clinical Stage, hemoglobin level, adherence to drugs, Functional status, TB status at baseline, disclosure and ART regimens taken.

2.1. Longitudinal Data Analysis Model

A longitudinal study is a result of repeated measurements on each subject. Hence in this study, HIV positive patients were followed over time and monthly measures such as CD4 cell counts were recorded. Such like this data are correlated within subjects and it requires special advanced statistical techniques for valid analysis and inference. Generalized linear mixed effects and Generalized Estimation Equation model are used to modeling the change in CD4 cell count over given time. Mixed model takes into account both the within and between sources of variations these are flexible enough take to account for the natural of heterogeneity in the population [8].

2.2. Exploration Data Analysis

Exploratory data analysis is the starting analysis, it is an important to create graphs that expose the patterns relevant to the scientific question and this helps to observe the structure as well as the pattern of data. This gives a direction to select the appropriate statistical models for the given data. This study explored the data using basic descriptive statistics and also a profile plot of the CD4 cell count over the period of the study along with other determinant factors to assess the nature of the data by exploring individual profiles, the average evolution, and the variance function.

2.3. Generalized Estimating Equations

Generalized estimating equation (GEE) is an extension of GLMs in order to accommodate a correlated data. In fitting models using the GEE approach has been shown to give consistent estimators of the regression coefficients and their variances under weak assumptions about the actual correlation among a subject's observations and the parameters were estimated by using quasi likelihood.

In order to select the important factors related ART drug on the recovery of CD4 counts over time of HIV patients taking ART treatment, the backward selection procedure was used. To select significant variables, firstly, under the GEE model building strategy started by fitting a model containing all possible covariates in the data. This was done by considering three working correlation assumptions (exchangeable, independence and autoregressive). Since GEE isn't a likelihood approach, the quasi-likelihood counterpart to the AIC is the QIC, or the "quasi-likelihood under the independence model information criterion" [8]. To better select "working" correlation structure Hin K. and Wang M. (2009) proposed correlation information criterion (CIC).

2.4. Generalized Linear Mixed Model

GLMMs are the extensions of GLMs to a longitudinal data that allows a subset of the regression coefficients to vary randomly from one individual. They enable for accounting the within subject association [6]. Unlike the models fit in GEE, generalized linear mixed models have the flexibility to specify random effects and also to generate subject-specific parameter estimates.

To study in GLMM the primary interest is in estimating the parameters or a set of covariates in the generalized linear mixed-effects model. The subject-specific random effects model has become a well-known model to analyze different types of longitudinal data as it effectively shows the pattern of repeated measurements over time. In this model, the average progression was described using some function of time, which is a fixed effect, and subject-specific deviations from this average evolution are introduced by using random effects [9].

Maximum likelihood (ML) by Laplace approximation technique was used to estimate the parameters. ML estimates standard deviations of the random effects assumed the fixed-effect estimates were correct. The following derivations were done with respect to ML. Such likelihood may involve high-dimensional integrals that cannot be evaluated analytically so that much software are able to solve such complex manipulation using iteration technique. Akaike's information criteria (AIC) and Bayesian information criteria were used for model selection method.

3. Results

The total numbers of patients included in this study were 632. The mean of these continuous independent variables for age and weight were 32.41 years, 54.73 kilograms and with standard deviations of 9.213 years and 10.562 kilograms, respectively.

The descriptive statistics of independent categorical variable value as shown in the table 1: the total number of females were 408 (64.56%) and 224 (35.44%) were males. The CD4 count of the patient varies across the stage. The highest number recorded in WHO stage I, 251 (39.71%) patients and followed by 184 (29.11%) stage II, stage IV has the lowest recorded in the study. Among the total number of the patient 318 (50.32%) of patients had ART regimens taken AZT-3TC-EFV, 96 (15.19%) were AZT-3TC-NVP, 84 (13.29%) were at TDF-3TC-NVP, 61 (9.65%) patients had d4t-3TC-NVP and 55 (8.7%) of the patient had taken TDF-3TC-EFV. The patient also vary with functional status among those, 397 (62.81%) had good functional status (were "working" classification), 125 (19.78%) were ambulatory and the rest 110 (17.41%) were bedridden. Additionally, about 457 (72.31%) of the patient had a good adherence and 175 (27.69%) had not good adherence, the same is true about 513 (79.88%) had negative TB status and about 119 (20.12%) had positive TB status. Patients who were TB negative at baseline have higher mean CD4 cell count at all time points than patients with Positive TB status. And the patient live in urban were 391 (61.86%) and about 241 (38.14%) were lived in rural.

The CD4 cell score were measured values were from 5 to 1941. The mean of CD4 cell count of patients increases with an increasing rate until time 30-36, with the maximum average of 784.8342 and their standard deviation of 412.79 at the last time point. Therefore the mean CD4 cell count of HIV positive patients increases with an increasing rate.

Table 1. Baseline demographic and clinical characteristics of ART data taken from Ayder hospital.

Characteristics	Category	N	Percentage (%)
Sex	Female	408	64.56
	Male	224	35.44
WHO stage	I	251	39.71
	II	184	29.11
	III	142	22.47
	IV	55	8.70
Hemoglobin level	Severe anemia	32	5.06
	Moderate anemia	93	14.72
	Mild anemia	187	29.59
	Normal	320	50.63
ART Regimens	AZT-3TC-EFV	318	50.32
	AZT-3TC-NVP	96	15.19
	TDF-3TC-NVP	84	13.29
	D4t-3TC-NVP	61	9.65
	TDF-3TC-EFV	73	11.55
Functional Status	Working	397	62.81
	Bed ridden	110	17.41
	Ambulatory	125	19.78
TB status	Negative	513	79.88
	Positive	119	20.12
Place of residence	Urban	391	61.86
	Rural	241	38.14
Disclosure	Yes	421	66.61
	No	211	33.39
Adherences	Good	457	72.31
	Bad	175	27.69

3.1. Exploring Individual Profile Plots of CD4 Cell Count over Time

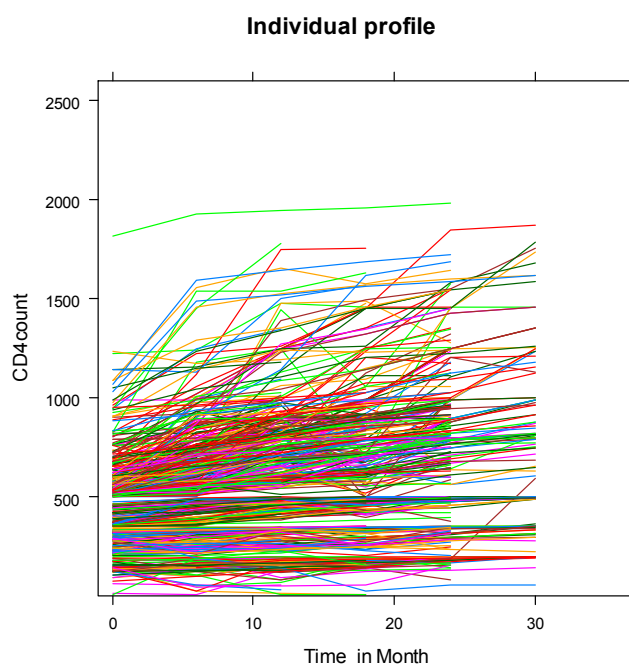


Figure 1. Individual profile plots for CD4 counts by time.

Figure 1 indicates that the individual profile plot of CD4 cell count of HIV infected patients included in this study and shows that there is large variability between CD4 cell counts of patients. These individual profiles can also provide some information on between patient's CD4 cell count variability and illustrate that there is change among patient's CD4 cell count over time. Considering the fluctuation of CD4 counts of patients and irregularity of changes over time, it is with good news that this variability may handle by mixed model.

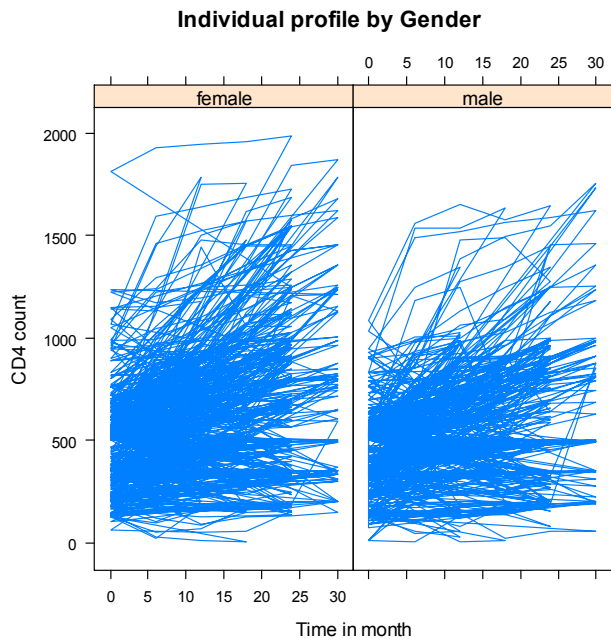


Figure 2. Individual Profile plot by Sex.

The individual profile plot of CD4 count for both male and female groups is displayed in Figure 2. This result seems that there is high within variation in female patients as compared

with the male patients. The between patients variation is high at the end as compared with at baseline for both groups. As researcher observed in this figure the CD4 cell count of the female patient was highly erratic than male.

3.2. Exploring the Variance Structure of CD4 Cell Count over Time

The observed variance of CD4 count is given in figure 3. Plot of variance appears that the observed variance was not constant through time evolution and shows variability of high variability of CD4 count measurements over time the observed variance plot shows the variability is small at baseline and increases until almost all months.

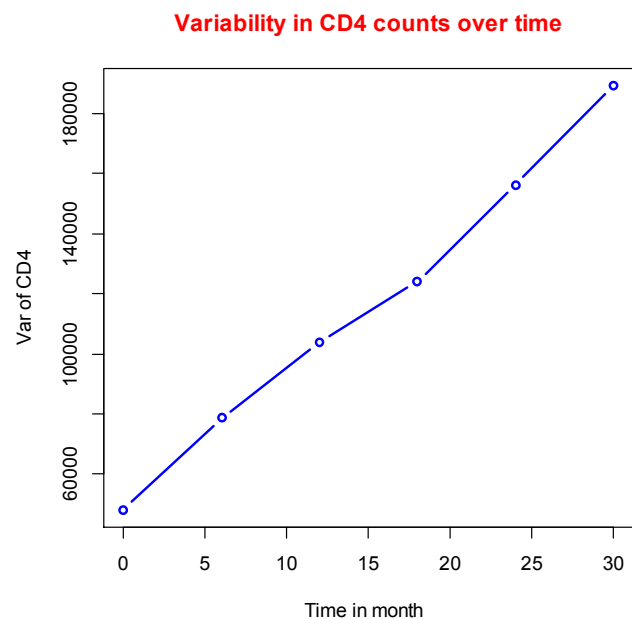


Figure 3. Variance Function of CD4 Count.

Table 2. Descriptive Statistics of CD4 count score by time point.

Time	1	2	3	4	5	6
Mean (CD4)	486.728	518.291	578.190	606.8611	716.2625	784.8342
S.D (CD4)	251.42	287.65	323.15	362.26	390.85	412.79
Min (CD4)	10	5	8	8	48	45
Max (CD4)	1561	1847	1923	1941	1941	1822

Table 3. The actual Variance of CD4 count at each visit time taken at Ayder referral Hospital.

Time	0	1	2	3	4	5
Variance (CD4)	63212.02	82742.52	104425.9	131232.3	152763.7	170395.6

3.3. Analysis of Longitudinal Data Model

3.3.1. Generalized Estimating Equation

In order to select the best model, first important to specify the best working correlation and the result is shown in the following table 4.

Table 4. Model selection from the three correlation structures.

Independence	Exchangeable	autoregressive
QIC	7797194	7796532
CIC	60	72
		3146.745
		17.26

Based on these values the autoregressive working correlation is preferable with respect to minimum QIC and CIC compare to the other. Thus, researcher can conclude that model autoregressive is the best fit for this data and focused on this model. Then the researcher selected final model from

the model for CD4 cell count response was given as below by excluding the most non-significant variable that is place of resident and disclosure because this variable had largest p value implies there is no significant difference.

Table 5. Wald test estimates of the final GEE model with autoregressive correlation structure.

Coefficients	Estimate	Std. err	95%CI		Pr (> W)
			Lower	upper	
Intercept	6.14	1.016	4.148	8.131	<0.0001
Time	0.415	0.103	0.213	0.617	<0.0001
Male	-0.311	0.145	-0.044	-0.037	0.032
Severe anemia	-0.92	0.201	-1.314	-0.526	<0.0001
Moderate anemia	-0.44	0.163	-0.759	-0.121	0.007
Mild anemia	-0.134	0.094	-0.318	-0.050	0.154
Age	-0.136	0.177	-0.172	-0.159	0.004
TB status positive	-0.386	0.466	-0.172	-0.057	0.002
AZT-3TC-NVP	-1.172	0.647	-0.180	0.354	0.070
TDF-3TC-NVP	-0.461	0.632	-0.516	-0.459	0.007
d4t-3TC-NVP	-1.346	1.321	-0.657	-0.643	<0.0001
TDF-3TC-EFV	-1.446	0.379	-0.793	-0.706	<0.0001
Stage II	-1.165	0.587	-0.171	-0.054	0.047
Stage III	-0.179	1.295	-0.201	0.640	0.890
Stage IV	-1.825	0.391	-0.773	-0.713	<0.0001
Ambulatory	1.031	0.407	0.017	0.401	0.010
bed ridden	-0.475	0.514	-0.084	0.879	0.801
Weight	0.199	0.133	0.002	0.271	<0.0001
Bad	-0.644	0.466	-0.115	0.272	0.168
Time*(sex) male	0.131	0.165	-0.001	0.123	0.425
Time*Stage II	-0.406	0.138	-0.005	-0.007	<0.0001
Time*Stage III	-0.141	0.055	-0.012	-0.006	<0.0001
Time*Stage IV	-0.440	0.106	-0.012	-0.002	<0.0001
Time*weight	-0.026	0.025	-0.002	-0.001	<0.0001

Model of GEE with autoregressive correlation structure model in the table 5 shows that, the value of the intercept ($e^{\beta_0} = e^{6.14} = 464.054$) is represented that the mean of an estimate of the CD4 count at base line (Time=0) for females which is significantly different from zero ($p < 0.0001$) the same is true for the parameter working, those patient who used AZT-3TC-EFV, those patient who had good adherence, those patient who are did not attacked by TB and WHO stage

I categories. The average of CD4 count was found to be 464.0536.

3.3.2. Generalized Linear Mixed Model (GLMM)

From the results in table 6 which shows the values of information criteria's (values of AIC and BIC) and uses to select the model that fits the ART data well.

Table 6. Comparison of models with different random effects using AIC and BIC test for the ART data.

	Random intercept effects	Random time effects	Random intercept and time effects.
AIC	33432	58461	25814
BIC	33617	58537	25905

Based on the output in table 6, the model with Intercept + time as random effect was best model fit for the ART data. After choosing the appropriate random effects for the data, the researcher had also assessed the significance of the fixed effects and its interaction effects. From the final GLMM model the linear effect of time is significant. And also age, sex, weight, regimen class and TB status are the significant

main effect terms on the change of CD4 count. The interaction effect of WHO Stage and weight with time are among the significant interaction terms. But, time by sex interaction is not significant and the adherence of the patient also not significant 5% level of significance and then the final model is shown below table 7.

Table 7. Final model for GLMM and Covariance parameter estimates for the ART data.

Parameter	Estimate	Std. Error	95% CI		P-value	Random effect variance estimates
			Lower	Upper		
Intercept	6.41373	0.483	5.466	7.361	<0.0001	
Time	0.02946	0.093	0.026	0.033	<0.0001	
Male	-0.02918	0.158	-0.052	-0.006	0.012	
Severe anemia	-0.874	0.206	-1.278	-0.471	<0.0001	
Moderate anemia	-0.361	0.125	-0.606	-0.116	0.0083	
Mild anemia	-0.127	0.083	-0.289	0.036	0.126	
Age	-0.00457	0.125	-0.006	-0.003	<0.0001	
Rural	-0.01234	0.153	-0.009	0.034	0.276	
Positive	-0.10163	0.123	-0.138	-0.065	<0.0001	
AZT-3TCNVP	-0.04926	0.333	-0.097	-0.001	0.045	D11=0.022131
TDF-3TCNVP	-0.09147	0.374	-0.146	-0.037	<0.0001	D22=0.0042532
d4t-3TC-NVP	-0.34169	0.549	-0.421	-0.262	<0.0001	Covariance
TDF-3TC-EFV	-0.37537	0.619	-0.465	-0.286	<0.0001	D ₂₁ =0.2454220
Stage II	-0.42483	0.300	-0.105	-0.018	0.005	Residual variance
Stage III	-0.01994	0.460	-0.047	0.087	0.558	$\delta^2 = 0.9528$
Stage IV	-0.06162	0.629	-0.516	-0.334	<0.0001	
Ambulatory	0.08996	0.261	0.052	0.128	<0.0001	
bed ridden	-0.00450	0.471	-0.073	0.063	0.896	
Weight	0.00761	0.113	0.006	0.008	<0.0001	
time:* male	0.00132	0.053	-0.001	0.003	0.213	
time*Stage II	-0.00504	0.061	-0.007	-0.003	<0.0001	
time*Stage III	-0.00587	0.072	-0.009	-0.003	<0.0001	
time*Stage IV	-0.01071	0.084	-0.014	-0.007	<0.0001	
time*weight	-0.00027	0.021	-0.0003	-0.0002	<0.0001	

From above Table 7, results showed that the variances and covariance's of the random effects were significantly different from zero. The variances of the intercepts and linear effects of time were significantly different from zero. This indicates that the CD4 cell count values at baseline vary across subjects and the change of CD4 cell counts over time vary within subjects.

The estimated value intercept is ($e^{\beta_0} = e^{6.41373} = 610.1654$) in GLMM is an estimate of the " i^{th} " female subject average CD4 cell count provided that she is working, WHO-clinical stage-I, having good adherences and regimen class (AZT-3TC-EFV) categories. Similarly the estimated value of time ($e^{\beta_1} = e^{0.02946} = 1.030$), implies the mean CD4 count increases 1.030 times per month every individual patients.

In addition the coefficient for sex ($\beta_2 = -0.02918$) verifies that the mean CD4 cell count for " i^{th} " male individual is $e^{-0.02918} = (0.971)$ times lower than female individual with the same random effects b_i at base line and the difference is highly significant at 5%. The estimated value of weight is $e^{0.00761} (1.008)$ this is indicated that the mean CD4 count increased by 100.8% for the following time. In particular, rate of increase in the mean CD4 count for i^{th} subject in WHO stage II category is estimated to be $e^{-0.42483} (0.654)$ times per month lower than the rate of increase for any stage I category patient with the same random effects. Similarly in WHO stage IV category is estimated to be $e^{-0.06162} (0.9402)$ times lower than the rate increasing stage I category and similar interpretation can made for the others.

4. Discussion

The purpose of this study was to examine the evolution of

HIV infection using longitudinally measured CD4 count for HIV positive patients initiated to ART in Ayder comprehensive specialized Hospital. The profile plots indicated that there is variability in CD4 cell count within as well as between individuals in the data. The result of exploratory analysis for the mean structure also suggested that, CD4 cell count increases in a linear trend over time. This supports the results of [10, 11] that identified after the patients initiated to the ART their CD4 cell count were increased due to the therapy.

When selecting a correlation structure form GEE model only minimum QIC and CIC considered the same as the previous literature [12]. In the generalized estimation equation model, AR (1) was selected. And also the generalized linear mixed model the change of CD4 cell count analysis was used for sack of determines fixed and random effect components in the model. In GLMM the random effect that random intercept only, random slope only and both random intercept and random slope models were compared for the purpose of selecting. The three models were compared using the AIC value and researcher got a model with intercept and slope as random effect is the best [4, 13] and based on minimum standard error value a GLMM model fitted a data better than comparing to GEE model.

The result of this study indicated that age has significant association with the change of CD4 cell count and supported by [11]. The study also found the male sex group has statistically significant difference with female for the progression of CD4 counts over time. This implies that the progressions of CD4 cell counts for female patients are more likely higher than male counter parts over time which is supported by [13]. Different studies showed that Weight was

a factor that is affecting the change of CD4 cell count under HIV patients. According to Haftu (2015) a high risk of death of patients was found to be associated with lower initial weight. A study in Ethiopia showed that weight was statistically significant in the joint model [10]. This study also found that weight was statistically a significant risk factor the change of CD4 cell counts.

Hemoglobin level is associated with CD4 counts, patients those with severe anemia are less to develop more CD4 cells i.e. as the level of hemoglobin increase, the number of CD4 cell increases. This is supported by [17]. ART regimen class also shown to be significantly determining a patient's CD4 cell count. This implies that the patients those used TDF-3TC-EFV are 68.7% time's lower change of CD4 cell count than those using AZT-3TC-EFV drug in Ayder referral hospital Ethiopia and this is in agreement with a study in Nigeria which reported that ART regimen class was indeed a risk factor for change of CD4 cell counts [14]. Time was among the significant determinant factors, this means that as the time duration increased, patients going to be showing improvement [4, 15, 16].

Getting to ART treatment at early WHO clinical stages is positively related with progression of CD4 cell count of HIV patients over time. In this study researcher revealed that a patient starting ART treatment with WHO stage I is beneficial in recovering his or her CD4 count relative to with WHO stage II. Keeping the other covariates constant, a patient who started ART treatment with WHO stage IV has a disadvantage of 0.9402 times CD4 count of a patient with WHO stage I, or the CD4 count of a patient who started ART treatment with WHO stage IV decreases by 94.02% as compared with patients started ART treatment at WHO stage I. This result is supported by [10, 16].

Functional status has been found significant variable for the change of CD4 count. A study was carried out in Ghana aimed the risk factor of change in CD4+ cell counts of HIV patients on ART. During follow up functional status under ambulatory category was statistically significant in the longitudinal study model [3]. This means the risk of change of CD4 cell counts in HIV patients under ambulatory category was higher working category in generalized linear mixed model. The same is true under this study TB status has been found a significant variable for the change of CD4 count. This implies that TB positive HIV patients are lower change of CD4 cell count than TB negative HIV patients and this was supported by study in Debre Markos [16].

5. Conclusions

CD4 count increases in a linear trend over time after patients initiated to ART program. GLMM had shown best fit for this data with small standard error than GEE. The study has found factors that contributed to the risk factor of the progression of CD4 cell count under HIV positive patients. Age, sex, weight, WHO stage, TB status, functional status, regimen class duration of time by WHO stage and duration of time by weight were identified as significant predictors for

the progression of CD4 count (HIV infection). Patients with higher current CD4 cell count have less likely of practicing events than patients with smaller current CD4 cell count. Patients with higher CD4 cell count have lower risk of disease. For HIV patients, researcher are advised to start antiretroviral therapy treatment as early as possible, with higher CD4 cell counts and while at lower WHO stage to improve their CD4 cell count progression.

Consent for Publication

Not applicable.

Competing Interests

The author declares that they have no competing interests.

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