Journal of Scientific Research & Reports

24(5): 1-8, 2019; Article no.JSRR.51508
ISSN: 2320-0227

Evaluation of the Trend of CD4 Cell Count Over Time in Case of HIV/AIDS Patients under ART Follow-up

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Authors' contributions

This work was carried out in collaboration between both authors. Authors KTG and MAE conceived and designed the study, developed data collection instruments and supervised data collection. They participated in the testing and finalization of the data collection instruments and coordinated the study progress. Authors KTG and MAE performed the statistical analysis and wrote all versions of the manuscript. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JSRR/2019/v24i530167
Editor(s):
(1) Dr. Karl Kingsley, PhD, MPH, Associate Professor of Biomedical Sciences, Director of Student Research, University of Nevada, Las Vegas - School of Dental 1001 Shadow Lane, B313, Las Vegas, Nevada 89106, USA.
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Complete Peer review History: https://sdiarticle4.com/review-history/51508

Original Research Article

Received 13 July 2019
Accepted 21 September 2019
Published 01 October 2019

ABSTRACT

Background: Globally 36.7 million people living with HIV, 1.8 million new HIV infection, and 1 million AIDS-related deaths in 2016.Patient mortality was high during the first 6 months after therapy for all patient subgroups and exceeded 40 per 100 patient years among patients who started treatment at low CD4 count. The aim this study was to evaluate the trend of CD4 cell count over time and to determine the progress of patient characteristics measured at baseline on CD4 cell count of HIV-infected patients who were under ART treatment in Arba Minch Hospital. **Methods:** This study was retrospective follow up study using data extracted from medical records, patient interviews, and laboratory work-up. The study was employed among 550 adult patients that were selected by simple random sampling. The continuous outcome variable CD4 cell count has measured at months 0, 6, 12, 18, and 24. Longitudinal data analysis were used because the set of measurements on one patient tend to be correlated, measurements on the same patient close in time tend to be more highly correlated than measurements far apart in time, and the variability of longitudinal data often changes with time and the data handled through linear mixed effect models.

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Result: The fitted result of the linear mixed model showed that linear visit time effect and the baseline characteristics education status, condom, tobacco, degree of Disclosure, and weight effects had significant effect on CD4 measurements. Also, the interaction age with linear visit time effect had significant effect on the evolution of CD4 cell count. However, no significant difference between sex, WHO stage, and marital status groups.
Conclusion: This study find that the CD4 cell count of HIV/AIDS patients is significantly determined by the visit time, education status, condom, tobacco, degree of Disclosure, and weight effects of patients.

Keywords: CD4 cell count; individual profile; linear mixed model; longitudinal model.

1. INTRODUCTION

Globally, in 2016 there were 36.7 million people living with HIV, 1.8 million new HIV infection, and 1 million AIDS related deaths [1]. In eastern and southern Africa, young women (aged 15-24 years) accounted for 26% of new HIV infections in 2016 despite making up just 10% of the population. Young women (aged 15-24 years) in western and central Africa and the Caribbean accounted for 22% and 17% of new HIV infections in 2016 [1]. Sub-Saharan Africa was a region highly affected by the HIV epidemic. Ethiopia is one of the Sub-Saharan African countries with the highest numbers of people affected by the problem [2,3]. In Ethiopia, there were 710,000 patients infected with HIV/AIDS in 2016. Around 404,405 HIV patients were on an Anti retroviral therapy (ART) and around 20,000 AIDS-related deaths were reported in the same year [4].

Patient mortality was high during the first 6 months after therapy for all patient subgroups and exceeded 40 per 100 patient years among patients who started treatment at low CD4 count. This trend was seen regardless of region, demographic or disease-related risk factor [5]. Study at Jimma University Specialized Hospital showed that functional status, weight, linear time and quadratic time effects have significant effect on the mean change of CD4 measurement over time [6].

The CD4 count is like a snapshot of how well your immune system is functioning. CD4 cells (also known as CD4+ T cells) are white blood cells that fight infection [7]. The CD4 cell count provides information on the overall immune function of a person with HIV. The measurement is critical in establishing thresholds for the initiation and discontinuation of opportunistic infection (OI) prophylaxis and in assessing the urgency to start ART [8]. When the CD4 count drops below 200 cells/mm3, a person is diagnosed with AIDS. A normal range for CD4 cells is about 500-1,500 cells/mm^3. Usually, the CD4 cell count increases when the HIV virus is controlled with effective HIV treatment [7]. It is recommended that after 3 months of treatment with ART, a patient should gain 50-100 CD4 cells/mm^3 per year and that an increment below this range could imply poor response to the treatment [9]. Patients' CD4 count is also required to reach at least the lower limit of the CD4 count for the general healthy adult population (500 cells/mm^3) [9] which otherwise can be an indication of immunologic failure.

It can be seen from the report that even though there were many people on antiretroviral treatment, there were also many AIDS-related deaths registered in 2017. Thus, further studies are needed to identify factors related to ART. In this study, CD4 cell counts of HIV-infected patients undergoing ART treatment in Arba Minch Hospital were used to evaluate CD4 cell count over time and to identify baseline patient characteristics that might affect evolution CD4 cell count of HV-infected people who are on ART. The study employed linear mixed models to fit CD4 count over time of HIV-infected people.

2. METHODOLOGY

2.1 Study Area and Design

The study was conducted in Arba Minch hospital, Gamo Gofa zone, Southern Ethiopia. Arba Minch town is located about 505 km South West from Addis Ababa, about 275 km from Hawassa, the capital city of the Southern region. Arba Minch General Hospital provides HIV/ AIDS interventions, including free diagnosis, treatment, and monitoring. The retrospective cohort study was conducted from January 2007 to October 2017 at Arba Minch General Hospital, Ethiopia.

2.2 Study Population

The source population was all adult people living with HIV who were under ART regime follow-up at Arba Minch General Hospital from January 2007 to October 2017. The population of our study includes all HIV/AIDS patients under ART follow-up at Arba Minch General Hospital and who fulfill the inclusion criteria. The study excluded adult patients who were below 16 years and those patients who started ART follow-up before January 2007 or after October 2017. Simple random sampling technique was used to select 550 samples from the total of 3,405 HIV/AIDS patients who had been under ART follow-up.

2.3 Study Variables

The dataset contains data from 550 adults enrolled ART at Arba Minch General Hospital, 2007 to 2017. The response variable considered for this study was the CD4 cell count. Numbers of CD4 cell counts per cubic millimeter of blood were measured approximately every 6 months interval. The CD4 cell count of the patient was recorded five times at months 0, 6, 12, 18, and 24. The covariate variables are assumed to influence the longitudinal response of the patient included in the model are: sex, age, weight, visit time, WHo clinical stage, marital status, education status, functional status, condom, tobacco, degree of disclosure, and knowledge about ART.

2.4 Linear Mixed-effect Model

The continuous outcome variable CD4 cell count contains measured at months 0, 6, 12, 18, and 24. Since measurements are taken from the same subject over time, observations cannot be considered as independent. Thus, in such cases, the use of a standard regression model assuming independence of observations taken from the same subject may not be appropriate. So, appropriate random effect models that account for the correlated nature of the data will be presented. The random-effects approach is extending the univariate linear regression model to longitudinal settings is based on subject-specific regression model [10].

A longitudinal model is the estimation of changes in response over time and testing whether these changes are covariate dependent [11]. Special methods of statistical analysis are needed for longitudinal data because the set of measurements on one patient tend to be correlated, measurements on the same patient close in time tend to be more highly correlated than measurements far apart in time, and the variability of longitudinal data often changes with time. These potential patterns of correlation and variation may combine to produce a complicated covariance structure. This covariance structure must be taken into account to draw valid statistical inferences. Therefore, standard regression and Analysis of Variance (ANOVA) may produce invalid results, because two of the parametric assumptions (independent observations and equal variances) may not be valid. The general form of the linear mixed model employed for which assumes that the outcome vector Y_i of all n_i outcomes for subject i satisfies [12]

$$\boldsymbol{Y_i = X_i\beta + Z_i b_i + \epsilon_i}$$

In which $\boldsymbol{\beta}$ is a vector of population average regression coeffcients, called fixed effects, and where $\boldsymbol{b_i}$ is a vector of subject-specific regression coeffcients. The $\boldsymbol{b_i}$ are assumed normal with mean vector $\mathbf{0}$ and covariance D, and they describe how the evolution of the ith subject deviates from the average evolution in the population. The matrices $\mathbf{X}_i$ and $\mathbf{Z}_i$ are $(n_i \times p)$ and $(n_i \times q)$ matrices of known covariates. Note that p and q are the numbers of fixed and subject-specific regression parameters in the model, respectively. The residual components ϵ_i are assumed to be independent $N(\mathbf{0}; \Sigma_i)$, where Σ_i depends on i only through its dimension n_i. D and Σ_i are the variance components, where D is the covariance matrix of random effects, and Σ_i is the measurement error matrix. The vector $\boldsymbol{\beta}$ and b_i are the fixed effects (the predicted variables are supposed to have the same effects for all individuals) and the random effects (the predicted variables also have an additional individual-specific effect, allowing variation between individuals), respectively.

2.5 Model Selection Criteria

A key part of the analysis of data is model selection, which often aims to choose a parsimonious model. To have an appropriate model for the linear mixed model most commonly known model selection criterion; Akaike Information Criterion (AIC) [13] was considered for this study.

2.6 Data Analysis Software

The statistical software used in this study was the Statistical Analysis Software (SAS) version 9.4 and R Version 3.3.1.

3. RESULTS

In this section summary statistics of our data, data analysis, and interpretation are presented. The study begins with presenting summary statistics of factors/covariates considered in the study, then exploring mean, variance, and correlation structures CD4 cell count over the ages, fitting the model and interpretation of the results.

3.1 Exploratory Data Analysis

Some patient's baseline characteristics and CD4 cell count over time were presented in Table 1. Regarding the sex composition of patients, the mean age of female/male were 37.22 and 38.22 respectively. The mean weight of the patient was 49.60 for the female group while it is 56.34 for the male group. Moreover, when the patients are female the mean CD4 cell count for female were 190.22, 351.66, 412.41, 466.46, and 522.92 at months 0, 6, 12, 18, and 24, respectively.

3.2 Individual Profile

To understand the association between the CD4 measurement and time, individual profile plot was employed. In Fig. 1, the evolution of CD4 cell count for each individual profile plots suggested that there was high variability between subjects. This plot also shows that different baseline values at the start of the study were recorded which indicated that a random intercept in the model. Additionally, the CD4 cell count evolution seems different across subjects and this again suggests the for need a random slope during model fitting.

3.3 Mean Structure

In order to see the average evolution of the CD4 cell count over time and to have some idea what the mean structure looks like, a plot of the average evolution overtime was depicted. The average evolution describes, how the profile of a number of a relevant subpopulation (or the population as a whole) evolves over time. From Fig. 2(a), the results of this exploration will be useful in order to choose a fixed-effects structure of the linear mixed model. The average of the profiles increases from baseline month to month 24. From individual profiles and the average evolution plots, our results suggest modeling the CD4 cell count as a linear over time. This results in an average intercept and an average linear time effect.

3.4 The Variance Structure

Besides the average evolution, the evolution of variance over time is important to build a proper subject-specific or marginal longitudinal model. The plot of the average evolution of variance as a function of time was done to show the variance structure Fig. 2(b). The overall variance

Table 1. Summary measures of covariates and response at each time points for CD4 cell count data

		Gender			
		Female		Male	
Study time (months)	**Variable**	**Mean**	**St.dev**	**Mean**	**St.dev**
Baseline	Age	37.22	10.48	38.32	9.65
	Weight	49.60	7.95	56.34	7.70
Baseline		190.52	117.42	170.92	108.45
6		351.66	192.91	320.94	191.10
12	CD4	412.41	209.53	367.35	182.26
18		466.46	231.67	362.47	194.08
24		522.92	299.16	380.31	186.34

Table 2. Correlation matrix

	CD4 at baseline	CD4 at month 6	CD4 at month 12	CD4 at month 18	CD4 at month 24
CD4 at baseline	1.0000				
CD4 at month6	0.3645	1.0000			
CD4 at month 12	0.3493	0.6959	1.0000		
CD4 at month 18	0.3358	0.6292	0.7069	1.0000	
CD4 at month 24	0.3388	0.5772	0.7224	0.7715	1.0000

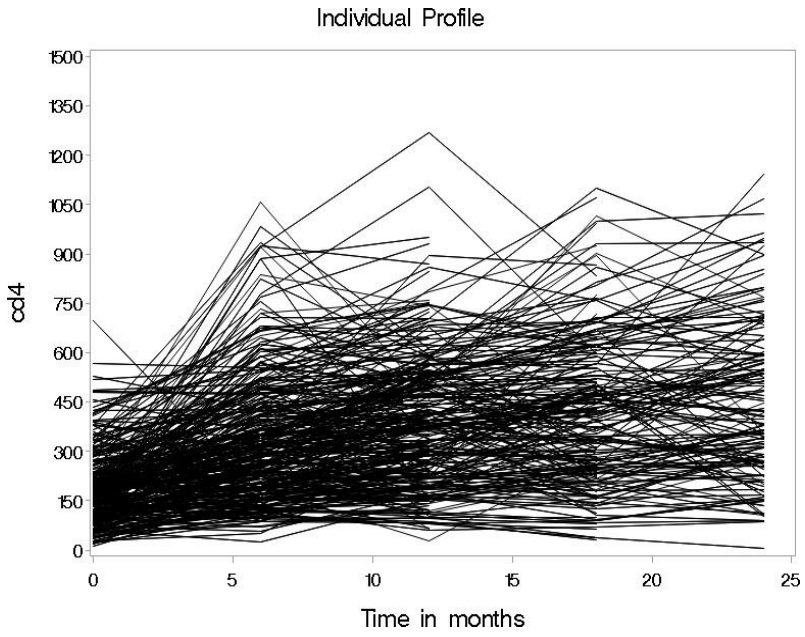

Fig. 1. Individual profiles of IQ test score

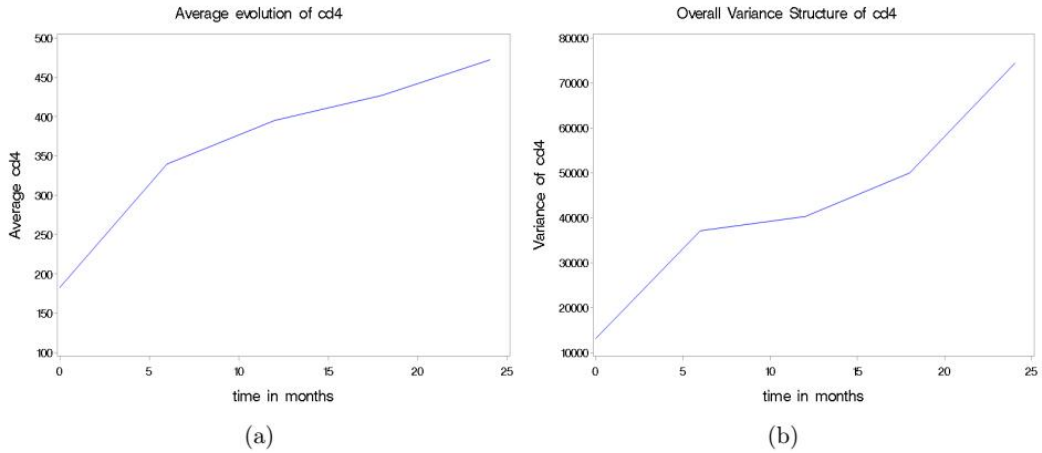

Fig. 2. Overall average evolution (a) and over all variance evolution (b) for CD4 cell count during a visit time

function seems relatively stable, showing an increasing pattern over time and hence a constant variance model could be a plausible starting point for longitudinal modeling approach.

3.5 The Correlation Structure

The correlation structure describes how measurements within a subject correlate. The correlation matrix presented in Table 2 shows the pairwise correlation between measurements at any pair of time points. It was observed that there were high correlations between the pair of measurements. Also, scatter plot matrices are a way to roughly decide if we have a linear correlation between multiple variables. The scatter plot matrix shown in Fig. 3 shows that CD4 cell count at months (0, 6, 12, 18 and 24) are highly correlated. So, we could not ignore the correlation of the data.

3.6 Result of Linear Mixed Model

The outcome variable of interest is the CD4 cell count by which evolution over time may be assessed. Based on results of exploratory data

analysis, the evolution of the CD4 cell count was assumed to have a linear time effect as a preliminary mean structure and unstructured variance-covariance structures seemed a plausible starting for performing linear mixed model. To assess the need for serial correlation inclusion, the criterion of fitting linear mixed models with the same mean and random-effects structure was used as proposed by Verbeke and Molenberghs [10]. The models were compared using the likelihood ratio test based on REML and results showed that there was no need of including the serial correlation.

The possibility of random-effects structure reduction was also assessed using the likelihood ratio test (mixture of chi-squares with equal weights 0.5) by deleting random effects in a hierarchical way starting from the highest order time effect comparing it with the previous model. After this, simultaneous contrast statements were used to explore the possibility of reducing the mean structure, starting from the unstructured mean effect which was rejected. In all cases, the possibility of simplification of random effects from the models was model with random intercept and random slope. The fixed effects considered were sex, age, weight, who stage, marital status, education status, condom, tobacco, disclosure, functional status, knowledge about ART, the linear time effect of CD4 cell count, and the interaction age with linear time effect. After model selection, the final result was given in Table 3 with AIC= 29832.9 obtained:

From the fitted result of linear mixed model of Table 3, it can be seen that the estimates of linear visit time effect and the baseline characteristics education status, condom, tobacco, degree of Disclosure, and weight effects had significant effect on CD4 measurements. Also, the interaction age with linear visit time effect had significant effect on the evolution of CD4 cell count. However, no significant difference between sex, who stage, and marital status groups observed.

The fitted result of linear mixed model at baseline the CD4 cell count of always condom use group were 171.77 greater and sometimes condom use patients group was 25.3447 greater CD4 measurements in comparison with not condom used group. Furthermore, the model showed with a unit increase in weight of the patients increases the mean CD4 measurements by 1.7577 and linear time also has positive effects on the mean change of CD4 measurements.

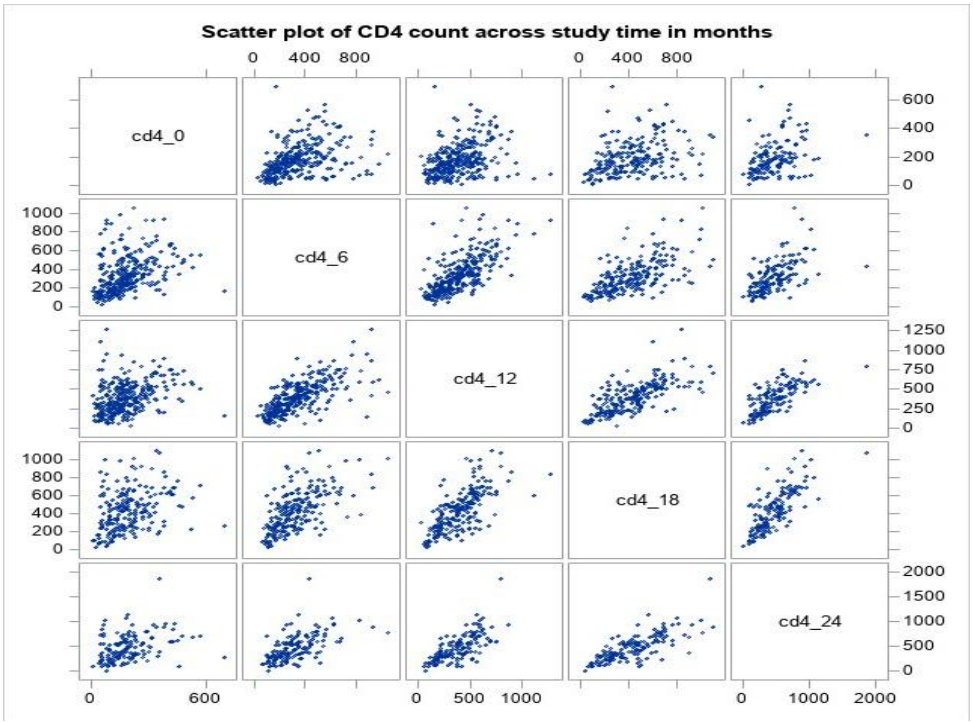

Fig. 3. Scatter plot matrix for the CD4 cell count at 5 visit time points

Table 3. Parameter estimates using REML for CD4 cell count data

Variables	Parameter		Estimate	St. error	P-value
Intercept		β_0	116.3200	44.7991	0.0097
Time		β_1	17.1160	1.9567	<.0001
Sex	Male	β_2	-18.0405	11.4685	0.1160
	Female(ref.)				
WHO	Stage II	β_3	3.4682	16.3988	0.8325
	Stage III	β_4	-5.3816	13.8683	0.6980
	Stage IV	β_5	51.5145	27.3430	0.0598
	Stage I(ref.)				
Marital status	Single	β_6	10.7523	15.4028	0.4853
	Divorced	β_7	-26.6275	27.2602	0.3289
	Separated	β_8	13.1856	22.3698	0.5557
	Window	β_9	72.1710	29.9572	0.0161
	Married(ref.)				
Education	Elementary	β_{10}	-17.1876	12.4039	0.1661
status	High school	β_{11}	-17.0315	13.7248	0.2149
	Certificate and above	β_{12}	-84.8181	30.4084	0.0054
	Not educated(ref.)				
Condom	Use always	β_{13}	171.7700	100.7300	0.0884
	Sometimes	β_{14}	25.3447	9.8879	0.0105
	Not use always(ref.)				
Tobacco	No	β_{15}	-58.0645	54.7379	0.2890
	Yes	β_{16}	-25.8750	10.9540	0.0183
	No opinion(ref.)				
Disclosure	Friend only	β_{17}	35.5790	29.0067	0.2202
	Disclosed for all	β_{18}	53.9153	9.9771	<.0001
	Family only(ref.)				
Age		β_{19}	-0.2621	0.4749	0.5811
Time*Age		β_{20}	-0.1128	0.05004	0.0244
Weight		β_{21}	1.7577	0.6364	0.0058
Covarience of b_i	Var (b_{1i})	d_{11}	2572.78		
	Cov (b_{1i}, b_{2i})	d_{12}	571.30		
	Var (b_{2i})	d_{22}	71.3010		
Residual	Var (ε_{ij})	σ^2	14950		

4. CONCLUSION

The objectives of this research were to evaluate the trend of CD4 cell count over time and to determine the progress of patient characteristics measured at baseline on CD4 cell count of HIV infected patients who were under ART treatment in Arba Minch Hospital. The results of this study used longitudinal data analysis to assess the association between visit time and outcome CD4 cell count. The fitted result of linear mixed model showed that linear visit time effect and the baseline characteristics education status, condom, tobacco, degree of disclosure, and weight effects had significance effect on CD4 measurements at 5% level of significant. The interaction age with linear visit time had significant effect on the evolution of CD4 cell count. But the difference between sex group, who stage, and marital status groups had no significant effect on CD4 cell counts at 5% level significant. A significant number of HIV patients are found in the study area and so greater attention and intervention needed on identified risk factor.

ETHICAL APPROVAL

The research proposal for this study was checked and approved by ethical clearance committee of Arba Minch University, and the medical director's office of Arba Minch Hospital granted permission to use the patients' data for this study. For the purpose of confidentiality, there were no linkages with individual patients and all data had no personal identifier and were kept confidential and therefore did not require informed consent.

ACKNOWLEDGMENTS

We would like to acknowledge Arba Minch General Hospital administrator, health professionals and data collectors who contributed to this work. We would also like to extend our gratitude to Arba Minch University for all support and opportunity provided for us to conduct this study.

COMPETING INTEREST

The authors declare that they have no competing interest availability of data and materials the raw data documents are available upon request from the corresponding author.

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The peer review history for this paper can be accessed here:
https://sdiarticle4.com/review-history/51508