# Statistical Joint Modeling of Longitudinal CD4 Cell variation and Time-to-Lost Follow-up from ART Predictors on HIV/AIDS Patients: A case of Mekelle General Hospital

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**Research**

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# Statistical Joint Modeling of Longitudinal CD4 Cell variation and Time-to-Lost Follow-up from ART Predictors on HIV/AIDS Patients: A case of Mekelle General Hospital

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## Abstract

**Back ground**: Time-to-lost follow-up and CD4 cell variation measures are the outcome variables of infection in HIV/AIDS patients after starting ART in this study. The time-to-lost follow-up from ART was determined by month time interval among dates of ART commencement to drop-out, as documented by the health information data administrator. The main goal of this study was to identify association of CD4 cell variation measurements on time-to-lost follow-up and main predictors of HIV/AIDS positive patients.

**Methods:** Institution based retrospective cohort study design was used among 216 HIV/AIDS patients under ART follow-up from period September 11, 2013 to September 5, 2016 at Mekelle General Hospital, Ethiopia and employed both survival and longitudinal outcome to fit separate and statistical joint modeling approach.

**Results:** A total of 216 HIV/AIDS patients were selected using systematic random sampling technique to analyze the longitudinal and survival outcome using joint model study. The result of this study showed that relationship between CD4 cell variation on hazard of time-to-lost follow-up was negatively statistical significant. Thus, time-to-lost follow-up from ART is less probable to occur in HIV/AIDS patients which have higher CD4 cell evolution. In survival sub-model Baseline CD4, sex of male, living in rural and comorbidity HIV/TB were significant factors of risk to time-to-lost follow-up from ART of HIV/AIDS patients. The longitudinal sub-model shows Baseline CD4 cell and being bedridden were significant factors of $\sqrt{CD4\ cell}$ variation at 5% significance levels.

**Conclusions:**The author assessed relationship of repeated measured CD4 cell variation on hazard of time-to-lost follow-up was negatively statistical significant and performance of both separate and statistical joint sub-models in terms model parsimony, smaller AIC & smaller

standard error in statistical joint model performs. Thus, the author concluded that statistical joint model was preferred for simultaneous analyses of repeated biomarker CD4 cell and survival time-to-lost follow-up data.

**Key Words:** ART, HIV/AIDS, Time-to-lost Follow-up, Statistical Joint Modeling, Mekelle

# Background

Human Immunodeficiency Virus/Acquire Immune Syndrome (HIV/AIDS) is caused huge problems in worldwide. Globally, around 36.9 million individuals living on HIV/AIDS, two million fresh HIV positive and 1.2 million mortality due to the infection in 2014 [1,2].

From the world, There were approximately 25.8 million people living with HIV and accounted for 70 % were new and still accounted for 74% of individuals mortality by AIDS associated reasons at sub Saharan Africa in 2013 [3,4].

Ethiopia is one of the highly affected negatively by HIV/AIDS in its entire indicator in sub-Saharan African countries. There had been expecting 793,700 persons alive on HIV based the latest EPP/Spectrum modeling in 2013 [4].

Antiretroviral treatment grow-up is continuing worldwide and can reduce HIV replication and also it improves the immune capacity [5, 6]. Although,14.9 million people were eligible to use ART but only 40 % of the patients were on ART of them, 13.5 million were lived in low and middle income countries in 2014 [7]. Around, 780, 000 HIV/AIDS positive were on ART in Ethiopia [8]. Out of these patient's, starting ART, 249,174 are adhering to their treatment regimen and there were 55,200 AIDS associated mortality in 2013 [9].

Lost follow-up from ART is a main problem to the success on HIV/AIDS treatment. Based on WHO report, out of the registered HIV patient's the measurement of achievement was only 23%. ART lost from follow-up negatively affects the improvement of an immunological advantage and increases HIV/AIDS related mortality [10]. Lost follow-up of ART will be the reason for drug toxicity, treatment poor adherence and medication resistance this results to mortality [11]. 40% of all HIV positive on ART were loss from follow-up in sub-Saharan Africa region and 46% of them had passed away their life [12-13].

Moreover, lost to follow-up is more familiar in low income countries due to low adherence and poor health care looking for behavior of patient and lost to follow-up after 1 year of ART

initiation is greater than 40% that is mainly factors with advanced WHO clinical stage and too poor baseline CD4 due to late beginning [14-15].

In the Tigray region, based on the Federal HIV/AIDS Prevention and Control Office estimated that there were about 56,900 HIV/AIDS positive patients in 2012 [16].

Additionally, the Mekelle General Hospital has been started ART facilities since September, 2011 and still has given a service for more than 10,000 HIV/AIDS patients [11].
In ART follow-up, CD4 cell is measured repetitively over time and this rise of CD4 cell change at every visiting time inspires the patient to be a good adherent to their regimen [17-19].

Statistical Joint models are used to describe the joint behavior of the two response variables simultaneously. These responses may have varied characteristics. These outcome variables are maybe binary, ordinal or continuous in nature and several preceding investigations had used joint models of two longitudinal responses variables [20-22]. Many of these models were employed statistical joint modeling of longitudinal responses variables, which have typically used a bivariate longitudinal outcome [20, 22]. Such investigations had not incorporate the association of longitudinal CD4 cell with time-to-lost follow-up as an observed measure of repeatedly from the same patient and have a shortage of information the effect of repetitively measured longitudinal data on time-to-event data. Statistical Joint modeling between longitudinal response variables on time-to-lost follow-up has advantages in reducing type I error on the same patient and improves efficiency in estimating parameters [22, 23].

Therefore, the recent investigation was carried out with the purpose of studying the statistical joint modeling approach that can be extended for CD4 cell count variation & time-to-lost follow up data by assuming an associated effect on each response variable. So, this problem can be solved through combining a statistical joint model approach, and used to compare the separate and joint models with respect to their parameter estimation in longitudinal and event sub-model process. With the greatest of our awareness, no other investigation has done to determine association parameter and the major predictors that affecting together these two outcomes CD4 cell variation & time-to-lost follow-up in Mekelle General Hospital.

# Methods and data analysis

## Study design

Institution based retrospective follow up study was carried out to measure statistical joint predictors of CD4 cell count change and time-to-lost follow-up among ART users registered from September 11, 2013 to September 5, 2016 followed-up time. Statistical Joint modeling between CD4 cell count variation and time-to-lost follow-up was employed.

## Study area and population

Mekelle General Hospital is located in the Northern part of Tigray National Regional State, which is about 783 km far from Addis Ababa, the capital of Ethiopia. The target population of the study was included HIV positive patients whose age greater than 15years old and started ART treatment in Mekelle General Hospital from September 11, 2013 to September 5, 2016,.

## Sample size and sampling procedure

Out of, 865 totals HIV positive patient's that begin ART treatment in Mekelle General Hospital from September 11, 2013 to September 5, 2016, 216 were selected using systematic random sampling technique. In this investigation HIV/AIDS patient has a minimum measured CD4 count two visits and maximum six visits were incorporated.

## Data collection procedures

The study used secondary data and a data extraction check list was prepared to collect the data by reviewing their records. A baseline CD4 cell count variation was identified and collected from the recording documents of ART subjects. The first month baseline hemoglobin level was also considered as a predictor variable for longitudinal and time-to-lost follow-up joint study. Similarly, other characteristics like socio-demographic variables, visiting times and clinical data were also collected from the recording papers of HIV/AIDS patient's charts. The data were collected by health expert workers after they had given adequate training about the variables included in the study.

## Quality of data

The quality of the data was controlled by data controllers from an ART section of the Mekelle General Hospital. The necessary amendments were made on the final data extraction format and the filled formats were checked daily by the supervisor and authors. The mechanism data extraction and variables included in this investigation were checked its reliability of understanding and the completeness of data.

## Variables included in the study

The survival and longitudinal response variables in this recent study were CD4 cell count variation and time-to-lost follow-up after ART treatment started. The survival and longitudinal response variables are various in natures. The longitudinal response variables was the variations of CD4 cell count (in cells/$mm^3$) of HIV/AIDS Positive patients during the follow up time from the date of ART initiation to the last visit follow-up time.

On the other hand, the survival response variable was time-to-lost follow-up from Antiretroviral Therapy was determined by months based on the time interval among dates of ART commencement to drop-out, as documented by the health information data administrator. In this study, the authors were focused on the statistical joint modeling of longitudinal outcomes with time-to-lost follow up data. Moreover, the predictor variables for the two responses variables were given in **Table 1**.

## Inclusion and Exclusion Criteria

Patients whose age was above 15 years old that are attending a minimum of two visit of ART treatment at Mekelle General Hospital for refilling their prescription and who were initiated on ART from September 11, 2013 to September 5, 2016 GC. And Patients whose age was below 15 years old that are attending ART treatment at Mekelle General Hospital for refilling their prescription, patients who are not registered in the ART clinic and who are not initiated on ART were not included in this study. In addition patients out of the study period are not included.

## Data Management, Structure and Analysis Strategy

The secondary data was entered in to SPSS version 20 and transferred to R version 3.6.1 software for analysis. For the sample selection to be involved in this study, CD4 cell count

variation measurement just before the beginning of ART was reflected as a covariate such that there should be at least two visit responses later the starting of ART in order to include in the analysis. Descriptive statistics were used to describe the percentage and frequency of the HIV positive patients in reference to all covariates. Patients' time at risk was measured starting from the time of initiation of treatment until each patient ended the follow-up time.

# Statistical Models of data analysis

In this study the author was used the following three types of different statistical data models:

- A linear mixed effects model used for continuous response variables for the longitudinal data like CD4 cell count.
- Survival model for the continuous survival time-to-lost follow-up from ART response variable like cox proportional hazard model.
- Statistical Joint model of longitudinal (CD4 cell count) analysis for longitudinal measurements with survival time-to-lost.

## Linear Mixed Model

This model arises when multiple observations are made on the same subject over time. Measurements made on the same variable for the same subject are likely to be correlated and another important outcome that is commonly measured in a longitudinal study is the time until a key clinical event of interest occurs such as disease recurrence or lost (time-to-event data).

A LMM is a parametric linear model for repeatedly measured data that quantifies the relationships between a continuous dependent variable and various predictor variables when the response variable have been follow a normal distribution and also have included to account for the correlation and this might include both fixed-effect parameters associated with one or more continuous or categorical covariates and random effects associated with one or more random factors. Whereas fixed-effect parameters describe the relationships of the covariates to the dependent variable for an entire population, random effects are specific to subjects within a population.

Let $\beta$ denotes a p*1 vector of unknown population coefficients for the fixed effect and $x_i$ be known $n_i$*p design matrix values of the fixed predictors linking $\beta$ to the set of the longitudinal measurements $y_i$ is given as $y_{i0}$, $y_{i6}, y_{i12}$ ..... $y_{i30}$ for the $i^{th}$ subject at times $t_{i0}$, $t_{i6}, t_{i12}$

,,,,,,,,,,,,,,,,,,,, $t_{i30}$. Since, the CD4 cell of HIV/AIDS patients is measured after 6 months for 3 years respectively. The Linear Mixed Model is defined as:

$$y_i = X_i\beta + Z_i b_i + \epsilon_i; \quad (1)$$

(Fixed) (Random)

$$\begin{cases} b_i \sim N(0, D) \\ \epsilon_i \sim N(0, \sum_i) \\ b_1, \ldots\ldots, b_n, and\ \epsilon_i, \ldots\ldots \epsilon_n\ are\ independent \end{cases}$$

Where $y_i$ is the $n_i$*1 longitudinal outcome vector for observations in the $i^{th}$ subjects and $\epsilon_i$ is distributed as $N(0, \sum_i)$ is a vector of residuals components, combining measurement error and serial correlation. And also $b_i$ is random-effects parameters distributed as N (0, D), with independently of each other and of the within-subjects residuals $\epsilon_i$. That is, $cov(b_i; \epsilon_i) = 0$. Furthermore, $\sum_i = \delta^2 I_{ni}$ is the $n_i * n_i$ positive-definite variance-covariance matrix for the errors in subject i, where $I_{ni}$ denotes the $n_i * n_i$ identity matrix.

Marginally, the vector $y_i$ is normally distributed with mean $X_i\beta$ and variance-covariance matrix of $v_i = Z_i D Z_i^T + \delta^2 I_{ni}$. Here D is a k * k positive-definite covariance matrix for random effects. Conditional on $b_i$; $y_i$ is normally distributed with mean $X_i\beta + Z_i b_i$ and with variance-covariance matrix $\sum_i$. It can also be rewritten as $y_i / b_i \sim N(X_i\beta + Z_i b_i, \sum_i)$. That is, given the random effects $b_i$, the dependent variable $y_i$ is normally distributed with variance covariance structure [24-26]. In this study longitudinal model used to recognize determinant factors that affect longitudinal change of CD4 cell count progression

## Cox proportional hazard model

This model used to investigate the association between survival time of patients and one or more predictor Variable in medical research. Let $t_j$ (j = 1, 2,…, n) be the time to lost from ART for patient i; and $X^T_{i2} = (x_{12}, x_{22}, \ldots x_{k2})$ be a p-dimensional fixed effects vector of covariates for patient i that is associated with the p-dimensional vector $\beta_2$ of fixed effects. Then the semi parametric models for $t_j$ have hazard functions at the time t of the form:

$$h_i(t) = h_0(t) exp\ [X^T_{i2}\beta_2\ ] \quad (2)$$

Where $h_0(t)$ baseline hazards function and the semi-parametric model (unspecified to $h_0(t)$) is the widely used Cox Proportional Hazards model [27-28]. Hence, the author was used survival model to investigate the determinant factors that can affect survival time-to-lost follow-up after patients started taking treatment.

## Statistical Joint Modeling of Longitudinal and Survival Data Analysis

In many longitudinal studies, the outcomes recorded on each subject include both a sequence of repeated measurements at pre-specified times and the time at which an event of particular interest occurs: e.g, lost,death from the study. The term statistical joint modelling refers to the statistical analysis of the resulting data while taking account of any association between the repeated measurement and survivl time-to-event outcome [29]. Joint longitudinal and survival models had been formed where the association between the two endpoints is due to shared random effects.

This study was mainly focus on the use of a joint model, where the longitudinal and survival processes are assuming to be conditionally independent may be has given unobserved random effects. That is, the key assumption of a joint model is that the random effects underlie both the longitudinal and survival processes. This means that these random effects account for both the association between the longitudinal and event outcomes, and the correlation between the repeated measurements in the longitudinal process. These types of joint model have also called a shared parameter model, as both processes share these random effects [30].

Therefore, in this study, the author was used some of the methodologies, notations and equations used [31]. and employed the statistical joint models that belong to the random effects shared parameter models framework as both sub-models share the same random effects. Let $T_i$ represent the failure time for the $i^{th}$ individual such that either censoring or the event has occurred. Without loss of generalizability, our aim is to associate the true and unobserved value of the longitudinal outcome at time t, denoted by $m_i(t)$, with event outcome $T_i$. The longitudinal and survival components of the joint model are typically linked through the trajectory function. Specifically, Joint models of longitudinal with survival Time-to-lost follow-up from ART:

$$\begin{cases} y_i(t) = X_i\beta + Z_i b_i + \in_i (t); \\ \lambda_i(t) = \lambda_0(t) exp\{\alpha^T * \mathrm{Ш}_i + [\Upsilon . m_i(t)]\}, t > 0; \end{cases} \quad (3)$$

Where, $y_i(t)$ are longitudinal sub model, $\lambda_i(t)$ , is survival sub model.

$m_i$(t) Represents the history of the true (unobserved) longitudinal response. $\mathrm{Ш}_i(t)$ Represents the vector of baseline covariates with corresponding parameter estimates $\alpha_i$ and $\Upsilon$. measures the effect of the longitudinal outcome to the risk of an event (i.e., in our case effect of number of CD4 cells to the risk of time-to-lost). Hence with this formulation, the risk of an event at time t is

dependent on the true value of the longitudinal endpoint at that time. The main goal of this statistical Joint longitudinal and survival data analysis were used to identify the association of longitudinal change of CD4cell count change on time-to-lost follow-up from ART and major risk factors of longitudinal and event process on HIV/AIDS patients [32].

## Model Selection Criteria

Model selection is the process of selecting a statistical model from a set of candidate models, for given HIV/AIDS patient's data. There are different mechanisms that can be used to select an appropriate statistical JM or for the $univariate$ LMM most commonly known model selection criterions; $Akaike$ Information Criterion (AIC) and the Bayesian Information Criterion (BIC) had considered for this study that can predicted survival status of HIV/AIDS patients on ART follow-up. AIC and BIC are measures of likelihood, penalized for the complexity of the model [33].

$$AIC = -2\log L + 2p \quad (3)$$

$$BIC = -2\log L + npar \log(N)$$

# Results

## Baseline characteristics of HIV/AIDS Positive patients at ART Follow-up

A total of 216 HIV infected patient records enrolled on ART were included in this study. Above half 134(62%) of the study subjects were females, and 128(59.3%) had lived in rural, 49 (22.7%) had both HIV/TB status and 19% patients were lost from the follow-up. The median and std. Deviation time-to-lost follow up from ART for the cohort study was 28.7 and 6.5 months respectively **(Table 2).**

### Statistical Joint Model Analysis on $\sqrt{CD4\ cell}$ Change on Time-to-Lost Follow-up from ART

Based on the above sub-titles, the researcher tried to find the association between the two responses and the major factors that affect $\sqrt{CD4\ cell}$ count change and time-to-lost Follow-up from ART of HIV/AIDS patients by fitting simultaneously. The statistical joint model analysis of longitudinal change of $\sqrt{CD4\ cell}$ count change on HIV/AIDS patient and survival time-to-lost follow-up was analyzed by applying R software. **Table 3** shows that the separate analysis of longitudinal linear mixed model, Cox proportional hazard model and statistical joint model were given. Based on this Table, Baseline CD4 cell and being bedridden were significant factors of $\sqrt{CD4\ cell}$ count variations. The Baseline CD4 cell, being sex of male, being living in rural and being comorbidity HIV with TB was significant factors of risk to short Time-to-Lost follow-up of HIV/AIDS patients. The associations of the $\sqrt{CD4\ cell}$ count on survival time-to-lost follow-up from ART on HIV/AIDS patients were statistically significant.

# Discussion

In this paper, the authors found that factors affecting $\sqrt{CD4\ cell}$ count variations on time-to-lost follow-up predictors of HIV/AIDS patients by fitting simultaneously. Therefore, Based on **Table 3,** Baseline CD4 cell count, being sex of male, being living in rural and being comorbidity HIV with TB were significant factors of risk of time-to-lost follow-up of HIV/AIDS patients. On the other hand, Baseline CD4 cell and being bedridden were significant factors of $\sqrt{CD4\ cell}$ count variations. The association parameter of the $\sqrt{CD4\ cell}$ count variation on time-to-lost follow-up of HIV/AIDS patients was negatively significant when we fitted simultaneously. This study was similarly found by [21].

The risk of time-to-lost follow-up of patients for those who had developed HIV/TB patients was more risk than those had not developed HIV/TB patients when controlling other independent variables. These results conformed to the study conducted by [34]. This shows that, the main known risk factor for lost follow-up from ART in HIV/AIDS patients are TB development.

There was also significant sex differential among patients at risk of mortality of males had more affected as compared with females by controlling other predictor variables. This result had been supported by previous research [34, 35].

The risk of lost follow-up from ART in HIV/AIDS patients where lived in urban had lower than those where lived in rural area by controlling other predictor variables. This show that, HIV/AIDS patients those lived in urban have better understanding of the disease state and comprehension of instructions given on drug usage than those lived in rural areas. This result was Consistent with findings by [36].

Moreover, those patients who had lower baseline CD4 were associated with a higher risk of lost follow-up among the retrospective cohort. That means, Patient's baseline CD4+ count significantly impact on his or her survival attending follow-up time. This study was agreed to a study by [10] in Ethiopia.

The progression change about $\sqrt{}$ (CD4 cell) count on patients for those bedridden functional status patients was less than those working functional status when controlling other independent variables. This study agreed with the findings of [19].

The baseline CD4 cell count was positively associated with progression change of $\sqrt{}$ (CD4 cell) count during ART treatment. That means, High baseline CD4 count was contributed to increase of $\sqrt{}$ (CD4 cell) count change. This result was similar with some studies also reported positive associations between these characteristics [19, 37].

# Conclusions

Statistical joint model analysis was fitted for the survival time-to-lost follow-up and CD4 cell count variation data analysis under this study. An Improvement of statistical joint model has helped validate the observed correlation between the outcome variables. The result under this study indicated that some predictors were significantly correlated with the change of CD4 cell count and time-to-lost follow-up and improving of statistical joint model analysis for the two responses gave a powerful estimation as compared to the separation model. The result of this study identified a certain group of patients who were with the highest hazard of CD4 cell count change, but who had developed co-infected with HIV/TB, being the sex of male, bedridden functional status and lower Baseline CD4 cell count change. This group of patients needs high attention in counseling and awareness creation. Finally, the association parameter was negative

for the statistical joint models. Hence, this indicated that the higher √ (CD4 cell) count change is significantly associated with the lower risk of time-to-lost follow-up from ART.

## Abbreviations

AIDS: Acquired Immune Deficiency Syndrome; AIC: Akaike Information Criteria; CI: Confidence Interval; CD4: Classification Determinant Four; ART: Antiretroviral Therapy; HIV: Human Immune Deficiency Virus; LMM: Linear Mixed Model; WHO: World Health Organization.

## Availability of data and materials

The author used secondary data for this study obtained at Mekelle General Hospital.

## Consent for publication

Not applicable.

## Ethics approval and consent to participate

This study used secondary data from medical case records and patients were not contacted. The data from the case records were handled with strong responsibility and confidentiality. Ethics approval was delivered from the Research Ethics Review Committee of University of Gondar College of Natural and Computational Science and permission was taken from Mekelle General Hospital medical director to collect data from records.

# Competing interests

The author declares no competing interests.

## Authors' contributions

This research paper total activity was completed by GG. Finally, author read and approved the final manuscript.


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