The effect of longitudinal body weight and CD4 cell progression for the survival of HIV/AIDS patients
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It is about half a century since the HIV epidemic has been a menace to this world. Since then, several risk factors have been investigated for the prevalence of the disease, and the survival of Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) patients. The main purpose of the current study was to examine the current patient status in contrast with baseline facts and investigate the separate and joint effects of body weight and CD4 cell count progression for the survival of HIV/AIDS patients. A retrospective cohort study was conducted among HIV/AIDS patients, who were under Antiretroviral Therapy (ART) follow-up during 11 September 2013—5 September 2016 at Mekelle General Hospital, Ethiopia. A total of 216 HIV/AIDS patients were selected by using a systematic random sampling technique. Based on the complexity of the data and the desired objectives of the study, the authors have considered linear mixed-effects model (LMM) for continuous responses body weight and CD4 count, a Cox proportional hazard model for the survival outcome (time to death) and Joint model of longitudinal and survival outcome. The mean age, hemoglobin level, and body weight of HIV/AIDS patients at the start of ART were 34.8 years, 13.6 g/100 ml, and 49.2 kg, respectively. The average number of baseline CD4 cells count was 311.04 cells per mm³ with a standard deviation of 161 cells per mm³ of blood implying that patients were at a higher risk of getting HIV/AIDS-related illness. Out of 216 HIV/AIDS patients, 134 (62%) were female and 130 (60%) lived in an urban area. Similarly, among the sampled HIV/AIDS patients 23 (10.6%) were with HIV/TB co-infected. The present study has concerned on the comparison of separate and joint modeling. The

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PUBLIC INTEREST STATEMENT
HIV is a major health problem worldwide despite enormous efforts to control its spread. This study would be used to the natural and most appropriate statistical models to study body weight & CD4 cell count progression on the survival time-to-death of HIV-infected patients under ART in which most efficient estimates would be obtained. Therefore, the importance of this study would have the most efficient statistical model to fit bodyweight & CD4 cell count progression on survival time-to-death of HIV-infected patients under ART follow-up. And also, it provides important information for both HIV patients and ART service providers (health experts) to give more attention and work on the risk factors that are responsible for a change in body weight & CD4 cell count on survival time-to-death of the HIV patients. It would also be useful to input other researchers who want to conduct research on a similar area/title.
results clearly demonstrate that the joint modeling of longitudinally CD4 count and weight measurements with survival outcomes fit the current dataset better than those obtained from the separate model, of course the authors realize in some specific cases both separate and joint analysis were consistent. However, the joint models were simpler as compared to the separate models as their effective member of parameters was smaller. In the analysis of joint modeling of longitudinal $\sqrt{CD4cell}$ and log (body-weight) progression with survival time to death of HIV/AIDS patients, considered various sub-models and various significant factors were identified. In the event process the sub-model, Baseline CD4, fair, and good adherence, HIV/Tuberculosis (TB), and sex were significant factors of risk to short survival Time-to-Death on HIV/AIDS patients. In the first longitudinal process sub-model, Baseline CD4, Ambulatory functional status, HIV/TB (yes), Time*Ambulatory functional status, Time*Working functional status, and Time*Baseline CD4 were the significant factors of $\sqrt{CD4cell}$ count progression. Moreover, In the second longitudinal process sub-model, visit time of follow-up, age, sex (male), baseline weight, Time*Ambulatory, and Time*Working functional status were the significant factors of log 10 (bodyweight) progression. In the present study, appropriate models were chosen and important significant factors also identified. Hence, the authors strongly suggest that special intervention, clinical practice, and health policy revision should be made on the risk factors that potentially determine the survival of HIV/AIDS patients.

**Subjects:** Medicine; Dentistry; Nursing & Allied Health

**Keywords:** ART; CD4 cell; HIV/AIDS; longitudinal data analysis; statistical joint modeling

1. **Introduction**

It is about half of a century since the HIV epidemic has been a menace to this world. Following the reports of the first case in the early 1980s, the spread of HIV/AIDS has increased at an alarming rate. Despite global awareness, more than 70 million people were affected and 35 million people died due to HIV infection (WHO, 2017). It is reported that, nearly 36.7 million people were living with HIV (UNAIDS, 2016, WHO, 2017) and that more than 1 million people died globally in 2016. While adults ranging in age between 15 and 49 years, which constitutes about 0.8% worldwide, were affected, the infection in Sub-Saharan Africa continues to be severe (4.2%), and this accounts for about two-thirds of HIV people living in the world. Although the infection varies considerably in different regions, the distribution of HIV/AIDS was more in Sub-Saharan Africa and represents about 60% of the victims of HIV/AIDS of the world. Among 800,000 new HIV cases reported in Eastern and Sub-Saharan Africa, 12.9% of the infected people were assessed for ART, and around 380,000 people died of HIV/AIDS in 2017 (UNAIDS, 2018).

Ethiopia is one of the most highly affected among the seven countries that are the greatest hit by the HIV/AIDS pandemic diseases in Sub-Saharan Africa (Seyoum & Temesgen, 2017). Approximately about one million people living with HIV becomes the leading cause of mortality among 15–49 years of age that accounts for 43% of all population deaths in 2016, and approximately a total of 114,690 people died of AIDS-related conditions (Tadege, 2018).

Antiretroviral treatment (ART) was started in Ethiopia in 2003, formally with cost-sharing. However, the country initiated free ART in 2005 with the support of the Global Fund for Tuberculosis, AIDS, and Malaria (GFTAM), and the US President’s Emergency Plan for AIDS Relief (PEPFAR). In the study area, Mekelle General Hospital has begun ART delivery services follow up since September 2011 and has been given a service, more than 10,000 HIV/AIDS patients (Gezae et al., 2019). But, the effectiveness of ART initiatives is not yet fully investigated, especially how much support is to prolong the survival of HIV patients in the study area and a nation to the larger
domain. Thus, we have focused on examining the existing status and determining the potential predictors that could affect the survival of HIV patients and suggesting realistic interventions to optimize patient's life quality. The CD4 cell count of a healthy individual must have at least 500 cells/mm³ and below this level is an indication of an unhealthy condition, and when CD4 cell count reduces below 200/mm³, the person requires a diagnosis for AIDS (Kaufmann et al., 2003; Seyoum & Temesgen, 2017).

CD4 counts decrease over time in persons who are not receiving ART, of course, the other way is also true. Moreover, CD4 cell counts are affected by various demographic factors (Florence et al., 2003).

Authors have focused on the longitudinal change of body weight and CD4 cell count progression on survival time-to-death of the HIV/AIDS patients. Survival analysis involves the modeling of time to event data; in this context, death or failure is considered as “an event.” In fact, separate modeling could be possible, but usually, joint modeling is suggested for such studies and comparisons have been made with the separable models. Joint modeling is appropriate when one wants to predict the time to an event with covariates that are measured longitudinally and are related to the event. An underlying random effects structure links the survival and longitudinal sub-models and allows for individual-specific predictions.

Thus, the main purpose of the current study was to examine the current patient status in contrast with baseline facts and determine potential predictors through appropriate statistical models. The present paper is organized as follows. Section 2 describes data and methods. The basic findings of the study are presented and discussed in Sections 3 and 4, respectively. Finally, concluding remarks are provided in Section 5.

2. Data and methods

2.1. Study area and period
This study was conducted at Mekelle General Hospital, Tigray Region, and Northern Ethiopia on HIV/AIDS positive patients who initiated ART follow-up from 11 September 2013 until 5 September 2016.

2.2. Study design and data source
In the present study, authors have obtained data through a retrospective cohort study design where basically joint longitudinal and survival modeling have considered determining potential predictors.

2.3. Study population
All HIV/AIDS positive patients whose ages were 15 years and above treated on ART follow-up from 11 September 2013 to 5 September 2016, in Mekelle General Hospital. These would be the study population if they fulfilled the inclusion criterion considered in this study.

2.4. Sample size determination and sampling procedure
In this, the researcher used a systematic random sampling procedure to select sample subjects from the list of the study population. Then, the researcher has used the survival sample size determination formula to achieve statistically significant results. Sample size calculation formula, the required sample size for this study was obtained as follows (Collett, 2015).

\[
\text{Death} = \frac{(z_2 + z_\alpha)^2}{2 \log(\text{HR})^2}
\]

The sample size was determined by taking the mortality rates in two groups of HIV positive on ART based on their WHO clinical stage as exposure status. Where \( z_{1.96} = 1.96 \), \( z_{0.84} = 0.84 \), HR of exposures \( = 7.36 \), \( 1 = \) Proportion of exposed group (WHO stage-IV) = 0.84, \( 2 = \) Proportion of non-exposed group (WHO stages-II & III) = 0.16. Therefore, \( \text{Death} = \frac{(1.96^2 + 0.84^2)}{0.84 - 0.16} \approx 77 \) and also the probability of death was 35.5%.
Then, \( n = \left\lfloor \text{Death} \right\rfloor = \frac{72}{0.0353} = 216 \). The study participants were selected using a systematic random sampling method of patients’ unique identification number and were retrospectively from 11 September 2013 to 5 September 2016. Then, the sample size for this current study has become 216 HIV positive subjects (Damtew et al., 2015).

2.5. **Data collection procedure**
The relevant data were taken from HIV/AIDS patients under ART follow-up charts and have been collected by two professional collectors and also one supervisor.

2.6. **Quality of data**
The quality of the data was controlled by data controllers from the ART section of the hospital. The controllers were taken intensive training by the Ministry of Health for different services. The data extraction tools and the variables included in the study were tested. Necessary amendments were made to the final data collection sheet.

2.7. **Study variables**
The response and predictor variables considered in this study were defined as follows.

2.7.1. **Response variables**
The longitudinal response variables were the progression of body weight (in kg) and CD4 cell count (in cell/mm\(^3\)) of HIV/AIDS positive patients during the follow-up time from the date of ART initiation. The survival response variable was the survival time-to-death or censored (in the month) HIV/AIDS positive patients during the follow-up time from the date of ART initiation. This was measured from the starting of treatment till the patient’s time-to-death or censored of the last visit.

2.7.2. **Independent variables**
The covariate (predictor) variables in the current study were considered potentially affect the body weight and CD4 cell count progression and then, aggravate the death of HIV/AIDS patients. Thus, the study variables selected based on authors experience and empirical-related literature (Ayalew, Moges et al. 2014; Reda et al., 2013; Tadege, 2018; Temesgen & Kebede, 2016).

2.8. **Statistical models**
In this study, the authors used the survival model to investigate the determinant factors that can affect survival time after patients started taking treatment to death of the patient’s, and the univariate longitudinal model analysis had been used to recognize determinant factors that affect the longitudinal change of CD4 cell count and body weight progression separately. And also, the statistical joint longitudinal and survival analysis were used to assess the impact of the longitudinal change of body weight and CD4 cell count progression on survival time-to-death of the HIV/AIDS patients. Based on the complexity of the data and the desired objectives of the study, the authors have considered the following three types of different statistical data models:

- A linear mixed-effects model (LMM) was used for continuous response variables for the longitudinal data like bodyweight & CD4 cell count.
- Survival model for the continuous survival time-to-death response variable like the Cox proportional hazard model.
- Statistical Joint model of longitudinal (bodyweight & CD4 cell count) analysis for longitudinal measurements with survival time-to-death.

3. **Results**

3.1. **Descriptive statistics of baseline covariates was illustrated, Table 1**
Descriptive statistics of baseline covariates was illustrated in Table 1. Thus, among 216 HIV/AIDS positive patients considered in the current study, 31 (14.4%) of them died, while the remaining 185
(85.6%) were censored and they may still alive, death with other case/competing risks and lost follow-up. The mean age, hemoglobin level, and body weight of HIV/AIDS patients at the start of ART were 34.8 years, 13.6 g/100 ml and 49.2 kg, respectively. The average number of baseline CD4 cells count was 311.04 cells per mm$^3$ with a standard deviation of 161 cells per mm$^3$ of blood implying that patients were at higher risk of getting HIV/AIDS related illness. Out of 216 HIV/AIDS patients 134 (62%) were female, and 130 (60%) were lived in an urban area. Similarly, among the sampled HIV/AIDS patients 23 (10.6%) were with HIV/TB co-infected. Table 1 also revealed that the percentage of death in males (9.7%) was higher than that of females (4.6%) in HIV positive patients. Moreover, the percentage of death HIV/TB co-infected patient's (43.48) was higher than that of patients who did not have TB diseases (10.88%). Finally, the percentage of death of HIV/AIDS positive patients who lived in rural (9.3%) areas was higher than those who lived in urban (5%) areas.

3.2. Separate and joint model analysis on longitudinal $\sqrt{CD4}$ cell Progression and Survival time-to-death, Table 2
In this section, we determined the variables to be included in the statistical joint model, authors have considered an automatic backward variable selection method (step AIC in R). The survival sub-model was consistent with the results from the separate survival analysis. The differences in magnitudes of the parameter estimates were very small, and there was some parameter difference in terms of statistical significance. The results from the separate and joint analysis were slightly similar to each other. In the survival sub-model fair adherence, good adherence, Baseline CD4, HIV/TB, Baseline weight, and sex were statistically significant predictors of the risk of death. However, the category of functional status and education level was not statistically significant (Seid et al., 2014; Seyoum & Temesgen, 2017).

Longitudinal analysis sub-model of the joint model time, Baseline CD4, Baseline weight, HIV/TB (Yes), married, divorced, ambulatory functional status, age, time*Baseline CD4, time*ambulatory, time*working, and time*HIV/TB (yes) all predictors included in the model were statistically significantly associated with the progression of $\sqrt{CD4}$ cell count. Therefore, from this result Baseline, CD4, and Baseline weight is positively associated with the trajectory of the $\sqrt{CD4}$ cell count. And also, significantly lower risk for shortening the survival time to death associated with HIV/AIDS patients having higher Baseline CD4 and Baseline weight. While the estimated parameters of the two models were slightly similar to each other and not identical, the estimate of the association parameters in the Joint Model was significantly different from zero. This association indicates that higher $\sqrt{CD4}$ cell progression was associated with a lower risk of survival time and time to death.

The residual variability was smaller in the joint analysis (5.9731) compared to the relative linear mixed effects analysis (6.0025), which was probably because the standard errors were adjusted for the correlation between the longitudinal and survival responses. Finally, when we assessed the overall performance of both, the separate and joint statistical models in terms of a model less complex and goodness of fit, the joint statistical model performed better. As a result, the joint model was better as it has a smaller total AIC than the separate model. Also, the statistical significance of both the association parameters was also evidence that the statistical joint model analysis was better than the separate models (Grover et al., 2015).

3.3. Separate and joint model analysis on Log$_{10}$ (Body-Weight) progression and survival time-to-death, Table 3
In this subsection, the survival sub-model was consistent with the results from the separate model of survival analysis, Table 3. The differences in magnitudes of the parameter estimates were minor and there was some parameter difference in terms of statistical significance. The results from the separate and joint model analysis were slightly similar to each other. This survival sub-model is
| No | Covariates | Categories | Total No of patient’s (%) | Observed death (%) |
|----|------------|------------|----------------------------|-------------------|
| 1  | Sex        | Female     | 134 (62%)                  | 10 (4.6%)         |
|    |            | Male       | 82 (38%)                   | 21 (9.7%)         |
| 2  | Education level | Illiterate | 57 (26.4%)                | 16 (7.4%)         |
|    |            | Elementary | 45 (20.8%)                | 8 (3.7%)          |
|    |            | Secondary  | 74 (34.3%)                | 6 (2.8%)          |
|    |            | Tertiary   | 40 (18.5%)                | 1 (0.46%)         |
| 3  | Marital status | Single    | 54 (25%)                  | 7 (3.2%)          |
|    |            | Married    | 109 (50.5%)               | 11 (5%)           |
|    |            | Divorced   | 39 (18%)                  | 5 (2.3%)          |
|    |            | Widowed    | 14 (6.5%)                 | 8 (3.7%)          |
| 4  | Functional status | Working | 146 (67.6%)               | 10 (4.6%)         |
|    |            | Ambulatory | 55 (25.5%)                | 13 (6%)           |
|    |            | Bedridden  | 15 (6.9%)                 | 8 (3.7%)          |
| 5  | WHO clinical stage | Stage-I | 93 (43%)                  | 8 (3.7%)         |
|    |            | Stage-II  | 63 (29.2%)                | 5 (2.3%)          |
|    |            | Stage-III | 45 (20.8%)                | 12 (5.6%)         |
|    |            | Stage-IV  | 15 (6.9%)                 | 6 (2.8%)          |
| 6  | HIV/TB infection | No      | 193 (89.4%)               | 21 (10.9%)        |
|    |            | Yes       | 23 (10.7%)                | 10 (4.6%)         |
| 7  | Adherence on treatment | Good | 96 (44.5%)                | 5 (2.3%)          |
|    |            | Fair      | 74 (34.2%)                | 10 (4.6%)         |
|    |            | Poor      | 46 (21.2%)                | 13 (6%)           |
| 8  | Occupational status | Unemployed | 163 (75.5%)               | 23 (10.7%)        |
|    |            | Employed  | 53 (24.5%)                | 8 (3.7%)          |
| 9  | Place of residence | Urban | 130 (60.2%)               | 11 (5%)           |

(Continued)
| No | Covariates               | Categories          | Total No of patient’s (%) | Observed death (%) |
|----|--------------------------|---------------------|---------------------------|--------------------|
|    |                          | Rural               | 86 (39.8%)                | 20 (9.3%)          |
| 10 | Type of ART regiment    | TDF+3TC+EFV         | 135 (62.5%)               | 12 (5.6%)          |
|    |                          | D4t+3TC+NVP         | 20 (9.25%)                | 13 (6%)            |
|    |                          | AZT+3TC+NVP         | 40 (18.5%)                | 13 (6%)            |
|    |                          | AZT+3TC+EFV         | 21 (9.7%)                 | 3 (1.4%)           |
| 11 | Continuous variables    | mean                |                           | standard deviation |
|    | CD4 at base line        | 311                 |                           | 163.6              |
| 12 | Body weight at base line| 49.2                |                           | 9.85               |
| 13 | Hemoglobin at base line | 13.6                |                           | 1.98               |
| 14 | Age at base line        | 34.8                |                           | 11                 |
Table 2. Shows the comparison of separate and joint model analysis √(CD4 cell) with survival time-to-death

| No. | Parameter          | Separate model analysis of survival analysis | Joint model sub model |
|-----|--------------------|---------------------------------------------|-----------------------|
|     |                    | Fixed effect | Se(i) | z-value | Pr>|z| | Fixed effect | Se(i) | z-value | Pr>|z| |
| 1   | Function status    |              |       |         |     |              |       |         |     |     |
|     | Bedridden (R)      |              |       |         |     |              |       |         |     |     |
|     | Ambulatory         | −0.732       | 0.595 | −1.231  | 0.218 | −0.5247       | 1.0577 | −0.496 | 0.125 |     |
|     | Working            | −0.4316      | 0.7092| −0.609  | 0.5428| −0.42         | 1.0332 | −0.4065| 0.178 |     |
| 2   | Baseline CD4       | −0.00513     | 0.001433| −3.578 | 0.00037* | −0.0045      | 0.0015 | −3.053 | 0.0023* |     |
| 3   | Adherence          |              |       |         |     |              |       |         |     |     |
|     | Poor (R)           |              |       |         |     |              |       |         |     |     |
|     | Fair               | −1.493       | 0.513 | −2.914  | 0.00357*| −1.5526       | 0.5323 | −2.92  | 0.0035* |     |
|     | Good               | −1.837       | 0.64098| −2.866  | 0.004163*| −1.735        | 0.6405 | −2.709 | 0.0068* |     |
| 4   | Baseline weight    | 0.0402       | 0.0229 | 1.755  | 0.04791* | 0.0433       | 0.0227 | 1.9755 | 0.04793* |     |
| 5   | Sex; female (R)    |              |       |         |     |              |       |         |     |     |
|     | Male               | 1.443        | 0.494 | 2.921   | 0.00349*| 1.227         | 0.486 | 2.522  | 0.0117* |     |
| 6   | HIV/TB status      |              |       |         |     |              |       |         |     |     |
|     | No (R)             |              |       |         |     |              |       |         |     |     |
|     | Yes                | 1.899        | 0.745 | 2.55    | 0.023* | 2.101         | 0.676 | 3.1    | 0.0210* |     |

Separate model analysis of longitudinal

| Parameter          | Separate model analysis | Joint model sub model |
|--------------------|-------------------------|-----------------------|
|                    | B | Se(i) | z-value | Pr>|z| | B | Se(i) | z-value | Pr>|z| |
| 1                   | Time | −0.826 | 0.274 | −3.01  | 0.0027* | −0.827 | 0.2702 | −3.06 | 0.0022* |     |
| 2                   | Baseline CD4             | 0.0213            | 0.0018 | 12.2   | 0.0000* | 0.0234  | 0.00051 | 10.5  | 0.0000* |     |
| 3                   | Baseline weight          | 0.061             | 0.0267 | 2.268  | 0.0244* | 0.0605  | 0.0258 | 2.346  | 0.019* |     |

(Continued)
| No. | Parameter | Separate model analysis of survival analysis | Joint model sub model |
|-----|-----------|---------------------------------------------|-----------------------|
|     |           |Fixed effect | B       | Se(B) | z-value | Pr(>|z|) | B       | Se(B) | z-value | p-value |
| 5   | HIV/TB status |             |         |       |        |         |         |       |        |         |
|     | HIV/TB(R)    |             |         |       |        |         |         |       |        |         |
|     | HIV/TB(yes)  | −3.2        | 1.276   | −2.51 | 0.0130*| −2.169  | 1.245   | −1.735 | 0.109  |
| 6   | Marital status |             |         |       |        |         |         |       |        |         |
|     | Single(R)    |             |         |       |        |         |         |       |        |         |
|     | Married      | −1.181      | 0.564   | −2.094| 0.0375*| −1.178  | 0.544   | 2.164  | 0.00304*|
|     | Divorced     | −1.3357     | 0.731   | −1.827| 0.059  | −1.338  | 0.7086  | −1.988 | 0.049  |
|     | Widowed      | −0.647      | 1.037   | −0.624| 0.533  | −0.6537 | 0.998   | −0.655 | 0.5125 |
| 7   | Time*Baseline CD4 | 0.0028 | 0.00037 | 7.512 | 0.0000*| 0.00194 | 0.000191 | 5.322  | <0.0001*|
| 8   | Time*HIV/TB  |             |         |       |        |         |         |       |        |         |
|     | Time*No(R)   |             |         |       |        |         |         |       |        |         |
|     | Time*Yes     | 0.531       | 0.236   | 2.25  | 0.025* | 0.5209  | 0.233   | 2.239  | 0.025* |
| 9   | Time*function-status |         |         |       |        |         |         |       |        |         |
|     | Time*Bedridden(R) |         |         |       |        |         |         |       |        |         |
|     | Time*Ambulatory | 0.923    | 0.297   | 3.102 | 0.002* | 0.926   | 0.2925  | 3.165  | 0.0015*|
|     | Time*working  | 0.905      | 0.296   | 3.06  | 0.0023*| 0.91    | 0.291   | 3.126  | 0.0018*|
|     | Random effect variance | 19.98 | 4.47 | 18.49 | 4.3 |  |
|     | Std.Dev | 4.47 | 18.49 | 4.3 | 4.3 |  |

*P-value < 0.05 
R = reference group
given below. Fair Adherence, good Adherence, Baseline CD4, Baseline weight, ambulatory Function status, working Function status, primary education level, secondary education level, tertiary education level, and sex (male) were statistically significant predictors with the risk of affecting survival time-to-death.

Table 3, longitudinal analysis sub-model of the joint model age, Baseline CD4, Baseline weight, Ambulatory Function status, working Function status, time: Baseline CD4, and sex (male) all predictors included in the model were significant predictors of progression on the log (bodyweight). Finally, the estimated parameters of the two models (separate and joint models) were slightly similar to each other but not identical. However, the estimates of the association parameters in the statistical Joint model analysis were significantly different from zero. This provides that there was enough evidence of an association between the two sub-models. The estimate of association (\( \text{Gamma}_2 = -1.975 \)) indicating that the higher Log10 (Body-Weight) progression is associated with the lower risk of shortening survival time-to-death. When evaluating the overall performance of the separate and joint models in terms of a model less complex and goodness of fit, the joint model was performed better. As a result, the joint model was better as it has a smaller total AIC than the separate model. The statistical significance of both the association parameters was also a strong evidence that the joint model analysis was better than the separate models (Grover et al., 2015).

3.4. Statistical joint model analysis on \( \sqrt{CD4cell} \) and Log10 (Body-Weight) progression with Survival Time-to-Death, Table 4

Table 4 shows that the first longitudinal process sub-model was for \( \sqrt{CD4cell} \) count and the second was for log (bodyweight). Based on this table, Baseline CD4, Ambulatory functional status, HIV/TB (yes), Time*Ambulatory, Time*Working, and Time*Baseline CD4 were significant factors of \( \sqrt{CD4cell} \) count progression. The visit time of follow-up, age, sex(male), Baseline weight, Ambulatory, and working functional status were significant factors of log(bodyweight) progression and Baseline CD4, fair adherence, good adherence, HIV/TB, and sex were significant factors of risk to short survival Time-to-Death of HIV/AIDS patients. The associations of the \( \sqrt{CD4cell} \) count on survival time-to-death and log (Bodyweight) on survival time-to-death of HIV/AIDS patients were statistically significant when those two biomarkers of longitudinal repeated measurements with survival time-to-death were fitted simultaneously. The association parameters were negative for both statistical joint sub-models.

4. Discussions

In the present paper, the researchers tried to find the factors that affect log (bodyweight) and \( \sqrt{CD4cell} \) count progression sub-models on the short survival time-to-death of HIV/AIDS patients by fitting simultaneously. Baseline CD4, Fair, Good adherence, HIV/TB, and sex were significant factors of risk to affect survival time-to-death of HIV/AIDS patients. Baseline CD4, Ambulatory functional status, HIV/TB, Time*Ambulatory functional status, Time*Working functional status, and Time*Baseline CD4 were significant factors of \( \sqrt{CD4cell} \) count progression. On the other hand, visit time of follow-up, age, sex, Baseline weight, Ambulatory functional-status, and working functional-status were significant factors of log (bodyweight) progression. The associations of the count on survival time-to-death and log (Bodyweight) on survival time-to-death of HIV/AIDS patients was statistically significant when the two biomarkers of longitudinal repeated measurements with survival Time-to-Death were fitted simultaneously. That means, the association parameters were negative for both statistical joint models (Hickey et al., 2016).

The risk of survival time to death on patients who had developed HIV/TB (yes) patients was more risk than those who had not developed HIV/TB (No) patients when controlling other independent variables. These results conformed to the studies conducted (Damtew et al., 2015; Tadege, 2018). This shows that the significant risk factor for mortality in HIV/AIDS patients was TB development. There was also a significant sex differential among patients on the risk of mortality of males had
Table 3. Shows comparison of separate and joint model analysis of Log_{10}(Body-Weight) progression with survival Time-to-death

| Parameter                  | Fixed effect | Separate model analysis of survival | Joint model sub model |
|----------------------------|--------------|-------------------------------------|-----------------------|
|                            |              | $\beta$ | $\text{SE}(\beta)$ | z-value | $p(>|z|)$ | $\beta$ | $\text{SE}(\beta)$ | z-value | $p(>|z|)$  |
| Function status            |              |        |                    |         |           |        |                    |         |           |
| Bedridden(R)               | ——           |        |                    |         |           | ——     |        |                    |         |           |
| Ambulatory                 | 0.732        | 0.595  | 1.231              | 0.218   | 1.060     | 0.0001 | 1.6$\times 10^{-6}$| <0.0001*|
| Working                    | 0.4316       | 0.7092 | 0.609              | 0.543   | 0.6241    | 0.0001 | 4.79$\times 10^{-3}$| <0.0001*|
| Baseline CD4%              | 0.00513      | 0.001433 | 3.578          | 0.0037* | 0.035     | 0.0014 | 2.46               | 0.0137* |
| adherence                  | ——           |        |                    |         |           | ——     |        |                    |         |           |
| Poor(R)                    | -1.493       | 0.513  | -2.914             | 0.00357* | 1.6216    | 0.0000 | -2.17$\times 10^{-3}$| <0.0001*|
| For Good                   | -1.837       | 0.6409 | -2.866             | 0.004163* | -1.55     | 0.0000 | -3.11$\times 10^{-3}$| <0.0001*|
| Baseline weight            | -0.0402      | 0.0229 | -1.755             | 0.04791* | -0.084    | 0.0119 | -7.0768           | <0.0001*|
| Sex                        | ——           |        |                    |         |           | ——     |        |                    |         |           |
| female(R)                  | ——           |        |                    |         |           | ——     |        |                    |         |           |
| male                       | 1.443        | 0.494  | 2.921              | 0.00349* | 0.7139    | 0.0001 | 4.9$\times 10^{-3}$ | <0.0001*|
| Education                  |              |        |                    |         |           |        |                    |         |           |
| Illiterate(R)              | ——           |        |                    |         |           | ——     |        |                    |         |           |
| Primary                    | 0.5475       | 0.4964 | 1.103              | 0.2699  | 0.6073    | 0.0001 | 5.29$\times 10^{-3}$| <0.0001*|
| secondary                  | -0.5036      | 0.547  | -0.929             | 0.3527  | -0.479    | 0.0001 | -8.88$\times 10^{-3}$| <0.0001*|
| Tertiary                   | -1.287       | 1.096  | -1.175             | 0.2400  | -1.13     | 0.0000 | -5.28$\times 10^{-3}$| <0.0001*|

Parameter (Continued)
Table 3. (Continued)

| Parameter | Separate model analysis of survival | Joint model sub model |
|-----------|------------------------------------|-----------------------|
|           | $\delta$  | $\text{Se}(\delta)$ | $z$-value | $P(>|z|)$ | $\delta$  | $\text{Se}(\delta)$ | $z$-value | $P$-value |
| Fixed effect |          |                        |                  |           |          |                        |                  |            |
| female (R) | ——       | ——                    | ——              | ——-       | 0.000    | 0.00394      | 4.619    | <0.0001 |
| male       | 0.036    | -0.0030               | 4.39            | 0.0086    | 0.000    | 4.619        | <0.0001 |
| Marital    |          |                        |                  |           |          |                        |                  |            |
| single (R) | ——       | ——                    | ——              | ——        | 0.0137   | 0.0078       | 1.7782   | 0.0754  |
| married    | 0.0155   | 0.0137                | 1.13            | 0.2599    | 0.0153   | 0.0102       | 1.5075   | 0.1317  |
| Widowed    | 0.00449  | 0.019                 | 0.236           | 0.8135    | 0.0036   | 0.0086       | 0.4217   | 0.6732  |
| Baseline CD4 | 0.00012  | 0.00004              | 3.012           | 0.0029    | 0.0001   | 0.0000       | 3.3336   | 0.0009* |
| Baseline weight | 0.0066   | 0.00061              | 10.83           | 0.0000*   | 0.0068   | 0.0006       | 11.80    | <0.0001* |
| Function status |        |                        |                  |           |          |                        |                  |            |
| Bedridden (R) | ——       | ——                    | ——              | ——        | 0.036    | 0.0182       | 1.97     | 0.048*   |
| Ambulatory  | 0.0718   | 0.0173                | 4.146           | 0.0000*   | 0.0714   | 0.0058       | 10.43    | <0.0001* |
| Working     | 0.0002   | 0.000008              | 1.907           | 0.0467*   | 0.0001   | 0.0000       | 2.0466   | 0.0407* |
| Random effect |        |                        |                  |           |          |                        |                  |            |
| (Intercept) | 0.007    | 0.0038                | 2.832           | 0.0070    | 0.007    | 0.0838       | 0.0000   | <0.0001 |
| Time        | 0.0025   | 0.0015                | 1.370           | 0.0000    | 0.0025   | 0.0015       | 1.370    | <0.0001 |
| Residual    | 0.0015   | 0.0000                | 1.975           | 0.0000    | 0.0015   | 0.0000       | 1.975    | <0.0001 |
| Association | ——       | ——                    | ——              | ——        | -1.975   | 0.0005       | -1.9627  | 0.02798 |

*P-value < 0.05.
Table 4. Result of joint model of longitudinal \( \sqrt{CD4 cell} \& \log \text{ (body weight)} \) progression with survival Time-To-Death of HIV/AIDS patients

| Parameters | \( B \) | \( \text{Se}(\beta) \) | z-value | \( \text{Pr}(>|z|) \) | \( B \) | \( \text{Se}(\beta) \) | z-value | \( \text{Pr}(>|z|) \) |
|------------|--------|----------------|--------|----------------|--------|----------------|--------|----------------|
| Sex        |        |                |        |                |        |                |        |                |
| female(R), male | 1.3408 | 0.6136 | 2.1851 | 0.0289* |        |        |        |                |
| Baseline CD4 | -0.0052 | 0.0016 | -3.2072 | 0.0013* | -0.0048 | 0.0015 | -3.20 | 0.00104* |
| Adherence  |        |                |        |                |        |                |        |                |
| poor(R)    |        |                |        |                |        |                |        |                |
| fair       | -1.6769 | 0.8610 | -1.9476 | 0.0515 |        |        |        |                |
| good       | -1.2532 | 0.6704 | -1.8693 | 0.0616 |        |        |        |                |
| HIV/TB     |        |                |        |                |        |                |        |                |
| HIV/TB(R)  |        |                |        |                |        |                |        |                |
| HIV/TB(yes)| 2.101  | 0.676 | 3.100 | 0.0210* |        |        |        |                |
| Associations|        |                |        |                |        |                |        |                |
| Gamma_1    | -0.6693 | 0.336 | -1.992 | 0.0367* |        |        |        |                |
| Gamma_2    | -1.975  | 1.0065 | -1.9627 | 0.02798* |        |        |        |                |
| AIC        | 6602.83 |        |        |        | 2833.126 |        |        |                |

Parameters |
|------------|--------|----------------|--------|----------------|--------|----------------|--------|----------------|
| Longitudinal process sub model of \( \text{M}_i \) on Time-To-Death | \( B \) | \( \text{Se}(\beta) \) | z-value | \( \text{Pr}(>|z|) \) | \( B \) | \( \text{Se}(\beta) \) | z-value | \( \text{Pr}(>|z|) \) |
| (Intercept)_1 | 10.356 | 2.0583 | 5.0314 | <0.0001* | 10.46  | 2.0199 | 5.176 | <0.0001* |
| time_1      | 0.0259 | 0.3835 | 0.0676 | 0.9461 | 0.0309 | 0.2480 | 0.1247 | 0.900 |
| Baseline CD4_1 | 0.0208 | 0.0022 | 9.48  | <0.0001* | 0.0207 | 0.0019 | 10.977 | <0.0001* |
| age_1       | -0.0015 | 0.0251 | -0.0586 | 0.950 | -0.0040 | 0.0274 | -0.1453 | 0.88 |
| Functional status |        |        |        |        |        |        |        |                |
| Bedridden(R)_1 |        |        |        |        |        |        |        |                |

(Continued)
| Parameters | \( B \) | \( \text{Se}(B) \) | \( \text{z-value} \) | \( \text{Pr}(>|z|) \) | \( B \) | \( \text{Se}(B) \) | \( \text{z-value} \) | \( \text{Pr}(>|z|) \) |
|------------|---------|---------|---------------|----------------|---------|---------|---------------|----------------|
| Ambulatory_1 | 1.8094  | 1.6722  | 1.082         | 0.02792*       | 2.49687 | 1.14876 | 2.183        | 0.01857*       |
| Working_1   | -0.4411 | 1.6919  | -0.2607       | 0.07943        | -0.5106 | 1.5874  | -0.3217      | 0.0748         |
| HIV/TB      | ———    | ———    | ———          | ———           | ———    | ———    | ———          | ———           |
| Yes_1       | -1.8287 | 1.4197  | -1.288        | 0.01977        | -2.0019 | 0.914   | -2.191       | 0.00847*       |
| Time\(^*\) BaselineCD4 | 0.0025 | 0.0004  | 6.0157        | <0.0001        | 0.0026  | 0.0003 | 8.152        | 0.0001*        |
| Time\(^*\) Functional Ambulatory | 0.7346 | 0.3631  | 2.0231        | 0.0431         | 0.7347  | 0.2233  | 3.3          | 0.0009*        |
| Time\(^*\) Working | 0.7906 | 0.3453  | 2.289         | 0.0220         | 0.7927  | 0.2205  | 3.595        | 0.0003*        |
| Parameters | Longitudinal process sub model of \( \log(\text{weight}) \) on Time-To-Death | Longitudinal process sub model of \( \log(\text{weight}) \) on Time-To-Death_2 |
| Parameters | \( B \) | \( \text{Se}(B) \) | \( \text{z-value} \) | \( \text{Pr}(>|z|) \) | \( B \) | \( \text{Se}(B) \) | \( \text{z-value} \) | \( \text{Pr}(>|z|) \) |
| (Intercept)_2 | 1.261  | 0.0431  | 29.24         | <0.0001        | 1.2610  | 0.0473  | 26.65        | <0.0001*       |
| time_2      | 0.0305 | 0.0094  | 3.2402        | 0.0012         | 0.0305  | 0.0106  | 2.885        | 0.0039*        |
| age_2       | 0.0010 | 0.0005  | 2.00          | 0.0075         | 0.0011  | 0.0004  | 2.76         | 0.0058*        |
| Sex         | ———    | ———    | ———          | ———           | ———    | ———    | ———          | ———           |
| female(R)_2 | ———    | ———    | ———          | ———           | ———    | ———    | ———          | ———           |
| male_2      | 0.0061 | 0.0086  | 0.7099        | 0.04778        | 0.0067  | 0.00338 | 1.995        | 0.0417*        |
| Baseline weight | 0.0067 | 0.0009  | 7.2           | <0.0001*       | 0.0067  | 0.0010  | 6.589        | <0.0001*       |
| Functional status | ———    | ———    | ———          | ———           | ———    | ———    | ———          | ———           |
| Bedridden(R)_2 | ———    | ———    | ———          | ———           | ———    | ———    | ———          | ———           |
| Ambulatory_2 | 0.0372 | 0.024   | 1.55          | 0.0135*        | 0.0395  | 0.0150  | 2.625        | 0.0087*        |
| Working_2   | 0.0364 | 0.0575  | 0.633         | 0.0092*        | 0.0506  | 0.0176  | 2.866        | 0.0042*        |
more affected than females by controlling other predictor variables. This study contradicts the previous study (Reda et al., 2013). The risk of death of HIV/AIDS patients whose Adherence Fair and Good had lower than those whose Adherence Poor by controlling other predictor variables. This shows that HIV/AIDS patients whose Adherence was Fair and Good have better survival time and understanding of the disease condition and comprehension of instructions given on drug usage than Adherence poor patients, and this observation agrees with the study conducted earlier (Ahunie & Ebrahim, 2017; Tegegne, 2021; Temesgen & Kebede, 2016).

Moreover, patients with lower baseline CD4 were associated with a higher risk of death among the retrospective cohort. That means the patient’s baseline CD4+ count significantly impacts their survival time. This study was agreed with a study (Damtew et al., 2015; Tadege, 2018).

The progression change of $\sqrt{CD4_{cell}}$ count on patients for those who had developed HIV/TB (yes) patients was less than those who had not developed HIV/TB patients when controlling other independent variables. This study agreed with the findings of (Damtew et al., 2015; Farhadian et al., 2021; Mengesha et al., 2014). On the functional status of patients on ART, The progression change of $\sqrt{CD4_{cell}}$ count for Ambulatory Functional status patient’s more as compared to Bedridden Functional status patients by controlling other independent variables. This shows that patients whose Bedridden Functional statuses have a higher probability of risk of death than patients whose Ambulatory Functional status. This result is in agreement with the earlier findings (Ahunie & Ebrahim, 2017; Temesgen & Kebede, 2016). 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 the increase of $\sqrt{CD4_{cell}}$ count progression. This result was similar to an earlier study that reported positive associations between these characteristics (Adams & Luguterah, 2013).

When an interaction effect is present, the impact of one factor depends on the level of the other factor. In another way, it can be stated that it is a complex multivariable effect, which provides more precise information than a simplified main effect (Cox, 1984; Kemphorone, 1952). In the present study, the interaction effect of time with working functional status and time with baseline CD4 count were identified. This finding is consistent with various literature (Brennan et al., 2013; Egger et al., 2009; Hughes et al., 2011).

The interaction effect of visit time follow-up by functional status had a statistically significant effect on the mean $\sqrt{CD4_{cell}}$ count, this suggesting that as the number of visit time increased, the average $\sqrt{CD4_{cell}}$ count of HIV/AIDS patients who were ambulatory and working functional status was higher than the average $\sqrt{CD4_{cell}}$ count of patients who were bedridden functional status by 2 times (p-value = 0.0009) and 2.2 times (p-value = 0.0003), respectively, when other variables constant. The length of stay of follow-up on ART was an important predictor of improvement on the log of bodyweight progression of patients (p =0.0305; p-value = 0.0039). Such kind of result also found (Tegegne, 2021; Temesgen & Kebede, 2016). The progression change of log (bodyweight) has positively associated with the baseline body weight. This indicated higher body weight at baseline was found to be associated with higher progression on the log (bodyweight). The results of the present study confirmed the study reported previously (Reda et al., 2013).

Similarly, the longitudinal joint sub-model of log (bodyweight) ambulatory and working functional status was significant factors for contributing to the prediction of HIV/AIDS patients of bodyweight progression. That means that ambulatory and actively working patients had better log body weight than bedridden patients as reported earlier (Tegegne, 2021; Temesgen & Kebede, 2016). It means, higher age predicted improvement in the log of body Weight progression which is similar to the earlier study (Mengesha et al., 2014; Reda et al., 2013).

5. Conclusion
In the present study, both separate and joint analyses were considered, and across all statistical comparison criteria, the latter performed better. Thus, through the joint analysis, important significant factors were identified, and special attention should be given for HIV-positive adults, especially for those who had
developed HIV/TB, male by sex, bedridden functional status, poor adherence, and lower Baseline CD4 cell count progression. Among various potential interventions, optimize patient awareness through intensive training may help to qualify adherence status, and also, continuous and timely medical care should be made to minimize the risk of death. Moreover, the authors strongly suggest that health experts should measure the repeated biomarkers to have updated health status of HIV/AIDS patients so that they can make realistic and timely solutions. The higher repeated biomarkers (Log10 (Body-Weight) and $\sqrt{CD4_{cell}}$) indicates the lower risk of survival time-to-death.

6. Limitations of the study
We were unable to include important various socio-demographic and socioeconomic variables like consumption of alcohol, viral load, smoking, income level, physical activity, and diet style that might have contributed to the survival times death of the HIV/AIDS patients. Globally, Tobacco, Alcohol, and Obesity are the major causes of death that have increased substantially since 1990 in some large populations, and thus, missing such variables have never been missed in any death-related studies. Moreover, the present study was restricted to age group ≥15 due to their different measures of CD4 cell count HIV/AIDS patients for children and adults.

Abbreviations
AIC: Akaike Information Criteria
AIDS: Acquired Immune Deficiency Syndrome
ART: Antiretroviral Therapy
BIC: Bayesian Information Criteria
CD4: Cluster Differentiation4
GFTAM: Global Fund for Tuberculosis, AIDS and Malaria
HIV: Human Immunodeficiency Virus
HAART: High Active Anti-Retrieval Virus
LMM: Linear Mixed Model
ML: Maximum Likelihood
PEPFAR: President Emergency Plan for AIDS Relief
REML: Restricted (or residual) maximum likelihood
JM: Joint Modeling
TB: Tuberculosis
UNAIDS: United Nations Program on HIV/AIDS
WHO: World Health Organization Clinical Stage

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Disclosure statement
The authors declare that they have no competing interests.

Ethics approval and consent to participate
Ethical clearance was obtained from the Ethical Review Committee of the University of Gondar College of Natural and Computational Science. The names of the subjects
were not extracted to ensure the privacy of HIV/AIDS patients, and confidentiality was maintained throughout the data collection process and analysis. To collect the data, permission was obtained from administrative officers of Mekelle general hospital.

Data availability statement
The authors have considered HIV/AIDS datasets from Mekelle General Hospital patient history card and are now attached as supplementary materials of the submission system.

Authors’ contributions
GGG has made contributions on conceptualized the research problem, acquisition of data, designed the study, performed the statistical analysis, interpretation of data, and revised & drafting the manuscript. ZGA and DMC have played a great role in the re-vision of the research design, data analysis, manuscript write-up, editing the entire manuscript, and being ready for publication. Finally, all authors have read and approved the final manuscript before submission.

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