Socio-demographic and Clinical Variables associated with the variation of CD4 Cell Count and Body Mass Index (BMI) for HIV Positive adults receiving HAART, a joint longitudinal data analysis

CURRENT STATUS: POSTED

Awoke Seyoum Tegegne
Bahir Dar University

bisrategebrail@yahoo.comCorresponding Author

Principal Ndlovu Ndlovu
University of South Africa

Temesgen Zewotir Zewotir
Kwazulu-Natal

DOI: 10.21203/rs.3.rs-17312/v2

SUBJECT AREAS
Infectious Diseases

KEYWORDS
Socio-demographic, clinical factors, individual characteristics, Joint modelling, CD4 cell count, BMI
Abstract

Background: The rate of prevalence of HIV among adults has been increasing in Sub-Saharan African countries over the last decade. Currently, an estimated number of 722,248 people are living with HIV, 23,000 people are newly infected with HIV and 11,000 people are died because of AIDS related illness. The objective of this study was to identify the most significant variables associated with the variation of CD4 cell count and body mass index (BMI) of HIV positive adults who initiated HAART at Felege Hiwot Teaching and Specialized Hospital, North-West Ethiopia. This study also aimed to compared the precision of parameter estimates conducted by separate and joint models.

Methods: To analyze the long-term CD4 cells count and body mass index of HIV infected adults, a cohort longitudinal study of 792 HIV-infected patients was performed. A joint model was employed to identify the variables associated with the variation of CD4 cell count and body mass index of adults receiving treatment at Felege Hiwot Teaching and specialized Hospital. A random of 792 samples was taken among patients using individual charts in the hospital.

Results: Among the main effects, Socio-demographic variables (Level of education, level of disclosure of the disease to persons living together and Marital status ), individuals factors(age, weight and gender), economic factors (ownership of cell phone, level of income), clinical factors (baseline CD4 cell count) retention (food and medication adherence, follow-up time/visit) significantly affected the variables of interests. Similarly, the interaction effects of follow-up times/visits * cell phone ownership, follow-up times/visits * gender, age * gender of patients significantly affected both response variables in current investigation.

Conclusion: Socio-demographic, individual and Clinical variables had significant effect on CD4 cell count and BMI in HAART medication program. Follow-up time/visit in the HAART program had also direct and significant effect on the variables of interest. Older HIV patients should be targeted by appropriate public health actions, such as opportunistic screening and easier access to healthcare service. The patients should be advised to disclose the disease to get support from communities around them.

Background
Currently, about 37.9 million people are living with human immunodeficiency virus (HIV) in the world and Sub-Saharan Africa accounted for 71% of the global total [1]. In Ethiopia, about 722 248 people are living with HIV and the prevalence of HIV among adults is 1%. Hence, 23, 000 people are newly infected with HIV and 11,000 people are died because of AIDS related illness[2]. Among all people living with HIV, 81% of them are on treatment [3]. Amhara region, one of the eleven regions in the country, had a prevalence rate of 1.6%, which is a serious case as compared to the national one [4, 5]. Hence, the region needs special attention to decrease the prevalence of HIV and to reduce HIV related problems of patients who are receiving HAART[6]. Both CD4 cell count and BMI are two of the strongest predictors of progression of HIV and death[6, 7]. The amount of CD4 cell count provides a picture of immune system health, with higher CD4 counts leads to healthier immune systems [6, 8]. A previous study indicates that low BMI and injection drug use associated with lower CD4 cell count[7]. Previous researches conducted for analysis of CD4 cell count also indicate that medication adherent HIV patients are more probable to have large CD4 cell count [9]. Therefore, socio-demographic disadvantageous HIV positive adults are associated with lower CD4 cell count in the era of HAART [10]. The social-demographic factors are related to disclosure of the disease and communication with people living together[11, 12], level of education and residence area[13]. Successful strategies to get better retention in HIV care require an understanding of retention and adherence behaviour and the complex relationship between biological, psychological, behavioural, social and health system [14, 15].

In Ethiopia, separated researches on factors affected for the variation of BMI of HIV patients has also widely been done[16, 17]. However, detailed researches about socio-demographic, individual characteristics and clinical variables associated with the variation of CD4 cell count and BMI of HIV positive adults under HAART using joint and advanced methods are limited[18]. The knowledge and understanding of joint predictors of CD4 cell count and BMI is important in a situation that large number of patients enrolled in HAART and further helps to reduce dropouts from the treatment[19]. Joint models are more precise and reliable in assessing the joint predictors of the variables of interests[20]. The interaction effects observed in current investigation were not assessed in the
Therefore, the objective of current investigation was to assess the joint predictors of two longitudinal response variables; CD4 cell count and BMI of patients who are receiving treatment at Felege Hiwote Teaching and Specialized hospital. In addition, this research aimed to compare the precision and reliability of parameter estimation conducted by separate and joint models.

Methods

Study design

A retrospective cohort study was conducted to assess joint predictors of CD4 cell count and BMI among adult HAART users enrolled in the first 10 months of 2012 and followed-up to June 2017. Joint modeling between count and binary responses was conducted.

Study area and population

The study was conducted at Felege-Hiwot Teaching and Specialized Hospital located in North-western Ethiopia, Amhara Region. Patients in the hospital were given regimens containing two nucleoside reverse transcriptase inhibitors and one non-nucleoside reverse transcriptase inhibitor. Patients in the urban and rural clinics received different regimens. The reason for this was patients in rural clinics could be co-administered with anti-tuberculosis (TB) medication as suggested by the Ethiopia’s HIV treatment strategy. Pregnant patients received Nevirapine (NVP) rather than EFV.

Inclusion criteria

Adult patients, whose ages were 15 years and above, with a CD4 cell count below 200 cells/mm3 or patients with World Health Organization (WHO) stage IV of HIV disease regardless of CD4 cell count, enrolled at Felege-Hiwot Referral and Teaching Hospital were included under this study. Hence, from the total HIV positive adults who enrolled in the first 10 months of 2012 and started HAART in the hospital from September 2012 to June 2017 and patients with a minimum of 2 follow-up time/visit responses of CD4 count and BMI were included in the study. The nature of longitudinal study forced us to have at least two follow-up times/visits responses of the variable of interest.

Sample size and sampling technique

Out of the targeted HIV/AIDS patients, 792 were selected using stratified random sampling technique.
considering their residence area as strata using 95% level of confidence and 5% marginal error.

**Data collection tools and extraction procedures**

In data collection procedures, the available information was first observed and discussed with health staff at ART section in the hospital. Data was extracted using data extraction format developed by the authors in consultation with health staffs. All relevant information was collected by health staffs after theoretical and practical orientations. Charts of patients were retrieved using the patients’ registration card number which was found in the electronic database system. A secondary data extraction check-list was designed and used to adopt the routinely collected data. A baseline CD4 cell count was identified and collected from the registration cards of HAART attendants. Similarly, other characteristics like socio-demographic, economic and clinical data were also collected from the registration cards of patients. Data analysis was conducted using Statistical System Analysis (SAS) software version 9.2.

**Variables under investigation**

[Please see the supplementary files to view this section.]

**Statistical models for current investigation**

[Please see the supplementary files to view this section.]

**Results**

The summary statistics of the baseline socio-demographic and clinical variables of patients included in the study are indicated in Table1. Table1 shows that out of the sample of 792 patients: 40.9% were rural residents; 50.6% were females; 56.3% were living with their partner; 33.6 % disclosed their disease to family members, 49.2% were owners of cell phones, 25.5% were medication adherent, only 11.5% had high income and 20.6% had no education. The average(median) weight was 58kg (IQR: (52,64)), average years of all patients was 36 years (IQR: (28,48)). Among the participants, 80.1% of the patients were abnormal BMI( either under-weight or over-weight baseline BMI). The average (median) baseline CD4 cell count for all patients was 134 cells/mm3(IQR: (113,180))(Refer to Table1).

In the analysis, patients who disclosed the disease reported that they got better social support from communities around them. To investigate this, HIV/AIDS stigma scale was used by the health staff at each
visiting time. Among those patients disclosed the disease (266 patients), more than half of them (165 or 62%) got social support. Similarly, mental depression of participants was also invented using Beck’s depression inventory scale at each visit and 180 (22.7%) were mentally depressed.

The exploratory data analysis of each visit in current investigation indicates that the expected CD4 cell count for all follow up times/visits varies 150 cells/mm³ with standard deviations 18 cells/mm³ at the first visit and 494 cells/mm³ with standard deviations 27 cells/mm³ at the 23rd visit in the study period. Hence, the distribution was over-disperssed (variance > mean) and the expected CD4 cell count was linearly increased with corresponding follow-up times/visits (Refer to Figure1). This was supported by the Cochran–Armitage test ($z = 16.34, p-value < 0.0001$) [24].

Figure1:
Check for Missing Completely at Random (MCAR) for current study
Missing completely at random (MCAR) refers to missingness in such a way that the missing values at the jth visit are independent of both the observed and unobserved values in the (j-1)th visit. There have been different approaches to check the MCAR assumptions when the missingness pattern is monotone(dropout). The nature of missingness pattern in current investigation was monotone(dropouts). This pattern in Figure2 indicates that there was no missing observation in the first two visits and the number of dropouts increased linearly with follow-up times/visits. Hence, at the last visit(23rd visit), about 174 (21.5%) of the HAART attendents were dropouts among 792 sampled data under current investigation.

Figure2:

[Please see the supplementary files to view this section.]

Table1: Baseline Socio-demographic, clinical and individual characteristics of HIV positive adults
| Variables                          | Median (IQR) | Categories                          | No (%)       |
|-----------------------------------|--------------|-------------------------------------|--------------|
| Weight (kg)                       | 58 (52, 64)  | -                                   | -            |
| Age (years)                       | 36 (28, 48)  | -                                   | -            |
| Height (meter)                    | 1.45 (1.28, 1.68) | -                                   | -            |
| Gender                            | -            | Male                                | 392 (49.4)   |
|                                   | -            | Female                              | 400 (50.6)   |
| Baseline BMI                      | -            | Normal                              | 158 (19.9)   |
|                                   | -            | Abnormal (over/under weight)        | 634 (80.1)   |
| Baseline CD4 cell count/ mm³      | 134 (113, 180)| -                                   | -            |
| WHO HIV stage                     | -            | Stage I                             | 101 (12.8)   |
|                                   | -            | Stage II                            | 259 (32.7)   |
|                                   | -            | Stage III                           | 199 (25.1)   |
|                                   | -            | Stage IV                            | 233 (29.4)   |
| Follow-up times/visits            | -            | -                                   | 23           |
| Medcation adherence               | -            | Adherent                            | 202 (25.5)   |
|                                   | -            | Non-adherent                        | 590 (74.5)   |
| Dietary instruction adherence     | -            | Adherent                            | 245 (30.9)   |
|                                   | -            | Non-adherent                        | 547 (69.1)   |
| Educational status                | -            | no education                        | 163 (20.6)   |
|                                   | -            | Primary                             | 209 (26.4)   |
|                                   | -            | Secondary                           | 274 (34.6)   |
|                                   | -            | Tertiary                            | 146 (18.4)   |
| Residence area                    | -            | Urban                               | 468 (59.1)   |
|                                   | -            | Rural                               | 324 (40.9)   |
| Marital status                    | -            | living with partner                 | 446 (56.3)   |
|                                   | -            | living without Partner              | 346 (43.7)   |
| Disclosure of the disease         | -            | Yes                                 | 266 (33.6)   |
|                                   | -            | No                                  | 526 (66.4)   |
| Level of income                   | -            | low income (< 500 ETB per month)    | 41 (5.2)     |
|                                   | -            | middle income (5001-999 ETB per month) | 660 (83.3) |
|                                   | -            | high income (1000ETB per month)     | 91 (11.5)    |
| Ownership of Cell phone           | -            | Yes                                 | 390 (49.2)   |
|                                   | -            | No                                  | 402 (50.8)   |
Table 2 shows that after controlling for some basic covariates, the existence of missingness in the previous \((j-1)^{th}\) visit has insignificant effect for the existence of missingness at the \(j^{th}\) visit which implies that there is no evidence against the null hypothesis (MCAR) (p-values > 0.05). Hence, the result in \((j-1)^{th}\) visiting time had no any effect for the missing observation obtained at the \(j^{th}\) visiting time. Hence, the missingness occurred at the \(j^{th}\) follow up visit was independent on observed and unobserved values of the variable of interest which implies that the missingness pattern in current uninvestigation was MCAR.

Table 2: The results from fitting the logistic regression model (6) for checking MCAR assumptions

| Effect                        | Estimate  | Standard Error | t Value | Pr > |t| |
|-------------------------------|-----------|----------------|---------|-------|---|
| Intercept                     | -11.4015  | 3.8059         | -3      | < 0.001 |
| Follow-up time/visit          | 0.05463   | 0.02451        | 1.453   | 0.3245 |
| CD4 cell count                | 0.0534    | 0.03957        | 1.35    | 0.1772 |
| Baseline CD4 cell count       | 0.001768  | 0.005317       | 0.33    | 0.7394 |
| Age                           | 0.0229    | 0.03054        | 0.75    | 0.4532 |
| Residential area (Ref. = urban) |         |                |         |       |
| rural                         | -1.1643   | 1.3618         | -0.85   | 0.3926 |
| Gender (Ref. = female)        |           |                |         |       |
| male                          | -0.3117   | 0.2353         | -1.32   | 0.1854 |
| Adherence (Ref. = adherent)   |           |                |         |       |
| non-adherent                  | 5.7708    | 4.3239         | 1.33    | 0.182 |

To fit the joint models of CD4 cell count and BMI data collected from the hospital, first quasi-Poisson for CD4 cell count data and binary logistic model for BMI data were considered separately [29]. The reason for doing this was to visualize the advantage of joint models over the separate models.

Table 3 shows the separate or joint marginal models of CD4 cell count and BMI with link function of log and logit functions respectively. As it is indicated in Table 3, age, weight, baseline CD4 cell count, follow up times/visits, baseline CD4 cell count, residence area, gender, level of disclosure of the disease to people living together, medication and dietary instruction adherence, marital status and ownership of cell phone significantly affected both response variables. The separate model shown in Table 3 was univariate distribution. The combination of separate models of the two response variables are indicated in Table 4.

Table 4 was created by imposing joint multivariate distribution of random effects. The conditional independence random intercept model in Table 4 indicates that age, weight, follow up times/visits, baseline
CD4 cell count, gender, medication adherence, dietary instruction adherence, marital status and level of income significantly affected both response variables. The two response variables, CD4 cell count and BMI in Table 4 had the same sign in parametric estimation which indicates that the two outcomes are positively correlated to each other.

The conditional independence assumptions in Table 4 was too restrictive in introducing estimation errors and the parameter estimation is not reliable. During this time, relaxation of conditional independence by re-fitting the joint random inrcepts model with possible correlated errors is important[19]. However, the relaxation of conditional independence approach for the current investigation lacked to be converged. In this condition, it is important to introduce conditional dependence of one response in terms of the other using linear predictor[19] which validates the observed correlation between the two responses arising from the association of random intercepts. This was done using generalized linear mixed effect model for BMI as a response and CD4 cell count as a linear predictor. The generalized linear mixed effect model of BMI considering CD4 cell count as linear predictor is indicated in Table 5.

In Table 5, the main effect predictors like age of patients, weight of patients, baseline CD4 cell count, the number of followed-up visits, marital status, sex, residence area, cell phone ownership, level of disease disclosure, level of education, residence area, medication and food adherence and level of income had significant effect on the variables of interests. Hence, as age of patients increased by one year, the odds of being normal BMI of HIV patients decreased by by 2.7% (AOR = 0.9732, 95% CI:(0.42315, 0.9999), P-value = 0.0153)) given the other variables constant. As baseline CD4 cell count increased by one cell per mm3, the odds of being normal BMI for HIV patients was increased by 5.4% (AOR = 1.0538, 95% CI:(1.0032, 1.2489), P-value = 0.0231)) given the other variables constant.

Gender had significant effect for the variables of interests. Thus, comparing female patients with males, the odds of being normal BMI for females was smaller by 24.1% than males (AOR = 0.7590, 95% CI:(0.5231,0.8999), P-value = 0.0231)) given the other variables constant.

The odds of being normal BMI for patients who did not disclosed their disease to people around them was
decreased by 12% as compared to those patients disclosed their disease (AOR=0.8795, 95%CI:(0.6232, 0.9892), p-value=0.0153) keeping the other variables constant. Similarly, the odds of being normal BMI for medication non-adherent patients was decreased by 76.9% as compared to those of medication adherent patients (AOR=0.2312, 95% CI:(0.1231, 0.4982), p-value = 0.0231) given the other conditions constant. The odds of being normal BMI for patients who did not adhere dietary instruction given by the health staff was decreased by 29.2% as compared to those HIV positive adults who adhere their prescribed dietary instruction (AOR=0.7081, 95% CI:(0.5231, 0.8972), p-value = 0.0142) keeping the other conditions constant. Among the socio-demographic covariates, marital status has significant effect on BMI of HIV patients. Thus, the odds of being normal BMI of HIV patients living with their partner was increased by 43.8% as compared to those patients living without their partner (AOR= 1.4378, 95% CI:(1.3489, 1.5245), p-value = 0.0164) keeping the other conditions constant.

The odds of being normal BMI for patients without cell phone was decreased by 38.3% as compared those patients with cellphone (AOR=0.6175, 95% CI:(0.4232, 0.8982), p-value = 0.0324) keeping the other conditions constant. Similarly, level of education, residence area and level of income had significant effect on the variables of interest.

Some of the interaction effects of covariates also had significant effect on the response variable. In Table5, only significant interaction effects are present for the table to be manageable in one page. Hence, follow-up times/visits * cell phone ownership, follow up times/visits * gender and age * gender significantly affected both response variables through a linear link function (Refer to Table5).

Table5 indicate that, as patients’ follow-up times/visits increased by one unit, the increasing rate of odds of being normal BMI for patients without cell phone was decreased by 3% (AOR=0.9704, 95% CI:(0.7342, 0.9989), p-value = 0.0324) (P-value < 0.01) keeping the other conditions constant. Whenever, the number of follow-ups of patients increased by one unit, the rate of increasing the odds of being normal BMI for female patients was increased by 4.1% as compared to males, keeping the other variables constant (AOR= 1.0408, 95% CI:(1.0184, 1.1893), p-value = 0.0324). In Table5, it is also indicated that as
patients’ age increased by one year, the decreasing rate of the odds of being normal BMI for female patients was decreased by 1% as compared to males (AOR = 0.9900, 95% CI: (0.6543, 0.9998), p-value = 0.0321) keeping the other conditions constant.

Table 3: Parameter estimates and corresponding standard errors of joint marginal / separate analysis for CD4 cell count and BMI data with AR (1) working covariance
| Effect                                      | BMI                        | CD4 cell count                  |
|--------------------------------------------|----------------------------|--------------------------------|
|                                            | Estimate  | Standard Error | Pr > |t| | Estimate  | Standard Error | f |
| Intercept                                  | -6.1123   | 0.9131         | 0.0152 | 3.0243 | 0.0392 | 0 |
| age                                        | -0.0272   | 0.0134         | 0.0153* | -0.0182 | 0.0821 | 0 |
| weight                                     | 0.2034    | 0.0431         | 0.0125* | 0.0194 | 0.0278 | 0 |
| Follow up visits                           | 0.0524    | 0.0154         | 0.0231* | 0.0346 | 0.0124 | 0 |
| Baseline CD4 cell count                    | 0.0163    | 0.0182         | 0.0141* | 0.0192 | 0.0351 | 0 |
| Residence(Ref.=Urban)                      |           |                |        |        |        |    |
| Rural                                      | -0.1162   | 0.0825         | 0.1921 | -0.0265 | 0.8637 | 0 |
| Gender(Ref.=Male)                          |           |                |        |        |        |    |
| Female                                     | -0.2757   | 0.08289        | 0.0231* | 0.0352 | 0.8343 | 0 |
| Disclosed(Ref.=Yes)                        |           |                |        |        |        |    |
| No                                         | -5.1284   | 0.1435         | < 0.0153* | -0.9251 | 0.6432 | 0 |
| Who(Stage4)                                |           |                |        |        |        |    |
| Stage1                                     | 0.8642    | 0.3252         | 0.8452 | 0.0723 | 0.9152 | 0 |
| Stage2                                     | 0.9433    | 0.2145         | 0.0546 | 0.0562 | 0.8251 | 0 |
| Stage3                                     | 1.1452    | 0.1262         | 0.0752 | -0.0254 | 0.9245 | 0 |
| Medication adherence(Ref.=Adherence)       |           |                |        |        |        |    |
| Non-adherent                               | -1.4643   | 1.0228         | 0.0231* | -1.4365 | 0.8729 | 0 |
| Food adherence(Ref.=adherent)              |           |                |        |        |        |    |
| Non-adherent                               | -0.9452   | 0.9435         | 0.0142* | -0.8263 | 0.2384 | 0 |
| Marital status(Ref.= without partner)      |           |                |        |        |        |    |
| With partner                               | 0.7631    | 0.7857         | 0.0164* | 0.2482 | 0.8281 | 0 |
| Phone(Ref.=Yes)                            |           |                |        |        |        |    |
| No                                         | -1.4821   | 0.6404         | 0.0324* | -0.8354 | 0.0653 | 0 |
| Education (Ref.=Tertiary)                  |           |                |        |        |        |    |
| No education                               | -0.7837   | 0.7245         | 0.04532 | -0.0431 | 0.7862 | 0 |
| Primary                                    | -0.0263   | 0.1465         | 0.8854 | 0.0652 | 0.8549 | 0 |
| Secondary                                  | -0.6321   | 0.8432         | 0.3821 | 0.0224 | 0.6543 | 0 |
| Income(Ref.=Low)                           |           |                |        |        |        |    |
| High                                       | 0.3554    | 0.9228         | 0.2182 | 0.7336 | 0.8432 | 0 |
| Middle                                     | 1.7951    | 0.2523         | 0.0134* | -0.2845 | 0.7869 | 0 |

*stands for statistically significant variables.
Table 4: Parameter estimates and corresponding standard errors for conditional independence random intercept models of CD4 cell count and BMI data (Laplace approximation)
| parameter                          | BNI Estimate | BNI Standard Error | BNI Pr > |t| | CD4 cell count Estimate | CD4 cell count Standard Error | f |
|-----------------------------------|--------------|--------------------|---------|---|-----------------------|-------------------------------|---|
| Intercept                         | 6.1123       | 0.6131             | 0.0152  |   | 3.0243                | 0.0192                       |   |
| age                               | -0.0272      | 0.0034             | 0.0153* |   | -0.0182               | 0.0321                       | 0 |
| weight                            | 0.2034       | 0.0331             | 0.0125* |   | 0.0194                | 0.0178                       | 0 |
| Follow up visits                  | 0.0524       | 0.0054             | 0.0231* |   | 0.0346                | 0.0114                       | 0 |
| Baseline CD4 cell count           | 0.0163       | 0.0082             | 0.0231* |   | 0.0192                | 0.0151                       | 0 |
| Residence(Ref.=Urban)             |              |                    |         |   |                       |                              |   |
| Rural                             | -0.1162      | 0.0425             | 0.1921  |   | -0.0265               | 0.6637                       | 0 |
| Gender(Ref.=Male)                 |              |                    |         |   |                       |                              |   |
| Female                            | -0.2757      | 0.05289            | 0.0231* |   | 0.0352                | 0.4343                       | 0 |
| Disclosed(Ref.=Yes)               |              |                    |         |   |                       |                              |   |
| No                                | -5.1284      | 0.0435             | < 0.0153* |   | -0.9251               | 0.3432                       | 0 |
| Who(Stage4)                       |              |                    |         |   |                       |                              |   |
| Stage1                            | 0.8642       | 0.1252             | 0.8452  |   | 0.0723                | 0.2152                       | 0 |
| Stage2                            | 0.9433       | 0.1145             | 0.0546  |   | 0.0562                | 0.3251                       | 0 |
| Stage3                            | 1.1452       | 0.1162             | 0.0752  |   | -0.0254               | 0.2245                       | 0 |
| Medication adherence(Ref.=Adherence) |          |                    |         |   |                       |                              |   |
| Non-adherent                      | -1.4643      | 1.0128             | 0.0231* |   | -1.4365               | 0.1729                       | 0 |
| Food adherence(Ref.=adherent)     |              |                    |         |   |                       |                              |   |
| Non-adherent                      | -0.9452      | 0.5435             | 0.0142* |   | -0.8263               | 0.3384                       | 0 |
| Marital status(Ref.= without partner) |          |                    |         |   |                       |                              |   |
| With partner                      | 0.7631       | 0.5857             | 0.0164* |   | 0.2482                | 0.2281                       | 0 |
| Phone(Ref.=Yes)                   |              |                    |         |   |                       |                              |   |
| No                                | -1.4821      | 0.2404             | 0.0324* |   | -0.8354               | 0.0153                       | 0 |
| Education (Ref= Tertiary)         |              |                    |         |   |                       |                              |   |
| No education                      | -0.7837      | 0.4245             | 0.04532* |   | -0.0431               | 0.1862                       | 0 |
| Primary                           | -0.0263      | 0.0465             | 0.0254* |   | 0.0652                | 0.3549                       | 0 |
| Secondary                         | -0.6321      | 0.3432             | 0.3821* |   | 0.0224                | 0.2543                       | 0 |
| Income(Ref=Low)                   |              |                    |         |   |                       |                              |   |
| High                              | 0.3554       | 0.0228             | 0.0182* |   | 0.7336                | 0.3432                       | 0 |
| Middle                            | 1.7951       | 0.1523             | 0.0134* |   | -0.2845               | 0.2869                       | 0 |

*stands for statistically significant variables.
Table5: Parameter estimates for joint model of BMI data considering CD4 cell count as linear predictor
| Parameter                                      | Estimate | Standard Error | Adjusted odds Ratio(AOR) | Wald 95% CI for AOR |
|------------------------------------------------|----------|----------------|--------------------------|---------------------|
| Intercept                                      | 1.1123   | 0.2131         | 3.0413                   | 1.2345 6.3245       |
| age*dist                                       | -0.0272  | 0.0024         | 0.9732                   | 0.42315 0.9999      |
| weight*dist                                    | 0.2034   | 0.0231         | 1.2256                   | 1.0874 2.3425       |
| Baseline CD4 cell count*dist                   | 0.0524   | 0.0024         | 1.0538                   | 1.0032 1.2489       |
| CD4 cell count *dist                           | 0.5242   | 0.0024         | 1.6891                   | 1.0032 1.2489       |
| dist*residence(Ren.=Urban)                    |          |                |                          |                     |
| Rural                                          | -0.1162  | 0.0225         | 0.8903                   | 0.42315 0.9982      |
| dist*gender (Ren.=Male)                        |          |                |                          |                     |
| Female                                         | -0.2757  | 0.02289        | 0.7590                   | 0.52315 0.8999      |
| dist*disclosed(Ren.=yes)                       |          |                |                          |                     |
| No                                             | -0.1284  | 0.0335         | 0.8795                   | 0.0565 0.9993       |
| dist*who (Ren.=stage4)                         |          |                |                          |                     |
| Stage 1                                        | 0.8642   | 0.1152         | 2.3731                   | 1.2999             |
| Stage 2                                        | 0.9433   | 0.1045         | 2.5684                   | 1.2999             |
| Stage 3                                        | 1.1452   | 0.0162         | 3.1431                   | 1.2999             |
| Medication adherent*dist(Ren.=adherent)        |          |                |                          |                     |
| Non-adhe.                                      | -0.4643  | 1.0118         | 0.8592                   | 0.62315 0.9892      |
| Food adh.*dist(Ren.=adherent)                  |          |                |                          |                     |
| Non-adherent.                                  | -0.3452  | 0.2435         | 0.7081                   | 0.5231 0.8972       |
| dist*marital status stat(Ren.=Without partner) |          |                |                          |                     |
| With partner                                   | 0.3631   | 0.2857         | 1.4378                   | 1.3489 1.5245       |
| dist*phone(Ren.=Yes)                           |          |                |                          |                     |
| No                                             | -0.4821  | 0.1104         | 0.6175                   | 0.4232 0.8982       |
| dist*education (Ren.=Tertiary)                 |          |                |                          |                     |
| No educ.                                       | -0.7837  | 0.1245         | 0.4567                   | 0.22315 0.6982      |
| Primary                                        | -0.0263  | 0.0365         | 0.9740                   | 0.72315 0.9982      |
| Secondary                                      | -0.6321  | 0.1432         | 0.5315                   | 0.42315 0.6982      |
| dist*income (Ren.= Low)                        |          |                |                          |                     |
| High                                           | 0.3554   | 0.0128         | 1.4268                   | 1.3489 1.7245       |
| Middle                                         | 1.7951   | 0.1123         | 6.0201                   | 1.3489 4.3245       |
| Visiting time*dist                             | 0.0521   | 0.0145         | 1.0513                   | 1.0245 1.1542       |
| Follow up times/visits *dist* ownership of cell phone(Ren.=Yes) |          |                |                          |                     |
| No                                             | -0.0332  | 0.03341        | 0.9704                   | 0.7342 0.9989       |
| Follow up times/visits *dist*gender (Ren.= Male) |          |                |                          |                     |
| Female                                         | 0.0421   | 0.0343         | 1.0408                   | 1.0184 1.1893       |
| Age*dist*gendr (Ren.=Male)                     |          |                |                          |                     |
| Female                                         | -0.0122  | 0.01224        | 0.9900                   | 0.6543 0.9998       |
*stands for statistically significant variables

Discussion

The result in this investigation revealed that socio-demographic factors, economic factors and individual characteristics have direct and significant association with CD4 cell count. This findings is agreed with one of the previous investigation [26].

Level of education plays significant effect on the BMI of HIV patients in which more educated patients had normal BMI as compared to non-educated patients. Education helps to know about balanced diet and use of physical fitness for health status of them selves. The result obtained in this study is consistent to previous research[17].

Female patients are more underweight in BMI as compared to males. The potential reason for this might be that males are more weighted as compared to females. However, the result in this regard is contradicted with previous study[27] and agreed with another study[28]. This needs further investigation. As age of HIV patients increased, CD4 cell count as well as BMI decreased. This result agreed with many previous researches conducted separately[29-31].

Retention and close flow ups in medication care had also direct and significant effect on BMI which means patients which closely follow their prescribed medication given by the health staff had good adherence competence and this further leads to normal BMI. This result agreed with previous researches [32, 33]. Retention in medication care and adherence competence had direct and significant effect on CD4 cell count which has similar argument with previous researches[26, 32]. Retention in HIV medication care is a crucial activity for achieving optimal CD4 cell count and to have normal BMI[34].

The economic factors such as patients with cell phone and those who had high income associated with high retention in the medication care. Hence, patients with high income may use different alternatives to get pills and he/she also uses proper food adherence schedules for the treatment to be effective and this encourages the patient to attend the visits of health institution and to have normal BMI[13, 35]. Patients’ cell phone can play significant role in taking pills on time and to remind the date that the patient should visit the hospital and this has indirect effect on the status of CD4 cell
count change[36]. Cell phone helped patients to be HAART adherent because of its alarm (memory aid) for reminding the time pills are taken and this also helps to obtain normal BMI [37, 38]. Patients with high income and with ownership of cell phones belongs to urban areas and such patients had better CD4 cell count and normal BMI[23].

Previous researches also indicated that HIV positive adults who lived in rural areas exposed for shortage of food as compared to urban residents and this leads to be under weight and low CD4 cell count. Access to balanced diet is to a large extent correlated with normal BMI of patients. Hence, HIV patient with high income can have good accesses for food adherence and this further leads for good medication adherence[6, 39].

Clinical factors such as patients' baseline CD4 cells count significantly affected their retention of medication care. High number of baseline CD4 cell count encouraged the patient to be good medication adherent and this further leads to have normal BMI[40-43]. HIV positive adults with high baseline CD4 cell count had high number of CD4 cell count/mm3. This result is similar with previously conducted research[32] but contradicted with another previously conducted study[6].

Conclusion

The separate and joint modelling approache in current investigation revealed a good opportunity to compare the two approaches. Hence, the joint model occurred at Table5 had smaller standared errors as compared to separate model at Table3. This shows that joint model is better in parameter estimation as compared to separate models and revealed more precise and reliable result inferring about the study variable. In current investigation, Age of patients, weight, Baseline CD4 cell count, residence area, gender, disclosure of the AIDS, medication adherence, dietary instruction adherence, marital status, ownership of cell phone, level of education, level of income, follow up time/visits had significant effect on the two response variables. Among the interaction effects, follow up times/visits *ownership of cell phone, follow up times/visits *gender and age *gender significantly affected the variable of interests.

The analysis in the current investigation identified a certain group of patients, such as males and rural residents, patients without owner of cells phone; non-adherent and aged patients were a relatively
maximum risk of treatment response (CD4 cell count change and BMI). Poor adherent patients had low results in the variable of interests which indicates that BMI and CD4 cell count are positively correlated to each other. Patients with good performance of adherence to medication had better CD4 cell count change as well as normal BMI. Non-adherent patients in this long-term treatment program were at risk and should receive interventional treatment.

Consequently, due attention should be given to address the specific needs of each group of the patients. Health related education should be given to patients to be adherent and this leads for high progress of CD4 cell count and BMI [44, 45]. Moreover, interventions need to be designed to promote both food and medication adherence and patients should be advised to disclose the disease to individual living together. Identifying factors affecting the level of CD4 cell count and BMI of HIV positive adults jointly would help health professionals to facilitate proper management and monitoring of the health care intervention on ART program.

One limitation of current investigation was that, self reported data by the patients made uncertainty, since patients may discard unused pills and considered them as used once. There was no means of control such data. Why the interaction effect occure in current investigation can not be answered currently and can be considered as a gap for further investigation.

Abbreviations
HIV= Human Immunodeficiency Virus; AIDS= acquired Immune deficiency syndrome; BMI= Body Mass Index; HAART= Highly Active Antiretroviral Therapy; CD4 = Calcification Determinant Four; PLWHIV= People living with Human Immunodeficiency Virus.

Declarations

**Ethics approval and Consent for participants**

To get the secondary data from the hospital in the study area, Ethical clearance certificate had been obtained from two universities namely Bahir Dar University, Ethiopia with Ref RCS/1412/20012 and University of South Africa (UNISA), South Africa, Ref. We can attach the ethical clearances certificate up on request. Authors did not get consent for participants because the sendary data was obtained in the hospital,
**Competing interests**
As no individual or institution funded this research, there is no conflict of financial interest between authors or between authors and institutions.

**Funding**
Not applicable

**Authors’ contributions**
The first author wrote the proposal, develop data collection format, supervise the data collection process, analyzed and interpreted the data. The second and third authors participated in design and data analysis and critically read the manuscript and gave constructive comments for the betterment of the manuscript applying their reach experience. All authors contributed on manuscript preparation and discussed on order of authors.

**Availability of data and materials**
We confirm that the data used for this study is available at corresponding authors and can be submitted upon request.

**Consent for publication**
This manuscript has not been published elsewhere and is not under consideration by any other journal. All authors approved the final manuscript and agreed with its submission. We agreed about authorship and order of authors for this manuscript.

**Author’s information**
AST is an associate professor of statistics department at Bahir Dar University, Ethiopia with seven publications previously. Currently, he successfully completed his PhD entitled “Modelling binary, ordinal and count response data; application of adherence and CD4 cell count change data” with the close supervision of the second and third authors. All the three authors together had five publications using the same data with the current one and on the same study area. This will be the six\textsuperscript{th} article for our PhD paper. The previous five articles are;

1. Seyoum et al. (2016): AIDS Res Ther (2016) 13:36, DOI 10.1186/s12981-
016-0119-6

Available on line: https://aidsrestherapy.biomedcentral.com/articles./Comparison-of-quasi-Poisson-and-nega..

2. **Seyoum et al. AIDS Res Ther (2017):** AIDS Res Ther (2017): DOI 10.1186/s12981-017-0141-3).

Available on line: https://aidsrestherapy.biomedcentral.com/articles/.../s12981-017-0141

3. **Tegegne et al. (2018): Journal:** BMC Infectious Diseases (2018):18:83, DOI 10.1186/s12879-018-2977-0

Available on line: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5819083

4. **Tegegne et al (2018):**

**Journal:** BMC Infectious Diseases (2018) 18:197, https://doi.org/10.1186/s12879-018-3108-7).

Available on line: https://bmcinfectdis.biomedcentral.com/articles/10.../open-peer-review

5. **Awoke Seyoum et al. (2019): AJOL, J. Sci. & Technol. 11(3): 165-193,2018:**

Available on line: https://www.ajol.info/index.php/ejst/article/download/.../174355

**Acknowledgement**

Felege Hiwot Teaching and Specialized Hospital, Ethiopia is gratefully acknowledged for the data supplied in our health research.

**References**

1. Indravudh, P.P., A.T. Choko, and E.L. Corbett, *Scaling up HIV self-testing in sub-Saharan Africa: a review of technology, policy and evidence*. Current opinion in infectious diseases, 2018. **31**(1): p. 14.

2. Wondimeneh, Y., et al., *HIV and Malaria Infections and Associated Risk Factors Among Febrile Illness Patients in Northwest Ethiopia*. Türkiye Parazitolojii Dergisi, 2018. **42**(3): p. 180.

3. Mitku, A.A., et al., *Prevalence and associated factors of TB/HIV co-infection among HIV Infected patients in Amhara region, Ethiopia*. African health sciences, 2016.
4. Stover, J., et al., *What is required to end the AIDS epidemic as a public health threat by 2030? The cost and impact of the fast-track approach*. PLoS one, 2016. 11(5).

5. Unaids, J., *Fact sheet—latest global and regional statistics on the status of the AIDS epidemic*. Geneva: UNAIDS, 2017.

6. Tegegne, A.S. and T. Zewotir, *Determinants of CD4 cell count change and time-to default from HAART; a comparison of separate and joint models*. BMC infectious diseases, 2018. 18(1): p. 197.

7. Mariz, C.d.A., et al., *Body mass index in individuals with HIV infection and factors associated with thinness and overweight/obesity*. Cadernos de saude publica, 2011. 27(10): p. 1997-2008.

8. Macallan, D.C., *Nutrition and immune function in human immunodeficiency virus infection*. Proceedings of the Nutrition society, 1999. 58(3): p. 743-748.

9. Langebeek, N., et al., *Predictors and correlates of adherence to combination antiretroviral therapy (ART) for chronic HIV infection: a meta-analysis*. BMC medicine, 2014. 12(1): p. 142.

10. Do, N.T., et al., *Psychosocial factors affecting medication adherence among HIV-1 infected adults receiving combination antiretroviral therapy (cART) in Botswana*. AIDS research and human retroviruses, 2010. 26(6): p. 685-691.

11. Belle, D., *Poverty and women's mental health*. American psychologist, 1990. 45(3): p. 385.

12. Alok, R., et al., *Problem-focused coping and self-efficacy as correlates of quality of life and severity of fibromyalgia in primary fibromyalgia patients*. JCR: Journal of Clinical Rheumatology, 2014. 20(6): p. 314-316.

13. Kusunya, E., *Socio-Economic Factors Influencing Adherence to Utilization of*
Antiretroviral Therapy for People Living With HIV/AIDS: A Case Study of Dodoma
Municipal and Kongwa District—Tanzania, 2015, The University of Dodoma.

14. Guerrero, M., J. Rialp, and D. Urbano, *The impact of desirability and feasibility on entrepreneurial intentions: A structural equation model*. International Entrepreneurship and Management Journal, 2008. 4(1): p. 35-50.

15. Guerrero, J.M., et al., *Hierarchical control of droop-controlled AC and DC microgrids—A general approach toward standardization*. IEEE Transactions on industrial electronics, 2010. 58(1): p. 158-172.

16. Corrêa, R.d.A., et al., *Burden of disease by lower respiratory tract infections in Brazil, 1990 to 2015: estimates of the Global Burden of Disease 2015 study*. Revista Brasileira de Epidemiologia, 2017. 20: p. 171-181.

17. Berhe, N., D. Tegabu, and M. Alemayehu, *Effect of nutritional factors on adherence to antiretroviral therapy among HIV-infected adults: a case control study in Northern Ethiopia*. BMC infectious diseases, 2013. 13(1): p. 233.

18. Seyoum, A. and Z. Temesgen, *Joint longitudinal data analysis in detecting determinants of CD4 cell count change and adherence to highly active antiretroviral therapy at Felege Hiwot Teaching and Specialized Hospital, North-west Ethiopia (Amhara Region)*. AIDS research and therapy, 2017. 14(1): p. 14.

19. Grover, G., et al., *A Joint Modeling Approach to Assess the Impact of CD4 Cell Count on the Risk of Loss to Follow up in HIV/AIDS Patients on Antiretroviral Therapy*. International Journal of Statistics and Applications, 2015. 5(3): p. 99-108.

20. Seid, A., et al., *Joint modeling of longitudinal CD4 cell counts and time-to-default from HAART treatment: a comparison of separate and joint models*. Electronic Journal of Applied Statistical Analysis, 2014. 7(2): p. 292-314.

21. Prah, J., et al., *Factors Affecting Adherence to Antiretroviral Therapy among HIV/AIDS
Patients in Cape Coast Metropolis. Ghana. J HIV AIDS, 2018. 4(1).

22. Sarna, A. and S. Kellerman, *Access to antiretroviral therapy for adults and children with HIV infection in developing countries: Horizons studies, 2002–2008.* Public Health Reports, 2010. 125(2): p. 305-315.

23. Seyoum, A. and T. Zewotir, *Quasi-Poisson versus negative binomial regression models in identifying factors affecting initial CD4 cell count change due to antiretroviral therapy administered to HIV-positive adults in north-West Ethiopia (Amhara region).* AIDS research and therapy, 2016. 13(1): p. 36.

24. De Wit, L., et al., *Motor and functional recovery after stroke a comparison of 4 European rehabilitation centers.* Stroke, 2007. 38(7): p. 2101-2107.

25. Grady, J.J. and R.W. Helms, *Model selection techniques for the covariance matrix for incomplete longitudinal data.* Statistics in Medicine, 1995. 14(13): p. 1397-1416.

26. Bayou, T., et al., *Factors determinant for change of initial antiretroviral treatment regimen among patients on ART follow-up clinic of Mekelle Hospital, Mekelle, Ethiopia.* Int J Basic Clin Pharmacol, 2014. 3(1): p. 44-9.

27. Chandwani, S., et al., *Predictors of antiretroviral medication adherence among a diverse cohort of adolescents with HIV.* Journal of Adolescent Health, 2012. 51(3): p. 242-251.

28. Chen, X., et al., *HIV drug resistance mutations (DRMs) detected by deep sequencing in virologic failure subjects on therapy from Hunan Province, China.* PloS one, 2016. 11(2).

29. Gezie, L.D., *Predictors of CD4 count over time among HIV patients initiated ART in Felege Hiwot Referral Hospital, northwest Ethiopia: multilevel analysis.* BMC research notes, 2016. 9(1): p. 377.

30. Ayalew, J., H. Moges, and A. Worku, *Identifying factors related to the survival of AIDS
patients under the follow-up of antiretroviral therapy (ART): The case of South Wollo. International Journal of Data Envelopment Analysis and Operations Research, 2014. 1(2): p. 21-27.

31. Bitew, B.D., et al., Determinants of none-adherence to antiretroviral therapy among HIV-infected adults in Arba Minch General Hospital, Gamo Gofa Zone, Southern Ethiopia: a case control study. Am J Health Res, 2014. 2(2): p. 234-240.

32. Ezeamama, A.E., et al., Age, sex, and nutritional status modify the CD4+ T-cell recovery rate in HIV-tuberculosis co-infected patients on combination antiretroviral therapy. International Journal of Infectious Diseases, 2015. 35: p. 73-79.

33. Ye, R.-H., et al., Studies on the determinants and changes related to the natural CD4 (+) T cell counts among antiretroviral treatment-naive HIV/AIDS patients in Dehong prefecture, Yunnan province. Zhonghua liu xing bing xue za zhi= Zhonghua liuxingbingxue zazhi, 2011. 32(9): p. 882-887.

34. Rao, D., et al., A structural equation model of HIV-related stigma, depressive symptoms, and medication adherence. AIDS and Behavior, 2012. 16(3): p. 711-716.

35. Kipp, A.M., et al., Socio-demographic and AIDS-related factors associated with tuberculosis stigma in southern Thailand: a quantitative, cross-sectional study of stigma among patients with TB and healthy community members. BMC Public Health, 2011. 11(1): p. 675.

36. Lester, R.T., et al., The HAART cell phone adherence trial (WelTel Kenya1): a randomized controlled trial protocol. Trials, 2009. 10(1): p. 87.

37. Maqutu, D., et al., Determinants of optimal adherence over time to antiretroviral therapy amongst HIV positive adults in South Africa: a longitudinal study. AIDS and Behavior, 2011. 15(7): p. 1465-1474.

38. Suffoletto, B., et al., A mobile phone text message program to measure oral
antibiotic use and provide feedback on adherence to patients discharged from the emergency department. Academic Emergency Medicine, 2012. 19(8): p. 949-958.

39. Schneider, F. and B.S. Frey, Economic and political determinants of foreign direct investment. World development, 1985. 13(2): p. 161-175.

40. Ebonyi, A.O., et al., Factors associated with a low CD4 count among HIV-1 infected patients at enrolment into HAART in Jos, Nigeria. British Journal of Medicine and Medical Research, 2014. 4(13): p. 2536.

41. Florence, E., et al., Factors associated with a reduced CD4 lymphocyte count response to HAART despite full viral suppression in the EuroSIDA study. HIV medicine, 2003. 4(3): p. 255-262.

42. Montarroyos, U.R., et al., Factors related to changes in CD4+ T-cell counts over time in patients living with HIV/AIDS: a multilevel analysis. PloS one, 2014. 9(2): p. e84276.

43. Smith, C.J., et al., Factors influencing increases in CD4 cell counts of HIV-positive persons receiving long-term highly active antiretroviral therapy. Journal of Infectious Diseases, 2004. 190(10): p. 1860-1868.

44. Adams, M. and A. Luguterah, Longitudinal analysis of change in CD4+ cell counts of HIV-1 patients on antiretroviral therapy (ART) in the Builsa district hospital. European Scientific Journal, 2013. 9(33).

45. Asfaw, A., et al., CD4 cell count trends after commencement of antiretroviral therapy among HIV-infected patients in Tigray, Northern Ethiopia: a retrospective cross-sectional study. PloS one, 2015. 10(3): p. e0122583.

Figures
Figure 1

Average CD4 cell count versus Follow-up time/visit by patients
Figure 2

Number of dropout patients versus follow-up time/visit

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

ResultsFigure2.docx
Methods.docx