# 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

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# Abstract

Background: The rate of prevalence of HIV among adults has been increasing in Sub-Sahara 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 previous researches[21, 22].

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

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

he analysis, patients who disclosed the disease reported that they got better social support n communities around them. To investigate this, HIV/AIDS stigma scale was used by the lth staff at each visiting time. Among those patients disclosed the disease (266 patients), e than half of them (165 or 62%) got social support. Similarly, mental depression of ticipants was also invented using Beck's depression inventory scale at each visit and 180 .7%) were mentally depressed.

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

**re1:**

**ck for Missing Completely at Random (MCAR) for current study**

sing completely at random (MCAR) refers to missingness in such a way that the missing values at the jth are independent of both the observed and unobserved values in the(j-1)th visit. There have been different oaches to check the MCAR assumptions when the missingness pattern is monotone(dropout). The re of missingness pattern in current investigation was monotone(dropouts). This pattern in Figure2 cates that there was no missing observation.in the first two visits and the number of dropouts increased arly with follow-up times/visits. Hence, at the last visit(23$^{rd}$ visit), about 174 (21.5%) of the HAART ndents were dropouts among 792 sampled data under current investigation.

**re2:**

*[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/ $mm^3$ | 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) |

ıle2 shows that after controlling for some basic covariates, the existence of missingness in previous (j-1)$^{th}$ visit has insignificant effect for the existence of missingness at the jth visit ch implies that there is no evidence against the null hypothesis (MCAR) (p-values > 0.05). ıce, the result in (j-1) $^{th}$ visiting time had no any effect for the missing observation obtained the j$^{th}$ visiting time. Hence, the missingness occurred at the jth follow up visit was ependent on observed and unobserved values of the variable of interest which implies that missingness pattern in current unvestigation was MCAR.

Table2: 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 |

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

ble3 shows the separate or joint mariginal models of CD4 cell count and BMI with link function of log and it functions respectively. As it is indicated in Table3, age, weight, baseline CD4 cell count, follow up es/visits, baseline CD4 cell count, residence area, gender, level of disclosure of the disease to people living ether, medication and dietary instruction adherence, marital status and ownership of cell phone nificantely affected both response variables. The separate model shown in Table3 was univariate tribution. The combination of separate models of the two response variables are indicated in Table4. ble4 was created by imposing joint multivatiate distribution of random effects. The conditional ependence random intercept model in Table4 indicates that age, weight, follow up times/visits, baseline 4 cell count, gender, medication adherence, dietary instruction adherence, marital status and level of ome significantely affected both response variables. The two response variables, CD4 cell count and BMI Table4 had the same sign in parametric estimation which indicates that the two outcomes are positively related to each other.

e conditional independence assumptions in Table4 was too restrictive in introducing estimation errors and parameter estimation is not reliable. During this time, relaxation of conditional independence by re-fitting joint random inrcepts model with possible correlated errors is important[19]. However, the relaxation conditional independence approach for the current investigation lacked to be converged. In s condition, it is important to introduce conditional dependence of one response in terms of other using linear predictor[19] which validates the observed correlation between the two sponses arising from the association of random intercepts. This was done using generalized ear mixed effect model for BMI as a response and CD4 cell count as a linear predictor. The neralized linear mixed effect model of BMI considering CD4 cell count as linear predictor is icated in Table5.

Table5, the main effect predictors like age of patients, weight of patients, baseline CD4 cell count, the nber of followed-up visits, marital status, sex, residence area, cell phone ownership, level of disease closure, level of education, residence area, medication and food adherence and level of income had nificant effect on the variables of interests. Hence, as age of patients increased by one year, the odds of ng normal BMI of HIV patiens decreased by by 2.7% (AOR= 0.9732,95% CI:( 0.42315, 0.9999), P-value = 153)) given the other variables constant. As baseline CD4 cell count increased by one cell per mm3, the ds of being normal BMI for HIV patients was increased by 5.4% (AOR= 1.0538, 95% CI:( 1.0032, 1.2489), P-ue = 0.0231)) given the other variables constant.

nder had significant effect for the variables of interests. Thus, comparing female patients with males, the ds of being normal BMI for females was smaller by 24.1% than males (AOR= 0.7590, 95% CI:( 231,0.8999), P-value = 0.0231) given the other variables constant.

e odds of being normal BNI for patients who did not disclosed their disease to people around them was reased by 12% as comapared to those patients disclosed their disease (AOR=0.8795, 95%CI:( 0.6232, 892), p-value=0.0153) keeping the other variables constant. Similarly, the odds of being normal BMI for dication non-adherent patients was decreased by 76.9% as compared to those of medication adherent ients (AOR=0.2312, 95% CI:( 0.1231, 0.4982), p-value = 0.0231) given the other conditions constant. The ds of being normal BMI for patients who did not adhere dietary instruction given by the health staff was reased by 29.2% as compared to those HIV positive adults who adhere their prscribed dietary instruction )R=0.7081, 95% CI:( 0.5231, 0.8972), p-value =0.0142) keeping the other conditions constant. Among the io-demographic covariates, mariatal status has significant effect on BMI of HIV patients. Thus, the odds being normal BMI of HIV patients living with their partner was increased by 43.8% as compared to those ients living without their partner (AOR= 1.4378, 95% CI:( 1.3489, 1.5245), p-value = 0.0164) keeping the er conditions constant.

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

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

ble5 indicate that, as patients' follow-up times/visits increased by one unit, the incearing rate of odds of ng normal BMI for patients without cell phone was decreased by 3% (AOR=0.9704, 95% CI:( 0.7342, 989), p-value = 0.0324) (P-value < 0.01) keeping the other conditions constant. Whenever, the number of ow-ups of patients increased by one unit, the rate of increasing the odds of being normal BMI for female ients was increased by 4.1% as comapared to males, keeping the other variables constant (AOR= 1.0408, % CI:( 1.0184, 1.1893), p-value = 0.0324). In Table5, it is also indicated that as patients' age increased by

e year, the decreasing rate of the odds of being normal BMI for female patients was decreased by 1% as mpared to males(AOR= 0.9900, 95% CI:( 0.6543, 0.9998), p-value = 0.0321) keeping the other conditions nstant.

**le3:** Parameter estimates and corresponding standard errors of joint mariginal /separate analysis for CD4 cell nt and BMI data with AR (1) working covariance

| Effect | BMI | | | CD4 cell count | | |
|---|---|---|---|---|---|---|
| | Estimate | Standard Error | Pr > \|t\| | Estimate | Standard Error | Pr > \|t\| |
| Intercept | -6.1123 | 0.9131 | 0.0152 | 3.0243 | 0.0392 | 0.0156 |
| age | -0.0272 | 0.0134 | 0.0153* | -0.0182 | 0.0821 | 0.0226* |
| weight | 0.2034 | 0.0431 | 0.0125* | 0.0194 | 0.0278 | 0.0353* |
| Follow up visits | 0.0524 | 0.0154 | 0.0231* | 0.0346 | 0.0124 | 0.0145* |
| Baseline CD4 cell count | 0.0163 | 0.0182 | 0.0141* | 0.0192 | 0.0351 | 0.0245* |
| Residence(Ref.=Urban) | | | | | | |
| Rural | -0.1162 | 0.0825 | 0.1921 | -0.0265 | 0.8637 | 0.0435* |
| Gender(Ref.=Male) | | | | | | |
| Female | -0.2757 | 0.08289 | 0.0231* | 0.0352 | 0.8343 | 0.0182* |
| Disclosed(Ref.=Yes) | | | | | | |
| No | -5.1284 | 0.1435 | < 0.0153* | -0.9251 | 0.6432 | 0.0421* |
| Who(Stage4) | | | | | | |
| Stage1 | 0.8642 | 0.3252 | 0.8452 | 0.0723 | 0.9152 | 0.0432* |
| Stage2 | 0.9433 | 0.2145 | 0.0546 | 0.0562 | 0.8251 | 0.0241* |
| Stage3 | 1.1452 | 0.1262 | 0.0752 | -0.0254 | 0.9245 | 0.0354* |
| Medication adherence(Ref.=Adherence) | | | | | | |
| Non-adherent | -1.4643 | 1.0228 | 0.0231* | -1.4365 | 0.8729 | 0.0143* |
| Food adherence(Ref.=adherent) | | | | | | |
| Non-adherent | -0.9452 | 0.9435 | 0.0142* | -0.8263 | 0.2384 | 0.0139* |
| Marital status(Ref.= without partner) | | | | | | |
| With partner | 0.7631 | 0.7857 | 0.0164* | 0.2482 | 0.8281 | 0.0165* |
| Phone(Ref.=Yes) | | | | | | |
| No | -1.4821 | 0.6404 | 0.0324* | -0.8354 | 0.0653 | 0.0153* |
| Education (Ref.=Tertiary) | | | | | | |
| No education | -0.7837 | 0.7245 | 0.04532 | -0.0431 | 0.7862 | 0.0432* |
| Primary | -0.0263 | 0.1465 | 0.8854 | 0.0652 | 0.8549 | 0.1732 |
| Secondary | -0.6321 | 0.8432 | 0.3821 | 0.0224 | 0.6543 | 0.1432 |
| Income(Ref.=Low) | | | | | | |
| High | 0.3554 | 0.9228 | 0.2182 | 0.7336 | 0.8432 | 0.0345* |
| Middle | 1.7951 | 0.2523 | 0.0134* | -0.2845 | 0.7869 | 0.0421* |

*stands for statistically significant variables.

**Table4:** Parameter estimates and corresponding standard errors for **conditional independenc random intercept models** of CD4 cell count and BMI data(Laplace approximation)

| parameter | BNI | | | CD4 cell count | | |
|---|---|---|---|---|---|---|
| | Estimate | Standard Error | Pr > \|t\| | Estimate | Standard Error | Pr > \|t\| |
| Intercept | 6.1123 | 0.6131 | 0.0152 | 3.0243 | 0.0192 | 0.0156 |
| age | -0.0272 | 0.0034 | 0.0153* | -0.0182 | 0.0321 | 0.0226* |
| weight | 0.2034 | 0.0331 | 0.0125* | 0.0194 | 0.0178 | 0.0353* |
| Follow up visits | 0.0524 | 0.0054 | 0.0231* | 0.0346 | 0.0114 | 0.0145* |
| Baseline CD4 cell count | 0.0163 | 0.0082 | 0.0231* | 0.0192 | 0.0151 | 0.0245* |
| Residence(Ref.=Urban) | | | | | | |
| Rural | -0.1162 | 0.0425 | 0.1921 | -0.0265 | 0.6637 | 0.0435* |
| Gender(Ref.=Male) | | | | | | |
| Female | -0.2757 | 0.05289 | 0.0231* | 0.0352 | 0.4343 | 0.0182* |
| Disclosed(Ref.=Yes) | | | | | | |
| No | -5.1284 | 0.0435 | < 0.0153* | -0.9251 | 0.3432 | 0.0421* |
| Who(Stage4) | | | | | | |
| Stage1 | 0.8642 | 0.1252 | 0.8452 | 0.0723 | 0.2152 | 0.0432* |
| Stage2 | 0.9433 | 0.1145 | 0.0546 | 0.0562 | 0.3251 | 0.0241* |
| Stage3 | 1.1452 | 0.1162 | 0.0752 | -0.0254 | 0.2245 | 0.0354* |
| Medication adherence(Ref.=Adherence) | | | | | | |
| Non-adherent | -1.4643 | 1.0128 | 0.0231* | -1.4365 | 0.1729 | 0.0143* |
| Food adherence(Ref.=adherent) | | | | | | |
| Non-adherent | -0.9452 | 0.5435 | 0.0142* | -0.8263 | 0.3384 | 0.0139* |
| Marital status(Ref.= without partner) | | | | | | |
| With partner | 0.7631 | 0.5857 | 0.0164* | 0.2482 | 0.2281 | 0.0165* |
| Phone(Ref.=Yes) | | | | | | |
| No | -1.4821 | 0.2404 | 0.0324* | -0.8354 | 0.0153 | 0.0153* |
| Education (Ref.=Tertiary) | | | | | | |
| No education | -0.7837 | 0.4245 | 0.04532* | -0.0431 | 0.1862 | 0.0432* |
| Primary | -0.0263 | 0.0465 | 0.0254* | 0.0652 | 0.3549 | 0.1732 |
| Secondary | -0.6321 | 0.3432 | 0.3821* | 0.0224 | 0.2543 | 0.1432 |
| Income(Ref.=Low) | | | | | | |
| High | 0.3554 | 0.0228 | 0.0182* | 0.7336 | 0.3432 | 0.0345* |
| Middle | 1.7951 | 0.1523 | 0.0134* | -0.2845 | 0.2869 | 0.0421* |

*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 | | Pr > \|t\| |
|---|---|---|---|---|---|---|
| Intercept | 1.1123 | 0.2131 | 3.0413 | 1.2345 | 6.3245 | 0.0152 |
| age*dist | -0.0272 | 0.0024 | 0.9732 | 0.42315 | 0.9999 | 0.0153* |
| weight*dist | 0.2034 | 0.0231 | 1.2256 | 1.0874 | 2.3425 | 0.0125* |
| Baseline CD4 cell count*dist | 0.0524 | 0.0024 | 1.0538 | 1.0032 | 1.2489 | 0.0231* |
| CD4 cell count *dist | 0.5242 | 0.0024 | 1.6891 | 1.0032 | 1.2489 | 0.0231* |
| dist*residence(Ref.=Urban) | | | | | | |
| Rural | -0.1162 | 0.0225 | 0.8903 | 0.42315 | 0.9982 | 0.0121* |
| dist*gender (Ref.=Male) | | | | | | |
| Female | -0.2757 | 0.02289 | 0.7590 | 0.52315 | 0.8999 | 0.0231* |
| dist*disclosed(Ref.= yes) | | | | | | |
| No | -0.1284 | 0.0335 | 0.8795 | 0.0565 | 0.9993 | 0.0153* |
| dist*who (Ref.=stage4) | | | | | | |
| Stage 1 | 0.8642 | 0.1152 | 2.3731 | 0.42315 | 1.2999 | 0.8452 |
| Stage 2 | 0.9433 | 0.1045 | 2.5684 | 0.44315 | 1.2999 | 0.0546 |
| Stage 3 | 1.1452 | 0.0162 | 3.1431 | 0.8255 | 1.2999 | 0.0752 |
| Medication adherent*dist(Ref.=adherent) | | | | | | |
| Non-adhe. | -0.4643 | 1.0118 | 0.8592 | 0.62315 | 0.9892 | 0.0231* |
| Food adh.*dist(Ref.=adherent) | | | | | | |
| Non-adherent. | -0.3452 | 0.2435 | 0.7081 | 0.5231 | 0.8972 | 0.0142* |
| dist*marital status stat(Ref.=Without partner) | | | | | | |
| With partner | 0.3631 | 0.2857 | 1.4378 | 1.3489 | 1.5245 | 0.0164* |
| dist*phone(Ref.=Yes) | | | | | | |
| No | -0.4821 | 0.1104 | 0.6175 | 0.4232 | 0.8982 | 0.0324* |
| dist*education (Ref.=Tertiary) | | | | | | |
| No educ. | -0.7837 | 0.1245 | 0.4567 | 0.22315 | 0.6982 | 0.04532* |
| Primary | -0.0263 | 0.0365 | 0.9740 | 0.72315 | 0.9982 | 0.0254* |
| Secondary | -0.6321 | 0.1432 | 0.5315 | 0.42315 | 0.6982 | 0.3821* |
| dist*income (Ref.= Low) | | | | | | |
| High | 0.3554 | 0.0128 | 1.4268 | 1.3489 | 1.7245 | 0.0182* |
| Middle | 1.7951 | 0.1123 | 6.0201 | 1.3489 | 4.3245 | 0.0134* |
| Visiting time*dist | 0.0521 | 0.0145 | 1.0513 | 1.0245 | 1.1542 | 0.0123* |
| Follow up times/visits *dist* ownership of cell phone(Ref.=Yes) | | | | | | |
| No | -0.0332 | 0.03341 | 0.9704 | 0.7342 | 0.9989 | 0.0324* |
| Follow up times/visits *dist*gender (Ref.= Male) | | | | | | |
| Female | 0.0421 | 0.0343 | 1.0408 | 1.0184 | 1.1893 | 0.0324* |
| Age*dist*gendr (Ref.=Male) | | | | | | |

| Parameter | Estimate | Standard Error | Adjusted odds Ratio(AOR) | Wald 95% CI for AOR | | Pr > \|t\| |
|---|---|---|---|---|---|---|
| Female | -0.0122 | 0.01224 | 0.9900 | 0.6543 | 0.9998 | 0.0324* |

*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 aapproaches. 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 significante effect on the two reponse 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.


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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$^{th}$ 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

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# Figures

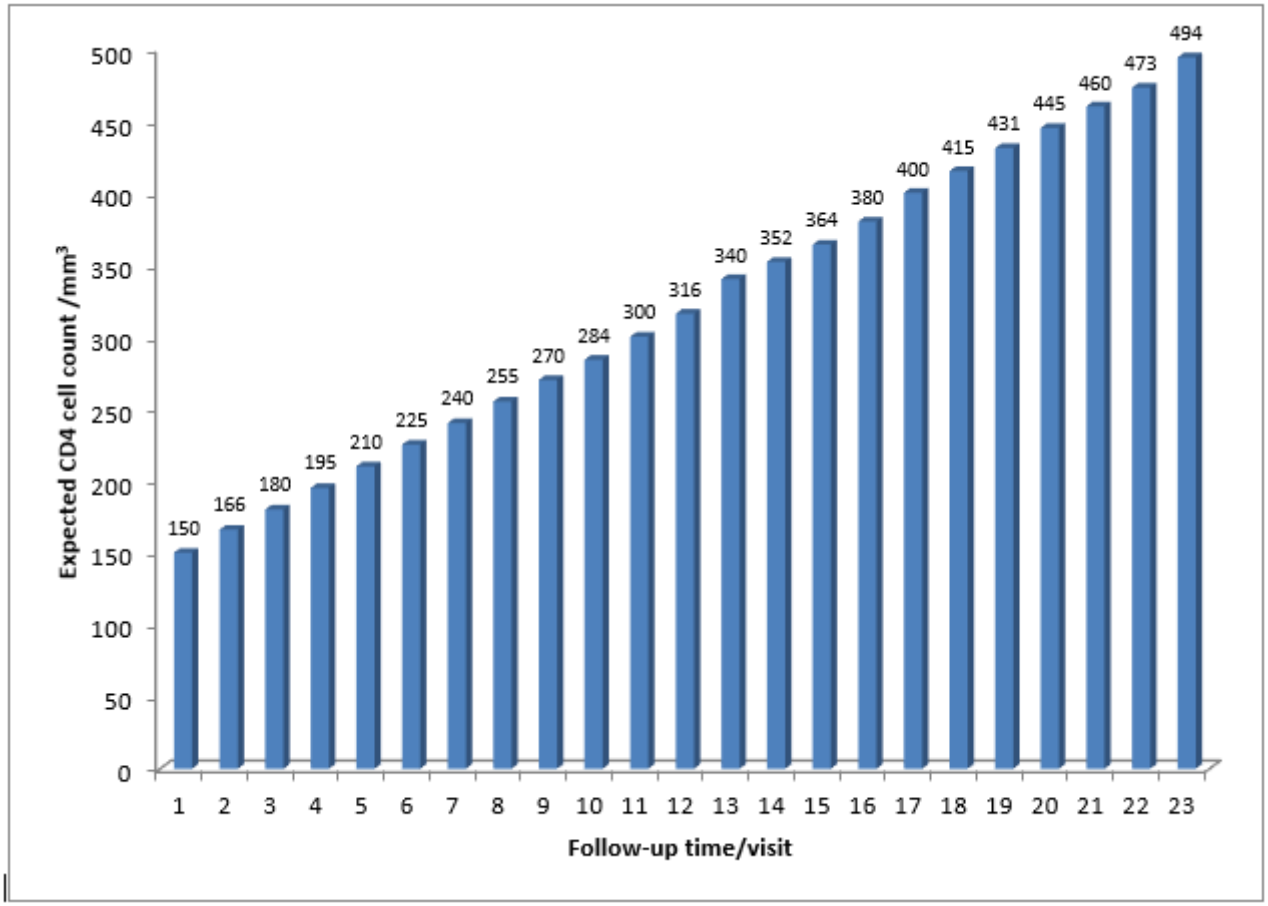


**Figure 1**

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

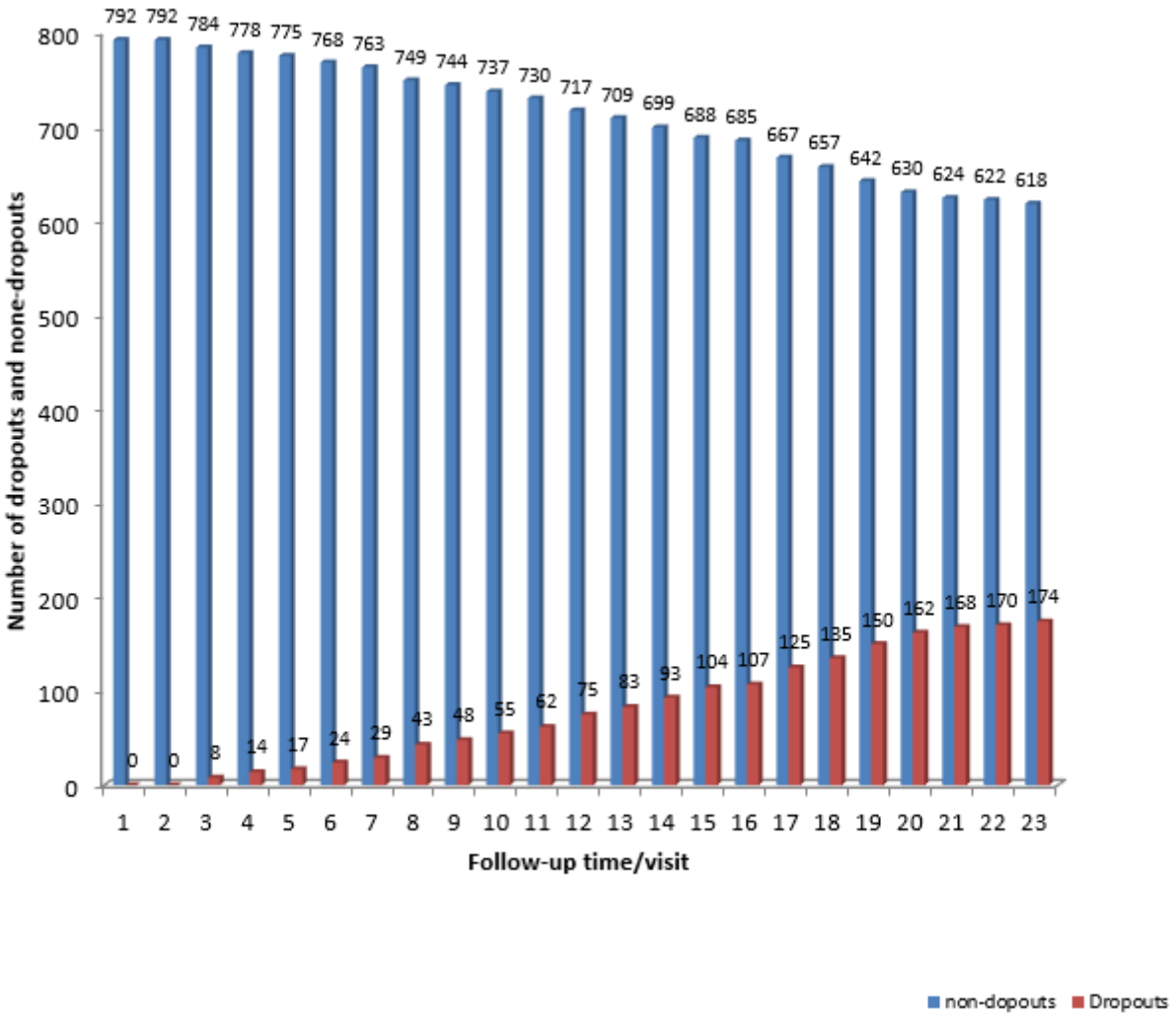


**Figure 2**

Number of dropout patients versus follow-up time/visit

# Supplementary Files

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- Methods.docx
- ResultsFigure2.docx