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Longitudinal study of change in CD4+ cell counts on HIV-Positive patients at Dalhatu Araf Specialist Hospital, Lafia

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Abstract

The aim of this study was the Longitudinal Study of Change in CD4+ Cell Counts on HIV-Positive Patients at Dalhatu Araf Specialist Hospital, Lafia. The study deployed linear mixed effects models to check if the mean response CD4+ cell count varies with time. The study also attempted to test if the mean response varies in the two groups. An attempt to estimate the relationship between the response and observations according to gender. The study revealed that the trajectory of the mean response over time has a very high variability where we see that there is a general rise in the CD4+ cell counts at the initiation of ART. It was further seen that the CD4+ cell counts in male patients is observed to be higher with higher median value after the sixth observation. A linear mixed effect model was used and tested where it was noted that there is evidence of between-individual heterogeneity which further shows that the decision to choose a mixed effects model instead of an only fixed effects model was in order. The model summary showed that the mean CD4+ cell counts at the baseline (OBS1) was averagely good, but at the initiation of ART, there was a significant increase in the mean response where it was further revealed that the pattern of the mean response over time is not flat. In modelling the group effects, we see the difference between the mean CD4 cell count of male versus female is -113.62 CD4 cell count (i. e. 95% CI= -290.64 to 63.39) lower than female, adjusting with time. Finally, the Wald test does not show any significant evidence of interaction between the observations and gender (p=0.2925) which suggests that the mean response based on gender may be parallel.

Keywords: CD4+ cell count; Longitudinal Analysis; Fixed Effects; Random Effects; R

1. Introduction

CD4+ T lymphocyte (CD4) cell counts are the primary laboratory markers used to study the progression from HIV to AIDS. However, it is a subject of debate among clinicians on the appropriate CD4 level to initiate HIV treatment. The 2013 WHO guideline recommends that HIV therapy be initiated when CD4+ cell counts is less than $500 cells / \mu L$ which is a departure from previous guidelines which gives a threshold of $350 cells / \mu L$. The debate of when to initiate therapy is also fuelled by the lack of evidence from HIV treatment initiation randomized clinical trials due to ethical implications, (WHO, 2013).

HIV infection causes severe depletion of CD4 T cells in the gut-associated lymphoid tissue with subsequent reduced levels of circulating CD4 lymphocytes in the peripheral blood. The CD4 T cells are terribly reduced in acute HIV infections but are seen to rebound over several weeks. If a patient remains untreated, CD4 T cells declines over several years. Studies have shown that prior to seroconversion, CD4 count is measured at around $1000 cells / mm^3$; it declines to an average of about $780 cells / mm^3$ at six months post seroconversion and to $670 cells / mm^3$ at one year of follow-

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up. Subsequently, the CD4 cell counts declines at a yearly average rate of approximately $50 cells / mm^3$. Significant depletion of CD4 T cells can give access to opportunistic infections and mortality in patients not undergoing therapy.

In longitudinal studies, measurements are taken from the same individual repeatedly over time. The primary goal of a longitudinal study is to characterize the change in response over time and to discover the factors that influence the change of the response. In longitudinal studies, responses between subjects may be independent but the repeated measurements within subjects are very likely to be correlated. When modelling longitudinal data, the within-subject correlation must be taken into account. The observed usually contains missing data, dropouts, censoring, outliers and measurement errors and are often unbalanced since the subjects were measured at different times and on different number of times.

Parametric models such linear mixed model are popularly useful in modelling longitudinal especially change in CD4 cell count over time., because the mixed effect models are parsimonious and efficient when the models are specified correctly.

1.1. Problem statement

Clinicians have used different markers to evaluate the progress of HIV in patients, among these markers are the viral load and CD4+ cell count. Viral load is quite expensive to use in terms of cost and technology. As such, the CD4+ cell count is commonly used, where a means of predicting future CD4+ count becomes very necessary. Since CD4 is the most important factor in deciding whether to initiate antiretroviral therapy, we hope to use this work to understand the prediction of future CD4+ cell counts for better administration of ART.

1.2. Justification

CD4+ count response to antiretroviral therapy (ART) are important measures of the efficacy of ART in individual patients. In Nasarawa State, almost no study is seen on long-term CD4+ response to ART among patients receiving care in resource limited setting. Among those patients who are able to remain on ART, robust immunologic response can be maintained for long periods and the risk of serious morbidity and mortality may eventually diminish. Hence the need for tools to predict CD4 cell counts into future times.

Aim

The aim of this research is the Longitudinal Study of Change in CD4+ Cell Counts on HIV-Positive Patients Initiated on Antiretroviral Therapy.

Objectives

- To identify the trajectory of the mean response over time.
- To obtain the average difference between groups of individuals.
- To estimate the relationship between the response and time vary according to groups of individuals.

2. Literature review

Many studies have been done on the change in CD4+ cell counts of HIV patients on ART. Nearly all studies in the first instance attempted to identify and establish factors in addition to HIV, that contributes to the change in CD4+ cell counts in HIV patients already enrolled in the antiretroviral therapy system. Some of these factors are seen to be demographic, such as, age, sex, area of residence, WHO clinical stage, initial CD4+ cell count, etc (Kauffmann et al, 2003; Florence et al, 2003; Gea-Banacloche & Clifford, 1998; Ebonyi et al, 2014; Cheaney, 2000; Tadese et al, 2019).The ability of health professionals to identify factors which influence the level of CD4+ cell count other than HIV and ART helps both care givers and patients to facilitate necessary monitoring and management technique of care interventions. Also, it helps check whether or not HIV patients who are enrolled in ART at low CD4 cell count baseline of $\leq 200 cell / mm^2$ get to recover. Other principal patient related factors associated with non-adherence included have been identified

Kulkarni et al (2011) and Xiuhong et al (2011) both used linear regression models to study some predictors of CD4+ cell counts recovery in HIV-1 positive patientsalready on ART beyond five (5) years of active ART. These studies majorly assumed that the change in CD4+ cell counts is linear, however, Adams & Luguterah (2013) suggested a longitudinal approach where they carried out a longitudinal analysis of change in CD4+ cell counts of HIV-1 patients on antiretroviral therapy (ART) in the Builsa district hospital. Secondary data sets were obtained from HIV/AIDS monitoring program at

the Builsa District Hospital, in which patients already enrolled into the ART were being monitored and thus generating repeated measurements of their CD4+ cell counts and other variables. The aim of the study was to investigate plausible determinants that affect change in CD4+ cell counts. Mixed effects modelling approach was deployed to model the CD4+ cell counts of different subjects. Results revealed that the correlation between CD4+ cell counts at different times had a first order autoregressive moving average variance-covariance structure. The CD4+ cell counts of subjects at initiation into ART, the duration of treatment and the drug type used in the treatment were seen to be predictor variables that determine the change in CD4+ cell counts. This study considered the changes in CD4+ cell count over the period of the study and the longitudinal approach was seen to be nonlinear and more advantageous.

Awoke, Principal and Zewotir (2017) looked at adherence and CD4 cell count change measure of the progression of the disease in HIV patients after the commencement of HAART. A retrospective longitudinal cohort study was conducted to examine the joint predictors of CD4 cell count change and adherence to HAART among HIV adult patients enrolled in the first ten months of the year 2009 and followed up till June, 20012. A joint model was deployed to detect determinants of two response variables. It was seen that joint model was more parsimonious than separate models as it reduces type-I error and subject-specific analysis improved its model fit. Also noted in the result is that as adherence increases, CD4 cell count also increased. Meaning that adherence to HAART boosts the immune system of subjects.

3. Methods and data analysis

3.1. Study Design

The study was a retrospective research that covered the duration 1st December, 2021 to 31st December, 2022. Data sets of fifty (50) patients already on ART was collected from Dalhatu Araf Specialist Hospital, Lafia, Nasarawa State. Gender, age at initiation of ART, Baseline weight, CD4+ cell count taken at the initiation of ART and thereafter every six-weekly CD4 cell count up to eight months, world health clinical staging at the initiation of ART and other factors were collected.

3.2. Sampling Procedure and Size

The sampling frame of this study was fifty (50) HIV-positive patients above 18 years started on ART between December 1st, 2021 and December 31st, 2022.

3.3. Selection Criteria

Data sets of fifty (50) patients above 18 years currently on ART who visited the Dalhatu Araf Specialist Hospital Lafia, Nasarawa State between the period December, 2021 to December, 2022 was used. The fifty patients were subjects whose records for six (6) observations were identified. Subject names were not used in this study.

3.4. Data Collection Criteria and Variables

The study used secondary data collected by well trained staff of the records unit of the health facility, where further orientation was given on the peculiar nature of the study. The data extraction template was designed and used to collect the data. The count variable of interest was the CD4+ cell count $(cells / mm^3)$ with repeated measurements every six (6) weeks, the gender, WHO clinical staging at initiation of ART, BMI from initiation of ART and age at start of study. Other variables of interests include water source, insect treated net, meals per day, food supplement, coping with medication, self reported adherence, educational level, occupational status, risk factors and drug allergies.

3.5. Ethical Consideration

The process of obtaining data sets for this study was based on permission received from prospective health facilities following guidelines stipulated by the Nasarawa State ministry of health. Data protection laws of Nigeria were strictly adhered to in carrying out this research. All facets of any other relevant ethics were adequately addressed.

3.6. Validity and Reliability

Content validity was based on the adequacy with which the items in an instrument measure the attributes of the study (Nunnally, 1978). This was ensured through constructive criticism from colleagues and those with extensive experience in research. Also, the reliability of the method was ensured through fitting of models to hypothetical data sets. Furthermore, the reliability and validity of results was obtained through member checks to help indicate whether the findings appeared to match with perceived authenticity. This was done in order to limit the distorting effects of random errors on the findings.

4. Data analysis and results obtained

4.1. Variable description

This analysis was conducted using data collected from fifty (50) patients at the Dalhatu Araf Specialist Hospital, Lafia, Nasarawa State. The data contains the variables as described below obtained from thirty-five (35) female and fifteen (15) male patients.

- PATID= Patients ID
- CD4COUNT= Measurement of CD4+ Cell Counts of patients, taken every 12 weeks for six times.
- GENDER= Sex of the participating patient
- OBSERVATION = Six observations of 12 weekly observations on patients
- AGE= Age of patient as at first introduction to ART and subsequent measurements.
- WEIGHT=Weight of patients as at first introduction to ART and subsequently.

4.2. Descriptive Plots

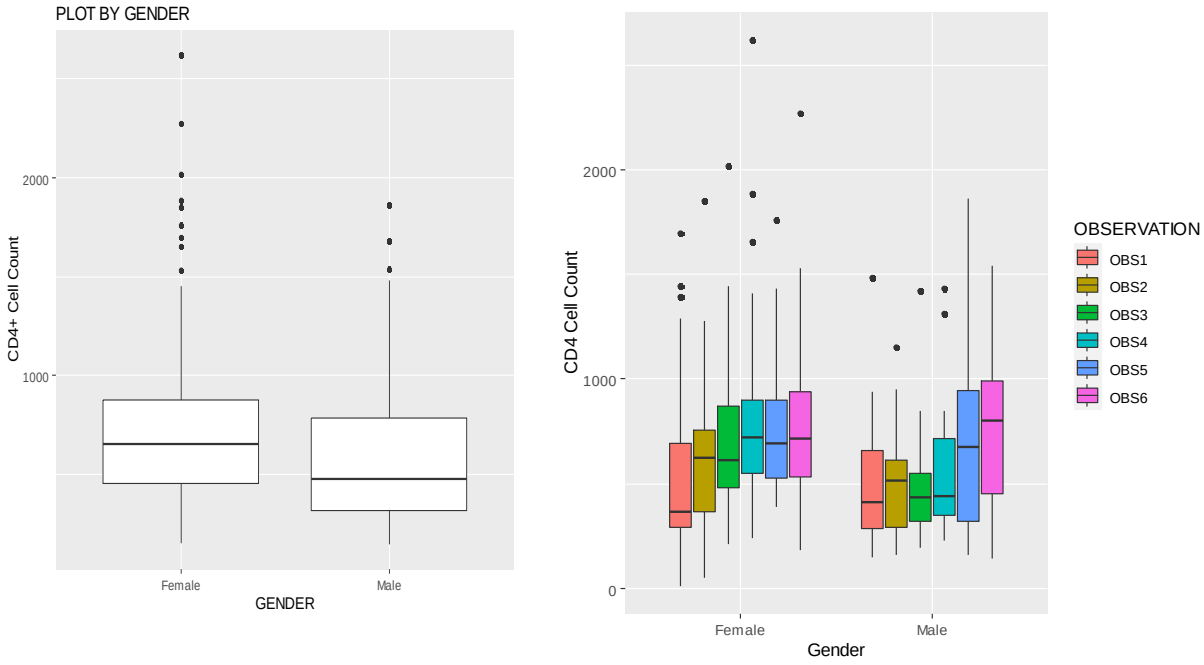

Figure 1 Box-plot of CD4+ Count Cell According to Gender and Observation

The first plot in Fig. 1 above shows that the female patients have a higher median CD4+ cell count than the male patients, although it is observed that they have the highest and lowest CD4+ cell count. This means that the female patients are observed to have a higher range of CD4+ cell count. The second plot in Fig. 1 also tells us same thing as the first except that based on the first observation, it further tells us that the female patients averagely came in with lower CD4+ cell count than the male. The observation (OBS2) shows that there is a rise in the CD4+ cell count after the commencement of ART with a slight drop in OBS3, rise in CD+ cell in OBS4 and OBS5, where we see that in the sixth observation, the CD4+ cell count is higher in male than female.

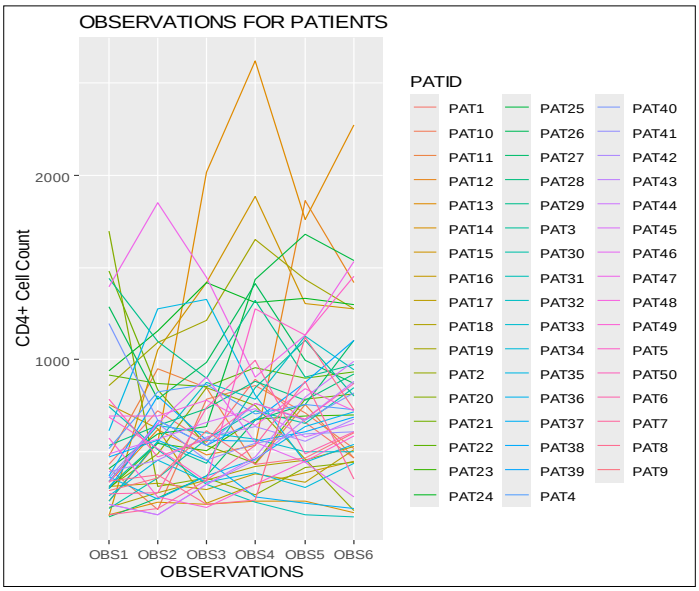

Figure 2 Individual line plot of Patients based on Observation

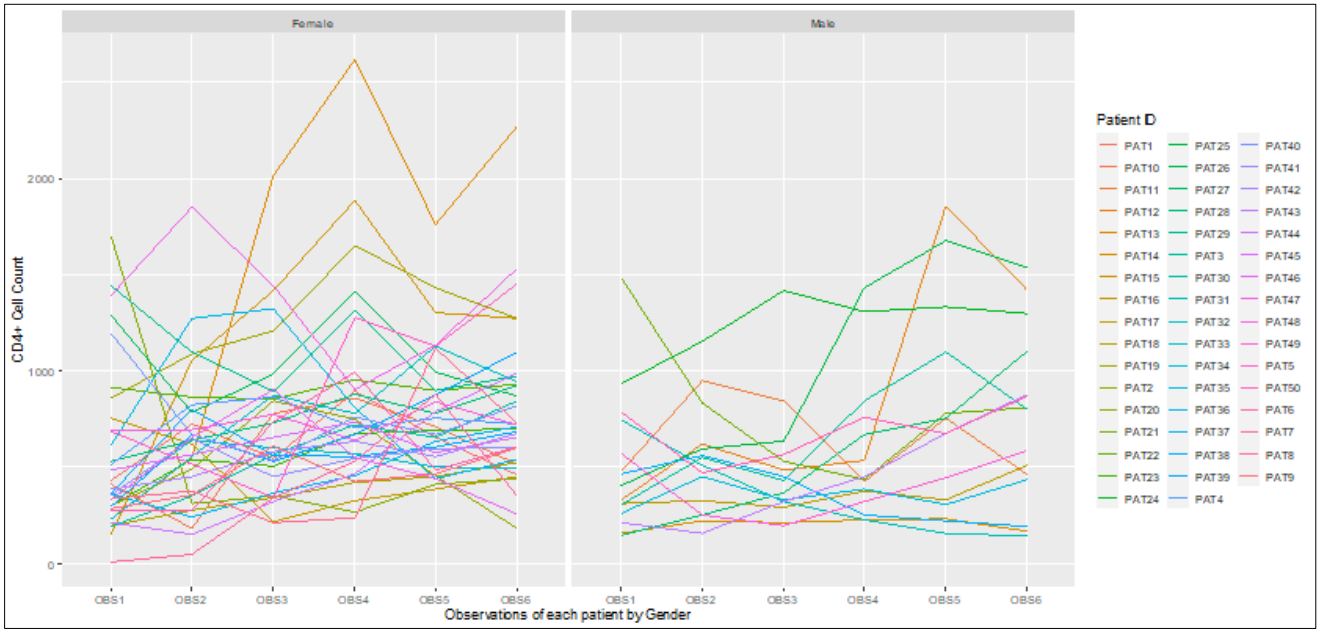

Figure 3 Individual line plot of Patients based on Observation and Gender

The plots in Fig. 2 and Fig. 3 shows the individual line plot of all participating patients where it was seen that the range of values in the female plot is wider and more variable than that of the male.

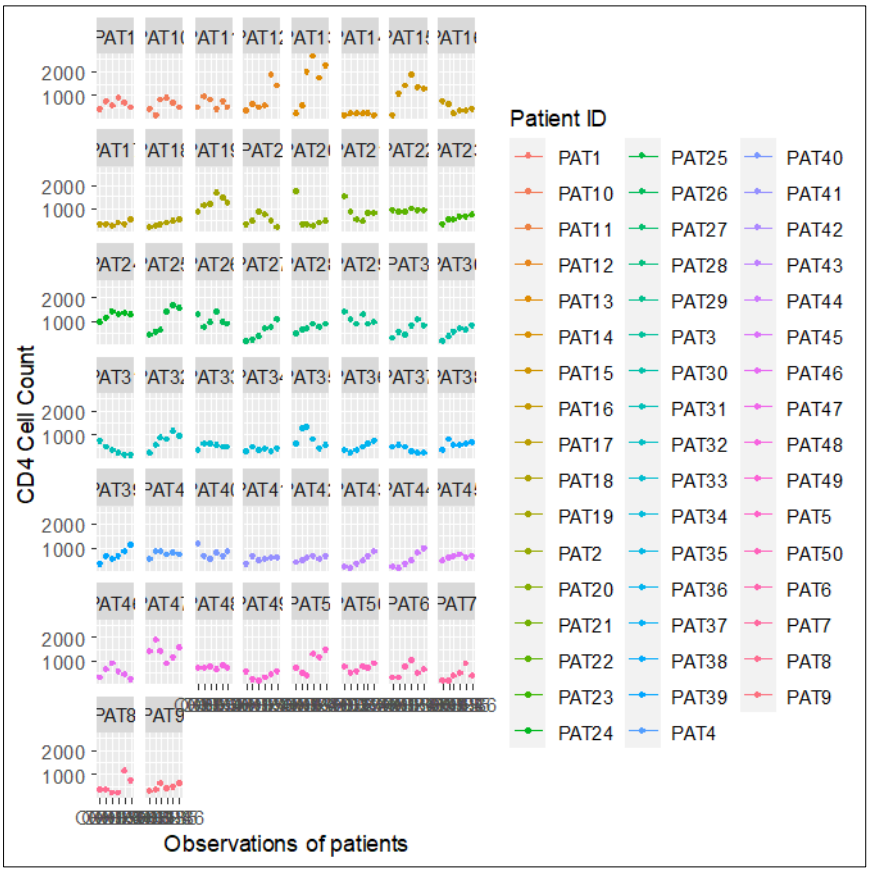

Figure 4 Plot of each patient data over time

4.3. Mean Response Over Time

```
> group_by(DATANEW,AGE,GENDER)%>%
+ get_summary_stats(CD4COUNT,show=c("mean","sd"))
# A tibble: 12 x 6
   GENDER   AGE variable      n  mean    sd
   <chr>  <int> <fct>     <dbl> <dbl> <dbl>
 1 Female     1 CD4COUNT     24  802. 472.
 2 Male       1 CD4COUNT     24  480. 302.
 3 Female     2 CD4COUNT     24  560  170.
 4 Male       2 CD4COUNT     12  283   99.8
 5 Female     3 CD4COUNT    102  690. 417.
 6 Male       3 CD4COUNT     24  848. 453.
 7 Female     4 CD4COUNT     48  832. 415.
 8 Male       4 CD4COUNT     18  641. 410.
 9 Female     5 CD4COUNT      6  692  276.
10 Male       5 CD4COUNT      6  674. 295.
11 Female     6 CD4COUNT      6  562. 280.
12 Male       6 CD4COUNT      6  550. 361.
```

The average responses for both male and female subjects based on age are seen to have a high variability with the least variability observed in the second observation for both male and female.

4.4. Linear Mixed Models

In order to test for a subset of fixed effects, a linear mixed-effects models was fitted using the lmer function in the lme4 package in R. The first section of the model states the fixed effects part of the model, while the second that is put in parenthesis indicate the random effect components.

```
> LIN1=lmer(CD4COUNT~1+(1|PATID),data=DATANEW)
> summary(LIN1)
Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]
Formula: CD4COUNT ~ 1 + (1 | PATID)
   Data: DATANEW

REML criterion at convergence: 4362.3

Scaled residuals:
    Min      1Q  Median      3Q     Max
-3.8572 -0.5945 -0.0567  0.4105  3.9382

Random effects:
 Groups   Name        Variance Std.Dev.
 PATID    (Intercept) 70977    266.4
 Residual             94154    306.8
Number of obs: 300, groups:  PATID, 50

Fixed effects:
            Estimate Std. Error     df t value Pr(>|t|)
(Intercept)   681.17      41.63  49.00   16.36   <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

The estimated marginal mean of the CD4 Cell count is 681.17 cells/mm3. The estimated variance of the random-effect that reflects the between-subject variability is 70977 while the estimated variance of the error term which reflects the within-subject variability is calculated to be 94154. Hence, the correlation between any two repeated measures (ICC) is equal to 70977/(70977+94154)=0.43.

We now go ahead to test the components using an ANOVA like table obtained from the ranova function and lmer test in R.

```
> ranova(LIN1)
ANOVA-like table for random-effects: Single term deletions


Model:
CD4COUNT ~ (1 | PATID)
            npar  logLik    AIC    LRT Df Pr(>Chisq)
<none>         3 -2181.2 4368.3
(1 | PATID)    2 -2222.2 4448.4 82.085  1  < 2.2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

The small p-value shows that there is evidence of between-individual heterogeneity which also shows that choosing a mixed-effects model instead of an only fixed effects model is in order.

4.5. Mean Response with Time

Here, the indicator variables are now used to contrast the mean responses at different occasions. We have measurements of the response at different time intervals OBS1(baseline CD4 Cell Count), OBS2, OBS3, OBS4, OBS5 and OBS6.

$$E[Y_{ij}] = \beta_o + \beta_1 X_{ij1} + \beta_2 X_{ij2} + \beta_{ij3} + \beta_{ij4} + \beta_{ij6}$$

Where $X_{ij1}, X_{ij2}, X_{ij3}, X_{ij4}$ *and* X_{ij5} are indicator variables for the other five CD4 cell count observations after the baseline observations respectively. As such, the second measurement (OBS2) is the referent.

```
> LINOBS=lmer(CD4COUNT~OBSERVATION+(1|PATID),data=DATANEW)
> summary(LINOBS)
Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]
Formula: CD4COUNT ~ OBSERVATION + (1 | PATID)
   Data: DATANEW
REML criterion at convergence: 4284.7
Scaled residuals:
    Min      1Q  Median      3Q     Max
-3.5988 -0.4878 -0.1533  0.3451  4.2695
Random effects:
 Groups   Name        Variance Std.Dev.
 PATID    (Intercept) 72438    269.1
 Residual             85387    292.2
Number of obs: 300, groups:  PATID, 50
Fixed effects:
                Estimate Std. Error     df t value Pr(>|t|)
(Intercept)       534.14      56.18 143.18   9.507  < 2e-16 ***
OBSERVATIONOBS2    61.82      58.44 245.00   1.058 0.291189
OBSERVATIONOBS3   120.42      58.44 245.00   2.060 0.040407 *
OBSERVATIONOBS4   217.56      58.44 245.00   3.723 0.000245 ***
OBSERVATIONOBS5   234.78      58.44 245.00   4.017 7.83e-05 ***
OBSERVATIONOBS6   247.60      58.44 245.00   4.237 3.21e-05 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
Correlation of Fixed Effects:
                (Intr) OBSERVATIONOBS2 OBSERVATIONOBS3 OBSERVATIONOBS4
OBSERVATIONOBS2 -0.520
OBSERVATIONOBS3 -0.520  0.500
OBSERVATIONOBS4 -0.520  0.500          0.500
OBSERVATIONOBS5 -0.520  0.500          0.500          0.500
OBSERVATIONOBS6 -0.520  0.500          0.500          0.500
                OBSERVATIONOBS5
OBSERVATIONOBS2
OBSERVATIONOBS3
OBSERVATIONOBS4
OBSERVATIONOBS5
OBSERVATIONOBS6  0.500
```

The model summary above shows that the mean CD4+ cell count at the baseline (OBS1) is 534.14cell/mm^3 but at the initiation of ART, it was observed that the difference between the mean responses of OBS1 and OBS2 is

$\beta_1 = 61.82 cell / mm^3$. The difference between the mean responses of OBS3 and OBS1 is $\beta_2 = 120.42 cell / mm^3$ .The difference between the mean responses and subsequent observations are as follows $\beta_3 = 217.56 cell / mm^3, \beta_4 = 234.78 cell / mm^3$ *and* $\beta_5 = 247.60 cell / mm^3$.

To test whether the mean response will be constant over time, we test the null hypothesis that all the regression coefficients used to model time are simultaneously equal to zero $\left(i.e.\ H_0 : \beta_1 = \beta_2 = \ldots = \beta_5 = 0\right)$.

```
> Anova(LIN)
Analysis of Deviance Table (Type II Wald chisquare tests)

Response: CD4COUNT
            Chisq Df Pr(>Chisq)
OBSERVATION 30.669  5  1.089e-05 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Our results from the Wald-test reveal that the pattern of the mean response over time is not flat. The estimated trajectory from the fitted model by using the predict function in R is shown below.

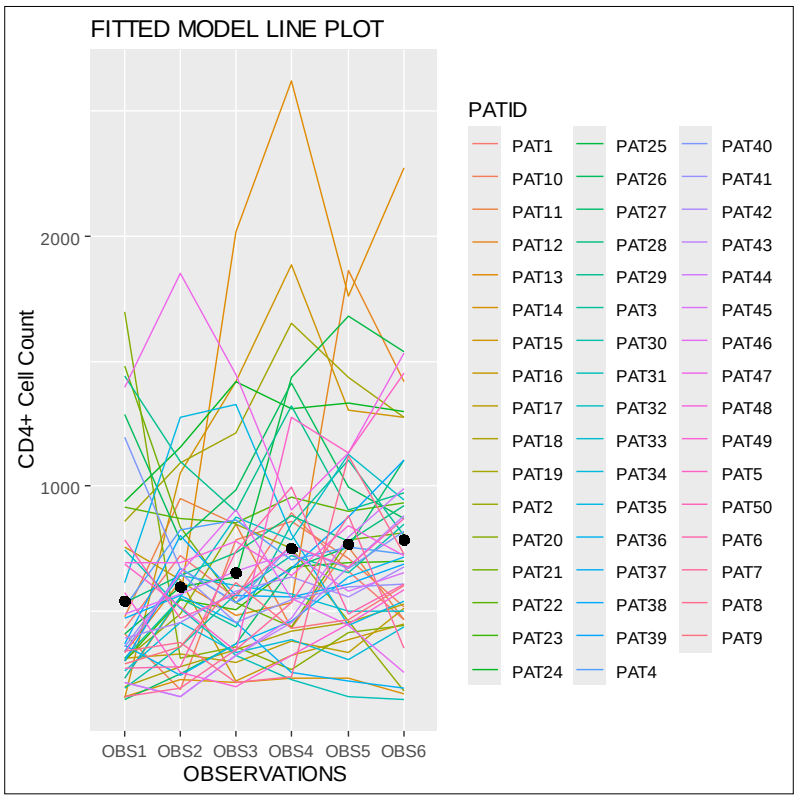

Figure 5 Fitted model plot

The trajectory of the fitted model shown in blue line where the points are the predicted mean response. It is seen to be slowly increasing.

4.6. Group Effect

The next objective is to test if the mean response varies in the two groups of individual that is gender (male =1 and female=2).

$$E[Y_{ij}] = \beta_o + \beta_1 X_{ij1} + \beta_2 X_{ij2} + \beta_{ij3} + \beta_{ij4} + \beta_{ij5} + \beta_{ij6}$$

Where $X_{ij1}, X_{ij2}, X_{ij3}, X_{ij4}$ *and* X_{ij5} are indicator variables for the other five CD4 cell count observations after the baseline observations respectively while X_{ij6} is the indicator variable for gender. The mean response for male and female is given as $E\left[Y_{ij} \mid X_{ij6} = 1\right] - E\left[Y_{ij} \mid X_{ij} = 0\right] = \beta_6$, that is adjusted for time.

```
> LINGGRP=lmer(CD4COUNT~OBSERVATION+GENDER+(1|PATID),data=DATANEW)
> summary(LINGGRP)
Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]
Formula: CD4COUNT ~ OBSERVATION + GENDER + (1 | PATID)
   Data: DATANEW

REML criterion at convergence: 4272.3

Scaled residuals:
    Min      1Q  Median      3Q     Max
-3.6122 -0.5081 -0.1581  0.3770  4.2494

Random effects:
 Groups   Name        Variance Std.Dev.
 PATID    (Intercept) 71419    267.2
 Residual             85387    292.2
Number of obs: 300, groups:  PATID, 50

Fixed effects:
                Estimate Std. Error      df t value Pr(>|t|)
(Intercept)       568.23      62.21  112.60   9.134 3.16e-15 ***
OBSERVATIONOBS2    61.82      58.44  245.00   1.058 0.291189
OBSERVATIONOBS3   120.42      58.44  245.00   2.060 0.040407 *
OBSERVATIONOBS4   217.56      58.44  245.00   3.723 0.000245 ***
OBSERVATIONOBS5   234.78      58.44  245.00   4.017 7.83e-05 ***
OBSERVATIONOBS6   247.60      58.44  245.00   4.237 3.21e-05 ***
GENDERMale       -113.62      90.32   48.00  -1.258 0.214459
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

> ci.lin(LINGEFFECT)
                Estimate   StdErr         z             P        2.5%     97.5%
(Intercept)     568.2271 62.21158  9.133784 6.614596e-20  446.294684 690.15960
OBSERVATIONOBS2  61.8200 58.44215  1.057798 2.901474e-01  -52.724504 176.36450
OBSERVATIONOBS3 120.4200 58.44215  2.060499 3.935084e-02    5.875496 234.96450
OBSERVATIONOBS4 217.5600 58.44215  3.722656 1.971382e-04  103.015496 332.10450
OBSERVATIONOBS5 234.7800 58.44215  4.017306 5.886722e-05  120.235496 349.32450
OBSERVATIONOBS6 247.6000 58.44215  4.236668 2.268608e-05  133.055496 362.14450
GENDERMale     -113.6238 90.31726 -1.258052 2.083730e-01 -290.642387  63.39477
>
```

The difference between the mean CD4 cell count of male versus female is -113.62 CD4 cell count (i. e. 95% CI= -290.64 to 63.39) lower than female, adjusting with time.

4.7. Interaction between observations and groups

Here, we try to find out if the change of the mean response over time varies according to the group of individuals. A mixed interaction model was fitted and results below were obtained.

```
> LINOBSGENDER=lmer(CD4COUNT~OBS*GENDER+(1|PATID),data=DATANEW)
> summary(LINOBSGENDER)
Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]
Formula: CD4COUNT ~ OBS * GENDER + (1 | PATID)
   Data: DATANEW

REML criterion at convergence: 4208.7

Scaled residuals:
    Min      1Q  Median      3Q     Max
-3.5627 -0.4871 -0.1064  0.4150  4.3365

Random effects:
 Groups   Name        Variance Std.Dev.
 PATID    (Intercept) 70885    266.2
 Residual             84595    290.9
Number of obs: 300, groups:  PATID, 50

Fixed effects:
                   Estimate Std. Error       df t value Pr(>|t|)
(Intercept)         549.857     66.650  141.227   8.250 1.00e-13 ***
OBSOBS2              79.429     69.527  240.000   1.142 0.254421
OBSOBS3             173.486     69.527  240.000   2.495 0.013261 *
OBSOBS4             276.200     69.527  240.000   3.973 9.41e-05 ***
OBSOBS5             225.486     69.527  240.000   3.243 0.001350 **
OBSOBS6             246.086     69.527  240.000   3.539 0.000481 ***
GENDERMale          -42.390    121.687  141.227  -0.348 0.728090
OBSOBS2:GENDERMale  -59.362    126.939  240.000  -0.468 0.640464
OBSOBS3:GENDERMale -186.886    126.939  240.000  -1.472 0.142263
OBSOBS4:GENDERMale -205.467    126.939  240.000  -1.619 0.106840
OBSOBS5:GENDERMale   20.981    126.939  240.000   0.165 0.868859
OBSOBS6:GENDERMale   -4.952    126.939  240.000  -0.039 0.968912
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

The mean response among female patients for the first observation 546cell/mm^3. At the second observation, the mean response is noticed to be 79.4cell/mm^3 higher than the first observation but is seen to be insignificant. The mean response at the third observation is 173.5 cell/mm^3 and was observed to increase significantly up till the sixth observation at 246.1 cell/mm^3. The mean response among male patients was observed to be insignificant. We get to see that the mean response among male and female depends on the time of observation but the change in the mean response over time does not depend on the gender of the patient.

4.8. Testing the interaction between gender and observations

```
> Anova(LINOBSGENDER, type=3)
Analysis of Deviance Table (Type III Wald chisquare tests)

Response: CD4COUNT
              Chisq Df Pr(>Chisq)
(Intercept) 68.0602  1  < 2.2e-16 ***
OBS         23.6653  5  0.0002517 ***
GENDER       0.1214  1  0.7275714
OBS:GENDER   6.1433  5  0.2925277
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

The Wald test does not show any significant evidence of interaction between the observations and gender (p=0.2925) which suggests that the mean response based on gender may be parallel.

```
> tidy(emmeans(LINOBSGENDER,c("OBS","GENDER")),conf.int=TRUE)
# A tibble: 12 x 9
   OBS   GENDER estimate std.error    df conf.low conf.high statistic  p.value
   <chr> <chr>     <dbl>     <dbl> <dbl>    <dbl>     <dbl>     <dbl>    <dbl>
 1 OBS1  Female     550.      66.7   141.     418.      682.      8.25 1.00e-13
 2 OBS2  Female     629.      66.7   141.     498.      761.      9.44 1.05e-16
 3 OBS3  Female     723.      66.7   141.     592.      855.     10.9  2.48e-20
 4 OBS4  Female     826.      66.7   141.     694.      958.     12.4  2.47e-24
 5 OBS5  Female     775.      66.7   141.     644.      907.     11.6  2.34e-22
 6 OBS6  Female     796.      66.7   141.     664.      928.     11.9  3.68e-23
 7 OBS1  Male       507.     102.    141.     306.      709.      4.98 1.79e- 6
 8 OBS2  Male       528.     102.    141.     326.      729.      5.18 7.45e- 7
 9 OBS3  Male       494.     102.    141.     293.      695.      4.85 3.18e- 6
10 OBS4  Male       578.     102.    141.     377.      779.      5.68 7.43e- 8
11 OBS5  Male       754.     102.    141.     553.      955.      7.41 1.08e-11
12 OBS6  Male       749.     102.    141.     547.      950.      7.35 1.44e-11
```

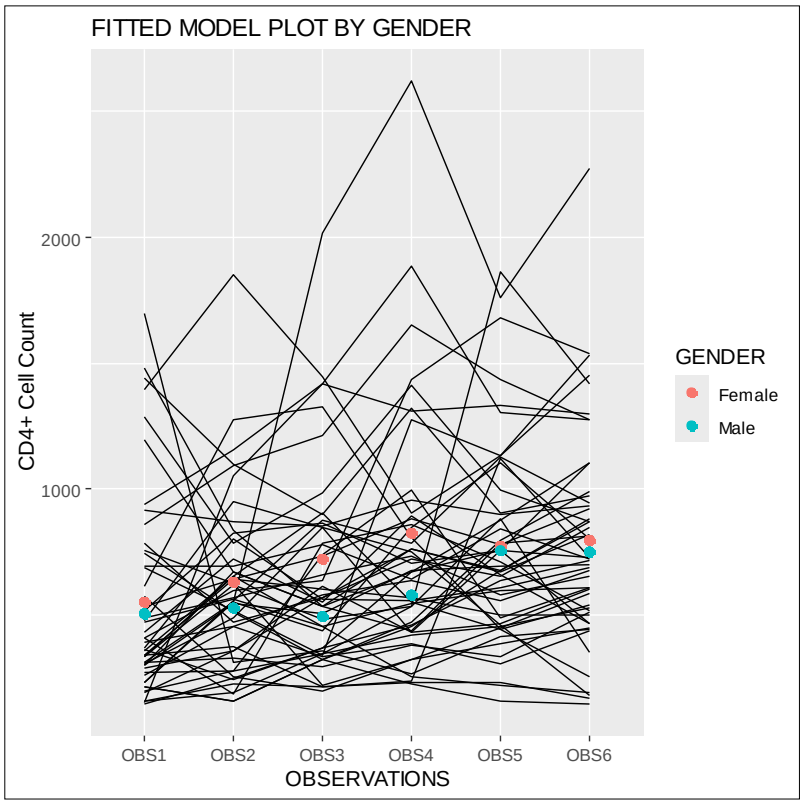

Figure 6 Fitted group model plot

The above plot confirms the Wald's test which suggested earlier that the mean response based on gender may be parallel.

5. Conclusion

A longitudinal study of the change in CD4+ cell count of fifty HIV-patients initiated on Antiretroviraltherapy at the Dalhatu Araf Specialist Hospital, Lafia, Nasarawa State was attempted in this study. The study deployed linear mixed effects models to check if the mean response CD4+ cell count varies with time. The study also attempted to test if the mean response varies in the two groups. An attempt to estimate the relationship between the response and observations according to gender.

The study revealed that the trajectory of the mean response over time has a very high variability where we see that there is a general rise in the CD4+ cell counts at the initiation of ART. It was further seen that the CD4+ cell counts in male patients is observed to be higher with higher median value after the sixth observation.

A linear mixed effect model was used and tested where it was noted that there is evidence of between-individual heterogeneity which further shows that the decision to choose a mixed effects model instead of an only fixed effects model was in order. The model summary showed that the mean CD4+ cell counts at the baseline (OBS1) was averagely good, but at the initiation of ART, there was a significant increase in the mean response where it was further revealed that the pattern of the mean response over time is not flat.

In modelling the group effects, we see the difference between the mean CD4+ cell count of male versus female is -113.62 CD4 cell count (i. e. 95% CI= -290.64 to 63.39) lower than female, adjusting with time.

Finally, the Wald test does not show any significant evidence of interaction between the observations and gender (p=0.2925) which suggests that the mean response based on gender may be parallel.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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