

# Growth Dynamics of CD4 cells in HIV-1 Patients on Antiretroviral Therapy (ART) at the Builsa District Hospital in Ghana

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**Abstract** The monitoring of CD4 counts are a basis for assessing the effectiveness of most HIV treatments. Understanding the way CD4 cells change over time among patients on ART could provide insight into the way Patients respond to treatment and how effective treatment is with time. This study examine the changes in CD4 count over time and the effect of some plausible factors on this change for Patients who were on Antiretroviral Therapy (ART) in The Builsa District Hospital in Ghana. Retrospective data from the HIV/AIDS Monitoring Program at the Builsa District hospital, in which patients had enrolled and their CD4 cell count were regularly being monitored every six months, forming repeated measures of CD4 counts, was used for our study: Profile analysis was used to study the pattern of change in the CD4 count. While treatment remained effective, the results showed that the trend of CD4 count over time was logarithmic indicating that the effectiveness of treatment, decreased with time. While the gender and marital status of the patients do not show any statistically significant differentials to this, the educational and religious status of the patients, as well as the drug used in the treatment do.

**Keywords:** HIV, CD4 cells, antiretroviral therapy, profile analysis

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## 1. Introduction

HIV/AIDS can be traced as far back as between 1884 and 1924 in the modern day city of Kinshasa in west central Africa, where a hunter killed a chimpanzee and some of the animal's blood entered the hunter's body: The blood carried a Simian Immunodeficiency Virus (SIV) that was harmless to the chimpanzee but harmful to humans [1]. Since the first recognised HIV/AIDS case in June 1981 [1], about 70 million people have contracted HIV and nearly 35 million people worldwide have died of HIV related causes of which 22.5 million are from Africa [2].

The CD4+ T-lymphocyte count is an important factor in the management of patients infected with HIV [8]. CD4 cells are a type of lymphocytes (white blood cell) of which are two main types: T-4 cells, also called CD4+, are helper cells and lead the attack against infections and T-8 cells (CD8+), which are suppressor cells, end the immune response [9]. The CD4 count in adults is expressed as the absolute number of CD4 cells per microlitre of blood and in children as a percentage of total lymphocytes or total T-lymphocytes: This has huge predictive and therapeutic implications and forms the foundation for most HIV treatment decisions [10].

Since the pandemic of HIV/AIDS in 2001 [11], Anti-retroviral therapy (ART) services have been available to HIV patients. Guidelines from the National AIDS Control

Program (NACP) recommend patients to initiate treatment when their CD4 cell count is less than 350 cells per microliter ( $\mu$ l) and or they become symptomatic with HIV infection as described in the world health organisation (WHO) stage I to IV.

The importance of CD4 counts to the health of the HIV/AIDS patient and in the treatment and management of this phenomenon, has attracted several studies on various aspects of these counts: As a means of understanding how CD4 cell counts decline in HIV/AIDS patients, [3] modelled the decline in the square root of CD4 cells counts from seroconversion onwards and demonstrated that the slope did not appear to be linear for the entire trajectory: they showed gender differentials in the CD4 counts at which persons developed and died from AIDS. [4] showed that in contrast to a strong correlation with HIV RNA load observed in adults, CD4 and CD8 T-cell activation in Ugandan children correlates significantly with CD4 T-cell status but not with viral load. [5] studied gender differentials in HIV treatments and outcomes with Indian women who had access to care having significantly higher CD4 counts than their male counterparts at enrolment into care, treatment initiation, and 1 year after initiating HAART. [6] study the relationship between the slope in CD4 counts and HIV viral load for patients who had been initiated of combination antiretroviral treatment (cART) and determined some factors to be associated with the slope in CD4 count: The consequence on long-term

outcomes through the possible development of HIV drug resistance however remains uncertain. [7] modelled the changing distributions at each level of CD4 cell count and used their model to estimate and compare the median life expectancy for Zambia to that of South Africa, at a CD4 count of 200 cells/mL. They concluded among other things that better data on time trends of CD4+ cell counts could help to refine their assumptions such as that of a linear decline. [12] studied the CD4+ cell counts in adults with HIV at the Time of initiation on ART and concluded that the majority of the patients having CD4 cell counts of less than 200 cells/mL was an indication of a relatively later start of ART treatment. Several studies into the effects and associations of socio economic and demographic factors on CD4 cells counts of HIV patients have also been done [13,14,15,16,17]. However, studies on the pattern of growth of the CD4 cells in HIV/AIDS patients on treatment, which could in addition to providing guidance into better modelling also provide insight into the long term effectiveness of treatment, are none existent or scarce. Questions on the long term effectiveness of the treatment of patients could be answered by the pattern of change over time of their CD4 counts.

This study therefore sought to answer the question of the effectiveness of the treatments with time, as well as the plausible differentials associated with it. A profile analysis of the repeated measures of the CD4 counts, of the patients over the study period, was done to provide these insights.

## 2. Materials and Method

### 2.1. Source of Data

We obtained historical data of patients' CD4 count from the HIV/AIDS Monitoring Program at the Builsa District hospital, in which patients who had enrolled and their initial CD4 cell count taken, had their CD4 cells regularly monitored every six months after treatment: This program included individuals who were diagnosed of HIV/AIDS and were enrolled in the centre's HIV/AIDS Drug Treatment Program. Our data was restricted to all individuals who had their therapy between January 1 2008 and December 2012; Patients who were 15 years or older at the time of diagnoses and had their CD4 cells counted at least thrice within the period were included in our study. Data on some plausible factors, such as gender, level of education, marital status and religious affiliation, taught to influence the change in the Patients CD4 count, were also obtained; also, data on the type of drug used by each patient was obtained.

The different drug combinations that were used in the treatment regimen include; Combivir/ Nevirapine (CBV/NVP), Combivir/ Efavirenz (CBV/EFV), Tenofovir /Lamivudine / Nevirapine (TDF/ 3TC/ NVP), Tenofovir/ Lamivudine/ Efavirenz (TDF/3TC/EFV) and Combivir/ Lopinavir/ Ritonavir (CBV/LPV/R). In all a total of 90 patients' information was used for this study.

### 2.2. Modelling Approach

We performed profile analysis on the CD4 counts of the patients and considered some covariates; gender, educational level, marital status, religion, time and drug

type. The duration to treatment ( $t$ ) was in intervals of 6 months, with the initial CD4 count taking at time  $t = 0$  and thereafter, every six months represented by a period such that  $t = 0$  representing the start of treatment,  $t = 1$  representing 6 months after treatment,  $t = 2$  representing 12 months after treatment, etc. The purpose of this approach is to observe the pattern of the average change in CD4 count over the period of study and to fit an appropriate model that would describe the trajectory of the average CD4 count over the period of study, and hence explain the effectiveness of the treatment with time. Several models were assessed and the best of the models, based on the amount of variability explained by the model (i.e. the model with the largest  $R^2$  value), was chosen. The appropriateness of our chosen model (the logarithmic model), was then assessed by incorporating the chosen model into a regression analysis on time. The Sharpiro-Wilks, Box-Ljung and ARCH-LM tests were also used to diagnose various aspects of the model.

We conducted a Multivariate Analysis of Variance (MANOVA) test to assess the universal equality of the different groups of each covariate tested. For each group that the MANOVA test determined their levels to be the same, we performed a profile analysis to examine specific aspects of the growth trajectory of the CD4 cells: Parallelism, equality and flatness were thus tested. These were to ascertain if the pattern of change in CD4 counts were the same between the groups, to determine if there were any between group differentials, and also if there were any changes over time respectively.

## 3. Results

**Table 1. Descriptive Statistics of CD4 Count of Patients on Treatment**

	Percentage	Min (CD4)	Max (CD4)
<b>Age</b>			
20-29	21	324	1032
30-39	42	226	1779
40-49	18	160	1264
50-59	12	150	1203
60-69	7	140	1195
<b>SEX</b>			
Male	81	8	1779
Female	19	79	935
<b>EDUCATION</b>			
Non	59	51	1203
Primary	9	172	618
JHS/middle	14	39	1779
SHS	10	176	1264
Tertiary	8	8	1195
<b>Marital status</b>			
Divorce	21	39	1779
Married	41	51	1203
Single	9	176	1264
Widow(er)	25	8	1195
Separated	2	172	618
<b>DRUG</b>			
CBV+EFV	27	244	1264
CBV+LPV/R	3	180	720
CBV+NVP	36	281	1779
TDF+3TC+EFV	14	155	769
TDF+3TC+NVP	20	238	1203
<b>RELIGION</b>			
Christianity	78	8	1779
Islam	11	150	1082
Traditionalist	7	185	634
Non	4	171	796

**Table 1** shows the descriptive statistics of the data: The ages of the patients ranges from 21 to 67 years with the mean and median age being 38 and 36 years respectively. There were more females (81%) than Males (19%): The mean change in CD4 count for males was 491 while that of the females was 479. Fifty-nine percent of the patients had no formal education. Of the 41% who had formal education, 9% attained primary education, 14% attained middle or junior high school education, 10% attained secondary education and 8% attained college or tertiary education (8%). The average change in CD4 count lowered with increasing education; the average change was 582 counts for Junior high school or middle education, 563 counts for SHS and 435 for Patients with tertiary education.

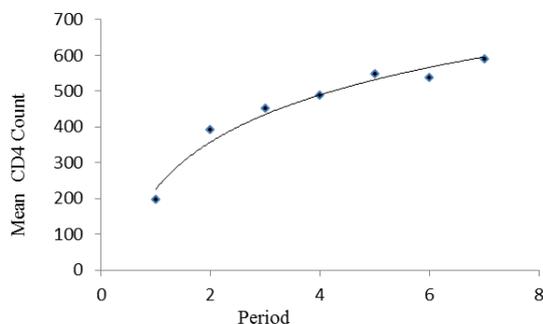
Forty-one percent of the patients (41%) were married, twenty-five percent were widowed, 21% divorced, 9% were single and 2% were separated. Divorced patients had the best mean CD4 change (564), followed by patients who were widowed (513) and patients who were separated (510): Patients who were single had the least mean change in CD4 count (499) followed by married patients (431).

A larger Percentage (77.8%) of the patients professed to be Christians with 11% professing to be Muslims and 6.67% traditionalist; Four percent of them do not belong to any religion.

Four types of treatment regimen were practised on the patients in the hospital: Thirty-six percent of the patients were issued CBV/NVP, twenty-seven percent were issued CBV/EFV, twenty percent took TDF/3TC/NVP and fourteen percent of the patients were also issued TDF/3TC/EFV.

### 3.1. The Trend of CD4 Count

Four models were assessed on their adequacy in describing the profile of the CD4 counts as shown in **Table 2**. The logarithmic model, which has the highest R<sup>2</sup> value (R<sup>2</sup> value = 0.9654), and therefore accounted for most of the variability in the data, was thus selected for the profile: The corresponding profile plot is shown in **Figure 1**. This model suggest that, even though the general pattern of the CD4 counts increased with time, the pattern increased at a decreasing rate.



**Figure 1.** Profile plot of CD4 count showing Logarithmic pattern

**Table 2. The Trend Model**

Assumed Model	Parameter estimates		R <sup>2</sup> value
Linear	$\alpha = 234.01$	$\beta = 55.804$	0.8284
Logarithmic	$\alpha = 225.39$	$\beta = 190.04$	0.9654**
Exponential	$\alpha = 241.2$	$\beta = 0.1472$	0.7121
Power	$\alpha = 229.83$	$\beta = 0.5231$	0.9043

Where  $\alpha$  = scale and  $\beta$  = slope parameters  
 \*\*Means highest variability accounted for

### Analysis of Variance (ANOVA)

The regression analysis on time, for the logarithmic trend model shown in the ANOVA table above (**Table 2**) shows that the trend model is very significant ( $p$ -value = 0.000). Particularly, the large value of the sum of squares and mean square error indicates that a large amount of the variability is accounted for by the logarithmic trend.

### Trend Model Diagnoses

The model was diagnosed to check for its adequacy as shown in **Table 4**. The Shapiro-Wilks test of normality indicated that the residuals of the model were normally distributed ( $p$ -value = 0.5524) while the Ljung-Box test shows that the model up to lag 2 is free from serial correlation ( $p$ -value = 0.2925). The ARCH-LM also indicates that the residuals were free from conditional heteroscedasticity ( $p$ -value = 0.5578). Hence the diagnostic test revealed that the model is adequate for the prediction of CD4 count.

**Table 3. Analysis of Variance**

Source	DF	SS	MS	F	P-value
Regression	1	101617	101617	139.69	0.000
Residual Error	5	3637	727		
Total	6	105255			

**Table 4. Trend model Diagnoses**

		DF	P-value
Shapiro-Wilks	W = 0.9302		0.5524
Box-Ljung test	Chi-Sq. = 4.9499	4	0.2925
ARCH-LM	Chi-Sq. = 3	4	0.5578

### 3.2. Profile Analysis

The pattern of change in CD4 counts over the period of observation by gender is shown in **Figure 2**. The profiles indicate that the average change in CD4 count for males and females are changing in about the same pattern over time. There appears not to be any significant differences in CD4 counts between the sexes until after the fourth period (2 years of treatment) when the Male CD4 count appear to be higher than that of the females. The MANOVA test for gender (**Table 5**) indicates that, there are no significant gender differentials.

**Table 5. MANOVA Test for Groups**

	Value	F Value	Num DF	Den DF	Pr >F
<b>Gender</b>					
Wilks' Lamda	0.9991	0.17	2	373	0.8432
Pillai's Trace	0.0009	0.17	2	373	0.8432
Hotelling-lawey T	0.0009	0.17	2	373	0.8432
Roy's Greatest T	0.0009	0.17	2	373	0.8432
<b>Marital Status</b>					
Wilks' Lamda	0.9757	2.32	4	373	0.0563
Pillai's Trace	0.0243	2.32	4	373	0.0563
Hotelling-lawey T	0.0243	2.32	4	373	0.0563
Roy's Greatest T	0.0243	2.32	4	373	0.0563
<b>Educational Attainment</b>					
Wilks' Lamda	0.9698	2.91	4	373	0.0217
Pillai's Trace	0.0302	2.91	4	373	0.0217
Hotelling-lawey T	0.0312	2.91	4	373	0.0217
Roy's Greatest T	0.0312	2.91	4	373	0.0217
<b>Treatment Regimen</b>					
Wilks' Lamda	0.9727	2.62	4	373	0.0351
Pillai's Trace	0.0273	2.62	4	373	0.0351
Hotelling-lawey T	0.0281	2.62	4	373	0.0351
Roy's Greatest T	0.0281	2.62	4	373	0.0351
<b>Religious Affiliation</b>					
Wilks' Lamda	0.9765	2.99	3	373	0.0309
Pillai's Trace	0.0235	2.99	3	373	0.0309
Hotelling-lawey T	0.0241	2.99	3	373	0.0309
Roy's Greatest T	0.0241	2.99	3	373	0.0309

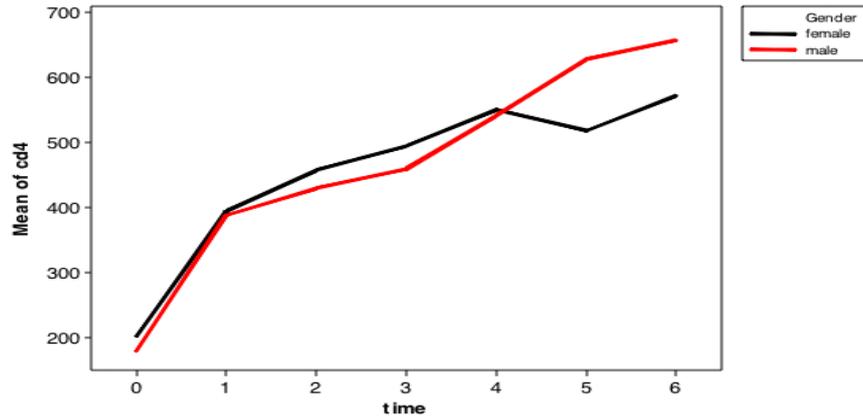


Figure 2. Means plot of CD4 count by gender

Figure 3 shows the average change in CD4 count by marital status. The profiles indicate that the average changes in CD4 count for all levels of marital status are changing in about the same pattern over time. There appears not to be any significant differences in CD4 counts among the various marital statuses until after the

fourth period (2 years of treatment) when Patients who are single, appear to be taking a consistently decreasing trend: All others, although fluctuating at times, show an increasing trend. The MANOVA Test for marital status in Table 5 indicates that the marital differentials are not statistically significant at the 5% significance level.

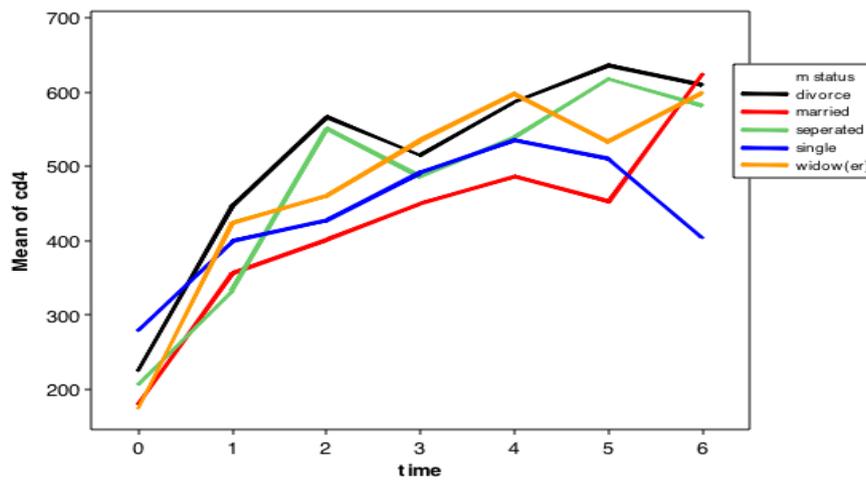


Figure 3. Profile plot of cd4 count by marital status

Figure 4, Figure 5 and Figure 6 show the change in CD4 count by educational level, treatment regimen and religion respectively, over time. The profiles for the various levels of education, apart from that for the patient

with Senior high School (SHS) level attainment, indicate a generally increasing trend with time: This suggests the profiles may not be parallel.

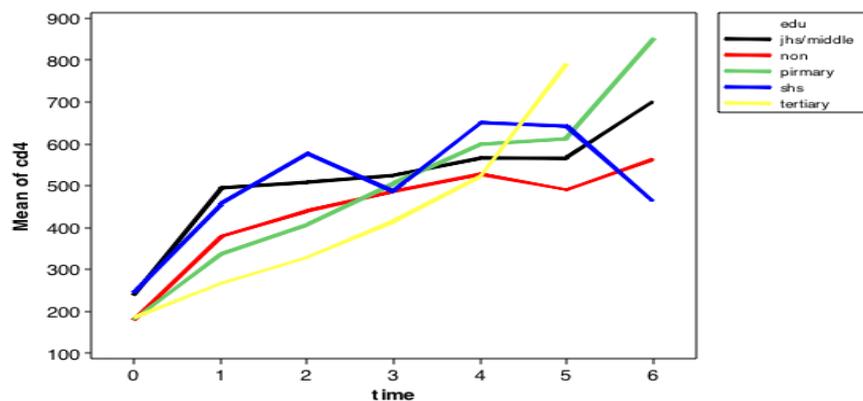


Figure 4. Profile plot of CD4 count by Educational level

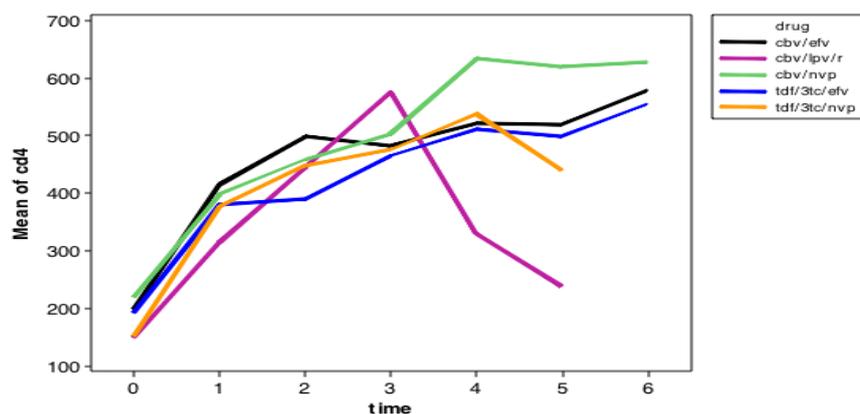


Figure 5. Profile plot of CD4 count by drug

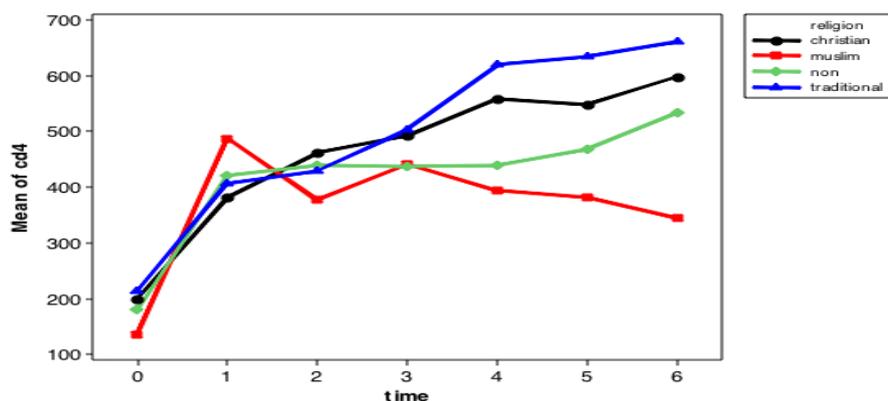


Figure 6. Profile plot of CD4 count by Religion

Similarly, while the profiles for all other drugs generally have an increasing trend with time, the profile for the Combivir/Lopinavir/Ritonavir (cbv/lpv/r) and Tenofovir/Lamivudine/Nevirapine (tdf/3tc/nvp) treatment regimens, although increasing in the initial stages, begin to fall after the third and fourth periods respectively (i.e. after one and a half years and two years of treatment respectively). This suggests that the profiles for treatment regimen may also not be parallel.

Again, all the religious groupings show that the average change in CD4 count of patients increases over time apart from the Islamic religion: This is shown in Figure 6. Worryingly, the Islamic religion shows a decreasing trend in the average CD4 count after the first period (i.e. after 6 months of treatment). The profiles for religious affiliations may thus not be parallel.

Results on The MANOVA test of Educational attainment, Treatment Regimen and Religious affiliation as shown in Table 5, confirm that the profiles for the levels of educational attainment, treatment regimen and religious affiliations, are significantly different at the 5 % significance level (P-Values < 0.05) and are therefore different in pattern. Consequently, each group cannot be identical at all of its levels. There are therefore educational, treatment regimen and religious differentials among the patients.

**Profile of CD4 count by Gender**

The test of parallelism for gender, shown in Table 6, is consistent with the MANOVA test and confirms that the pattern of change are not significantly different (P-Value of 0.5524 > 0.05) and can therefore be said to be the same

(parallel). The test of equality, shown in Table 7, confirm that, the parallel lines for the sexes are not significantly different (P-value of 0.4163 > 0.05) from each other and can therefore be said to be identical. Hence the change in CD4 counts by Gender, do not only follow the same pattern, but that they are exactly the same; thus there are not gender differentials.

Table 6. Test of parallelism for Gender

Source	Statistic	Df	F(df 1)	F (df 2)	F value	Pro>F
W	0.530	1	5	5	0.88	0.5524e
P	0.469		5	5	0.88	0.5524e
L	0.884		5	5	0.88	0.5524e
Residual	R	0.884	9	5	0.88	0.5524e

W= Wilks', Lamda, P = Pillai's Trace, L = Hotelling-lawey  
R =Trace Roy's Greatest Trace, e = exact, a = approximate, u = upper bound on F

Table 7. Test of Equality in Gender

Source	Statistic	Df	F (df 1)	F (df 2)	F value	Pro > F
W	0.9250	1	1	9	0.73	0.4163e
P	0.0740		1	9	0.73	0.4163e
L	0.0806		1	9	0.73	0.4163e
Residual	R	0.0806	9	1	0.73	0.4163e

The test of flatness, also shown in Table 8, confirms that the average CD4 count differed significantly with time (P-Value of 0.0111 < 0.05). CD4 count therefore does not remain the same over the period suggesting, as expected, that the treatment has an effect on the CD4

count. Thus while there are treatment effects, there are neither Gender effects, nor treatment Gender interactions.

**Table 8. Test for Flatness for Gender**

Source	Statistic	Df	F(df 1)	F (df 2)	F value	Pro > F	
W	0.403	1	5	15	4.44	0.0111e	
P	0.596		5	15	4.44	0.0111e	
L	1.479		5	15	4.44	0.0111e	
Residual	R	1.479	9	5	15	4.44	0.0111e

#### Profile plot of CD4 count by Marital Status

The test of parallelism for marital status is shown in Table 9. It is also consistent with the MANOVA test and shows that the seeming difference in the patterns of change in CD4 counts by Marital status, were not statistically significant at the 5% significance level (all P-Values > 0.05) and therefore the patterns cannot be said to be different. The test of equality, shown in Table 10, confirm that, the parallel lines for the Marital status are not significantly different (P-value of 0.7258 > 0.05) from each other and can therefore be said to be identical. Hence the change in CD4 counts by marital status, like that of Gender, do not only follow the same pattern, but that they are exactly the same; thus there are not significant Marital differentials.

**Table 9. Test of parallelism for marital status**

Source	Statistic	Df	F(df 1)	F (df 2)	F value	Pro > F	
W	0.105	4	20	17.5	0.86	0.6345a	
P	1.561		20	32	1.02	0.4644a	
L	3.436		20	14	0.61	0.8467a	
Residual	R	1.677	9	5	8	2.68	0.1035u

**Table 10. Test of level (Equality) for marital status**

Source	Statistic	Df	F (df 1)	F (df 2)	F value	Pro > F	
W	0.8132	4	4	9	0.520	0.7258e	
P	0.1868		4	9	0.520	0.7258e	
L	0.2296		4	9	0.520	0.7258e	
Residual	R	0.2296	9	4	9	0.520	0.7258e

The test of flatness, also shown in Table 11, confirms that the average CD4 count differed significantly with time (P-Value of 0.0111 < 0.05). Like that of Gender, CD4 count therefore does not remain the same over the period suggesting, as expected, that the treatment has an effect on the CD4 count. Thus while there are treatment effects, Marital Status has no effect neither are there any treatment and Marital Status interactions.

**Table 11. Test for Flatness for marital status**

Source	Statistic	Df	F (df 1)	F (df 2)	F value	Pro > F	
W	0.403	1	5	15	4.44	0.0111e	
P	0.596		5	15	4.44	0.0111e	
L	1.479		5	15	4.44	0.0111e	
Residual	R	1.479	9	5	15	4.44	0.0111e

## 4. Discussion

The results in this study indicate that generally, the pattern of the change in CD4 count for patients under ART is not only well described by the logarithmic model,

but that the logarithmic model better describes the change in CD4 profile than the linear model: Thus the change in CD4 count does not increase constantly with time but rather increases at a decreasing rate with time. This connotes that even though treatment remains effective, the effectiveness of the treatment decreased with time. Plausible factors for the decreasing effectiveness of treatment over time include the patient's failure to adhere to or be consistent in treatment [18,19,20], the virus' known ability to adapt to drugs thereby so far evading all attempts to find a cure to the disease [21], or the inherent failure of the drug or treatment procedure itself with time: It is therefore conceivable, at least theoretically, that over a long period of time, treatment will become ineffective. While the former can be addressed by educating and encouraging the patients as well as closely monitoring his or her therapy and drug intake, the latter two reasons underscore the need for regular review to ascertain the effectiveness of a treatment so as to enable possible change when a particular treatment is apparently failing.

The pattern of change did not differ significantly by gender or marital status and that, each level of gender and marital status had profiles that were identical in pattern and value to each other. The absence of gender-time and marital status-time interactions, as indicated by the parallelism of the profiles, indicate that patients responded to treatment in the same manner while the equality of the profiles indicate that the levels of response was also the same irrespective of patients gender or marital status. The lack of flatness indicate that treatment was effective

The presence of education and time, drug and time, as well as religion and time interactions, as shown by the absence of parallelism for educational, drug and religious status, shows that there are educational, drug and religious differentials in the effectiveness of treatment: At least one level of educational, drug and religious status differed from the others. Consequently, the levels, for each of these covariates, are not identical. These results are consistent with [13,14].

## 5. Conclusion

Generally all the patients that were considered in our study between January 2008 and December 2012 had their CD4 count increased at different levels after being put on treatment at a certain initial CD4 count. The overall mean CD4 count was 488 cell/ $\mu$ l. The profiles of CD4 growth by gender and marital status were parallel and equal but deviated from flatness. The growth profile in CD4 count however appeared better for patients with tertiary education than those with other levels of education. The logarithmic trend observed, indicates the failing effectiveness of treatment. It may therefore be clinically insightful to study whether consistency in treatment will affect this trend.

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