Global Scientific JOURNALS

GSJ: Volume 9, Issue 5, May 2021, Online: ISSN 2320-9186
www.globalscientificjournal.com

Modeling the Effects of Nutritional Withdrawal on CD4 Cell Count Among HIV/AIDS Patients Using Generalized Estimating Equations (GEE).

Samuel Redeemer Adornyo

Affiliation Model: Department of Mathematics and ICT, Methodist College of Education, Akim Oda, Ghana

Corresponding Author: Samuel R. Adornyo; Methodist College of Education, PMB, Akim Oda. Ghana. samueladornyo@gmail.com

ABSTRACT:

Background: HIV positive patients on antiretroviral (ARV) drugs requires increased calories to realize the full potential of their treatment. Therefore, nutritional intervention programs for People Living with HIV/AIDS (PLWHA) is a great relief to secure the nutrition insecurity of individuals receiving antiretroviral drugs. This study aims to examine the withdrawal effects of the nutritional intervention on CD4+ cell counts and model the effects of body mass index (BMI), blood hemoglobin levels (HB) on CD4+ cell counts before, during and after the initiation of the intervention among PLWHA.

Methods: The analysis was performed using data from a retrospective cohort study of 501 PLWHA who started ART from 2007 to 2011. Generalized Estimation Equations (GEE) was used to model the CD4+ cell counts before, during and after the initiation of the intervention. The technique based on repeated measurement within subjects, allows for modeling the within-subject variability. The quasi-likelihood method of estimation was adapted. The Autoregressive working correlation structure was use to account for correlation over time.

Results: There was a positive correlation between the HB levels of the HIV/AIDS patients and their CD4+ cell counts. There was an inverse relationship between age of patients and CD4 cell counts. The nutritional intervention positively influences the health indices of PLWHA during the intervention. The mean CD4+ cell count improved from 223.19cells/µL to 367.44cells/µL during the intervention. The withdrawal of the nutritional intervention decreases on the average CD4 cell count from 367.44cells/µL to 356.95cells/µL. BMI predicts a positive CD4+ cell count of patients. During nutritional intervention, patients gain weights and this improve on the CD4+ cell counts.

Contribution: The model strongly predicts the linear interaction of HB and time, suggesting the corresponding larger increase in the mean CD4 cell count. The withdrawal resulted in an average reduction of 172.88 cells/µL in the CD4 cell count.

Keywords: Cluster of differentiation 4 (CD4), Acquired Immunodeficiency Syndrome (AIDS), Generalized Estimating Equations (GEE), Generalized Linear Models (GLM), Human Immunodeficiency Virus (HIV), Longitudinal Data, Working Correlation Assumptions.

1. Introduction

Good nutrition is key to maintaining strength, energy, and a healthy immune system. It is little wonder that many studies all over the world have shown that poor nutritional status is highly associated with immunologic damage and adverse health out-comes among people infected with HIV.[1] Therefore, researches have noted that nutritional support can reasonably contribute to the clinical success of HIV programs thereby improving the general health condition and quality of life of people living with HIV/AIDS. Nutritional cares therefore are essential for the clinical success of HIV programs (ART) especially started in developing countries. It is on this score that nutritional interventions for PLWHAs, such as that of the Opportunities Industrialization Centres International (OICI), provided enhanced care and management of the disease. OICI was a donor organization in Ghana that used to provide nutritional support to orphanages and people living with HIV/AIDS. Key institutions that benefited from this nutritional support were; Bomso Clinic, SDA Hospital, Kwadaso, Bekwai Government Hospital, Adom HIV/Management Association, Step by Step Orphanage Centre and Liberty Foundation. Some PLWHAs who were put on the OICI nutritional intervention however were later withdrawn.

CD4+ T lymphocyte (CD4) cell counts is an important indicator of HIV progression since HIV/AIDS infects CD4 cells, CD4 count gives an immunologically significant measure for HIV/AIDS progression. The administration of ART for PLWHAs; where nutritional cares and supports form an integral part, is known to significantly increase CD4 count and thereby enhancing the immunity state of patients.

The peculiar nature of the withdrawal of the nutritional support and the rate at which the withdrawal could affect the CD4+ T lymphocyte (CD4) cell counts of people living with HIV/AIDS who were on the intervention led this research on the withdrawal effects of the nutritional interventions on the health outcome of PLWHA in Kumasi.

This study used Generalized Estimating Equations (GEE) to model CD4+ cell counts before, during and after the initiation of the intervention, given BMI and HB levels of PLWHA. The technique based on repeated measurement within subjects, allows for modeling the within-subject variability. The quasi-likelihood method of estimation was adapted. The autoregressive working correlation structure was used to account for correlation over time.

2. Purpose

This study seeks to examine the health outcomes of PLWHA before, during and after they were put on nutritional support. The study however has these two specific objectives:

a. to examine the withdrawal effects of the nutritional intervention on CD4+ cell counts
b. model the CD4+ cell counts before, during and after the initiation of the intervention, given BMI, HB levels and other characteristics of PLWHA, using Generalized Estimating Equations (GEE).

3. Methodology

Generalized Estimation Equations (GEE) was used to model the CD4+ cell counts before, during and after the initiation of the intervention. The technique based on repeated measurement within subjects, allows for modeling the within-subject variability. GEE factors Marginal Models for Longitudinal Data for the study. The quasi-likelihood method of estimation was adapted. The Autoregressive working correlation structure was used to account for correlation over time.

Analyses were conducted using STATA, version 12.1 (StataCorp LP, College Station, TX) and SAS (release 9.4) with significance level of $\alpha = 0.05$.

3.1 Data Source and Sample

The study population consisted of HIV-Positive patients above 18 years who had initiated ART between 2007 and 2011 and were receiving health care at the S.D.A hospital's Chronic Care Centre, Kwadaso, and the Bomso Clinic, Bomso, all in the

Ashanti Region of Ghana. A sample size of 501 was selected for the study which includes 490 PLWHA, and 11 health workers (8 counsellors, and 3 Nutrition Officer).

3.2 Variables.

CD4 cell count (cells/µL) with repeated measurements; before, during and after the food supplement intervention, linear time effect of BMI, linear time effect of HB level and age at the start of the study are other variables. The period within which respondents were not on any intervention was coded GROUP 1 (G1). The period when the intervention was introduced was coded GROUP 2 (G2) and the period of after the intervention was classified as GROUP 3 (G3).

Response Variable: CD4+ cell count (cells/µL) is the outcome or response variable in this study.

Covariates: The covariates for this study are listed below:

I. Age in years (at start of ART)
II. Hb*time (Linear interaction between Hb and time)
III. BMI*time (Linear interaction between BMI and time)
IV. G1
V. G2
VI. G3

4. Models Used for the Analysis:

[2,3] extended the generalized linear model to allow for correlated observations since there exit correlations between observations on a given subject. This extension is

referred to as Generalized Estimating Equations (GEE) model. The GEE model makes use of the Quasi-likelihood which specifies only the first two moments, mean (u) and variance v(u). The Quasi-likelihood also specifies a link function g(u) which links the mean to a linear predictor. Therefore, GEE model was adopted to cater for correlations between observations and to avoid underestimating standard errors for the between-subjects and overestimating the standard errors for the within-subjects.

GEE Model

Let y_i be the outcome on the subject Y with $y_i = (y_{i1}, y_{i2}, ..., y_{iT_i})'$ and $\mu_i = (\mu_{i1}, ..., \mu_{iT_i})'$, then $\mu_{it} = E(Y_{it})$ and a variance function of Y; $\upsilon(\mu_i)$.

Let $A_i = n \times n$ be an diagonal matrix with $V(\mu_{ij})$ as the jth diagonal element.

Define $R_i(\alpha) = n \times n$ working correction matrix of the *n* repeated measures. The working variance-covariance matrix for y_i equals $V(\alpha) = \phi A_i^{1/2} R_i(\alpha) A_i^{1/2}$; where $V(\alpha) = \phi R_i(\alpha)$ for normally distributed outcomes.

The GEE estimator of β is the solution of $\sum_{i=1}^{N} D_i' \left[V(\hat{\alpha}) \right]^{-1} \left(y_i - \mu_i \right) = 0$; where $\hat{\alpha}$ is a consistent estimate of α and $D_i = \partial \mu_i / \partial \beta$. In the normal case,

$$\mu_i = x_i \beta, \quad (1)$$

$D_i = X_i$, $V(\hat{\alpha}) = \phi R_i(\hat{\alpha})$, $\sum_{i=1}^{N} X_i' \left[R_i(\hat{\alpha}) \right]^{-1} \left(y_i - X_I \beta \right) = 0$ and

$$\hat{\beta} = \left[\sum_{i=1}^{N} X_i' \left[R_i(\hat{\alpha}) \right]^{-1} X_i \right]^{-1} \left[\sum_{i=1}^{N} X_i' \left[R_i(\hat{\alpha}) \right]^{-1} y_i \right].$$

The estimate of β is calculated iteratively by the reweighted Least-Squares, given $R_i(\alpha)$ and ϕ. The estimates calculated are quasi-likelihood because the solution depends on the mean and variance of y. The estimates of β and the Pearson residuals are used to consistently estimate α and ϕ. The Pearson residuals are calculated by;

$$r_{ij} = \frac{\left(y_{ij} - \hat{\mu}_{ij}\right)}{\sqrt{\left[V(\hat{\alpha})\right]_{jj}}} \qquad (2)$$

The square root of the diagonal elements yield the standard errors of $\hat{\beta}$; $V(\hat{\beta})$ There are two types of $V(\hat{\beta})$ in GEE;

i. Naive or "Model-based" Estimator

$$V(\hat{\beta}) = \sum_{\text{i}} \left[D_i^{'} V_i^{-1} D_i) \right] \qquad (3)$$

ii. Sandwich or "Empirical" or Robust Estimator

$$V(\hat{\beta}) = M_0^i M_i M_0^{-1} \;; \qquad (4)$$

where

$$M_0 = \sum_i^N D_i^{'} \hat{V}_i^{-1} D_i \text{ and } M_1 = \sum_i^N D_i^{'} \hat{V}_i^{-1} \left(y_i - \hat{\mu}_i\right)\left(y_i - \hat{\mu}_i\right)^{'} \hat{V}_i^{-1} D_i .$$

When $\hat{V} = \left(y_i - \hat{\mu}_i\right)\left(y_i - \hat{\mu}_i\right)^{'}$, the model-based and the empirical estimates becomes equal. This is achieved when a correct working correlation structure is specified. The empirical estimator gives a consistent estimator of $V(\hat{\beta})$ even if the working correlation structure is wrongly specified.

The following are the major correlation structure that can be specified:

i. Independent correlation structure assumes that correlation between time points is independent. $R_{u,v} = 1$ if $u = v$, othewise $= 0$.

$$\begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

ii. Exchangeable correlation structure is specified when the within subject observations are equally correlated.

$$R_{u,v} = 1 \text{ if } u = v, \text{othewise } = \rho_{jj'} . \begin{pmatrix} 1 & \rho & \rho \\ \rho & 1 & \rho \\ \rho & \rho & 1 \end{pmatrix}$$

iii. Autoregressive correlation structure is specified when repeated measures are mostly strongly correlated when close together in time and least correlated when furthest apart in time.

$$R_{u,v} = 1 \text{ if } u = v, \text{othewise } = \rho^{|u-v|} . \begin{pmatrix} 1 & \rho & \rho^2 \\ \rho & 1 & \rho \\ \rho^2 & \rho & 1 \end{pmatrix}$$

iv. Unstructured structure is specified when no constraints are placed on correlations. $R_{u,v} = 1$ if $u = v$, othewise $= \rho_{u,v} . \begin{pmatrix} 1 & \rho_{12} & \rho_{13} \\ \rho_{21} & 1 & \rho_{23} \\ \rho_{31} & \rho_{32} & 1 \end{pmatrix}$

GEE Model Parameters (Definitions)

Regression Parameters (*β*): The regression parameters express the relationship between the covariates and the outcome variable. For the analysis of this study, only the regression parameters are of primary interest.

Correlation Parameters (*α*): They express the within-cluster correlations of the response variable. This is achieved by the specification of a correlation structure.

These parameters are considered as nuisance parameters and are not of primary interest even though they add to the accuracy of the model

Scale Factor (ϕ): this parameter accounts for the extra variation of the response variable Y. The variation can be an under dispersion or overdispersion. It assumes 1 or estimated from the data.

The GEE Model for the study

The Generalized Estimating Equations model for this study is given by;

$$Y_{ij} = \beta_0 + \beta_1 G1 + \beta_2 G2 + \beta_3 G3 + \beta_4 age + \beta_5 BMI \times t_{ij} + \beta_6 HB \times t_{ij} + \varepsilon_{ij}$$
$$i = 1, 2, ..., n \quad \text{j=1,2,3 and } \varepsilon_{ij} \sim N(0, I_n \sigma^2) \tag{5}$$

$$E(Y_{ij}) = E(\beta_0 + \beta_1 G1 + \beta_2 G2 + \beta_4 Age + \beta_5 BMI \times t_{ij} + \beta_6 HB \times t_{ij} + \varepsilon_{ij})$$
$$\hat{Y}_{ij} = \hat{\beta}_0 + \hat{\beta}_1 G1 + \hat{\beta}_2 G2 + \hat{\beta}_3 G3 + \hat{\beta}_4 Age + \hat{\beta}_5 BMI \times t_{ij} + \hat{\beta}_6 HB \times t_{ij}$$

Where G1, G2 and G3 are Group 1 (No intervention), Group 2 (Intervention) and Group 3 (After Intervention) respectively.

Pearson Chi-Square Goodness of fit Test

For a generalized estimation equations model with y_i as the responses, weights w_i, fitted means $\hat{u}_i$, variance function v(μ) and dispersion ϕ, the Pearson goodness of fit statistic is;

$$X^2 = \sum \frac{w_i \left(y_i - \hat{\mu}_i \right)^2}{v(\hat{\mu})} \quad . \tag{6}$$

If the model is fitted correctly, $X^2 \sim \chi^2$ with the model's residuals degrees of freedom.

5. Results

Table 1 describes the study population's characteristics (n=501). The mean age was 35 years and the minimum age was 20 years. The maximum age was found to be 61 years. Thirty-five (35) years was the most frequent age of the respondents. A total of 501 patients were observed and their CD4+ cell counts measured from the start of ART, during the food supplement intervention and after patients were taken off the food supplement intervention. The mean CD4+ cell counts over each time period is as indicated in Table 1. The minimum CD4+ cell counts before the food supplement intervention is 1 (cells/µL) whilst and the maximum CD4+ cell count was 1068 cells/mm^3.

Table 1: Age and CD4+ Cell Count Characteristics of PLWHA

Variable	Obs	Mean	Std. Dev	Min	Max
Age	501	35.325	8.077	20	61
CD4 Counts Before Intervention (cells/µL)	501	223.190	156.476	1	1068
During Intervention (cells/µL)	501	367.443	154.423	10	1391
After Intervention (cells/µL)	501	356.946	139.667	70	1300

Ignoring the variations in CD4+ counts, the average CD4+ count of PLWHA increased from 223.1 (cells/µL) before the intervention to 367.4 (cells/ L) during the intervention and decreased substantially to 356.9 (cells/ L) after the intervention. The minimum CD4 +cell count now rose from to 1 (cells/ L) to 10 (cells/ L) and finally to 70 (cells/ L) and the maximum CD4+ cell count also increased from 1068 (cells/ L) to 1391 (cells/ L) and to 1300 (cells/ L) after the food supplement intervention. These results indicate that the food supplementation positively affected the CD4+ cell counts of respondents that were put on it and each one had their CD4+ cell count increased during the intervention.

The correlation structure is illustrated in **Table 2**. Correlation between CD4+ cell count before and during was highly significant and the CD4+ cell counts have a correlation that is very high for observations close together in time. The correlation however tends to reduce with increasing time separation between the CD4 counts. That is to say that, there is a correlation between CD4+ cell counts but this correlation weakens with distance between measurements. Hence, although an HIV-infected patient's CD4+ cell count de-pended on his/her past CD4+ cell count, the strength of the relationship was much stronger with immediate CD4+ cell count and vice versa.

Table 2: Correlation matrix on Repeated CD4+ cell counts

	CD4B	CD4D	CD4A
CD4B	1		
CD4D	0.8068	1	
CD4A	0.7451	0.8424	1

BMI Characteristics of HIV-Infected Patients are summarized in **Table 3**. The mean BMI of respondents was 18.9 kg/m^2 before the intervention but it in-creased to 23.6 kg/m^2 during the intervention and reduced to 20.5 kg/m^2 after the withdrawal of the intervention. This means that the nutritional status of respondent improved significantly during the food supplementation. The nutritional status of the PLWHA that were put on the intervention however decreased by a mean BMI of 3.13 kg/m^2. Descriptive Statistics on nutritional status; defined as BMI (Categories) are displayed in the tables below.

Table 3: BMI Characteristics of HIV-Infected Patients

Variable	Obs	Mean	Std. Dev	Min	Max
BMIB	501	18.948	2.533	.000048	26.5625
BMID	501	23.62703	2.456781	14.67876	31.99217
BMIA	501	20.49984	2.7808777	.000048	29.6875

The mean hemoglobin level of respondents increased during the intervention is shown in Table 4. The mean HB level of respondent increased significantly from 9.58 g/dl before the food intervention to 10.86 g/dl during the food supplementation. However, there was a slight decreased in the average hemoglobin level of respondent after the intervention.

Table 4: HB Characteristics of HIV-Infected Patients

HB (g/dl)	Mean	Std. Err	Min	Max
Before	9.577	1.630	3.3	16
During	10.857	1.458	7	17.9
After	10.405	1.278	7	17.0

Generalized Estimating Equations Model

Table 5 indicates the correction matrix. From the results, the correlations decrease over time as assumed by AR (1) working correlation and are similar to the correlation of the observed.

Table 5: AR (1) Correlation Matrix

	CD4B	CD4D	CD4A
CD4B	1.0000	0.8433	0.7112
CD4D	0.8433	1.0000	0.8433
CD4A	0.7112	0.8433	1.0000

From the **Table 6** below, the AR (1) parameter is 0.8236 which shows the AR (1) correlation structure is accurately specified.

Table 6: Covariance Parameter Estimates

Cov Parm	Subject	Estimate
AR (1)	ID	0.8236
Residual		19368

The empirical standard errors and model based standard errors (**Table 7**) are similar, indicating that the working correlation structure is adequate. G1, G2, age, HB*time and BMI*time were all statistically significant. The type 3 analysis is for testing the significance of the group effects. It indicates the p-values for the null hypothesis that there are no effects of Group (G1 and G2), age, HB*time and BMI*time on the CD4 cell counts of the HIV/AIDS patients.

Table 7: GEE Naive (Model-Based) Standard Error Estimates

Parameter	Estimate	Standard Error	95% Conf.	Limits	Z	**Pr > |Z|**
Intercept	-172.887	45.2350	-261.546	-84.2278	-3.82	0.0001
Group 1	272.8647	26.1064	221.6970	324.0323	10.45	< 0.0001
Group 2	182.1614	11.0217	160.5593	203.7634	16.53	< 0.0001
Group 3	0.0000	0.0000	0.0000	0.0000	.	
Age	-1.6534	0.7220	-3.0685	-0.2382	-2.29	0.0220
Hb*time	15.9896	1.0077	14.0146	17.9646	15.87	< 0.0001
BMI*time	1.5029	0.3874	0.7436	2.2622	3.88	0.0001
Scale	140.8382	.	.	.	.	.

From **Table 8**, the effect of Group, age, HB*time and BMI*time were also significant at the level of 0.05.

Table 8: Score Statistics For Type 3 GEE Analysis

Source	DF	Chi-Square	P r > ChiSq
Group	2	224.39	< 0.0001
Age	1	4.65	0.0310
Hb*time	1	67.49	< 0.0001
BMI*time	1	14.11	0.0002

Thus, the resulting equation for the GEE model is;

CD4 Cell Count = - 172.887 + 272.8647G1 + 182.1614G2 – 1.6534Age + 15.9896Hb*time + 1.5029BMI*time.

There was an average reduction of 172.887 cells/ L in the CD4 cell counts of respondents after the withdrawal of the nutritional intervention, holding all other variables constant. There is an inverse relationship between the age of respondents and their CD4 cell counts. An increase in the age of respondents is associated with a 1.6534 cells/ L decrease in the mean CD4+ cell counts of respondents.

Again, there was an average 15.9896 cells/ L increase in CD4 counts of respondents with every unit increase in their HB level. An increased in BMI of the HIV/AIDS patients result in an increase of 1.5029 cells/ L of the average CD4 cell count of respondents, holding all other variables constant. Also, the estimate of G1 (the contrast of G3 and G1) is 90.7033 larger than the estimate of G2 (the contrast of G3 and G2) meaning there was a significant increment in the average CD4 cell counts of respondents during the intervention.

6. Discussion

6.1 Characteristics of the Study Population

HIV/AIDS is no respecter of age even though the sexually active age groups of both sexes (male and female) are the most affected. The average age of the respondents was 35 years in this study. This age group falls within the projected range of 15-49 years of adult population in Ghana that is largely affected by the HIV/AIDS. [4]

Females are known to be more susceptible to HIV/AIDS a trend which shows that young women and adolescent girls are disproportionately vulnerable and at high risk. [5] The findings of this study revealed a consistent trend with majority (60%) of the PLWHAs were females.

6.2 Effect on the nutritional support on the outcome of the PLWHA

BMI was found to be a significant predictor of CD4 cell count and it predicts greater gains in CD4+ cell counts. This finding is in contrast to the results in the (6) study, which indicated that obese patients have smaller CD4+ cell count gains.

The significance of the linear interaction of BMI and time on the CD4 cell counts of respondents signifies the importance of the food supplementation intervention for the clinical success of HIV programs started in the country. The mean BMI of respondents was 18.9 before the intervention but it increased significantly to 23.6 during the intervention. There was a reduction in the mean BMI of respondents of 3.1 after the withdrawal of the intervention. The reduction can reduce the length of survival of patients since wasting assessed by reduced BMI is associated with an increased risk for death among both men and women.[7]

It was also discovered that majority (cum. freq of 97%) of respondents tend to have normal nutrition and overweight and obese during the intervention; ac-cording to the established classification of BMI. This can be compared with the cumulative frequency of 52.9% of respondents with normal nutrition and over-weight classification before the intervention.

Since appropriate enhancement in nutritional status of PLWHA helps boost their immune system, manage the frequency and severity of symptoms and promote good responses to medical treatment [8], there was an increase in the mean CD4+ cell count during the intervention.

CD4+ T lymphocyte (CD4) cell counts is an important indicator of HIV progression since HIV/AIDS infects CD4 cells, CD4 count gives an immunologically significant measure for HIV/AIDS progression. The administration of ART for PLWHA; where nutritional cares and supports form an integral part, is known to significantly increase CD4 count and thereby enhancing the immunity state of patients.

The study showed that there was a significant reduction in CD4 cell count of respondents after the intervention.

Also, an HIV-infected patient's CD4+ cell count depended on his/her past CD4+ cell count, the strength of the relationship was much stronger with immediate CD4+ cell count and vice versa. This suggests that a higher initial CD4+ cell count would result in a better rate of recovery of HIV-infected patients on ART. This is consistent with findings of [9].

The study showed that the linear interaction of HB and time is strongly associated with CD4 cell count. An increase in the HB of respondents causes a larger increase in the mean CD4 cell count of respondents. This positive correlation between the blood hemoglobin level of respondents and their respective CD4 cell counts confirms the findings of other studies [10] in the past.

The study confirmed the inverse relationship between age and CD4 cell counts of HIV/AIDS patients. Younger HIV/AIDS patients have a higher CD4 cell counts and the older an HIV/AIDS patient gets the lower his/her CD4 cell counts. This inverse correlation is consistent with other works.

6.3 Conclusion

The nutritional intervention positively affected the health outcomes of PLWHA during the nutritional intervention. After the intervention however, there was a significant reduction in the average CD4 cell count of respondents. BMI predicts a positive gain in CD4+ cell count of respondent and there was a positive correlation between the blood hemoglobin levels of the

HIV/AIDS patients and their CD4 cell counts. There was an inverse relationship between age and CD4 cell counts of HIV/AIDS patients. The increasing effect of the nutritional intervention on the outcome of PLWHA sets the tone for consistent provision of nutritional interventions for PLWHAs.

7. References

1. E. Liu, D. Spiegelman D, H. Semu, C. Hawkins, G. Chalamilla, A. Aveika, S. Nyamsangia, Mehta, D. Mtasiwa, W. Fawzi. Nutritional status and mortality among HIV-infected patients receiving antiretroviral therapy in Tanzania. J Infect Dis. 2011 Jul 15;204(2):282-90. doi: 10.1093/infdis/jir246. PMID: 21673040.
2. K. Y. Liang, & S. L. Zeger, (1986). Longitudinal data analysis using generalized linear models. Biometrika, 73(1), 13-22. https://doi.org/10.1093/biomet/73.1.13
3. S. Zeger, & K. Liang, (1986). Longitudinal Data Analysis for Discrete and Continuous Outcomes. Biometrics, 42(1), 121-130. doi:10.2307/2531248
4. GAC (2013). Ghana aids commission accessed January 2015.
5. UNAIDS (2014). Jc2656 (English original, July 2014, updated September 2014) ISBN 978-92-9253-062-4.
6. N.F Crum-Cianflone, M. Roediger, L.E. Eberly, (2010). Infectious Disease Clinical Research Program HIV Working Group. Obesity among HIV-infected persons: impact of weight on CD4 cell count. AIDS;24:10691072.[PubMed]
7. E. Mupere, L. Malone, S. Zalwango, A. Chiunda, A. Okwera, I. Parraga, C. Stein, J. Tisch, R. Mugerwa, W. Boom, H. Mayanja, and C. Whalen. (2012). DOI: http://dx.doi.org/10.1016/j.annepidem. 2012.04.007

8. S. N. Obi, N. A. Ifebunandu, A. K. Onyebuchi. Nutritional status of HIV-positive individuals on free HAART treatment in a developing nation. J Infect Dev Ctries. 2010 Nov 24;4(11):745-9. doi: 10.3855/jidc.863. PMID: 21252453.
9. V. D. Lima, V. Fink, B. Yip, R. S. Hogg, P. R. Harrigan, J.S. Montaner. Association between HIV-1 RNA level and CD4 cell count among untreated HIV-infected individuals. Am J Public Health. 2009 Apr;99 Suppl 1(Suppl 1): S193-6. doi: 10.2105/AJPH.2008.137901. Epub 2009 Feb 12. PMID: 19218172; PMCID: PMC2724944.
10. C. Obirikorang, F. A. Yeboah, (2009). Blood haemoglobin measurement as a predictive indicator for the progression of HIV/AIDS in resource-limited setting. Journal of Biomedical Science, 16(1), 102. http://doi.org/10.1186/1423-0127-16-102