

Effect of Antiretroviral Therapy on Selenium Level And Estimated Glomerular Filtration Rate Of HIV Patients In Yenagoa, Nigeria.

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Abstract: In humans, low CD4 count, chronic kidney failure and HIV infection are common incidence in Nigeria; however, selenium deficiency is not commonly prevalent across the country due to its variations in soil contents in the different geographical areas. A cross-sectional assessment of serum selenium level, CD4 count and eGFR status of HIV positive treatment naïve and HIV infected people on ART were done. Individuals on ART and treatment naïve were recruited. Subjects with diabetes mellitus, hypertension and age less than 18 and older than 60 years were excluded. Serum creatinine levels were determined to calculate the eGFR using Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI). Height and weight were measured to calculate the BMI and serum selenium and CD4 counts determined. There was significant negative correlation between eGFR status and BMI ($r = -0.181$, $p = 0.027$). The correlation between eGFR status and CD4 counts levels was not significant ($r = 0.073$; $p = 0.445$). eGFR status and selenium levels had very significant negative correlation ($r = -0.870$; $p = 0.000$). A weak negative correlation ($r = -0.055$; $p = 0.226$) was observed between BMI and CD4 counts, BMI and creatinine levels showed a positive correlation ($r = 0.213$; $p = 0.009$). There is a lucid relationship between the parameters so assayed in the HIV infected people. The negative correlation between eGFR status and BMI with significant difference show that muscle wasting among HIV infected people may have affected the eGFR status and BMI. Positive correlation between BMI and creatinine levels suggest that HIV infection inflicts direct assault on the kidney. The strong negative correlation between eGFR status and selenium levels is suggestive of the crucial role kidney play in the homeostasis of selenium levels in the body.

Keywords: Selenium, CD4 Cell, eGFR, human Immunodeficiency virus and antiretroviral therapy

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I. Introduction

The prevalence of HIV/AIDS is a major issue in developed and developing countries especially in sub-Saharan Africa. Nigeria due to its high population is rated second largest HIV disease burden in the world with 3.2 million people living with HIV (PLWHIV) after South Africa which has 6.8 million burden of the disease, however the prevalence of HIV has been constant at 3.4% with the introduction of antiretroviral drugs[1].

Major advances in HIV care, particularly the widespread implementation of antiretroviral therapy (ART), have improved survival and decreased rate arising from opportunistic infections worldwide [2]. With these advances, non-infectious causes of mortality such as cardiovascular, liver, and kidney disease have become more common sources of morbidity and mortality among HIV-infected patients in both high- and low-income countries [3]. Studies from several countries in sub-Saharan Africa have demonstrated a high prevalence of renal dysfunction in HIV infected individuals, reporting that 34% to 77% of patients have estimated glomerular filtration rates (eGFRs) ,90 ml/min/ 1.73 m² [4–6]. HIV-infected patients are at increased risk of premature comorbidities as a consequence of their HIV infection and the metabolic complications of ART combination; they have a nearly four-fold likelihood of developing renal disease compared to those without HIV[2] These findings were concerning given reports that renal dysfunction is associated with increased hazard of death among HIV infected patients initiating ART [5,7]. Several studies have followed patients for up to 12 years and demonstrated that baseline renal dysfunction improves after ART initiation in HIV infected patients, regardless of which ART regimen is used [8–11]. Others have reported no significant improvement and/or ongoing renal decline with similar follow-up periods, regardless of etiology of renal dysfunction or virologic suppression [12–14], though virologic suppression did appear to attenuate the rate of decline [15]

Incurrent clinical practice, the kidney function is assessed by the estimation of the glomerular filtration rate (eGFR)considered as the best overall indicator. ART is known to decrease the risk of renal disease in HIV

patients by 46% compared to naïve patients, however some treatments or boosted agents as part of ART regimens have been associated with renal impairment [3]

Furthermore, study [16] (Porter & Sutliff, 2012) have implicated the use of ART as a potential contributor to increase in reactive oxygen species. Increase in oxidative stress may worsen disease progression and increase HIV replication [17].

Selenium is an essential micronutrient that has been widely associated with vital role in HIV infection, due to its involvement in regulating oxidative stress and more so, selenium proteins have been shown to be a potent regulator in both NF- κ B activity and transcription of HIV. Selenium is also an essential factor in maintaining host immune competence, and it has been shown that optimal level decreases host suitability to viral pathogenesis [18, 19]. Most HIV infected persons are withdrawn or could not easily access the ART centers due social, emotional, psychological and financial constraints with the resultant increased HIV related diseases progression and death. This has probably affected their nutritional status and immune system as a result of limited resources to buy the needed food items, difficulty in eating food or malabsorption and malnutrition [20, 21], with the attendant decrease in certain essential micronutrients such as selenium in the body. There is paucity of information on the relationship of selenium, CD4 cell and renal status of patients on ART in Bayelsa. This study, therefore, assesses the magnitude of the changes in the study parameters that may be detected in the HIV infected as compared to the control group which is comprised of HIV uninfected individuals living in this study population.

II. Materials And Method

2.1. Study Design

This is a cross-sectional comparative study where the subjects include both female and male within the age bracket of 18 to 60 years. The total of 200 HIV infected subjects and 50 HIV negative control individuals were recruited for the study. Of the 200 subjects, 150 individuals are subjects who are on ART drugs and 50 individuals are ART naïve subjects. The age range was 18 – 60 years.

2.2. Ethical Considerations

The ethical clearance and experimental protocol were approved by the Ethics Committee of the Diete Koki Memorial Hospital, Opolo as attached in the appendix. Also, informed consent was obtained from all subjects through counseling and questionnaires. All subjects recruited for this study gave a written consent to be tested for HIV infection.

2.3 Selection Criteria

The subjects recruited for this study duly gave consent and within the age brackets of 18 to 60 years old. Only subjects that tested positive to HIV infection and those that were sero-negative to HIV antibodies were selected for the study. The HIV negative subjects constituted the controls, whereas HIV positive subjects were the experimental group. Both males and females were accepted for the study. Subjects on selenium therapy and the ones with history or with kidney disease or any chronic diseases such as TB and diabetes mellitus were excluded from the study. Smokers and/or alcohol consumers were also excluded, as well as pregnant women.

2.4 Collection of Samples

Five milliliters (5ml) of venous blood were collected from each subject through venipuncture, with 3ml dispensed into plain and 2ml into EDTA containers. The blood samples in the plain containers were allowed to clot. The sample was then centrifuged and the supernatant extracted into a sterile container for the laboratory analysis. Where the estimation was not carried out immediately the labeled serum sample was stored at minus 20°C for subsequent measurement.

2.5.1. HIV Testing

The HIV status of the study population was determined by immuno-chromatographic method. The brands include: Alere Determine (Alere Medical Co. Ltd. 2016), Trinity Biotech Uni-Gold (Trinity Biotech, 2016) and HIV 1/2 STAT-PAK (Chembio Diagnostics Systems, 2016).

2.5.2 Determination of Serum Creatinine, selenium and CD4 cell

Serum creatinine was analyzed using the ELITECH Clinical Systems Creatinine PAP SL Method (ELITECH 2016) using Selectra Pro S Clinical Chemistry Analyzer (Elitech Group Clinical Systems), While Selenium was determined by Agilent FS240 Atomic Absorption Spectrophotometer. The Partec CyFlow® Counter fully equipped portable Flow Cytometry System (FCM) was used in the identification and the enumeration of CD4 helper/inducer T-lymphocyte subset.

2.5.3 Estimated GFR

The eGFR was calculated using CKD-EPI method as shown below:

For females with Serum Creatinine (S_{Creat}) CKD-EPI formula

i) For females with $S_{Creat} < 62 \mu\text{mol/L}$

$$eGFR(\text{mL}/\text{min}/1.73\text{m}^2) = 144 \times (S_{Creat} \text{ in } \mu\text{mol/L} \times 0.0113/0.7)^{-0.329} \times (0.993)^{\text{age in years}}$$

ii) For females with $S_{Creat} > 62 \mu\text{mol/L}$

$$eGFR(\text{mL}/\text{min}/1.73\text{m}^2) = 144 \times (S_{Creat} \text{ in } \mu\text{mol/L} \times 0.0113/0.7)^{-1.209} \times (0.993)^{\text{age in years}}$$

For males with Serum Creatinine (S_{Creat}) CKD-EPI formula

i) For males with $S_{Creat} < 80 \mu\text{mol/L}$

$$eGFR(\text{mL}/\text{min}/1.73\text{m}^2) = 141 \times (S_{Creat} \text{ in } \mu\text{mol/L} \times 0.0113/0.9)^{-0.411} \times (0.993)^{\text{age in years}}$$

ii) For males with $S_{Creat} > 80 \mu\text{mol/L}$

$$eGFR(\text{mL}/\text{min}/1.73\text{m}^2) = 141 \times (S_{Creat} \text{ in } \mu\text{mol/L} \times 0.0113/0.9)^{-1.209} \times (0.993)^{\text{age in years}}$$

(Florkowski & Chew-Harris 2011; Lucas *et al.*, 2014)

2.6 Statistical Analysis

The statistical analysis of the data was done by using the Microsoft Excel 2010 and Graph Pad Prism 4.0. Pearson’s Correlation test was used to compare variables that did not follow normal distribution (e.g. CD4 counts). The statistical data were considered significant at $(p = 0.05)$.

III. Results

3.1: Comparison of Study parameters among HIV Subjects on ART, HIV Positive ART naïve Subjects and Control

The details of comparison of the study parameters in the test and control group shown in Table 3.1. Mean and standard deviation of BMI in ART subjects was $24.03 \pm 1.60 \text{ Kg/m}^2$, ART naïve subjects was $23.59 \pm 1.60 \text{ kg/m}^2$ and control group was $24.36 \pm 1.66 \text{ kg/m}^2$ at $(p = 0.0574; F=2.891)$. The average and standard deviation of serum selenium levels in ART subjects was $0.9329 \pm 0.03 \mu\text{mol/L}$, ART naïve subjects was $0.2229 \pm 0.02 \mu\text{mol/L}$ and control group was $0.4091 \pm 0.02 \mu\text{mol/L}$ at $(p < 0.000, F = 165.5)$. The mean and standard deviation of CD4 counts in HIV positive subjects on ART was $399.2 \pm 20.95 \text{ cells}/\mu\text{L}$, ART naïve was $299.1 \pm 37.43 \text{ cells}/\mu\text{L}$ and the control group was $806.7 \pm 33.28 \text{ cells}/\mu\text{L}$. The CD4 counts of the ART subjects was found higher than the counts of ART naïve group, comparison of the study group and control indicated significant difference $(p < 0.0001, F= 60.82)$. The average and standard deviation of creatinine levels in ART subjects was $80.8 \mu\text{mol/L}$, ART naïve subjects was $85.46 \mu\text{mol/L}$ and control group was $78.10 \mu\text{mol/L}$ at $(p= 0.6404, F= 0.4465)$. The mean and standard deviation of eGFR status in ART subjects was $108.6 \pm 27.19 \text{ mL}/\text{min}/1.73\text{m}^2$, ART naïve was $111.7 \pm 4.34 \text{ mL}/\text{min}/1.73\text{m}^2$ and HIV negative control group was $117.9 \pm 17.01 \text{ mL}/\text{min}/1.73\text{m}^2$. Also comparison of eGFR status among the respective groups indicated no significant difference $(p= 0.0655, F = 2.757)$.

Table 3.1: Comparison of Study Parameters among HIV Subjects on ART, HIV Positive ART naïve Subjects and Control

	BMI (kg/m²)	Selenium (μmol/L)	CD4 Count (cells/μL)	Creatinine (μmol/L)	eGFR (mL/min/1.73m²)
ART N=150	24.03 ± 1.60	0.9329 ± 0.03	399.2 ± 20.95	80.8 ± 3.19	108 ± 27.19
ART Naive N=50	23.59 ± 1.6	0.2229 ± 0.02	299.1 ± 37.43	85.46 ± 7.8	111.7 ± 4.34
Control N=50	24.36 ± 1.66	0.4091 ± 0.02	806.7 ± 33.28	78.1 ± 2.02	117.9 ± 17.01
p-Value	0.0574	< 0.0001	< 0.0001	0.6404	0.0655
F-value	2.891	165.5	60.82	0.4465	2.757

3.2: Comparison of Study Parameters between HIV Subjects on ART and Control Subjects

Table 3.2 showed a comparison between HIV positivesubjects on ART and the controls. The mean and standard deviation of age of ART subjects (40.14±8.87years) was significantly (p = 0.0005) higher than the control group (35.04±8.73years). There was no significant difference in mean and standard deviation of BMI of ART group (24.03±1.60kg/m²) and control subjects (24.36±1.66kg/m²) at(p = 0.2081). The mean and standard deviation of serum selenium level in ART subjects (0.9329±0.03µmol/L) was significantly (p = <0.0001) higher than the control subjects (0.4091±0.02µmol/L). Comparison of CD4 counts (399.2 ± 20.95cell/µL) of HIV positivesubjects on ART and the HIV negative control group (806.7±33.28cells/µL) showed a great reduction in CD4 counts of ART group (p = <0.0001). There was no significant difference in mean and standard deviation of serum creatinine level of ART subjects (80.8± 3.19µmol/L) had no (p = 0.6343) difference as compared to the control group (78.1±2.02µmol/L). Also, the mean and standard deviation of eGFR status indicated significant (p = 0.0168) difference between ART subjects (108.6±27.19mL/min/1.73m³) and control group (117.9±17.01mL/min/1.73m³).

Table 3.2: Comparison of Study Parameters between HIV Subjects on ART and Control Subjects

	BMI (kg/m ²)	Selenium (µmol/L)	CD4 Count (cells/µL)	Creatinine (µmol/L)	eGFR (mL/min/1.73m ³)
ART N=150	24.03± 1.60	0.9329 ±0.03	399.2 ±20.95	80.8 ± 3.19	108 ± 27.19
Control N=50	24.36 ± 1.66	0.4091 ±0.02	806.7 ±33.28	78.1 ± 2.02	117.9 ± 17.01
p-Value	0.2081	< 0.0001	< 0.0001	0.6343	0.0168

3.3: Comparison of Study parameters between HIV Subjects on ART and HIV Positive ART naive Subjects

The comparison of study parameters between HIV positive subjects on ART and HIV positive ART naïve subjects is depicted inTable 3.3. The mean and standard deviation of age of ART subjects was 40.14± 8.87years and ART naïve was 38.16± 8.6years at (p = 0.1547).No significant difference was also observed in the mean and standard deviation of BMI of ART subjects (24.03±1.60kg/m²) and control group (23.59±1.60kg/m²)at (p = 0.1016). The mean and standard deviation of serum selenium levels (0.9329 ± 0.03) of subjects on ART was significantly higher than ART naïve individuals (0.2229 ± 0.02) at (p = <0.0001). While the mean and standard deviation of CD4 count of ART subjects (399.2 ± 20.95cells/µL) was also significantly higher than ART naïve group at (p = 0.002). The creatinine level of ART individuals (80.8±3.19µmol/L) was not significantly different from ART naïve subjects (85.46±7.8mol/L) at (p = 0.3635). No significant (p = 0.1574) difference was observed in mean and standard deviation of eGFR of ART subjects (108.6±27.19ml/min/1.73m³) and ART naïve (111.7±4.34mL/min/1.73m³). The mean and standard deviation of serum selenium levels (p = <0.0001) and CD4 counts (p= 0.002) were significantly higher in ART subjects when compared with the ART naïve subjects.

Table 3.3: Comparison of Study Parameters between HIV Subjects on ART and HIV Positive ART naive Subjects

	BMI (kg/m ²)	Selenium (µmol/L)	CD4 Count (cells/µL)	Creatinine (µmol/L)	eGFR (mL/min/1.73m ³)
ART N=150	24.03 ±1.60	0.9329 ± 0.03	399.2 ± 20.95	80.8 ± 3.19	108 ± 27.19
ART Naive N=50	23.59 ± 1.6	0.2229 ± .02	299.1 ± 37.43	85.46 ± 7.8	111.7 ± 4.34
p-value	0.1016	< 0.0001	0.002	0.3635	0.1574

Table 3.4 Correlations among Subjects on ART (N=150)

Table 3.4 showed correlation analysis (Spearman’s correlation coefficient, r)results of studied parameters among subjects on ART. Correlation coefficient between serum selenium levels and BMI was (r = 0.102; p = 0.215), selenium and CD4 count was (r = 0.025; p = 0.757), selenium and creatinine levels showed a no significant negative correlation, (r = -0.140; p = 0.088), selenium levels and eGFR status indicated a correlation (r = 0.073;p = 0.376). The correlation between eGFR status and BMI was (r = -0.181;p = 0.027), eGFR status and CD4 counts levels gave correlation coefficient of (r = 0.073; p = 0.445), while correlation coefficient between eGFR status and creatinine was (r= 0.063; p = 0.376). There was strong native correlation

coefficient between eGFR status and selenium levels ($r = -0.870$; $p = 0.000$). A negative correlation ($r = -0.055$) was observed between BMI and CD4 counts with ($p = 0.226$) difference, BMI and creatinine levels showed significant positive correlation ($r = 0.213$; $p = 0.009$).

Table 3.4 Correlations matrix a

	r	p-Value
Selenium and BMI	0.102	0.215
Selenium and CD4 Counts	0.025	0.757
Selenium and Creatinine	-0.140	0.088
Selenium and eGFR	0.073	0.376
eGFR and BMI	-0.181	0.027
eGFR and CD4 counts	0.073	0.445
eGFR and Creatinine	0.063	0.376
eGFR and Selenium	-0.870	0.000
BMI and CD4 Counts	-0.055	0.226
BMI and Creatinine	0.213	0.009

mong Subjects on ART (N=150)

IV. Discussion

This present study assessed serum selenium levels, CD4 counts and estimated glomerular filtration rate (eGFR) of HIV infected persons living in Yenagoa. The result depicted significantly higher ($p=0.0001$) selenium values in the HIV patients on antiretroviral therapy compared to the control subjects as well as the naïve HIV patients. This finding is in accordance with findings of [22] that serum selenium levels were elevated in individuals on prolonged ART. Also, according to [23], selenium- containing enzymes are involved in the recycling of vitamin C (which is also a known organic antioxidant) from its spent form back to its active form; allowing for enhanced antioxidant protection. “Reported outcomes of different selenium intervention trials, although somewhat inconsistent, suggest that supplementation may delay the progress to AIDS, slow the depletion of CD4⁺ T cells, and reduce morbidity [24,25,26,27,28]. These observations may be due to the food intake and higher soil selenium content found in the northern region as reported by [29]. Studies reported below optimal levels of selenium content of soils in sub-Saharan Africa, particularly in the southern part of Nigeria where annual rainfall is high [29,30] which may have caused the low plasma selenium concentrations as indicated in this study location where low food selenium content was reported. However, this result is at variance with the work of [31], which reported that; susceptibility to oxidative stress had an association or otherwise a relationship with free-radical-mediated lipid peroxidation which is controllable partly by the “Master” antioxidant system (*Glutathione peroxidase*). Therefore, the increase in serum selenium could probably have resulted from the immune boost due to the ART. The statistically significant reduction in selenium levels of the ART naïve subjects may be due to the increased demand by HIV for production of its selenoenzymes and nutritional abnormalities of the infected.

Worthy of mention is the work of [33], which also stated that HIV in the infected individual synthesizes its own selenoproteins by utilizing the selenium pool of the host; again, suggesting the HIV infection to be the possible cause of selenium depletion. However, this finding is completely in contrast to the work of [34], which stated that the mean plasma selenium level is significantly lower in HIV negative human subjects than the levels in HIV positive individuals in their comparative study of plasma zinc and selenium levels amongst Human Immunodeficiency Virus (HIV) positive and negative subjects.

This study showed that CD4 cells counts of the HIV positive individuals on ART and ART naïve subjects were significantly lower when compared with that of the control group. This observation is in accordance with findings of [22], which reported reduced baseline CD4 cells counts of HIV positive subjects due to HIV assault leading to apoptosis of CD4 cells and immune cells deficiency. However, lower mean CD4 T-cells count was also observed in ART naïve HIV positive individuals when compared with HIV positive subjects on ART independent of the sex and age. This finding suggests the beneficial effects of ART on the treatment of HIV infected people by suppressing harmful effects of the HIV.

According to [29,35], the reduction in CD4 counts is probably due to the increased metabolic and oxidative stress caused by human immunodeficiency virus. This is in agreement with the work of [36], which earlier on reported HIV as a key factor in the development of chronic renal diseases and end stage renal disease (ESRD) which is capable of presenting a direct assault on the host’s immune system. This is probably a factor in the waning of the CD4 counts. And is also in consonance with the works of [37], which identified oxidative stress as a feature in the disease progression and probably responsible in the development of AIDS. A significantly normal eGFR status as compared with HIV negative control individuals was also observed from the study.

The findings of this study showed no significant difference in the mean and standard deviation of eGFR status among ART subjects, ART naïve and HIV negative control groups ($p = 0.7052$). This, though in contrast with the reports of [36], which published that the kidney is a receptacle for HIV and favourable site for HIV replication with a consequent renal dysfunction, could be due to effective management.

This present study showed a negative correlation between eGFR status and BMI ($r = -0.181$; $p = 0.027$). Whereas there was a significant positive correlation of glomerular filtration rate with BMI on treatment-naïve groups was reported in a retrospective comparative study [38], present study observed a negative correlation between eGFR and BMI, probably due to muscle wasting and the side effects of the antiretroviral therapy over time. Similarly, BMI and creatinine levels showed a positive correlation ($r = 0.213$; $p = 0.009$). This may probably suggest that a reduction in BMI could affect the creatinine concentration causing a rise in eGFR status hence; a decrease in the creatinine concentration of HIV infected individuals. Also, correlation between eGFR status and selenium levels showed a negative ($r = -0.870$; $p = 0.000$). There was no significant ($p = 0.445$) association between eGFR status and CD4 counts ($r = 0.073$). However, lower serum creatinine concentrations were seen in females than the males: and it is believed to be consequent upon the muscular mass of men.

High selenium levels amongst HIV positive patients on ART could be attributed to the effect of the ART as a result of immune recovery. However, there were no significant difference on the effect of the ART on the eGFR, as there was significant correlation between the selenium level and eGFR.

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