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Serum vitamin E levels in children with human immunodeficiency virus infection in Lagos Nigeria

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Abstract

Background Vitamin E supplementation in many adult populations has been found to reduce the impact of oxidative stress from chronic diseases which include HIV infection. With paucity of data among the pediatric population, this study was conducted to determine the mean serum vitamin E levels and its associations with the immunologic status, the nutritional status and the use of highly active antiretroviral drugs (HAART) in children with HIV aged 6 weeks to 13 years.

Methods Seventy HIV-infected children (35 HIV-infected on HAART, 35 HIV-infected HAART-naïve) and seventy age- and sex-matched HIV-uninfected children were recruited to the study. Social class, anthropometric measures, results of serum vitamin E (using HPLC), CD4 counts, and cholesterol levels were inputted into a pretested questionnaire.

Results The median (IQR) serum vitamin E levels among the children with HIV was 2.54 (1.55–5.27) µmol/L which was higher than the controls 1.87 (1.63–2.88) µmol/L, $p=0.03$.There was a positive correlation between serum vitamin E levels and immunological status using CD4% ($r=+0.141$, $p=0.53$) and CD4 counts ($r=+0.017$, $p=0.91$) among the children with HIV. There was no significant association between serum vitamin E levels and nutritional status. The vitamin E levels were higher in the HAART-exposed children compared to the HAART-naïve children but the difference was not significant $p=0.480$ and $p=0.485$ respectively.

Conclusion The children with HIV had higher serum vitamin E levels. Further research is needed to investigate possible reasons and implications for this including the role of the vitamin E carrier protein in HIV management.

Keywords Human immunodeficiency virus, Vitamin E, Highly active antiretroviral therapy

Key points

- Children with HIV can have higher vitamin E levels when compared to their HIV-negative counterparts.
- HAART-exposed children with HIV have higher levels of vitamin E when compared to their HAART-naïve counterparts
- There is a positive correlation between immunologic status and vitamin E levels in children with HIV.

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Background

HIV exerts oxidative stress on the body and vitamin E as an antioxidant may attenuate this effect. Infected people are at a high risk of vitamin E deficiency due to oxidative stress exerted by the disease, effects of some antiretroviral drugs [1–3] and increased urinary vitamin E excretion [4]. Vitamin E optimizes immune function by stimulating CD4 production, improving lymphocyte viability, decreasing viral load thus reducing the rate of progression in HIV [5–7]. It also protects cell membranes from oxidative damage by scavenging free radicals [3] and also attenuates anemia and renal compromise which are side effects of some antiretroviral drugs [8, 9].

Vitamin E is reported to have a positive correlation with immune status and a negative correlation with lipid peroxidation which is a consequence of oxidative stress [10, 11]. Few studies have reported vitamin E levels in HIV-infected children or found any association with their immune status or with the effect of the use of antiretroviral drugs on vitamin E. Hence, vitamin E status of these children has not been documented. Furthermore, these available studies [10, 11] did not use the HPLC method of analysis which is currently the most sensitive, specific and precise method of vitamin E analysis in comparison to methods such as colimetric assay, spectrophotometric assay, chemiluminescence assay, amperometric assay, and immunoassays [12].

This study aimed to determine vitamin E levels in HIV-infected children using the HPLC method of analysis and to identify any association between vitamin E levels, nutritional and immune status, and the use of antiretroviral drugs in HIV-infected children.

Methods

Study design and setting

This was a cross sectional study conducted in the Pediatric HIV Clinic of a 750 bedded tertiary hospital between 1 April 2017 and 31 October 2017. It manages about 100 to 150 children with HIV monthly including an average of 7 new cases monthly.

The study population included HIV-positive children aged 1 month to 13 years and age- and sex-matched controls who were HIV-negative. Documentary evidence of HIV infection was sighted from the medical records of the children with HIV following a positive DNA/PCR test for children aged 6 weeks to 18 months using a DBS Collection kit by Lasec^{R} which is a form of biosampling where samples are blotted and dried on a filter paper for analysis using DNA amplification or HPLC. For the children aged 18 months and above, documentary evidence of HIV infection was also sighted from their medical records.

The controls were screened for HIV using the highly sensitive Determine™ HIV–1/2 Set kit by Alere.™ However, the control subjects less than 18 months of age who tested positive were referred to the HIV clinic for a DNA PCR test after voluntary counseling and testing was conducted on their mothers.

Inclusion criteria

1. Children aged 6 months to 18 years who tested positive for HIV and whose primary caregiver provided a written informed consent.
2. Children aged > 7 years that tested positive for HIV and gave an informed assent in addition to the written consent provided by their respective care givers.

Exclusion criteria

1. Children who suffered acute illnesses 2 weeks prior to sample collection because the resulting oxidative stress and may confer a negative effect on antioxidant levels [1].
2. Children with severe acute malnutrition.
3. Children who were taking supplements containing vitamin E that was up to the recommended dietary allowance for the child's age.
4. Children on anti-epileptic drugs because drugs like sodium valproate, phenobarbitone, and phenytoin affect vitamin E [13].
5. Children with fat malabsorption syndromes because fat is involved in vitamin E metabolism [14].
6. Children with clinical signs of acute or chronic liver pathology because the liver is involved in vitamin E metabolism [15].

Data collection

Medical history and social class of each child determined using the Oyedeji classification of social class [16] was obtained.

Weight for age and height *z* scores, height for age *z* and body mass index for age *z* scores were computed using the WHO growth charts and interpreted using the WHO training course module on child growth assessment.

Blood samples were collected in a dimly lit room to prevent degradation. The newly diagnosed HAART-naive children had their blood samples taken upon initial presentation to the HIV clinic while the HAART-exposed children had their blood samples taken on routine clinic visits. The controls were recruited from the immunization and pediatric outpatient clinics. Five milliliters of venous blood was drawn from each child. From this

3 mls was removed into a universal bottle to obtain 2 mls of serum after undergoing centrifugation. This was then stored at − 20 °C to maintain stability. One milliliter of blood was put into a lithium heparin bottle for cholesterol analysis and one milliliter was also kept for CD4 analysis in an ethylenediaminetetraacetic (EDTA) bottle.

The samples were analyzed using the HPLC method. They were initially thawed then aliquots of 1 ml each were transferred into a plain sample bottle and 2 mls chilled methanol was then added. Each sample was then moved through a packed tube (column) by applying high pressure. Thereafter, they underwent protein precipitation to ensure that the sample is free from perceived impurities.

These were vortexed for 1 min at 3000 rpm then sonicated for 10 min using an ultrasonic bath to further enhance solubility and ensure partitioning of the analyte (vitamin E) before undergoing centrifugation. Standard concentrations were also prepared to ensure quality control to validate precision before vitamin E was analyzed.

Quality assurance was achieved by evaluation of samples using correlation coefficient, precision achieved and relative standard deviation (RSD) values.

Serum cholesterol was also analyzed because vitamin E: cholesterol ratio expresses the vitamin E status of individuals with a specificity as high as 94% [17].

CD4 was analyzed by qualitative flow cytometry using the Partec cyflow counter by Partec^{R}.

From the results obtained, the subjects with HIV were classified immunologically into 4 groups based on the WHO immunologic classification.

Statistical analysis

Data analysis was conducted using IBM SPSS Statistics for windows version 20.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as frequency distribution tables. The chi square test was used to test for statistical significance of categorical variables between or among groups. Continuous variables were presented as mean and standard deviation for the normally distributed variables and as median and interquartile range for the skewed variables. The Mann–Whitney *U* test was used to test for statistical significance of serum vitamin E levels between two groups while Kruskal–Wallis test was used to test for differences in median among more than two groups. The correlation between serum vitamin E levels and immunological state (CD4 counts) was determined using Spearman's rank order. In all analyses, a p value of less than 0.05 was considered statistically significant.

Ethical approval was sought and obtained from the health research ethics committee of the hospital involved in the study.

Results

Sociodemograghic characteristics of the study participants

A total of 140 children were enrolled in the study including 70 HIV-infected children (35 HIV-infected on HAART, 35 HIV-infected HAART naïve) and 70 confirmed HIV-negative healthy controls.

The median (IQR) age of the study participants with HIV infection was 87.60 (45–120) months which was similar to that of the controls.

There was a difference in the social class between the children with HIV and the control subjects (0.02) (Table 1).

Anthropometric characteristics and nutritional status of study participants

The mean (SD) BMI of the participants with HIV aged below 12 months (14.08 kg/m^2 ± 2.65) differed from that of the controls in that age group (16.58 kg/m^2 ± 2.08), $p = 0.04$.

There were differences in the weights and heights of the participants with HIV compared to the healthy controls aged 25–60 months, and 61–120 months, $p = < 0.05$, and in the BMI of the subjects with HIV compared to healthy controls aged 121–156 months $p = 0.01$.

There was a significant difference in the weight for length/height (among participants below 5 years), weight for age (among the participants below 10 years), height for age and BMI between the subjects with HIV and the controls $p < 0.05$ (Tables 2 and 3).

Serum vitamin E levels of study participants

The median (IQR) serum vitamin E levels of the HIV-infected subjects was 2.54 (1.55–5.25) µmol/L and it was significantly higher than that of the controls which was 1.87 (1.63–2.88) µmol/L, $p = 0.03$ (Fig. 1).

Correlation of serum vitamin E levels and immunologic status of the HIV-infected participants using CD4% and counts

There was a positive correlation between serum vitamin E and immunologic state in the children infected with HIV who were less than 5 years ($r = 0.141$, $p = 0.53$) and in the infected participants aged 5 years and above ($r = 0.017$, $p = 0.91$) (Figs. 2 and 3).

Relationship between serum vitamin E and nutritional status using BMI for age and length/height for age among the subjects with HIV

The serum vitamin E levels in the underweight HIV-infected subjects (3.3 µmol/L) was higher than their counterparts with normal weight (2.6 µmol/L) and those who were overweight (1.4 µmol/L) but the differences were insignificant $p = 0.48$.

Table 1 Sociodemographic status of the study participants

Parameter	HIV-positive *N* = 70	Controls *N* = 70	*p* value
Age months *median(IQR)*	87.60 (45.00–120.00)	87.60 (45.00–120.00)	1.00
Age group *n (%)*			
≤ 12 months	8 (11.4)	8 (11.4)	
13–24 months	4 (5.7)	4 (5.7)	
25–60 months	10 (14.3)	10 (14.3)	
61–120 months	32 (45.7)	32 (45.7)	
121–156 months	16 (22.9)	16 (22.9)	1.00
Gender			
Male *n (%)*	35 (50.0)	35 (50.0)	
Female *n (%)*	35 (50.0)	35 (50.0)	1.00
Socioeconomic class *n (%)*			
Class 1	0 (0)	2 (2.9)	
Class 2	10 (14.3)	22 (31.4)	
Class 3	24 (34.2)	27(38.6)	
Class 4	34 (48.6)	18 (25.7)	
Class 5	2 (2.9)	1 (1)	0.02

p values obtained by Student's *t* test and chi-square test

Table 2 Anthropometry of the study participants in the different age groups

Age group	Variable	HIV-positive	Control value	*p* value
≤ 12 months		Mean(SD)		
	Weight (kg)	6.52 (2.19)	7.50 (1.81)	0.06
	Height (cm)	0.68 (0.84)	0.68 (0.08)	0.61
	BMI (kg/m^2)	14.08 (2.65)	16.58 (2.08)	0.04
13–24 months				
	Weight (kg)	11.87 (2.76)	12.50 (4.04)	0.80
	Height (cm)	0.82 (0.08)	0.88 (0.03)	0.30
	BMI (kg/m^2)	17.18 (2.19)	15.66 (4.01)	0.59
25–60 months				
	Weight (kg)	13.52 (2.07)	18.65 (5.17)	0.01
	Height (cm)	0.93 (0.85)	1.09 (0.09)	< 0.01
	BMI (kg/m^2)	15.48 (0.91)	15.59 (2.26)	0.88
61–120 months				
	Weight (kg)	23.58 (5.72)	28.53(7.30)	< 0.01
	Height (cm)	1.23 (0.13)	1.33 (0.08)	< 0.01
	BMI (kg/m^2)	15.17 (1.70)	16.07 (3.30)	0.17
121–156 months				
	Weight (kg)	34.14(4.41)	42.63 (15.53)	0.05
	Height (cm)	1.46 (0.81)	1.51 (0.10)	0.11
	BMI (kg/m^2)	15.95 (1.48)	19.30 (4.73)	0.01

p values obtained from Student's *t* test

Table 3 Nutritional status of the study participants

	HIV-positive (*N*, %)	Controls (*N*, %)	*p* value
BMI for age			
Underweight	13 (18.6)	13 (18.6)	
Normal	55 (78.6)	45 (64.3)	
Overweight	2 (2.8)	12 (17.1)	0.01
Height for age			
Stunted	17 (24.3)	3 (4.3)	
Normal	50 (71.4)	47 (67.1)	
Tall	3 (4.3)	20 (28.6)	< 0.01
Weight for age			
Underweight	11 (20.4)	3 (5.6)	
Normal	41 (75.9)	36 (66.7)	
Overweight	2 (3.7)	15 (27.8)	< 0.01
Weight for height			
Underweight	8 (36.4)	3 (13.6)	
Normal	14 (16.6)	15 (68.2)	
Overweight	0 (0.0)	4 (18.2)	0.04

p value obtained by chi-square test

Vitamin E levels among the tall subjects with HIV was higher (4.57 µmol/L) than those who were stunted (2.84 µmol/L) or of normal height (2.47 µmol/L) though this was not significant, $p = 0.71$. Similrly, among the control subjects, no difference was noted across all groups $p = 0.80$.

There was no difference in vitamin E values among the underweight, normal and overweight subjects with regard to their weight for age ($p = 0.26$) and weight for height $p = 0.49$ (Table 4).

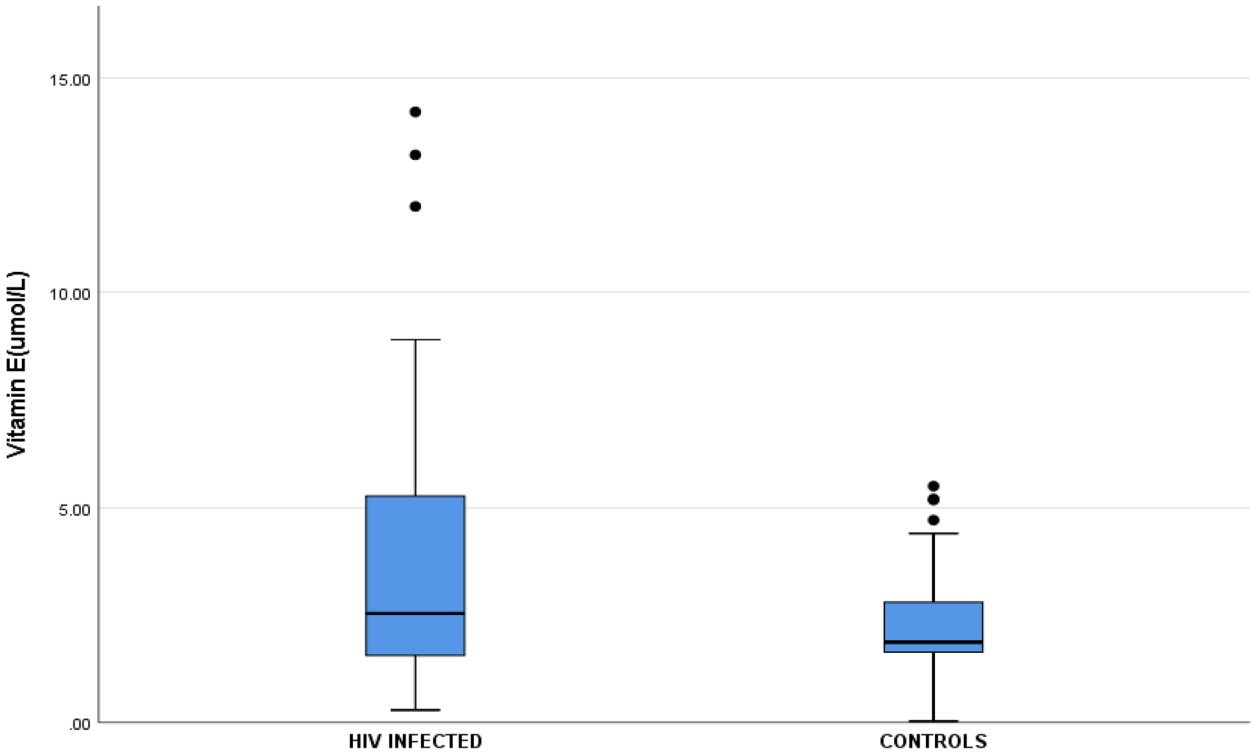

Fig. 1 Serum vitamin E levels of the study participants

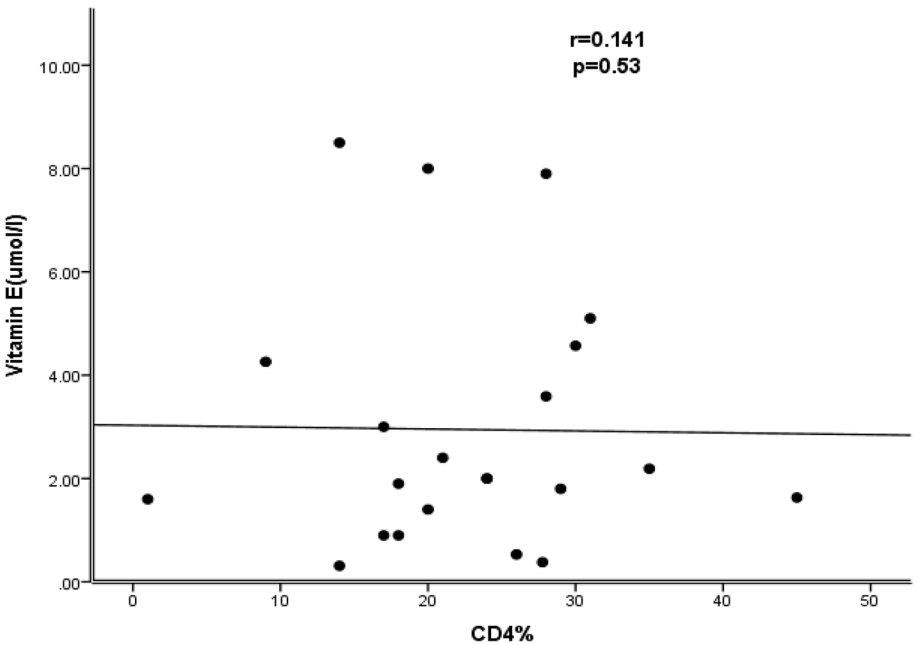

Fig. 2 Correlation of serum vitamin E and CD4% counts of the children with HIV below 5 years

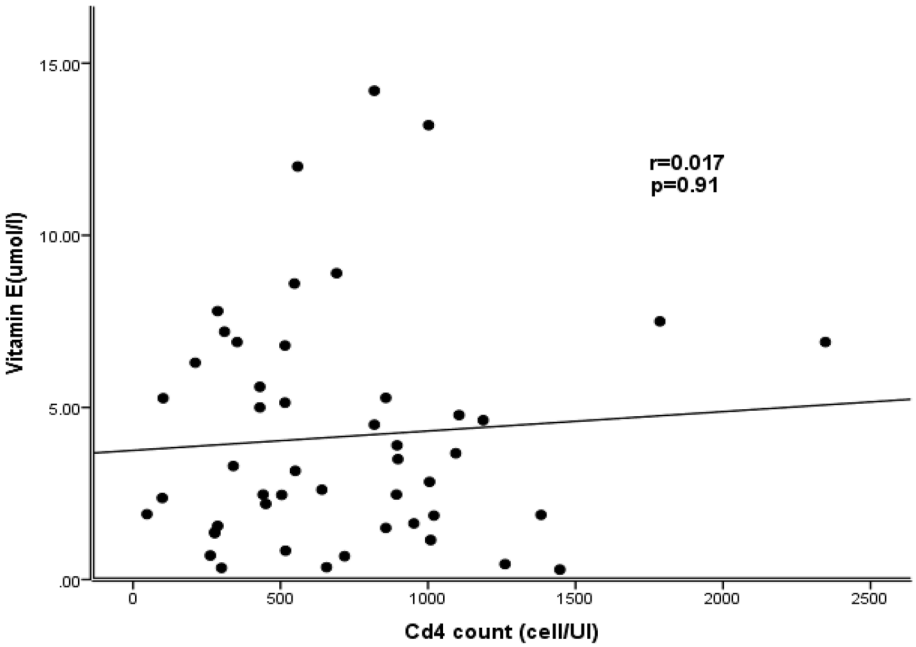

Fig. 3 Correlation of vitamin E and immune status of the participants greater than 5 years of age

Table 4 Distribution of serum vitamin E levels across the nutritional status of the participants with HIV

Parameter	Median (IQR)	*p* value
BMI for age		
Underweight	3.30 (2.04–5.08)	
Normal	2.60 (1.50–5.28)	
Overweight	1.40 (0.90–1.90)	0.48*
Height for age		
Stunted	2.84 (1.49–6.29)	
Normal	2.47 (1.47–5.17)	
Tall	4.47 (2.55–7.07)	0.71**
Weight for age		
Underweight	2.19 (0.68–3.59)	
Normal	2.40 (1.37–4.78)	
Overweight	5.27 (5.27–5.28)	0.26***
Weight for height		
Underweight	2.59(1.82–4.32)	
Normal	1.81(0.9–4.47)	0.49****

p value obtained from Kruskal–Wallis test

*p** *p* value comparing the median vitamin E values between the underweight, normal, and overweight HIV-infected children

*p*** *p* value comparing the median vitamin E values between the stunted, normal, and tall HIV infected children

*p**** *p* value comparing the median vitamin E values between the underweight, normal, and overweight children aged 10 years and below

*p***** *p* value comparing median vitamin E values between the underweight and normal HIV-infected children aged 5 years and below

Serum vitamin E levels between the HAART-exposed and HAART-naive participants

The vitamin E levels of the HIV-infected HAART-exposed subjects (3.16 μmol/L) was higher compared to the serum vitamin E levels of HIV-infected HAART-naïve subjects (2.2 μmol/L), though the difference was not significant, $p = 0.48$ (Fig. 4).

Discussion

In this study, the children with HIV had higher levels of vitamin E than the children in the control group. A similar pattern was also reflected in their vitamin E: cholesterol ratio which is a good index of expressing the vitamin E status of individuals [18]. Stephenson et al. [2] reported a similar finding among adolescents with HIV. Likely factors responsible for this include the presence of α tocopherol transfer protein [19] and TNF-α. The α tocopherol transfer protein which is involved in intracellular transport of vitamin E has been reported to have a direct relationship with vitamin E in tissues and plasma [15]. Oxidative stress directly stimulates transcription of the α tocopherol transfer protein gene resulting in higher α tocopherol transfer protein levels and therefore increased distribution and probably a falsely elevated serum level of vitamin E. TNF-α, an inflammatory mediator enhances the α tocopherol transfer protein promoter gene. Furthermore, it is documented that oxidative stress may enhance expression of the α TTP mRNA and the transcriptional activity of the α TTP promoter gene [15].

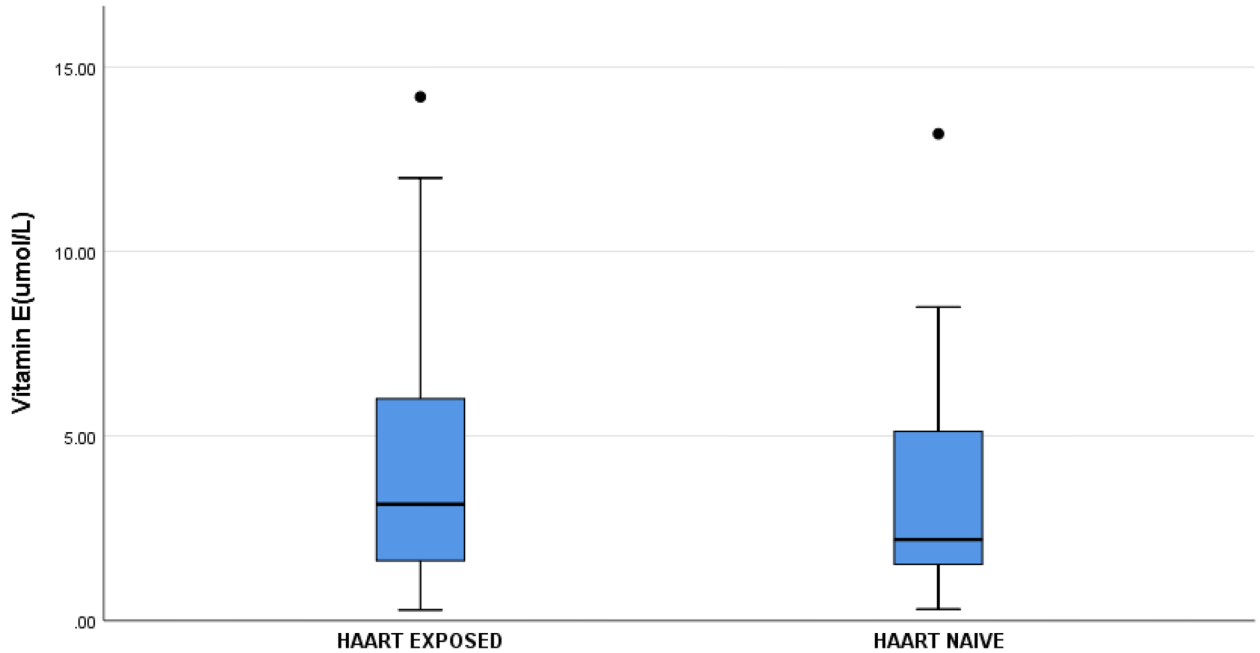

Fig. 4 Vitamin E levels of the HAART-exposed and HAART-naïve participants

HIV-induced oxidative stress may have been responsible for the higher levels of vitamin E reported among the HIV-infected children.

Nwosu et al. [11] on the contrary, reported lower vitamin E levels in the HIV-infected subjects in their study compared to their controls. It is possible that the children with HIV involved in the index study may have suffered a significant degree of oxidative stress compared to the controls hence resulting in higher levels of vitamin E considering the role of the alpha tocopherol transfer protein [15]. The participants in the index study may also have been on either unorthodox sources of vitamin E or on vitamin E rich diets.

Immunological status and vitamin E

There was a weak positive correlation between vitamin E levels and immune status of the subjects with HIV. Bilbis et al. [10] reported a significant correlation probably because their population size was larger and comprised of adults. This observation could be due to insufficient dietary intakes, malabsorption, diarrhea, impaired storage, and altered mechanism in HIV-infected individuals hence resulting in micronutrient deficiency, worsening of oxidative stress and immune suppression, and higher risk of progression to AIDS. HIV infection accelerates the release of pro-oxidants, cytokines, and reactive oxygen species resulting in increased utilization of antioxidants, an imbalance between pro-oxidants and antioxidants with consequent cell damage and eventual worsening of the ongoing oxidative stress. The decline in antioxidants including vitamin E whose role in immune function optimization, antibody production, stimulation of phagocytic and lymphocytic response, and resistance to viral and other infective diseases has been established, may predispose the HIV-infected individual to a worsened morbid state [20, 21]. Larger longitudinal studies in the pediatric HIV-infected population may however be needed to ascertain the relationship between immune status and vitamin E.

Nutritional status and vitamin E

There was a relative inverse relationship of vitamin E and nutritional status of the HIV-infected subjects with regard to the BMI of the HIV-infected subjects. This was similar to the reports from Stephenson et al. [2] and Garcia et al. [22] possibly because, with increasing BMI, there is a resultant predisposition to increased systemic and adipose tissue specific oxidative stress. Other possible factors include increased activity of the Renin Angiotensin Aldosterone System, reduction in erythrocyte glutathione and reduction in glutathione peroxidase antioxidant defense mechanisms have also been implicated. This would eventually lead to increased oxidative catabolism of the lipid soluble vitamins and increased levels of reactive oxygen species. Micronutrient deficiencies also tend to occur in individuals with high BMI due to possible reduced intake of micronutrients and increased intake of energy-dense foods instead [23]. Furthermore,

higher BMI values confer an inverse relationship between vitamin E levels and insulin resistance, lipid levels, and inflammation. This is because lipids are involved in vitamin E metabolism; therefore, low vitamin E levels may be a consequence of high lipid levels [22]. The underweight children had higher values of vitamin E than their counterparts with normal BMI possibly as a result of malnutrition-induced oxidative stress in underweight children [24, 25], which may have indirectly resulted in falsely elevated serum α tocopherol levels [2, 25]. However, larger studies may be needed to support this finding. The tall children with HIV had the highest levels of vitamin E, this pattern was similarly observed among the control subjects where the tall children had the highest vitamin E levels. There is little evidence supporting the effect of vitamin E on height especially in HIV-infected individuals. However, it has been hypothesized that vitamin E affects height positively by scavenging free radicals, stimulating trabecular bone formation and altering epiphyseal cartilage morphometry. Another theory is that vitamin E may protect against cellular lipid peroxidation in cartilage and indirectly sustain bone growth and modeling [26].

Vitamin E and HAART

Similar to a study conducted by Aniagolu et al. [27], there was no significant difference in vitamin E levels between the HAART-exposed and HAART-naïve HIV-infected population although, higher levels were seen among the HAART-exposed population. Therefore, larger studies may be needed to strengthen the finding in the index study.

Conclusion

Contrary to the finding of lower serum vitamin E levels demonstrated in earlier studies [11], children with HIV can have higher serum vitamin E levels compared to HIV-negative children. However, further studies may be needed to *study* reasons for this including the role of alpha tocopherol transfer protein in HIV and any effect it may have on tissue levels of vitamin E in these children including any overall health impact as this may affect HIV management. In addition, a positive correlation between vitamin E and immune status of the HIV-infected children was found while the HAART-exposed children had higher vitamin E levels compared to the HAART-naïve children.

Abbreviations

AIDS	Acquired immunodeficiency syndrome
ANOVA	Analysis of variance
APIN	AIDS Prevention Initiative Nigeria
BMI	Body mass index
CD4	Cluster of differentiation 4
CPU	Central processing unit
DNA	Deoxyribonucleic acid
DBS	Dried blood spot
ELISA	Enzyme-linked immunosorbent assay
FIA	FluoroImmuno Assay
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
IQR	Interquartile range
LUTH	Lagos University Teaching Hospital
NF	Nuclear factor
NRTI	Nucleoside reverse transcriptase inhibitors
NNRTI	Non-nucleoside reverse transcriptase inhibitors
PI	Protease inhibitors
RDA	Recommended dietary allowance
RIA	Radioimmuno assay
TNF-α	Tumor Necrosis Factor alpha
WHO	World Health Organization

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Authors' contributions

O.A was a major contributor in the data analysis of the anthropometric indices and in script editing. A.P analyzed and interpreted data of the HAART-naïve subjects involved in the study. S.O ensured the data on vitamin E was accurately interpreted in terms of conversion to the SI unit. All authors read and approved the final manuscript.

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Availability of data and materials

The dataset used and/or analyzed during this study is available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval was granted by the LUTH research ethics committee (registration number – NHREC 19/12/2008).

Consent for publication

Informed assent and written informed consent was obtained from all participants and their care givers.

Competing interests

The authors declare that they have no competing interests.

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