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Effect of Combined Antiretroviral Therapy on Selected Trace Elements and CD4$^+$T-cell Count in HIV-Positive Persons in an African Setting

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Abstract

In HIV-infected persons, low serum concentrations of trace elements have been associated with an increased risk of HIV disease progression and mortality. Few data are available to determine whether HAART ameliorates micronutrient deficiencies in HIV-positive persons. In the current study, we investigated the effects of HAART on selected trace elements such as selenium, zinc and copper and on CD4$^+$T-cell count in HIV-positive persons. Fifty HIV-positive individuals with 25 on HAART and 25 who were not on HAART were recruited for the study. Twenty five apparently health persons who were HIV-negative serve as a control group. Serum concentrations of selenium, zinc and copper were estimated by atomic absorption spectrophotometric method while CD4$^+$T-cell count was determined by flow cytometric method. Persons on HAART showed significantly ($P<0.05$) high Zn and CD4$^+$T-cell count compared to PRE-HAART. There was no significant difference in the serum selenium and copper levels between HAART and PRE-HAART persons. In conclusion, HAART significantly improved the immunological status as evidenced by increased CD4$^+$T-cell count and also significantly increased the zinc level in the same group. A large randomized placebo-controlled trial is recommended for future study.

Keywords: Micronutrients; Trace elements; HIV and AIDS; Immunological status and antiretroviral therapy

Introduction

The Human Immunodeficiency Virus (HIV) was unknown until the early 1980's but it has since then infected millions of persons in a global pandemic. At the end of 2005, it was estimated that about 40 million people have been infected with HIV, with over 60% of infections affecting people living in the sub-Saharan Africa [1,2]. The human immunodeficiency virus (HIV) infection continues to increase globally, with over 90% of new cases being reported in developing countries [3] and regarded as the primary cause of acquired immunodeficiency syndrome [4] in infected persons. Although major advances have been made in understanding the biology of HIV infection and significant progress in therapy has been made in the last few years, however, the basic role of host's nutrition in the pathogenesis of HIV infection still remains a major challenge in scientific knowledge. The concept that a malnourished host has a greater susceptibility to infections and a relatively worse prognosis has been generally accepted, however, it is often difficult to demonstrate that specific nutritional deficiencies contribute to poor clinical outcomes [5]. With the spread of HIV/AIDS pandemic in developing countries where nutritional problems are a common place and expensive drugs are generally unavailable, the identification and correction of micronutrient deficiencies may be increasingly important.

The use of Antiretroviral therapies (ART) is recommended globally for the management of HIV/AIDS. Different types of ART or combination therapies are available, and the prescription and use of a particular therapy depends on tolerability, the cost, and the therapeutic objectives [6]. WHO currently recommends first-line therapy with two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitors (NNRTI) [7]. A combination of nevirapine, stavudine, and Lamivudine or lamivudine with zidovudine is frequently prescribed [8]. Periodic blood plasma viral load and CD4$^+$T-cell count monitoring have been recommended to measure ART effectiveness since the goal of effective ART is a long term suppression of plasma viral load. While it cannot be assume that effective ART would eliminate transmission with individual exposure, evidence from several cohort, observational and mathematical modeling studies suggests that effective ART may be a promising way to reduce HIV transmission within population [9].

Trace metals are metals in extremely small quantities, almost at the molecular level, that reside in or are present in animal and plant cells and tissues. They are a necessary part of good nutrition, although they can be toxic if excess quantities are ingested. It has been shown that micronutrient deficiencies are common among HIV-infected persons, especially in those who are underprivileged and undernourished [9,10]. Under-nourished and micronutrient deficiencies in HIV-infected individuals exacerbate immunosuppression, oxidative stress, acceleration of HIV replication and CD4$^+$ T cell depletion [11]. Deficiency of antioxidant micronutrients in HIV positive populations is probably due to increased utilization of micronutrients because of increased oxidative stress rather than to inadequate dietary intake [12,13] and malabsorption [14].

Essential trace metals have a wide range of benefits among HIV-positive patients such as increased survival, improved oxidative stress, reduced hospitalization, increased weight gain, improved birth outcomes and infant immune status and reduced mother-to-child

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transmission [15]. The measurement of trace elements especially, selenium (se), zinc (zn), copper (cu) may be a useful marker to predict HIV infection progression. Better understanding of the mechanism of trace element abnormalities and the strategies to maintain optimal trace element abnormalities and the strategies to maintain optimal trace element balance could, thereby improve the immune function and life quality of these patients [16]. Zinc and Selenium supplementation alone or in combination with other micronutrients can be used to give a boost to HAART therapy and can also be a part of nutritional programme in HIV positive patients [17]. This study is aimed at determining plasma level of selected trace metals (selenium, zinc and copper) and T-lymphocyte ($CD4^+$T-cell count) levels among HIV-positive persons on ART attending a teaching Hospital in Osogbo, south-west Nigeria.

Materials and Methods

Study design and location

This cross-sectional analytical laboratory-based study was conducted in Osogbo, a city of approximately 500,000 people, based on the 2006 census. Located in the heart of southwestern Nigeria's Yoruba speaking people, Osogbo is served by two major government hospitals: Osun State Hospital, Asubiaro and Ladoke Akintola University of Technology Teaching Hospital and private hospitals. The city is 342 km south of Abuja (The Federal Capital Territory of Nigeria) and 194 km of Lagos. Osogbo is the capital of Osun State, a major distributor of electrical power supply for Nigeria and one of the foremost centers of Yoruba arts and culture in Africa.

Subjects

Participants were selected for this study based on the following criteria: HIV-positive persons older than 18 years and are not on antiretroviral drugs (PRE-HAART participants) or been on triple drugs therapy for at least 1 to 3 months (HAART participants). HIV positive out-patients (50) were recruited from LAUTECH teaching hospital (25 HIV-positive patients who were not on any form of antiviral therapy and 25 who were on the combination therapy). Participants were classified based on sex and immune status such as $CD4^+$T-cell count (lymphocytes/mm^3). The control group comprised 25 randomly selected age and sex-matched apparently healthy participants who showed no serological evidence for HIV and/or HCV infection and no abnormal laboratory findings. The study was approved by the university ethic committee. Informed consent was obtained from each participant after the protocol of the study was explained to them in the language they understood. Participants on antiviral therapy followed the following therapies: generic fixed-dose combination of zidovudine +lamivudine+nevirapine.

Blood collection

After an overnight fasting, 10ml of blood was collected from the antecubital vein using a sterile needle with syringe, distributed into an appropriate bottle (heparin, EDTA) for $CD4^+$T-cell count and trace metals. EDTA anticoagulated whole blood was required within 6 hours of sample collection for the estimation of $CD4^+$T-cell count and plasma from each bottle was separated by centrifugation for ten minutes at 4000 revolution per minute into plain bottles and stored at -20°C and analyzed within specified period.

Biochemical and immunological analyses

Serum concentrations of trace metals (Se, Zn, and Cu) were estimated by atomic absorption spectrophotometric method as described by Kaneko [18] and plasma $CD4^+$T-cell count was determined by flow cytometric method [19].

Principle and procedure

In the flame AAS, the principle is based on the dissociation of the element from its chemical bonds. This is then placed in an unexcited or ground state (neutral atom). Thus, the neutral atom is at a low energy level in which it is capable of absorbing radiation at a very narrow bandwidth corresponding to its own line spectrum. The amount of radiant energy absorbed at a characteristic wavelength in the flame is proportional to the concentration of the element present in the sample. For Zinc (Zn), **t**he serum was diluted 1:4 with water and aspirated to AAS. Standards and blanks were prepared by diluting with 5% glycerin (series of standards 1, 3 and 6 were recommended, however, 1 and 3 ppm were enough which have comparable concentration with sample).

Copper (Cu): The serum was diluted 1:1 with water, aspirated and read in AAS. Standards and blanks were prepared with 10% glycerin (recommended standards are 5 ppm and 15 ppm Cu; however, the lowest standard alone could be used). Selenium (Se): This element was read from samples prepared for Zn or Cu analysis. Standards and blanks were prepared accordingly.

Determination of $CD4^+$T-cell count

Cyflow counter flow cytometer was used to determine $CD4^+$T-cell count. In the cyflow counter, the fluorescence monoclonal antibody (CD4 mAb PE) binds to the CD4-antigen on the mononuclear cells (T lymphocytes and monocytes) and in a buffer suspension; the complex is passed through the flow cuvette in a single stream of flow. The complex is excited by the solid state laser high (green laser) at a wavelength of 532 nm causing the complex to emit light which is captured by a photomultiplier tube and transmitted into digital read out as counts. The procedure is as follows: the sheaths fluid bottle was filled to 800 ml mark and air was expelled from filter before corked tightly. The fluid was discarded in waste bottle and rinsed with 10% hydrochloride solution and corked tightly. The cable and electrical connection to the cyflow were checked and the automatic voltage regulator was switched on and allowed to stabilize. The UPS was switched on and allowed to stabilize before switching on the cyflow and allowing it to boot. The sample was prepared as follows: into a Rohren test tube, 20 µl of $CD4^+$T-cell count PE mAb was added and 20 µl of well mixed EDTA whole blood that was collected within 6 hours was added, mixed and incubated in the dark for 15 minutes at room temperature. 800 µl of $CD4^+$T-cell count buffer was added, mixed and read on the cyflow. The prepared sample was then plugged to the sample port of the cyflow and wait for acquisition and data analysis. The cyflow started from pre-run, run count and stopped and then it counted for a known volume of the sample and stopped. After getting, the result of the counting was displayed and used for analysis.

Statistical analysis

The SPSS software package was used for statistical analysis and values obtained from this study were expressed as mean and standard deviation when compared using the independent t-test and results were regarded as significant at $P<0.05$.

Results

The mean age of all HIV-positive patients was not significantly ($P>0.05$) different from those of the control group.

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Parameters & Groups		Mean ± SD	SEM
Zn (µg/dl)	HAART	10.60 ± 10.13	2.026
	PRE-HAART	102.16 ± 9.199	1.83
	CONTROL	90.11 ± 12.75	2.55
Cu (µg/dl)	HAART	19.75 ± 6.82	1.36
	PRE-HAART	17.70 ± 3.91	0.78
	CONTROL	82.08 ± 13.80	2.76
Se (µg/dl)	HAART	28.08 ± 7.80	1.56
	PRE-HAART	26.80 ± 5.04	1.00
	CONTROL	31.06 ± 7.48	1.50
CD4 count	HAART	481.06 ± 147.88	29.58
	PRE-HAART	174.16 ± 118.57	23.71
	CONTROL	886.16 ± 86.65	17.33

Table 1: Values of trace elements and CD4+T-cell count presented in mean ± SD in the study population.

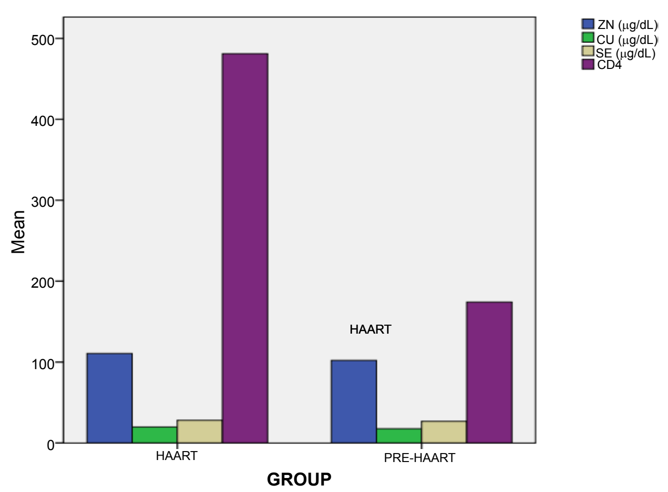

Figure 1: Values of selected trace elements and CD4+T-cell count in HAART and PRE-HAART HIV-infected persons. In this study, HAART significantly increased CD4+T-cell counts compared to participants in the pre-HAART group.

Biochemical and immunological variables

The mean serum levels of both biochemical and immunological variables in the three groups are shown in table 1. The mean ± SD values for the three groups are: CD4+T-cell-count (lymphocytes/mm^3): PREHAART patients 174.16 ± 118.573, HAART patients 481.04 ± 147.882 and control 886.1600 ± 17.33010 (Figure 1). Copper (Cu) (µg/dl): PREHAART patients 17.704 ± 3.9083; HAART patients 19.750 ± 6.8198 and control 82.076 ± 13.8027. Zinc (Zn) (µg/dl): PREHAART patients 102.16 ± 9.189, HAART patients 110.60 ± 10.132 and control 90.11 ± 12.747. Selenium (Se) (µg/dl): PREHAART patients 26.800 ± 5.0454, HAART patients 28.076 ± 7.8055 and control 31.064 ± 7.4819.

Comparison of mean ± SD of variables between PREHAART and HAART subjects

Patients on HAART had higher mean levels (P<0.05) of Zn and CD4+T-cell count compared to PREHAART (Figure 2). On the other hand, there was no significant (P<0.05) difference between the mean levels of Se and Cu in HAART patients compared to PREHAART patients (Table 1).

Comparison of mean ± SD of variables between control and PREHAART subjects

The mean serum concentrations of Se and Cu were significantly (P<0.05) lower in PREHAART patients compared to control subjects (Table 1).

Comparison of mean ± SD of variables between control and HAART subjects

Patients on HAART had higher (P<0.05) levels of Zn compared to control subjects (Figure 3). On the other hand, the mean serum levels of Cu and Se were significantly (P<0.05) decreased in HAART patients in comparison to control subjects (Table 1).

Discussion

The present study investigated the effect of antiretroviral therapy on CD4+T-cell count and selected trace elements (Zn, Cu and Se) in HIV-

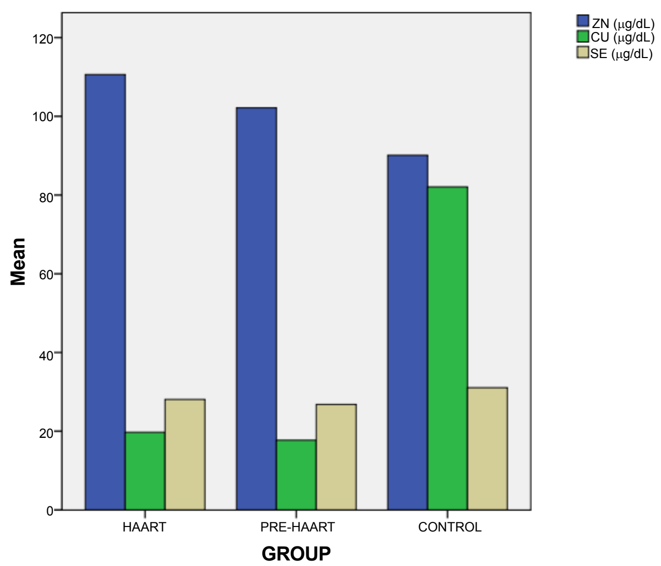

Figure 2: Values of selected trace elements in HAART, PRE-HAART and control groups. The level of Zn was significantly higher in HIV-negative control than in HIV-positive)pre-HAART and HAART groups).

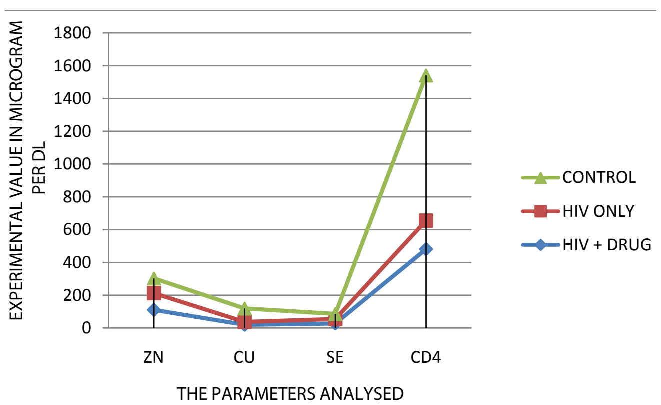

Figure 3: Values of selected trace elements in HIV-infected persons (HIV with HAART, HIV without HAART) and HIV-negative control group. In all the groups, Zn level was higher in HIV-negative control group than in HIV-positive participants without HAART and in participants who received HAART.

infected participants attending LAUTECH teaching hospital, Osogbo, Nigeria. Generally, when people are diagnosed as HIV positive, therapy is initiated when the CD4$^+$T-cell counts are less than 200 cells/mm^3. Our results showed that HIV infection decreases micronutrients such as copper and selenium and that antiretroviral therapy did not significantly improve them. Micronutrients are essential for maintaining immunological function however; deficiencies of certain minerals have been associated with impaired functions. For instance, zinc deficiency has been reported to decrease lymphocyte concentrations, copper deficiency reduced cytokine response while selenium deficiency negatively impacted on proper functioning of the neutrophils and T-lymphocytes [20-22]. Compared with HIV-negative person, HIV-infected persons have lower serum concentrations of various micronutrients and more commonly experience micronutrient deficiencies [23,24]. Among HIV-positive persons not receiving HAART, observational studies have shown that low or deficient serum concentrations of micronutrients including selenium and copper is individually associated with either low CD$^+$T-cell counts, advanced HIV-related diseases, increased disease progression and mortality [25,26]. In 1996, HAART became the new standard for HIV treatment and HAART regimens comprise 3 HIV medications among the following 4 categories: nucleoside-analog reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), Protease Inhibitors (PIs) and entry inhibitors [27] and initiation is generally recommended for patients with HIV-related opportunistic infections or a CD4$^+$T-cell count <200 cells/mm^3. HAART may restore immunological function [28] but does not eliminate weight loss and wasting [29] which continue to be strong independent predictors of mortality. It is thought that because low micronutrient concentrations are caused by similar mechanisms and several micronutrient concentrations are lower among individuals with HIV wasting syndrome, micronutrient deficiencies may also persist in the era of HAART [30]. In a study of 35 HIV adults receiving HAART, there was no significant difference in serum selenium between those on HAART and control group [31]. Another study determined concentrations of selenium, zinc and copper in 44 HIV-positive adults where 80% received combined therapy, after 23 of 30 participants with follow-up data had been initiated on HAART [32]. The percentage of persons with selenium deficiency decreased significantly from 77% to 10% and the percentage of persons with copper overload decreased significantly from 98% to 43% after HAART initiation. Interestingly, the authors reported that selenium, copper and zinc levels were neither significantly improved after HAART initiation nor higher in those receiving HAART at follow-up, and the study suggests that HAART may reduce selenium deficiency and not increasing its level.

We indirectly assessed the oxidative status by measuring the levels of the antioxidant elements such as selenium, copper and zinc and the presence of oxidative stress was observed by significant decrease in trace metals levels (Cu and Se). Oxidative cellular damage mediated by free radicals may be prevented or moderated by a normal antioxidant defense system that scavenges the ROS. This antioxidant system depends first on the integrity of an enzymatic system that requires adequate intake of trace minerals such as selenium, copper and zinc and secondly on adequate concentration of vitamin E, A and C in the cytoplasm and lipid membrane of the cells [33]. Micronutrients are critical components of essential metalloenzymes such as superoxide dismutases, glutathione peroxidases, cytochrome C oxidases, tyrozinases, uricases etc. in which most of them have antioxidant properties. The results of this study support the report of Constans et al. [34] who also confirmed that HIV-positive patients had significant lower plasma antioxidant micronutrients than control subjects.

In our study, the level of zinc was significantly higher in HIV-infected persons on HAART compared with control group and this agrees with the report of Arinola et al. [15]. The increased level of zinc in HIV-infected and even in HAART patients compared with controls may possibly reflect an unregimented measure to manage this disease in this environment. Most infected individuals accept all forms of unorthodox treatment, part of which usually include the use of herbs and dietary advice. Some of these may be a source of zinc thus contributing to the total pool of zinc in the serum of the study population. High zinc level in these patients could be beneficial since zinc could be both an inhibitor of reverse transcriptase and activator of the 'tat protein'. As earlier documented, most trace element studies are usually linked directly or indirectly with several metalloenzymes having antioxidant activities. The differences in micronutrient levels between PREHAART and HAART patients may be explained by their nutritional status. Although HAART results in increased CD4$^+$T-cell count and significant improvement in clinical, immunological and nutritional status [29] however, complications such as weight loss and wasting could be still observed in some patients on antiretroviral treatment.

We reported that HAART significantly increased CD4$^+$T-cell count compared to pre-HAART group. Previous studies have reported on significant increase in CD4$^+$T-cell count following HAART [35-37]. Significantly elevated CD4$^+$ T cell count in patients on HAART (zido vudine+lamivudine+nevirapine) compared with those not on HAART indicates an improved therapeutic efficacy of the HAART combination.

Conclusion

This study showed that HAART significantly improved immunological status of HIV-positive persons evidenced by increased CD4$^+$T-cell count and also significantly increased the concentration of zinc in the same group. However, HAART did not demonstrate a significant effect on plasma antioxidant micronutrients (selenium and copper). The decrease in antioxidant micronutrients that accompanies HIV infection suggests a potentially important role of nutritional supplementation and good nutrition in general in the proper management of HIV/AIDS.

Limitations of the Study

There are limitations in this study. Firstly, this is a cross-sectional analysis and a finding of association does not necessarily mean causation. Secondly, we cannot ascribe the lower level of selenium and copper directly to HAART. We equally recognized that serum concentrations may not be the best measure of total body stores for micronutrients since serum levels are tightly regulated across a range of dietary intake. Large randomized placebo-controlled trials should be conducted in HIV-positive persons receiving HAART to determine effects on clinical and laboratory rather than just laboratory HIV-related outcomes.

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