Effect Of Haart On Zinc Level In Hiv Positive Women: A Nigerian Study

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Abstract: This study aimed at establishing the effects of highly active antiretroviral therapy (HAART) on the distribution of zinc in the body of HIV seropositive women in their reproductive ages in both follicular and luteal phases of their menstrual cycle. Age ranges of 18-40years (mean 29years) were considered. The study was prospective, cross sectional and targeted for a particular group in a tertiary institution in Midwestern Nigeria. A targeted population of 100 HIV seropositive women of reproductive age group and 50 seronegative women of same age group as control were recruited into the study. They were recruited before the commencement of HAART and monitored for nine months at three months interval after initiation. The parameter that was measured was zinc distribution in both follicular and luteal phases of their menstrual cycles. Mean values and their standard errors of means (SEM) were computed on Microcal Origin 5.0 statistical software. Comparism of means was done using ANOVA and Student t-test. HAART significantly ($P<0.05$) elevated zinc levels in the first three months of therapy in both phases and later decreased gradually till the ninth month, with higher reductions recorded in the luteal phases at all times. **Conclusion:** In this group of young reproductive women, HAART led to elevated values of zinc in the first three months (repletion) of therapy with subsequent decrease thereafter and at all stages, lower in the luteal phase than follicular phase showing a tie with the type of sex hormones.
[Victoria N. Mokwenye and Raphael M. Mordi. **Effect Of Haart On Zinc Level In Hiv Positive Women: A Nigerian Study.** *Rep Opinion* 2015;7(11):30-35]. (ISSN: 1553-9873). http://www.sciencepub.net/report. 4. doi:10.7537/marsroj071115.04.

Key words: HIV-seropositive females; Luteal; Follicular; menstrual period; Zinc level

Introduction

The human immunodeficiency virus (HIV) is a retrovirus made up of two copies of positive single-stranded ribonucleic acid (RNA) that codes for the virus's nine genes. It is a lentivirus and one of its survival strategies is a long latency period, before severe illness or death occurs, during which time the host may pass the virus to others. This is a strategy to ensure continuity of the virus as the infection, if there is no intervention, ends in the death of the host, and consequently the end of the virus (Levy 1993).

HIV is a retrovirus which slowly but steadily attacks and destroys vital organs of the immune system and also depletes essential elements including iron and zinc. In recent times, the use of highly active antiretroviral therapy (HAART) for the treatment of HIV infected patients has generated some research findings as regards its micronutrients, vitamins and hormone levels. The aim of this study is to determine the effects of HAART on the measurement of zinc level in HIV positive women at the different phases of their menstrual cycle as HAART progresses. There are numerous reports in the literature on the role of zinc in the body (Prasad 2008; Singh 2011). Among others, zinc ions are effective antimicrobial agents even at low concentrations. There is 2-4gm of zinc distributed throughout the human body and most of it is in the brain, muscles, liver, kidney and bones, with the highest concentration in the prostrates and parts of the eye (Rink and Gabriel 2000).

However, despite the abundant reports in the literature on the roles of zinc in the body, there is no report on the effects of HAART on zinc levels on a target population of reproductive aged women on short intervals in their menstrual cycle. This study is targeted on the effects of HAART on these HIV seropositive women during the follicular and luteal phases of their menstrual cycles. Zinc, being connected with so many enzyme systems in the body, the importance of its measurement as HAART progresses cannot be over emphasized and the findings of this research can be used as a yard stick in assessing the efficiency of HAART on these patients.

Subjects And Methods

This study was done at the University of Benin Teaching Hospital (UBTH), a tertiary institution in Midwestern part of Nigeria. It has a compliment of over 800 beds and serves the whole of Edo State and beyond in the country.

Subjects: The subjects were HIV seropositive women of reproductive ages who were attending clinics and receiving treatment in UBTH.

Blood specimens were collected from these patients who were seen at the Infectious Diseases Clinic. All ethical standards as regards specimen collection were observed. Verbal and written consents were sought from willing patients before recruitment for the study using prepared forms which were attached to their case notes. Ethical standards permission was obtained from the hospital management before commencement of the programme. Only willing patients were used for the study. Only female adults of reproductive ages who were confirmed HIV positive and referred to the Infectious Disease Clinic for treatment and monitoring were used in this study. The women selected were not more than 40years old to eliminate menopausal women. Information on age, marital status, last menstrual periods (LMP) were obtained with the weight and height measured with standard scales, using prepared Data forms.

Estimation of Zinc was done using AAS Model-Solar 969 Unicam Services, an Atomic Absorption Spectrometric method. The technique is based on the ability of pyridine-2-aldehyde-2-pyridyl hydrazone (PAPHY) to form stable cationic bis complexes with zinc in the +2 oxidation state while in an aqueous medium. When the pH of the medium is shifted towards alkalinity, the charged complexes attain neutrality and are quantitatively extractable into an organic solvent. Thus the metals are free of the interfering effects of serum constituents and are easily estimated by AAS, based upon the absorption of radiation of free atoms.

Statistical Analysis

Mean values and their standard error of means (SEM) were computed on Microcal Origin 5.0 statistical software. Data analysis and graphic presentations were done using this package. Values are presented as Mean ± SEM and comparisons of means were done using ANOVA and student t-test. P-value <0.05 was considered significant for two independent variables.

Results

Zinc (Zn) responses

HIV infection led to significant elevations in zinc levels of this studied group in all phases (Fig 1). The distribution of this increase was not phase dependent (Fig.2). At the follicular phase, HAART led to significant elevation by the third month followed by decreases to the end of the study period (fig.3). The luteal phase showed the same elevation by the third month and decreases thereafter (fig.4). The same pattern of change was observed even in the amenorrhea phase (fig.5) for those that experienced amenorrhea. The comparative analysis showed that by the ninth month of study, zinc levels in all phases were comparable with the negative control values and consistently lower in the luteal phase than the follicular phase (fig. 6).

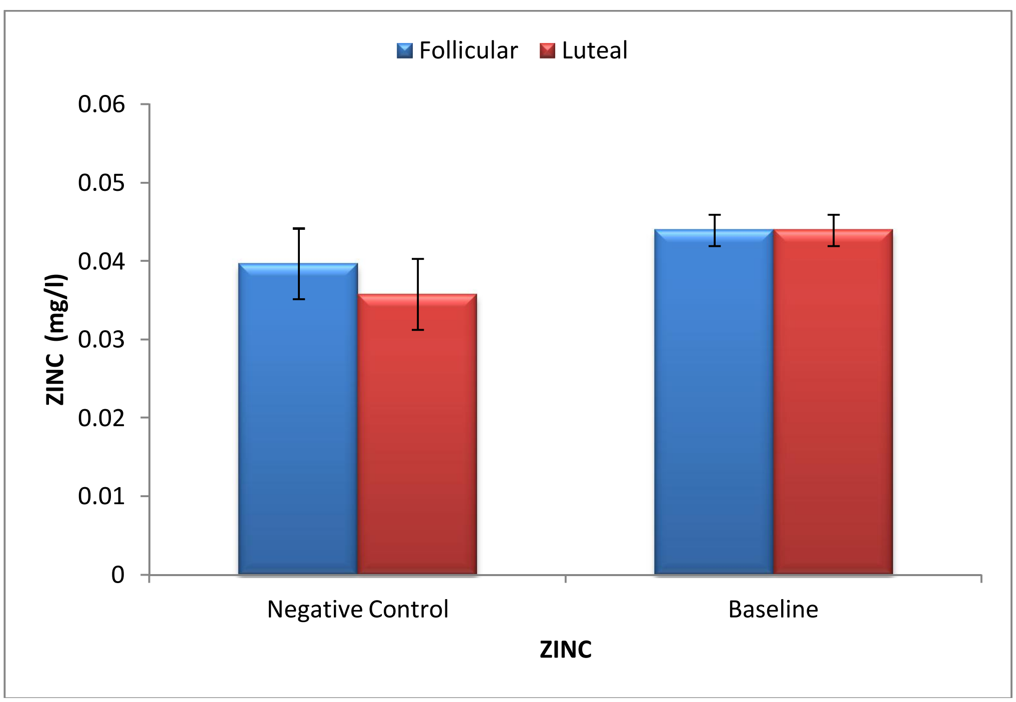

Fig. 1: Zinc Statistical Analysis Of Hiv-Positive (Baseline) And Hiv Negative Controls At The Follicular And Luteal Phases.

Infection with HIV significantly increased zinc levels at both phases.

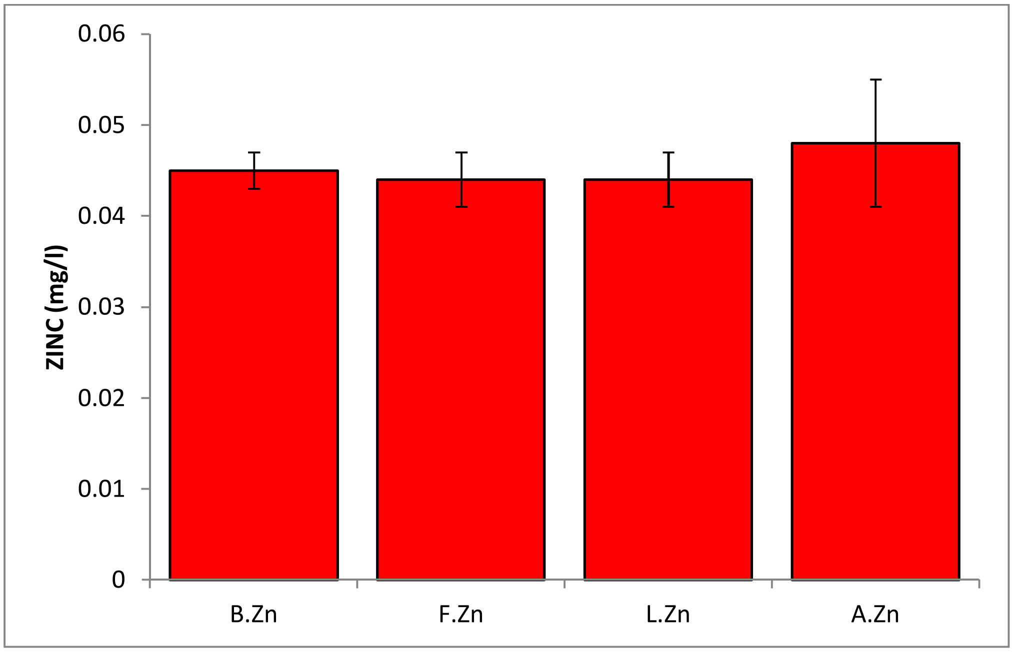

Fig. 2: Baseline Zinc Statistical Comparative Analysis

There was no statistically significant difference in the various phases.

N.B:	*P < 0.05
B.Zn	Total Baseline Zn (n = 100)
F.Zn	Follicular Baseline Zn (n = 53)
L.Zn	Luteal Baseline Zn (n = 38)
A.Zn	Amenorrhea Baseline Zn (n = 9)

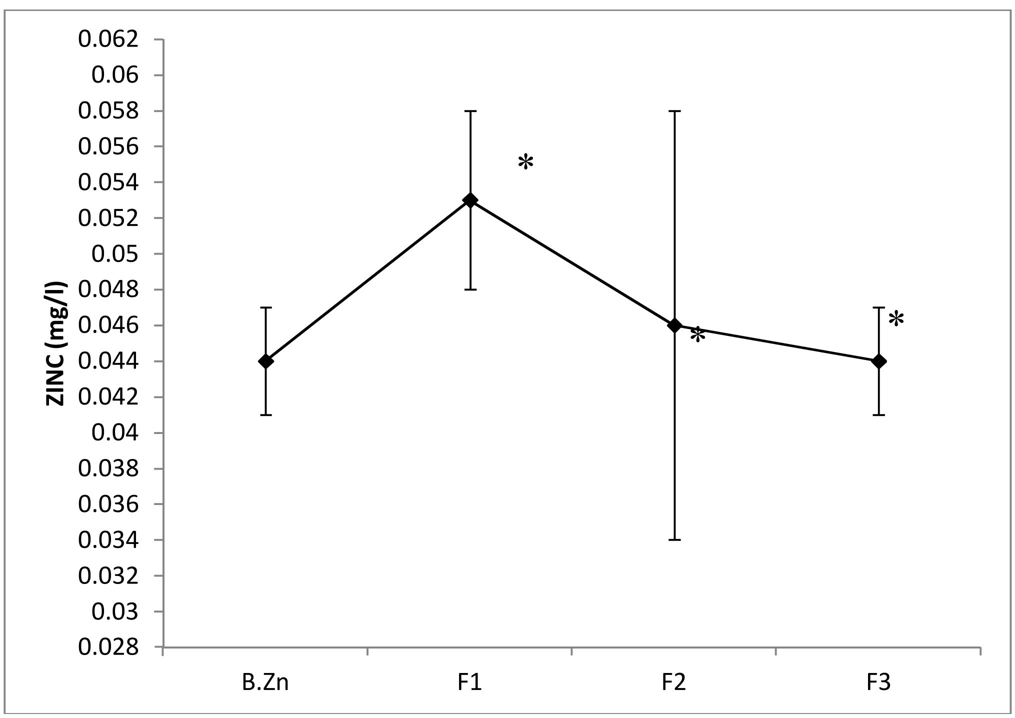

Fig. 3: Zinc Changes At Different Periods Of Haart

Administration During The Follicular Phase.

There was a statistically significant increase recorded at the 1st follow-up which thereafter decreased throughout the study period.

N.B: *P < 0.05
B.Zn: BASELINE ZINC
F1: 1ST MONITORING AT 3-MONTHS.
F2: 2ND MONITORING AT 6-MONTHS
F3: 3RD MONITORING AT 9- MONTHS

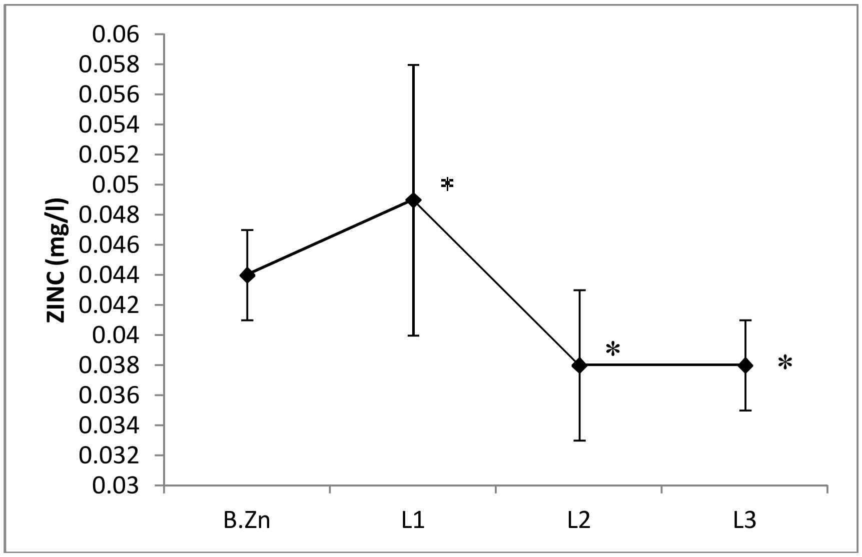

Fig. 4: Zinc Changes At Different Periods Of Haart

Administration During The Luteal Phase.

There was a statistically significant increase by the 1st monitoring with significant decreases thereafter.
N.B: *P < 0.05
B.Zn: BASELINE ZINC
L1: 1ST MONITORING AT 3-MONTHS.
L2: 2ND MONITORING AT 6-MONTHS
L3: 3RD MONITORING AT 9- MONTHS

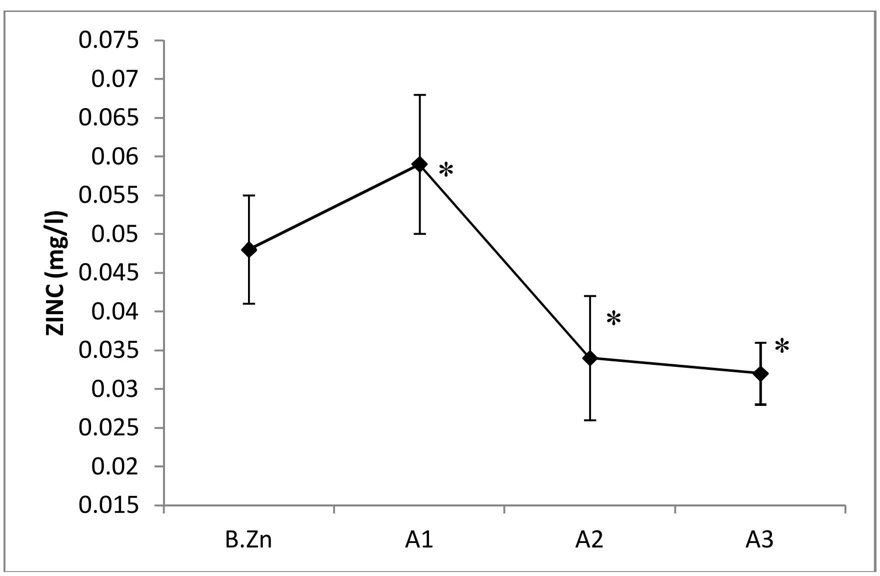

Fig. 5: Zinc Changes At Different Periods Of Haart

Administration During The Amenorrhea Phase.

There was significant increase by the 1st monitoring which dropped below the basal value by the 6th month and maintained the same trend thereafter.

N.B: *P < 0.05
B.Zn: BASELINE ZINC
A1: 1ST MONITORING AT 3-MONTHS.
A2: 2ND MONITORING AT 6-MONTHS
A3: 3RD MONITORING AT 9- MONTHS

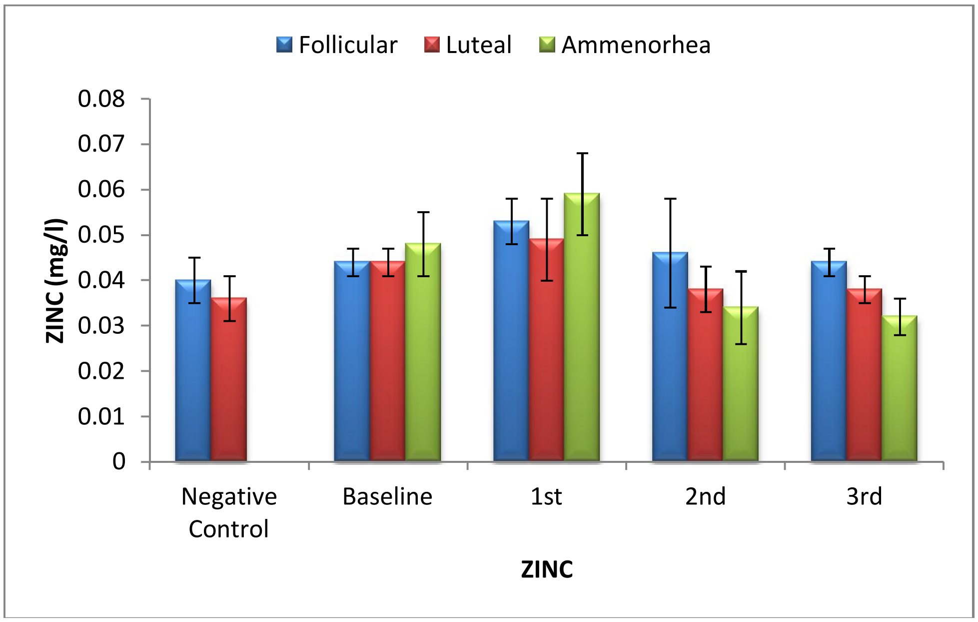

FIG. 6: Zinc Statistical Analysis Of All Phases

There were statistically significant alterations in zinc at the different phases and levels of monitoring as HAART progressed. The Luteal phase consistently maintained lower values than the follicular phase on HAART throughout the study period. By the end of the monitoring period, zinc levels had almost decreased to the negative control equivalent.

N.B: *P < 0.05
1ST MONITORING AT 3-MONTHS.
2ND MONITORING AT 6-MONTHS
3RD MONITORING AT 9-MONTHS

Discussion

In HIV infection, Zinc plays specific roles as antioxidant immune modulator (Tanaka et al., 1990) and a possible antiviral agent (Favier and Odeh 1994; Sprietsma 1999). Selenium and Zinc deficiencies are dependent on immune status and sex in HIV/AIDS patients (Rousseau et al., 2000; Wellinghausen et al., 2000). In this study, fluctuations in zinc levels in association with menstrual phases have been established. The study focused on females between ages of 18-40yrs (average 29years) and as such at peak of their sex hormone functions. Zinc levels showed significant elevations with HIV infection and not depletion, in all phases. HAART led to further elevations (repletion) by the third month of therapy. This is consistent with findings recorded in other studies (Rousseau et al.,2000; Mocchegiani et al., 2001). This shows that HAART can lead to repletion in the values of this micronutrient. By the sixth month interestingly, HAART led to reduction in zinc levels at all phases to the end of the study period.

The interesting finding in this study is that the luteal phase, at all stages of monitoring, recorded consistently lower values than the follicular phase. This disparity in serum zinc levels shows that zinc metabolism is probably tied to types of reproductive hormone levels present at each stage.

Progesterone and Estrogen are dominant in luteal phase. The persistently lower values of zinc obtained in the luteal phase indicates that these hormones are probably influencing its distribution. Zinc level recorded significant increase by the third month of therapy but had significantly depressed values at the sixth and ninth month of study in the all phases. It is assumed that elevated levels of the steroid hormones impact negatively on serum zinc levels. There will be need to do further studies on the exact mechanism involved in this finding. The finding at the follicular phase also suggests that follicule stimulating hormone (FSH) and the lutenizing hormone (LH) favours increased levels of zinc.

The relevance of zinc in resistance to infections by virus, fungi and bacteria is recognised because of its pivotal role in the efficiency of the entire immune system and in conferring biological activity to the rhythmic hormone called thymulin which has differentiation properties on T-cell lines. In infection with HIV, the zinc-bound thymulin (active thymulin) is strongly reduced with concomitant decreases in CD4+ cell counts as well. The zinc-unbound form of thymulin (inactive thymulin) is in contrast, very high (Drain et al., 2007; Fraker et al., 2000). The in-vitro addition of zinc to plasma samples induces a recovery of thymulin active form, thus, suggesting low zinc bioavailability as the cause of impaired thymic functions with consequent CD4+ cell count depletion.

Conclusion:

The emerging issue at this point is that the sex hormones have a relationship with zinc availability with prolonged HAART administration. Infection by HIV showed increased zinc levels at the untreated stage. Increasing values of progesterone and estrogen correlated with low serum levels of zinc while FSH and LH favoured serum zinc level elevations. So, zinc levels in females are tied to levels of some sex hormones.

Acknowledgement:

We thank Mr. Olumide for typing and editing this manuscript.

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11/5/2015