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Oxidative Stress and Serum Selenium in HIV Patients on Different Antiretroviral Regimen

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ABSTRACT

Background: **Two major Highly Active Antiretroviral Therapy naming as HAART-1(zidovudine, lamivudine and nevirapine) and HAART-2 (zidovudine, lamivudine and efavirenz) are considered for HIV positive patients. HIV as well as antiretroviral drugs can cause free radical formation with or without compensatory increase in serum selenium. This study was aimed at knowing serum levels of malonaldehyde (evidence of free radical production) and selenium.**

Method: **A total of 240 persons were surveyed, comprising subjects and controls. The respondents were in four groups each comprising 60 persons. The four groups are: HIV positive patients not yet on HAART termed Prehaart patients, HIV positive patients on HAART-1, HIV positive patients on HAART-2 and HIV negative patients (control). Serum levels of malonaldehyde (MDA) and selenium were assayed in each of study groups.**

Result: **CD4/mm^3 was significantly lower in subject groups when compared with control ($p<0.05$). MDA (µmol/l) was found to be higher in all subject groups but significant elevation was only found in HAART-2 group ($p<0.05$). Serum Se (µg/dl) levels were found to be significantly lower in all the groups when compared with control ($p<0.05$).**

Conclusion: **Production of free radicals was worse in patients on HAART-2. Decreased serum selenium levels in all groups may suggest reason for oxidative stress found in HIV positive patients on antiretroviral therapy.**

Abbreviation: ***HAART-1(zidovudine, lamivudine and nevirapine), HAART-2(zidovudine, lamivudine and efavirenz), MDA (Malonaldehyde),Se (Selenium).***

INTRODUCTION

Since the occurrence of HIV about two decades ago, little is known about the therapeutic regimen that can provide curative measures in its management. It has been said to affect about 40million persons worldwide (Zarocostas et al, 2005) out of which about 60% are living in African. Several mechanisms have been suggested for the course of the disease entity caused by this virus, it is generally believed and confirmed to having immunosuppressive effect and this encourages superimposed opportunistic infection (Wiwanitkit et al, 2001). Furthermore, oxidative stress has also been suggested in explaining its pathogenesis (Mollace et al, 2001) in this free radical (oxidant) production overwhelms available antioxidants.

HIV multiplies faster on the background of immunosuppression and people who are malnourished are prone to having their immunity depressed. In addition micronutrient like selenium, a trace metal enhancing some antioxidant enzymes action is also low (Dworkin et al 1994) (Favier et al,1994). However, it has been reported that low serum level of selenium observed in HIV infected patients is due to an increase demand of microelements in them. Increase free radical formation as evident by measured malonaldehyde (MDA), a product of lipid peroxidation and with decrease trace metals like selenium leads to oxidative stress. Free radical formation is not only due to HIV infection itself but can also be due to effect of some chemotherapeutics targeted on this disease condition. This may give an additive effect on lipid peroxidation caused by disease condition, worsens oxidative stress as a result of overwhelming oxidant production.

Different drug combinations are given to HIV positive patients having the expected criteria by WHO standard to commence therapy (WHO, 2003); this is called Highly Active Antiretroviral Therapy (HAART). The following combination are given in our environment based on patients' tolerability; zidovudine, lamivudine and nevirapine or zidovudine, lamivudine and efavirenz; these are referred to as 'HAART-1' and 'HAART-2' respectively. Different drug combinations have different effects and are bound to have different adverse effects in susceptible population.

In view of morbidity and mortality as well as adverse drugs reaction associated with HIV infection, this study was designed to see effects of various antiretroviral regimen on lipid peroxidation and oxidative stress, checked by serum level of MDA and selenium as an "antioxidant" as well as the disease burden itself using CD4+ count.

MATERIALS AND METHODS

This study was carried out in HIV clinic of Ladoke Akintola University of Technology Teaching Hospital, Osogbo. This is a tertiary hospital that serves medical needs of about 2million people of Osun State, Nigeria. This hospital was chosen because it is the only hospital in the state where free HIV/AIDS treatments are offered. This hospital also receives patients from neighboring villages. Patients above 18 years of age were recruited into the study, total of 240 people comprising subjects and controls. 60 subjects each for HIV positive patients not yet placed on HAART termed PREHAART patients, HIV positive patients on HAART-1(zidovudine, lamivudine and nevirapine), HIV positive patients on HAART-2 (zidovudine, lamivudine and efavirenz) and HIV negative patients (control). Controls were recruited from volunteered members of staff and their age and sex matched, they have no serological evidence of HIV and HCV infection.

After an overnight fasting, 10ml of blood was withdrawn from antecubital fossa and 5ml each was dispensed in plain and EDTA specimen bottles respectively. Both were centrifuged at 3000g and serum and plasma were extracted each into another screw cap plain specimen bottle respectively. Both set of samples were collected from subjects and controls and were kept frozen at -20^{o}C till analysis. Serum was used for selenium and MDA analyses while plasma was used for CD4+ count. MDA was analyzed by thiobarbiturate reactive substances method by Satoh *et al* (1978); Selenium was estimated by Flame Atomic Absorption Spectrophotometry using Flame Atomic Absorption Spectrophotometer serial number SN 115863752 DJ from Beckman Laboratory, Germany and CD4+cell count was estimated by Scan flow Cytometry (Becton-Dickinson, Rutherford, New Jersey, USA).

Results of the individual variable obtained were analyzed with the aid of SPSS version 18.0. Frequency tables and cross tabulations were generated and statistical significance was determined at less than 0.05. Ethical clearance was sought and gotten from the Ethics and Research Committee of Ladoke Akintola University of Technology Teaching Hospital, Osogbo.

RESULTS

TABLE I DEMOGRAPHIC TABLE OF THE STUDY POPULATION

AGE	PREHAART (n=60)		HAART-1 (n=60)		HAART-2 (n=60)		CONTROL (n=60)	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
21-30	4	8	6	14	16	10	18	16
31-40	8	14	12	14	12	10	6	4
41-50	8	12	2	6	6	2	4	-
Above 50	2	4	4	2	4	-	8	4

TABLE II MEAN±2SD OF VARIABLES BETWEEN CONTROL AND EACH SUBJECT GROUP

VARIABLES	PREHAART MEAN±2SD	HAART-1 MEAN±2SD	HAART-2 MEAN±2SD	CONTROL MEAN±2SD
AGE (years)	38.73±9.00 (p>0.05)	35.07±9.49 (p>0.05)	34.43±8.45 (p>0.05)	34.90±13.68
CD4 (lymp/mm^3)	505.53±389.73 (<0.05)	699.63±539.85 (<0.05)	471.37± 276.60 (<0.05)	1094.83±278.86
MDA (µmol/L)	0.22± 0.20 (>0.05)	0.28± 0.19 (>0.05)	0.37± 0.10 (<0.05)	0.19± 0.13
Se (µg/dl)	30.01± 5.18 (<0.05)	18.02± 2.89 (<0.05)	17.36±2.21 (<0.05)	32.79±5.46

TABLE III COMPARISON OF MEAN ±2SD OF VARIABLES WITHIN PREHAART, HAART-1 AND HAART-2 SUBJECTS

VARIABLES	PREHAART/ HAART-1 MEAN±2SD	PREHAART/ HAART-2 MEAN±2SD	HAART-1/ HAART-2 MEAN±2SD
CD4	505.53± 389.73/ 699.63±539.85 (p<0.05)	505.53± 389.73/ 471.37± 276.60 (p>0.05)	699.63± 539.85/ 471.37± 276.60 (p<0.05)
MDA	0.22± 0.26/ 0.28± 0.36(p>0.05)	0.22± 0.26/ 0.37± 0.10 (p<0.05)	0.28± 0.36/ 0.37± 0.10 (p<0.05)
Se	30.01± 5.18/ 18.02±2.89 (p<0.05)	30.01± 5.18/ 17.36±2.21 (p<0.05)	18.02± 2.89/ 17.36±2.21 (p>0.05)

TABLE IV PEARSON CORRELATION AMONG VARIABLES IN CONTROL AND TEST SUBJECTS

	MDA (µmol/L)	Se (µg/dl)
MDA (µmol/L)	1	-0.569(**)
Se (µg/dl)	-0.569(**)	1
Controls		

	MDA (µmol/L)	Se (µg/dl)
MDA (µmol/L)	1	-0.110
Se (µg/dl)	-0.110	1
PREHART subjects		

	MDA (µmol/L)	Se (µg/dl)
MDA (µmol/L)	1	-0.017
Se (µg/dl)	-0.017	1
HAART-1 subjects		

	MDA (µmol/L)	Se (µg/dl)
MDA (µmol/L)	1	0.030
Se (µg/dl)	0.030	1
HAART-2 subjects		

Correlation is significant at the 0.05 level
Correlation is significant at the 0.01 level

There was no significant difference in mean age of controls and various subject groups. Mean age values in years compared with control of 34.90±13.68 are 38.75±9.00 ($p>0.05$), 35.07±9.49 ($p>0.05$), 34.45±8.45 ($p>0.05$) for PREHAART, HAART-1 and HAART-2 respectively. CD4/mm^3 was significantly lower in subject groups when compared with control mean value of 1094.83±278.86. The mean values of 505.53±389.73 ($p<0.05$), 699.63±539.85 ($p<0.05$), 471.37±276.60 ($p<0.05$) in PREHAART, HAART-1 and HAART-2 were respectively observed. MDA (µmol/l) was found to be elevated in all subject groups but significant elevation was only found in HAART-2 group when all compared with control of mean value of 0.19±0.13. The values of 0.22±0.20 ($p>0.05$), 0.28±0.19 ($p>0.05$), 0.37±0.10 ($p<0.05$) were observed among PREHAART, HAART-1 and HAART-2 respectively. Serum Se (µg/dl) levels were found to be significantly reduced in all the groups when compared with control with mean value of 32.79±5.46. Values of 30.01±5.18 ($p<0.05$), 18.02±2.89 ($p<0.05$), 17.36±2.21 ($p<0.05$) were observed among PREHAART, HAART-1 and HAART-2 groups respectively.

Mean values within the subject groups were compared as shown in table III. CD4 was significantly elevated among patients on HAART-1 when compared with PREHAART patients (505.53±389.73 Vs 699.63±539.85 ($p<0.05$). Also there was significant reduction of CD4 among patients on HAART-2 than HAART-1 (699.63± 539.85/ 471.37± 276.60 ($p<0.05$). There was significant elevation of MDA in patients with HAART-2 than HAART-1 and PREHAART groups; 0.28± 0.36/0.37± 0.10($p<0.05$) and 0.22± 0.26/ 0.37± 0.10 ($p<0.05$) respectively. Furthermore, there were significant elevation of serum Se in PREHAART group when compared with HAART-1 and HAART-2. Values of 30.01± 5.18/18.02± 2.89 ($p<0.05$) and 30.01± 5.18/17.36±2.21 ($p<0.05$).

DISCUSSION

HIV infected individual on antiretroviral therapy is exposed to two courses of free radical injury, from the virus itself and also from antiretroviral drugs. Reacting oxygen species (ROS) may potentiate viral gene expression as well as viral replication by activating nuclear transcription factors. HIV positive Patients placed on zidovudine had been observed to having oxidative damage to DNA (De la Asuncion et al, 1998). Antiretroviral therapy also plays a role in oxidative damage to DNA and membrane polyunsaturated fatty acid, which later on, generate more free radical potentiating the cellular damage (Masia et al, 2007). In managing HIV positive patients in most part of the world, any of the regimens is not commenced until when among other criteria CD4 count is below 200/mm3; the disease burden and antiretroviral therapy put them at more risk of oxidative stress damage (Israel et al,1997)(Hurwitz et al,2004). In counteracting free radical injury, oxidant, antioxidant is most necessary, out of which trace metals are of importance (Chaturvechi et al, 2004). They are critical component of metalloenzymes such as glutathione peroxidase that also have antioxidant property; infact they are called antioxidant enzymes. Patient with free radical injury copes well with compensated increase in antioxidant level, this was observed in a study by Arinola et-al where serum zinc level was observed to be elevated in both HIV positive not on HAART and those on HAART (Olaniyi et al, 2007). This is contrary to our findings on serum selenium level; serum selenium was significantly reduced in PREHAART, HAART-1 and HAART-2 subjects compared with control. Similar result has been obtained in previous studies (Jones et al, 2006) (Paul et al, 2007).

In our study the mean age distribution of all the subject groups and control was not statistically significant; this gives a good comparative study. The disease burden was evident as a result of significant reduction in CD4 count in all the subject groups when compared with seronegative controls. CD4 is still used in this environment to monitor therapeutic effectiveness, it is reflected from this study that mean value of CD4 in PREHAART group is higher than patient on HAART-2. However, patient on HAART-1 had it elevated than patient without HAART, this could be as a result of early presentation of patient in which their CD4 count had not been seriously depressed. CD4 count in patient with HAART-2 is lowered than those on HAART-1, patient in

their pharmacogenetic variation may respond differently to the same or different therapeutic regime. However, HAART-1 has been proving to be more effective than HAART-2 (Munderi et al, 2010).

We talk about the free radical generation from viral load and antiretroviral drugs, this study shows elevated free radical formation as evident by increase MDA in all the groups, although significant elevation was only observed in patient on HAART-1. On the other hand, serum selenium levels are significantly elevated in all the groups when compared with controls. This is contrary to the work of Look Tang *et al* in which compensatory antioxidant accumulation is expected with increase in free radical production to prevent imbalance in oxidant- antioxidant levels. The decrease selenium level may be due to insufficient intake but could be more due to increase body demand as a result of disease burden because control group were drawn from the environment with the dietary available as well as the similar age group and similar body built (Monique et al, 2004). Similarly, MDA is significantly elevated in patient on HAART-2 when compared with PREHAART and HAART groups respectively; efaverenz is the only drug included in HAART-2 and included in HAART-1 that cause more free radical formation than other antiretroviral drugs.

CONCLUSION

Bearing in mind all above explained, one could conclude that compensatory accumulation of trace metals like selenium can potentiate some antioxidant enzyme effect against free radicals, oxidant are not observed in HIV positive patients as well as those on HAART-1 and HAART-2. The disease burden that increases demand for selenium may be responsible for low selenium seen in them.

RECOMMENDATION

We recommend that HIV positive patients on antiretroviral therapy should be placed also on antioxidants such as selenium.

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