Evaluation of $CD4^+$ T Lymphocytes and Renal Function Status of Naïve Human Immunodeficiency Virus-Infected Premenopausal Females

Romanus Ogai Ogalagu (Ph.D)

Department of Biochemistry, Faculty of Natural and Applied Sciences, Tansian University, Umunya, Anambra state, Nigeria.

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ABSTRACT

There is no known cure for HIV infection. However, effective preventive interventions are available that will enhance the sustainability and overall wellbeing of the patients as well as prevent vertical transmission from mother to child. This study was aimed at evaluating the renal function status of Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome – infected pre-menopausal females relative to the matched control group. The subjects used in the study were 80 HIV- positive females aged between twenty to thirty five years at the President's Emergency Plan for AIDS Relief (PEPFAR), HIV clinic, University of Nigeria Teaching Hospital (UNTH), Enugu. Samples from 80 apparently healthy non-HIV positive age-matched female volunteers served as the control group. The blood samples were collected using standard methods. HIV re-screening and confirmation were carried out using WHO HIV test algorithm. Automated method using Flow cytometry was used for the enumeration of $CD4^+$ T Lymphocytes while renal function parameters of the test subjects and the control group were carried out using standard methods. There was a significant increase $P < 0.05$ in the mean serum protein amongst the test subjects and their various groups as $CD4^+$ T lymphocyte count decreased compared with the control. The Mean serum albumin (g/L) of the overall patients/test subjects and their various sub- groups showed marked decrease $P < 0.05$ as the HIV progressed. There was a marked increase of serum urea (mmol/L) concentration $p < 0.05$ among the overall patients and their sub-groups when compared with their control counterparts. Mean serum creatinine (mmol/L) of the patients were significantly higher $p < 0.05$ than that of the control group. This study revealed a progressive renal function impairment as there was serious alterations in renal function parameters as the $CD4^+$ T lymphocytes count of the test subject decreased to 200 cells/µl and below.

Key words; $CD4^+$ T lymphocytes, HIV/AIDS, Pre-menopause and Retroviral therapy.

INTRODUCTION

There is no known cure for HIV infection. However, effective preventive intervention are available: preventing vertical transmission from mother to child, the use of condom for both sexes, pre- and post-exposure prophylaxes, voluntary medical male circumcision and the use of highly active antiretroviral therapy can control the virus and prevent it's onward transmission to other people [1]. Studies have it that over half of all people living with HIV (PLWH) globally are female [2]. This proportion is lower in many resource-rich settings, 35.3% of new HIV diagnoses in Europe in 2018 were in women [3]. The various stages of HIV-infection, asymptomatic stage inclusive, are closely associated with quantifiable medical laboratory findings spanning from HIV screening and confirmation, $CD4^+$ T lymphocyte counts, viral load test, sexually transmitted diseases tests, Tuberculosis test and serum chemistry panel tests amongst others. The most characteristic feature of AIDS is a selective depletion of the $CD4^+$ T-helper-inducer subset of T-cells. The degree of $CD4^+$ T-cell depletion is currently the single most important laboratory findings taken into consideration when recommendations are made regarding therapy with antiretroviral drugs [4]. Other functions of these surrogate markers of clinical AIDS include formulation of the decision on timing of future health care expenditure and to discriminate between apparently equivalent stages and further refine antiretroviral treatment which have been found to suppress HIV replication and rapidly increased peripheral blood $CD4^+$ T-cell counts and reversed immunodeficiency[5, 6].

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According to scholars, women living with HIV experience a high burden of co morbid diseases with common traditional risk factors and are often poorly managed. The same study also highlighted the magnitude of differences between women and men living with HIV beyond the pathophysiological state. A notable physiological difference between men and women which may contribute to differing health outcomes, is the difference between sex hormones, reproductive capability and transition through the menopause [7]. It has been reported that human immunodeficiency virus (HIV) infection and its treatment cause renal diseases which are associated with an increasing cause of morbidity and mortality in HIV positive individuals than in the general population. It has been also associated with adverse outcomes, such as complications of decreased renal functions and progression to renal failure [8]. Human Immunodeficiency virus (HIV) affects every organ system in the body by direct damage or by rendering the host susceptible to opportunistic infections. The commonest sites of HIV infection are lung, brain, heart, gut, kidney, skin, and lymphoid tissues [9]. However, kidney ailment has been reported as fourth leading condition contributing to death among those who have progressed to acquired immunodeficiency syndrome (AIDS) patients after sepsis, pneumonia, and liver disease [10].

Renal damage caused by antiretroviral drugs were reported to result in a variety of toxic drug effects presenting as acute renal failure, tubular necrosis, kidney stones and subsequently chronic renal failure [11]. There are marked changes of morbidity and shortened life expectancy in HIV–infected females and the resultant evolving epidemiology and stigmatization has seen an escalating impact on women. Menopause is a major clinical event that is universally experienced by women, but affects each individual woman differentially, uniquely or in a customized manner. For women with HIV, menopause is an important part of aging process to consider due to physiological and clinical manifestations during this period. These may include, accelerated development and progression of other age-related co morbidities, particularly cardiovascular disease, neurocognitive dysfunction, and bone mineral disease; all of which are potentially heightened by HIV or its treatment [12]. It has been reported that within the HIV-positive community, the average age of menopause is lower than the general population meaning that women with HIV are at higher risk of developing early and premature menopause [13]. There is paucity of information on naive pre – menopausal HIV/AIDS infected females in Nigeria with reference to renal function status, more especially, rural areas where the HIV scourge is quite alarming. In fact, data on this particular group of productive women not on antiretroviral therapy in Nigeria is almost nonexistent, hence this study.

MATERIALS AND METHODS

A formal approval for this work was obtained from the Medical Ethical Committee of the University of Nigeria Teaching Hospital, Ituku Ozalla, Enugu State. Informed consent was obtained from the patients prior to their inclusion in this study. Two categories of subjects were used. The first category was 80 HIV positive females aged between twenty to thirty Five years at the President's Emergency Plan for AIDS Relief (PEPFAR), HIV clinic, University of Nigeria Teaching Hospital, Enugu, Nigeria. They were counseled one on one and data on their demographic characteristic and behavioural factors obtained during the interview. Pregnant women and breast feeding mothers were excluded from the study. Similarly, patients who were on antiretroviral therapy prior to this study were not selected. The HIV/AIDS patients were divided into three groups according to Centre for Disease Control and Prevention Criteria (CDC) system [14]. This system is based on three ranges of $CD4^+$ counts *viz*: (1) ≥500, (2) 499-200 and (3) <200 cells/µl. The second category of subjects was the control group of 80 apparently healthy and HIV negative age-matched female volunteers. All the venous blood samples (10 ml) were collected from the medial cubital vein with minimal venous stasis and were dispensed into plain tubes, allowed to clot and the sera separated by centrifugation at 3,000 g for 10 minutes. The sera were used for HIV serology and analyses of other biochemical assays. Where the analyses were not possible the same day, the samples were stored at 4^0 C till the next day for analyses. HIV re-screening and confirmation tests were carried out using two enzyme linked immunosorbent assay rapid screening kits based on WHO system two, serial algorithm for detecting antibodies to HIV I & 2 [15]. Determine, a rapid screening kit (Alere Medical Company Ltd, Japan) and Immunocomb II (Organics, France) were used in the study. The first test was done using Determine HIV rapid test kit. Those that tested negative were declared negative. Those that tested positive for the first test were retested using Immunocomb II . Concordant or discordant positive samples were confirmed using western blot. The results were expressed as Mean ± Standard deviation (M ± S.D). The data were

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analyzed using graph pad Instat version 3.01, Graph pad software, San Diego, California, USA, while the test of significance was based on probability p - values of < 0.05. Comparisons between groups were performed using One-way-ANOVA, Bonferroni's multiple comparison test and student t-tests depending on the number of variables.

RESULTS

Demographic parameters of the test subjects.

Table 1.0 shows the mean age (years) 29.1 ± 3.52., 29.25 ± 2.79, 29.51 ± 3.61 and 28.35 ± 3.5 for the overall test subjects, test subjects with $CD4^+$ (cells/µl) ≥ 500, 499 - 200 and < 200 respectively. On comparison of the control value (29.78 ± 3.18) with the patients and their subgroups based on $CD4^+$ classification showed no significant difference ($p > 0.05$). The table also showed the breakdown of the 80 HIV patients based on the type of HIV they have as follows; HIV- 1 – 53, HIV-2 – 7 and HIV- 1 and HIV-2 – 20 patients. Different HIV types were further sub-divided by the CDC HIV staging depending on the levels of $CD4^+$. The result of the patients also showed massive proteinuria with the declining $CD4^+$ count. However, the 6.4 % proteinuria found in the control group may be as a result of latent sicknesses not captured in the course of this study since the controls were only apparently healthy.

Table 1: Demographic Characteristics of the Patients and the Control Group.

	Control	Test subjects	$CD4^+ \geq 500$ (Cclls/µl)	$CD4^+$ 499 -200 (Cellc/µl)	$CD4^+ < 200$ (Cells/µl)
Mean Age (yrs.)	29.78 ± 3.18	29.1 ± 3.52[aa]	29.25 ± 2.79[aa]	29.51 ± 3.61[aa]	28.35 ± 3.5[aa]
HIV - 1 (n)	-	53	10	26	17
HIV -2 (n)	-	7	2	3	2
HIV 1 and 2 (n)	-	20	8	8	4
Proteinuria (%)	6.4	47	35	45	69

[aa] represents $P > 0.05$.

RENAL FUNCTION PARAMETERS

Table 2.0 shows the serum levels of renal function parameters of the test subjects, various sub-groups and the control. Mean serum total protein (g/l) of the patients were 92.04± 2.68, 88.05 ± 0.05, 94.46 ± 0.59, and 91.22 ± 0.57 for overall patients, patients with $CD4^+$ counts (cells/µl) ≥ 500, 499 - 200 and < 200 respectively, while that of the control subjects was 79.34 ± 2.46. There was a significant increase ($P < 0.05$) in the serum protein amongst the test subjects and their various groups as $CD4^+$ count decreased. Mean serum albumin (g/l) in the test subjects were 29.97 ± 3.30, 34.82 ± 0.51, 29.24 ± 1.42, and 27.07 ± 1.26 for overall patients, patients with $CD4^+$ T-lymphocyte count (cells/µl) of ≥ 500, 499 - 200 and < 200 respectively while that of the control subjects was 41.05 ± 2.35 g/l. The overall patients and various groups of the test subjects showed marked decrease ($P < 0.05$) as the HIV progressed. Mean urea (mmol/L) of the test subjects were 49.92 ± 6.38, 43.41 ± 0.74, 47.52± 0.53, and 59.61 ± 1.06 for overall patients, patients with CD4+ T lymphocyte count (Cells/µl) ≥ 500, 499 - 200 and < 200 respectively while that of the control subjects was 8.86 ± 1.41 mmol/L. There was a marked increase of serum urea, concentration ($p < 0.05$) among the overall patients and their subjects when compared with

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their control group. Mean serum creatinine (mmol/L) of the patients were 174.49 ± 51.40, 87.60 ± 0.49, 193.52 ± 0.56, and 219.43 ± 4.74 respectively for the overall patients, patients with CD4 counts of ≥ 500, 499 - 200 and < 200 cells/µl. These values were significantly higher ($p < 0.05$) than that of the control group, 69.48 ± 8.97 mmol/L.

Table 2: Effects of HIV/AIDS on Renal Function Parameters

$CD4^+$ counts (cells /µl).

			≥ 500	499 - 200	< 200
Parameters	Controls	Test subjects			
Total protein (g/L)	79.34 ± 2.46	92.04 ± 2.68**	88.05 ± 0.50**	94.46 ± 0.59**	91.22 ± 0.57**
Albumen (g/L)	41.05 ± 2.35	29.97 ± 3.30**	34.82 ± 0.51**	29.24 ± 1.42 **	27.07 ± 1.26**
Urea (mmol / L)	8.86 ± 1.41	49.92 ± 6.38**	43.41 ± 0.74**	47.52 ± 0.53**	59.61 ± 1.06**
Creatinine (mmol/L)	69.48 ± 8.97	174.49 ± 51.4**	87.60 ± 0.49**	193.52 ± 0.56**	219.43 ± 4.74**
	N = 80	N = 80	N = 20	n = 37	n = 23

MEAN±SD

**Indicates significant difference $P < 0.05$ using one-way ANOVA/Bonferroni's multiple comparison

DISCUSSION

There was no significant difference between the mean age of the pre- menopausal female subjects compared with their control groups in this study. The study was in effect in concurrence with the works of Imai et al [16] and Andany et al [17] who found no significant difference in the mean age at menopause between HIV-infected and HIV-uninfected women. However, Fanttry et al [18] reported that HIV infected females experienced earlier menopause compared with the general population of women without HIV infection. The reason may not be far from the report of Conde et al [19] that natural menopause typically occurs between the ages of 50 and 52 years. According to them, average age of menopause displays significant country-to-country variation and therefore, an examination of the age of onset of menopause in any subpopulation requires comparison to the national average. More so, within the HIV-positive community, several reports have demonstrated that the average age of menopause is lower than the general population, and that women with HIV are at higher risk of developing early and premature menopause, menopause generally occurring below the age of 40 [17, 38], which informed the bases for the choice of age range of 20 – 35 exclding 36 years and above for the subjects in this study. According to some scholars, monitoring and implementation of targeted interventions for premature or early menopause among HIV-infected women might prevent or delay complications such as osteoporosis, cardiovascular diseases, and mental health issues [20].

This study revealed a significantly higher total serum protein in the test subjects than in the control group. This corroborates the findings by Feldman *et al* [21] and Patil *et al [22]* who reported an elevated serum total protein and globulin fraction in HIV positive subjects compared with their HIV Negative counterparts. This high total protein probably reflects a generalized, polyclonal gammopathy, with increased antibody production, which is an attempt on the part of the immune system to compensate for cellular immunodeficiency. This increase in serum protein may also be that normally, the serum protein is increased when there is infection even in absence of malnutrition. This is as a result of antibody production to contain and prevent the spread of the infection. These antibodies which are mainly gamma-globulins will increase the serum total protein concentration. In the case of HIV-infection, the high serum total protein levels is normally attributed to tissue degeneration and breakdown. Subsequently, it has been suggested that factors such as infection, changes in

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vascular permeability and hydration status can affect circulating proteins, including total protein [23, 24]. Moreover, in wasting process such as HIV/AIDS, there is increased tissue protein breakdown. The catabolism of muscle tissue to provide protein for glucose production through gluconeogenesis is suspected to add to general high level of protein in the face of reduced albumin concentration in HIV/AIDS, since there is frequently the presence of loss of appetite and hence starvation in HIV/AIDS [25]. Two key forces were implicated in this regard – negative energy balance and the cellular effect of the virus and its opportunistic infections [26]. Finally, the dehydration that accompanies diarrhoea in HIV/AIDS especially in the tropics is also suspected to lead to increased total protein level in HIV/AIDS [27]. The low serum albumin levels in our study was in concurrence with the works of [28, 29] who reported that the base line level can be considered an independent predictor of mortality in HIV-1 infected women and can be used as an additional marker of HIV-1 disease progression since hypoalbuminaemia predicts progression of disease and mortality in patients with HIV/AIDS). Other mechanisms that may explain decrease in albumin levels HIV may include anorexia and acute renal dysfunction[30, 31].

There were significant increases of serum levels of urea and creatinine $p<0.05$ compared with their control counterparts in this study. This corroborates the work of Ani et al [32] who reported a subtle but significant increases in urea and creatinine levels, associated with HIV-infected patients on antiretroviral therapy (ART) and HIV-infected patients not on ART.

This study showed renal function impairments amongst the patients. This was consistent with findings reported from the Ethiopian study; which showed an increase in prevalence of renal impairment from 3.6% before antiretroviral drugs initiation to 11.7% after ART introduction [33, 34]. Other scholars also revealed that **renal function impairment** is a common complication of **HIV infection** in both the pre- and post-ART periods and is associated with increased risk of HIV disease progression, AIDS- and non-AIDS-related events, cardiovascular disease and mortality [35, 36]. There were other scholasr reported renal function improvement after initiation of ART [37, 12]. However, others have reported no significant improvement and/or progressive loss of renal function during follow-up [38].

This study however, did not cover the post ART period as most of the subjects were coming to the hospital for the first time unaware of their HIV status and were not even ready to enroll into the ART initiation programme due to ignorance and/or their rural origin. Sometimes, their residences were not accessible to health workers who would have even taken the ART medications to their domains.

CONCLUSION

In this study, the elevation of renal function parameters; urea, creatinine and total protein with the progressive decrease of the $CD4^+$ T lymphocyte counts of the subjects and the sub groups, clearly indicate gradual renal function impairments during HIV progression. From the above results, we conclude that HIV progression to AIDS involves a multiple cellular events such as a progressive decline of $CD4^+$ T lymphocyte count including impaired renal function amongst the subjects and sub-groups as evidenced in this study.

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