ECRONICON OPEN ACCESS

EC MICROBIOLOGY
Research Article

Changes in the Levels of CD4+ T-Cell Count, 8-Hydroxy-2-Deoxyguanosine, Total Dopamine, Cortisol and Neopterin at Different Stages of HIV1-Infection

Moses Akiibinu[1]*, Fola Tayo[2], John Maduabuchi[1], Titiloye Oyewumi[3], Timothy Olagunju[4] and Bunmi Kotun[5]

[1]Department of Biochemistry and Chemistry, Caleb University Lagos, Nigeria

[2]Pharmaco-Herbal Development Laboratory, Famot Health Care Ltd, Iyeri Estate, Ikorodu-Itoikin Road, Imota, Lagos State, Nigeria

[3]Immunology Unit, Department of Chemical Pathology, College of Medicine, University of Ibadan, Ibadan, Nigeria

[4]Department of Chemical Pathology, University College Hospital, Ibadan, Nigeria

[5]Department of Biological Science and Industrial Biotechnology, Ccaleb University Lagos, Nigeria

***Corresponding Author:** Moses Akiibinu, Department of Biochemistry and Chemistry, Caleb University Lagos, Nigeria.

Received: May 24, 2022; **Published:** June 13, 2022

Abstract

Background: CD4 + T-cell remains the golden biomarker that changes with progression/severity of HIV/AIDS. This study assessed the levels of certain selected metabolites in different stages of HIV1- infection.

Methods: Sixty newly diagnosed HIV1-infected patients with varied CD4 + T-cell counts participated in this study. They were classified as CD4 + T-cell counts > 250 cells/µl (group 1), CD4 + T-cell counts ranging from 180 to 250 cells/µl (group2), and CD4 + T-cells < 180 cells/µl (group3). Another 25 apparently healthy age and sex-matched individuals without HIV1-infection served as controls (group4). Plasma levels of 8-hydroxy-2-deoxyguanosine (8-OHdG), total dopamine (TD), cortisol and neopterin were determined in all participants using enzyme linked immunosorbent assay (ELISA) methods. CD4+T-cell count was determined using flow cytometry method.

Results: Significantly ($p < 0.05$) higher levels of 8-OHdG, TD and neopterin were observed in all groups compared with controls. There were no significant ($p > 0.05$) changes in the levels of cortisol in all groups compared with controls. There was a significant correlation ($r = -0.49$, $p < 0.05$) between TD and CD4 + T-cell in HIV1-infected patients. Neopterin, cortisol and 8-OHdG did not show any significant ($r = -0.14$, $p > 0.05$; $r = -0.11$, $p > 0.05$; $r = -0.25$, $p > 0.05$ respectively) correlations with CD4 + T-cells in HIV-1 infected patients.

Conclusion: HIV1 infection could induce oxidative DNA-damage, dopamine synthesis and macrophage activation. Total dopamine level could be used to assess the progression of HIV1-infection. Further investigation may be needed to ascertain the findings.

Keywords: *DNA-Damage; Dopamine; Cortisol; Macrophage Activation; HIV1; CD4-T-Cells*

Introduction

HIV1 is an intracellular pathogen that requires resting CD4+ T-cells, activated CD4+ T-cells and macrophages for survival in the earliest phases of infection. The first entry step of HIV1 into the cells involves interaction of envelop (Env) protein with negatively charged cell-

surface heparan sulfate proteoglycans [1], α4β7 integrin [2] or pattern recognition receptors such as dendritic-cell–specific-intercellular adhesion molecular 3-grabbing non-integrin (DC-SIGN). The second entry step involves binding of the envelop protein (Env) to the host protein CD4, which is the primary receptor [3]. Affinity of the virus gp120 for CD4 and CXCR4 makes the CD4+ T-cells the primary target of HIV1. The virus has potential to induce cellular activation, CD4 + T-cell destruction, collagen deposition, and inflammation [4]. The memory CD4 + T-cells are selectively depleted from circulation during infection; and as the disease progresses, CD4 + T-cells of both the naive and memory phenotype are also lost from circulation [5]. X4 strain of the HIV-1 has ability to use the CXCR4 coreceptor to infect thymocytes as well [6]. Progressive depletion of CD4 + T-cell subset is also aided by its failure to undergo cell division in almost all cases of untreated HIV-1 infection. In an advanced disease, significant CD4 + T-cell populations are lost from the circulation and from lymphoid tissue sites. This makes circulating CD4 + T-cell a golden tool widely used as a measure of immune competence and a predictor of the immediate risk for opportunistic illnesses.

Neopterin or 2-amino-4-hydroxy-6-(D-erythro-1',2',3'-trihydroxypropyl) pteridine is a catabolic product of guanosine triphosphate in a reaction catalysed by guanosine triphosphate cyclohydrolase I (GTPCH I) when monocytes/macrophages are activated by interferon-gamma [7]. Little quantity of neopterin is also produced by activated monocytes, dendritic cells, endothelial cells, renal epithelial cells, fibroblasts, and vascular smooth muscle cells upon stimulation mainly by interferon gamma and to a lesser extent by interferon alpha and beta, with its release being enhanced by tumor necrosis factor. In human, increased secretion of neopterin is indicative of a pro-inflammatory immune status and macrophage activation during infection [8]. Neopterin release in response to cytokines by T-lymphocytes and natural killer cells also make neopterin an indicator of activation of cell mediated immunity in diseases like tuberculosis, HIV/AIDS, malignancies and autoimmune diseases [9]. Berdowska and Zwirska-Korczala [9] suggested that neopterin levels predict HIV-related mortality more efficiently than clinical manifestations.

Dopamine is an intermediate product of tyrosine metabolism in the adrenal medulla. It is an important catecholamine neurotransmitter that modulates many physiological functions, and contributes to pathophysiology of many diseases [10]. Dopamine synthesized in both central nervous system and the periphery is a neurotransmitter that exerts its actions upon binding to G protein-coupled receptors. The receptors are widely expressed in the body and the hormone functions in both the peripheral and the central nervous system. Dopamine plays a role in mood, sleep, learning, memory, the ability to focus, and motor control [11]. Auto-oxidation and metabolism of accumulated synaptic dopamine can lead to generation of reactive oxygen species, quinines, semiquinones, and induction of apoptosis of neurons [12]. Excessive dopamine in circulation could enhance cellular vulnerability to HIV [13]. Peter., *et al*. [14] reported that dopamine increases the number of macrophages infected by HIV1 while Dopamine Receptor D2 (D2R) agonist increases HIV1 replication. Abnormal D2R accounts for problems in signal transferring between the nervous systems that may lead to diverse serious disorders like schizophrenia, autism and Parkinson›s disease [15]. Experimental evidence suggests that HIV proteins (e.g. Tat and gp120) can cause toxicity to dopaminergic neurons in-vitro and in rodent models [16]. The HIV has the potential to invade the basal ganglia and damage the dopamine neurone. However, Kure., *et al*. [17] reported that neuropathology is associated with high HIV1 viral burden in the basal ganglia that has the highest density of dopaminergic terminals. Excess dopamine plays significant roles in several mental disorders such as attention deficit hyperactivity disorder, obsessive-compulsive disorder, schizophrenia, paranoia, hallucinations, psychosis, manic phase of bipolar disorder [18]. Himelhoch *et al*. [19] reported that psychiatric disorders are common in HIV patients, and previous work suggests that these patients experience delays in treatment with highly active antiretroviral therapy (HAART). Since dopamine is implicated in several mental disorders, this study aimed to assess the status of dopamine in different stages of HIV1-infected patients.

Cortisol is a metabolic product of cholesterol synthesized in the adrenal cortex. Previous studies show enhanced cortisol synthesis in HIV patients more than in the general population [20]. Evidences of pathological effects of HIV1 infection on adrenal gland have also been documented. Bricaire., *et al*. [21] reported abnormal histology of adrenal glands in 64 of 83 patients with HIV disease at postmortem examination [22]. In human sepsis, the hypothalamo-pituitary–adrenal axis is upregulated, resulting in elevated cortisol level which in the acute phase of infection is associated with increased adrenocorticotrophic hormone release [23]. Increased cortisol level in HIV1-

infeection was hypothesized to enhance HIV1 progression. Increased cortisol secretion during severe infection could cause a shift in the balance of Th1/Th2 cell ratio towards a Th2 response [24]. Wisniewski., *et al*. [25] reported that plasma DHEA concentrations correlated positively with the CD4 cell count, while other studies also demonstrate a negative linear correlation between CD4 count and cortisol levels [26]. Some studies did not find any correlation between infections and cortisol levels [25]. Contrary to other studies, Eledrisi and Verghese [27] reported adrenal insufficiency as complication of HIV1 infection.

Free radicals are molecular products of many inflammatory cells during infections [28,29]. The molecules have the potentials to oxidize both macro and micro-components of the cells. Effects of the free radicals on the poly unsaturated fatty acid lead to generation of peroxidation products including malondialdehyde, hydroxyguanosine (OHdG) etc. Cellular DNA is damaged by excess free radicals generated during cellular respiration, cell injury, phagocytosis, and exposure to environmental oxidants [30]. It has been estimated that while OHdG is generated in human cellular DNA as a by-product of normal metabolic processes at the rate of 178 residues/cell/day, increased free radical load would enhance the OHdG generation significantly [31]. The guanine analogue 8-hydroxyguanine is an abundant base modification in mammalian DNA whose level increases with oxidative stress. Keith., *et al*. [32] demonstrated mutagenic replication of hydroxyguanine (oh'Gua) as template causing G + T substitutions and misincorporation of OHdG as substrate causing A + C substitutions. This damage to DNA bases may lead to cancer and other diseases [33]. The present study was designed to assess the correlations and possible changes in the marker of oxidative DNA-damage, neuroactivity, cortisol and macrophage activation with changes in CD4+ T-cell counts in different stages of HIV1-infection by determinining the levels of CD4+ T-cells, plasma levels of 8-hydroxy-2-deoxyguanosine (8-OHdG), total dopamine (TD), cortisol and neopterin in different stages of HIV1- infection.

Materials and Methods

Sixty newly diagnosed HIV-1 seropositive patients were recruited for this study. Twenty of them had CD4+T-cell counts > 250 cells/µl (group 1), 20 had CD4+T-cell counts ranging from 180 to 250 cells/µl (group 2), and 20 had CD4 + T-lymphocyte count < 180 cells/µl (group 3). Another 25 apparently healthy non-HIV1 infected individuals who were not on any medication, nor had metabolic diseases served as controls (group 4). None of the participants had diabetics, chronic ulcer, cancer, or renal diseases at the time this study was conducted. Pregnant/lactating women and HIV 1 infected patients on antiretroviral drugs were excluded from the study. The height and weight of the participants were measured with standard methods, and the body mass index calculated. This study was approved by the Institutional Review Board; and informed consent obtained from all participants before the commencement of the study. 5 milliliters (ml) of venous blood sample was taken from the anticubital vein of every participant. 2ml was put into EDTA bottle for the determination of CD4+ T-cell levels. The remaining 3ml was put into lithium heparin bottle, centrifuged, and the plasma separated and stored at -20oC for the determination of 8-hydroxy-2-deoxyguanosine, total dopamine, cortisol and neopterin.

Methods

Determination of CD4+ T-cell

Levels of CD4 + T-cells was carried out using a flow cytometer (BD FACS Count, model-337858). The principle is based on the fact that cells labeled with fluorescent dyes are forced through a nozzle in a single cell stream that passes through a laser beam. As the cells are forced through, the light from the laser beam is intersected causing forward scattering, side scattering or fluorescence which is detected by photomultiplier tubes. All the informations are processed by the central processing unit attached to the machine and displayed as histogram.

Determination of total dopamine

Total Dopamine was determined by using commercially prepared reagents by IBL International GMBH, a commercially prepared enzyme linked immunosorbent assay (ELISA) kits by Mybiosource (Cat. No- MBS494145) as described by Lee., *et al* [34].

Determination of cortisol

Cortisol was determined by using commercially prepared enzyme linked immunosorbent assay (ELISA) kits (cat. numbers 24, 94K032) by InterMedical S.R.I. Villanicca (NA) Italy.

Determination of 8-OHdG

DNA-8-hydroxyguanosine was determined by using commercially prepared enzyme linked immunosorbent assay (ELISA) kits by Mybiosource (Cat. Number-MBS808265) as described by Endo., *et al* [35].

Determination of neopterin

Neopterin was determined by using commercially prepared enzyme linked immunosorbent assay ELISA kits produced by IBL Tecan (Catalog number: RE59321) as reported by Murr., *et al*. [36] and Edén., *et al* [37].

Statistical analysis

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) for windows, version 21. The data were expressed as Mean ± SD. Student's t-test was used for the comparison of HIV1-infected patients and controls. Pearsonian correlation coefficient (r) was calculated. The changes were considered significant, when p-values were less than 0.05.

Results

As shown in table 1 and 2, the body weight and body mass index of HIV1-infected patients in groups 2 and 3 were significantly ($p < 0.05$) lower compared to controls. Meanwhile, there was no significant ($p > 0.05$) change in the body weight and body mass index of group 1 compared to controls. Figure 1 shows that CD4 + T-cells decreased significantly ($p < 0.05$) in HIV1-infected patients compared with controls. All HIV1-infected patients show significantly ($p < 0.05$) higher levels of 8-OHdG, TD and neopterin (Figure 2 to 4) compared with the controls. There were no significant ($p > 0.05$) changes in the levels of cortisol (Figure 5) in all groups of HIV1-infected patients compared with controls. When compared within HIV1-infected groups, the plasma levels of 8-OHdG were significantly ($p < 0.05$) higher in groups 1 and 2 compared with group 3. Plasma TD level correlated significantly ($r = -0.49$, $p < 0.05$) with CD4 + T-cell counts in HIV1-infected patients. Neopterin, cortisol and 8-OHdG did not show significant ($r = -0.14$, $p > 0.05$; $r = -0.11$, $p > 0.05$; $r = -0.25$, $p > 0.05$ respectively) correlations with CD4 + T-cell counts in HIV-1 infected patients.

	HIV1 (CD4+T-cell > 250 cells/µl-group 1)	HIV1 (CD4+T-cell 180 to 250 cells/µl--group2)	HIV1 (CD4+T-cell <180 cells/µl -group 3)	Non-HIV (Controls-group4)	pa-values	pb-values	pc-values
Age (years)	49.40 ± 10.12	51.40 ± 9.10	48.35 ± 12.11	46.17 ± 15.03	>0.05	>0.05	>0.05
Height(M)	1.70+0.10	1.66±0.14	1.71±0.12	1.68 ± 0.07	>0.05	>0.05	>0.05
Weight(Kg)	61.60 ± 9.84	54.48 ± 6.44	49.14 ± 8.50	69.56 ± 7.54	>0.05	<0.05*	<0.05*
BMI(Kg/M^2)	21.50±3.74	18.9±3.22	16.01±3.47	24.64 ± 3.54 2	>0.05	<0.05*	<0.05*

Table 1: *Demographic Characteristics of HIV1-infected Patients and Controls.*

pa = significance of the difference between controls and HIV1 (CD4+T-cell > 250 cells/ml-group 1);

pb = significance of the difference between controls and HIV1 (CD4+T-cell 180 to 250 -group2); pc =significance of the difference between controls and HIV1 (CD4+T-cell <180 cells / ml -group 3);

**= significantly different from controls.*

Group	R-Value	P-Value
CD4 T-cells/ Neopterin	-0.14	>0.05
CD4+ T-cells/ Total Dopamine	-0.49	<0.05*
CD4 T-cells/ DNA-8-OHG	-0.25	>0.05
CD4 T-cells/ Cortisol	-0.11	>0.05

Table 2: *Correlation between CD4+ T-cell counts, DNA-8-OHG, Total Dopamine and neopterin in HIV 1 infected individuals *= significant correlation.*

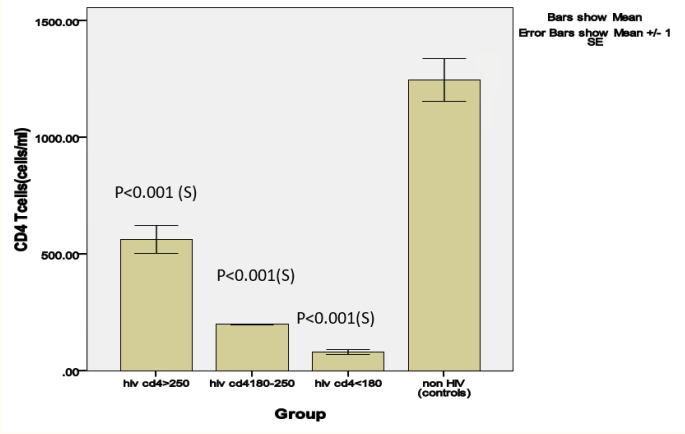

Figure 1: *Levels of CD4+ T-cells in Different Stages of HIV1 Infection and Controls.*

S= significantly different from controls.

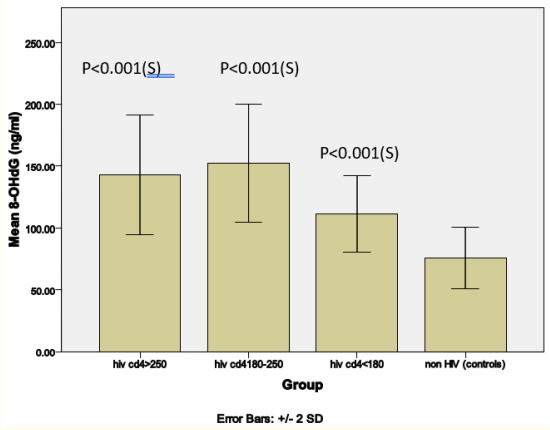

Figure 2: *Levels of 8OHdG in Different Stages of HIV1 Infection and Controls.*

S= significantly different from controls.

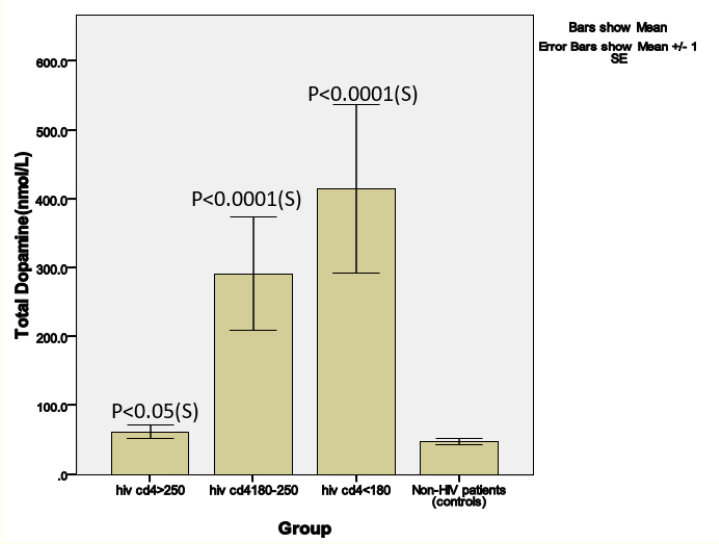

Figure 3: *Levels of Total Dopamine in Different Stages of HIV1 Infection and Controls.*

S= significantly different from controls.

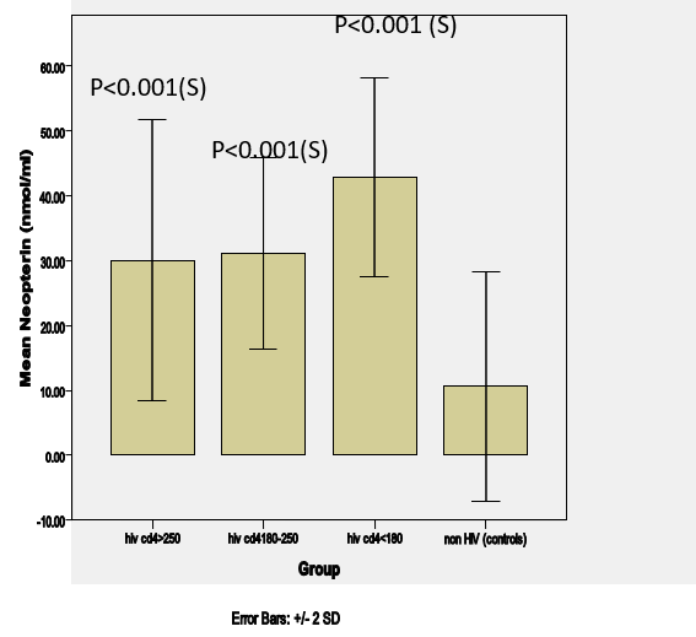

Figure 4: *Levels of Neopterin in Different Stages of HIV1 Infection and Controls.*

S= significantly different from controls.

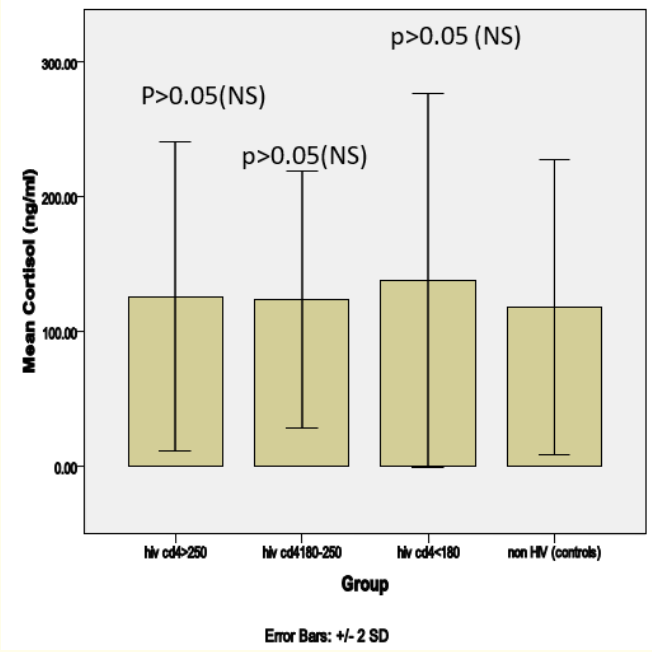

Figure 5: *Levels of Cortisol in Different Stages of HIV1 Infection and Controls.*

NS= insignificantly different from controls.

Discussion

It is evident that progressive destruction of lymphoid architecture by HIV/AIDS leads to reduced immunological activities and enhanced depletion of CD4 + T-cells in the infected patients [4]. Several studies show that susceptibility to opportunistic infection and waning of CD4+ T-cell count to a level less than 200/μL predict the risk of disease progression. Therefore, the progression of HIV1-infection can be determined by monitoring the rate of decrease of the circulating CD4+ T-cells over time. Our study also confirms progressive downregulation of CD4+ T-cells level with advancement of the disease in infected individuals recruited for this study. This CD4+ T-cells depletion could be due to the cytotoxic effect of HIV1, overactivation of other cells with cytotoxic potentials or oxidative DNA damage of the infected cells. Our result corroborates the findings of Mellors., *et al*. [38] who reported that CD4+ T-cell declines with progression of the disease. This study also agrees with Carter and Hughson [39] who reported that the CD4 + T-cell is the most important laboratory indicator of immune function and the strongest predictor of subsequent disease progression and survival in HIV-infected patients. Surprisingly, a significant correlation ($r = -0.49$, $p < 0.05$) existed between total dopamine and CD4 + T-cell counts in the HIV1-infected patients recruited for this study. Therefore, it could be hypothesized in this study that increase in total dopamine would predict the disease progression; a possible novel of this study.

Pro-inflammatory cytokines released during cellular activation trigger the production of reactive oxygen species, resulting in DNA and RNA lesions [40]. Excess production of reactive oxygen species during chronic inflammation may have damaging effects on biomolecules such as DNA, proteins, and lipids, leading to cellular dysfunction, metabolic syndrome, oxidative DNA damage and cell death [41]. Several studies reported that HIV1 induces oxidative stress and DNA damage in the infected cells via multiple mechanisms, including viral Tat protein [42]. Previous reports have implicated chronic inflammation and high free radical load in HIV1 infection as possible causes of DNA

damage and gene mutation [43]. Oxidation of guanine in the infected cells can lead to enhanced production of 8-oxo-7, 8-dihydroguanine. These and other factors might account for the significantly higher metabolic disorders and oxidative DNA damage previously reported in HIV-positive patients [41]. According to Shibutani., *et al*. [44], the oxidized guanine in genomic DNA causes transversion mutation which could contribute to DNA damage, genomic instability and protein metabolic dysfunction. Elevated levels of OHdG in the HIV1-infected patients recruited for this study could be due to the effects of the excess free radicals on the DNA of the infected cells. Our study therefore corroborates previous studies implicating HIV/AIDS as a factor in oxidative DNA-damage and certain malignancies [40]. This study also agrees with Aukrust., *et al*. [45] who reported that increased level of 7, 8-dihydro-8-oxoguanine is a marker of oxidative DNA damage in HIV1-infected CD4 + T-cells, since we also observed that the plasma level of OHdG increased progressively in the early stage of HIV1-infection and declined when the CD4 + T-cell fell below 180 cells/µl. It is therefore reasonable to hypothesize that OHdG production in HIV1-infected patients is dependent on functional impairment or population of the CD4+ T-cells.

Neopterin is a catabolic product of guanosine triphosphate in a reaction catalysed by guanosine triphosphate cyclohydrolase. It is predominantly produced by activated macrophages during infection. Available reports show that neopterin may be used as an additional parameter for differential diagnosis and prediction of HIV/AIDS progression [46]. Tsoukas and Bernad [47] also suggested that neopterin could be used as a marker of immune activation and determination of HIV1 infection prognosis. Previous studies also revealed that neopterin level increases early in the course of HIV1 infection, even before CD4 + T-cell depletion and clinical manifestation of AIDS. The present study also shows a significantly higher level of neopterin at early stage before depletion of CD4 + T-cells. Plasma levels of neopterin were consistently significantly higher in the three groups of HIV1-infected patients recruited for this study. Our findings seems to corroborate the report of Fuchs., *et al*. [7] who stated that neopterin level usually increases before first symptoms appear, and before formation of specific antibodies becomes detectable. This study does not corroborate other reports which state that neopterin level increases with the progression of HIV1 infection, and highest values detected in serum and urine in patients with AIDS [48].

Available reports show that adrenal gland can be directly infected by many microbial pathogens, including viruses, fungi, and bacteria. The adrenal glands activities are sensitive to stress, opportunistic infections; mostly cytomegalovirus and mycobacteria, and malignant tumours like non-Hodgkin's lymphoma and Kaposi's sarcoma [22]. These reports of Christeff., *et al*. [26] and Chittiprol., *et al*. [49] show that cortisol level increases in all HIV1-infected patients, independently of the ART treatment. In contrast to the increased plasma cortisol concentration reported in HIV1 infected patients by some previous researchers, our study did not show any significant change in the plasma levels of cortisol in the HIV1-infected patients recruited for this study. This could be due to many factors including suppressive effect of HIV1 on adrenal glands, malnutrition, malabsorption, mal-assimilation of lipids etc. Our finding agrees with Odeniyi., *et al*. [50] who reported that serum cortisol levels are within the normal range in many persons with HIV infections even in the presence of reduced adrenocortical function.

Dopamine is a neurotransmitter that plays several important roles in the brain and other parts of the body as an organic chemical of th e catecholamine and phenethylamine families. It constitutes about 80% of the catecholamine content in the brain. Therefore, hyperactivity of dopamine in the mesolimbic pathway mediates positive psychotic symptoms and aggression. Experimental evidence suggests that HIV1 infected proteins (e.g. Tat and gp 120) may cause toxicity to dopaminergic neurons in-vitro and in rodent models [19]. We observed significantly higher levels of total dopamine that increased progressively with decrease in the level of CD4 + T-cells in our HIV1-infected patients. The significantly higher level of total dopamine in this study could be due to possible activation or damaging effects of HIV1 on neurons and adrenal medulla containing dopamine. Hence, the release of excess dopamine into the circulation with progression of the disease. Peter., *et al*. [17] have previously reported that dopamine increases the number of macrophages infected by HIV1 while Dopamine Receptor-2 agonist increases HIV1 replication. Experimental evidence suggests that HIV1 proteins (e.g. Tat and gp120) can cause toxicity to dopaminergic neurons in-vitro and in rodent models [19]. Therefore, increased plasma dopamine could be an enhancer of HIV1 replication against immune protective strategies in an untreated HIV1-infection. The HIV/AIDS severity-dependent hyperdopaminemia

observed in this study could cause certain mental disorders like schizophrenia, paranoia, hallucinations, psychosis, manic phase of bipolar disorder in these patients [21]. Our study may therefore strongly agree with the report of Scheller., *et al*. [16] that excessive dopamine in circulation could enhance cellular vulnerability to HIV1.

Conclusion

In conclusion, HIV-1 infection could enhance oxidative DNA-damage, increase plasma dopamine level and macrophage activation. It could be speculated that total dopamine level increases with progression of HIV1-infection. This study may therefore suggest further evaluation of the relevance of total dopamine in the progressive HIV1 infection. There may be a need for dopamine antagonist therapy in patients with advanced stage of HIV/AIDS.

Authors' Contributions

MA, FT, JM, TO3, TO4 and BK designed the research, MA did the analysis and all authors contributed and approved the final manuscript.

Acknowledgements

The authors appreciate Mr. F.J. Abegunde and Mr. Dele Adigun, Department of Biochemistry and Chemistry, Caleb University Lagos, Nigeria for the material and technical supports.

Conflict of Interest

No conflict of interest declared by the authors.

Sponsorship

This study was funded by the Caleb University Lagos and the authors.

Bibliography

1. Saphire EO., *et al*. "Against HIV-1: A Template for Vaccine Design Crystal Structure of a Neutralizing Human IgG". *Science* 293 (2001): 1155.
2. Cicala C., *et al*. "The integrin α4β7 forms a complex with cell-surface CD4 and defines a T-cell subset that is highly susceptible to infection by HIV-1". *Proceedings of the National Academy of Sciences of the United States of America* 106.49 (2009): 20877-20882.
3. Maddon PJ., *et al*. "Axel R Cell 47 (1986): 333-348.
4. Schacker TW., *et al*. "Collagen deposition in HIV-1 infected lymphatic tissues and T cell homeostasis". *Journal of Clinical Investigation* 110 (2002): 1133-1139.
5. Roederer M., *et al*. "CD8 naive T cell counts decrease progressively in HIV-infected adults". *Journal of Clinical Investigation* 95 (1995): 2061-2066.
6. Berkowitz R D., *et al*. "CCR5- and CXCR4-utilizing strains of human immunodeficiency virus type 1 exhibit differential tropism and pathogenesis in vivo". *Journal of Virology* 72.12 (1998): 10108-10117.
7. Fuchs D., *et al*. "Neopterin as a marker for activated cell medicated immunity: application in HIV infection". *Immunology Today* 9 (1988): 150-155.

8. Immanuel C., *et al*. "Serum neopterin levels in HIV infected patients with and without tuberculosis". *Indian Journal of Medical Research* 121 (2005): 220-225.

9. Berdowska A and Zwirska-Korczala K. "Neopterin measurement in clinical diagnosis". *Journal of Clinical Pharmacy and Therapeutics* 26.5 (2001): 319-329.

10. Missale C., *et al*. "Dopamine receptors: from structure to function". *Physiological Reviews* 78 (1998): 189-225.

11. Klein MO., *et al*. "Dopamine: Functions, Signaling, and Association with Neurological Diseases". *Cellular and Molecular Neurobiology* 39.1 (2019): 31-59.

12. Purohit V., *et al*. "Drugs of abuse, dopamine, and HIV-associated neurocognitive disorders/HIV-associated dementia". *Molecular Neurobiology* 44.1 (2011): 102-110.

13. Scheller C., *et al*. "Dopamine activates HIV in chronically infected T lymphoblasts". *Journal of Neural Transmission* 107 (2000): 1483-1489.

14. Peter J Gaskill., *et al*. "Human Immunodeficiency Virus (HIV) Infection of Human Macrophages Is Increased by Dopamine. A Bridge between HIV-Associated Neurologic Disorders and Drug Abuse PMC2731133". *The American Journal of Pathology* 175.3 (2009): 1148-1159.

15. Seeman P., *et al*. "Brain receptors for antipsychotic drugs and dopamine: direct binding assays". *Proceedings of the National Academy of Sciences of the United States of America* 72.11 (1975): 4376-4380.

16. Nath A., *et al*. "Acceleration of HIV dementia with methamphetamine and cocaine". *Journal of Neuro Virology* 7 (2001): 66-71.

17. Kure K., *et al*. "Morphology and distribution of HIV-1 gp41-positive microglia in subacute AIDS encephalitis". *Acta Neuropathologica* 80 (1990): 393-400.

18. Tost H., *et al*. "Dopamine and Psychosis: Theory, Pathomechanisms and Intermediate Phenotypes". *Neuroscience and Biobehavioral Reviews* 34.5 (2010): 689-700.

19. Himelhoch S., *et al*. "Understanding associations between serious mental illness and HIV among patients in the VA health system". *Psychiatric Services* 58 (2007): 1165-1172.

20. Lo J and Grinspoon SK. "Adrenal function in HIV infection". *Current Opinion in Endocrinology, Diabetes and Obesity* 17.3 (2010): 205-209.

21. Bricaire F., *et al*. "Adrenocortical lesions and AIDS". *Lancet* 1 (1988): 881.

22. Arlt W and Allolio B. "Adrenal insufficiency". *Lancet* 361 (2003): 1881-1893.

23. Corley PA. "HIV and the cortisol connection: A feasible concept of the process of aids". *Medical Hypotheses* 44.6 (1995): 483-489.

24. Croxson TS., *et al*. "Changes in the hypothalamic-pituitary-gonadal axis in human immunodeficiency virus-infected homosexual men". *The Journal of Clinical Endocrinology and Metabolism* 68 (1989): 317-321.

25. Wisniewski TL., *et al*. "The relationship of serum DHEA-S and cortisol levels to measures of immune function in human immunodeficiency virus-related illness". *The American Journal of the Medical Sciences* 305 (1993): 79-83.

26. Christeff N., *et al*. "Changes in cortisol/DHEA ratio in HIV-infected men are related to immunological and metabolic perturbations leading to malnutrition and lipodystrophy". *Annals of the New York Academy of Sciences* 917 (2000): 962-970.

27. Eledrisi MS and Verghese AC. "Adrenal insufficiency in HIV infection: a review and recommendations". *The American Journal of the Medical Sciences* 321.2 (2001): 137-144.

28. Cerutti PA and Trump BF. "Inflammation and oxidative stress in carcinogenesis". *Cancer Cells* 3 (1991): 1-7.

29. Cotran RS., *et al*. "Robbins Pathologic Basis of Disease, 4th Edition., (1989): 925-937.

30. Kasai H., *et al*. "Carcinogenesis 7 (1986): 1849-1851.

31. Shigenaga MK., *et al*. "Urinary 8-hydroxy-2'-deoxyguanosine as a biological marker of in vivo oxidative DNA damage". *Proceedings of the National Academy of Sciences of the United States of America* 86 (1989): 9697-9701.

32. Keith C Cheng., *et al*. "8-Hydroxyguanine, an Abundant Form of Oxidative DNA Damage, Causes G to T and A to C Substitutions". *The Journal of Biological Chemistry* 267.1 (1992): 166-172.

33. Ames BN. "Dietary carcinogens and anticarcinogens. Oxygen radicals and degenerative diseases". *Science* 221 (1983): 1263.

34. Lee J., *et al*. "Carvedilol reduces plasma 8-hydroxy-2'- deoxyguanosine in mild to moderate hypertension. A pilot study". *Hypertension* 45 (2005): 986-990.

35. Endo K., *et al*. "Probucol and Atorvastatin Decrease Urinary 8-Hydroxy-2'-deoxyguanosine in Patients with Diabetes and Hypercholesterolemia". *Journal of Atherosclerosis and Thrombosis* 13 (2006): 68-75.

36. Murr C., *et al*. "Neopterin as a marker for immune system activation". *Current Drug Metabolism* 3.2 (2002): 175-187.

37. Edén A., *et al*. "CSF Biomarkers in Patients with COVID-19 and Neurological Symptoms: A case series". *Neurology* (2020).

38. Mellors JW., *et al*. "Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion". *Annals of Internal Medicine* 122 (1995): 573-579.

39. Mellors JW., *et al*. "Prognostic value of HIV-1 RNA, CD4 cell count, and CD4 cell count slope for progression to AIDS and death in untreated HIV-1 infection". *The Journal of the American Medical Association* 297 (2007): 2349-2350.

40. Zhang Y., *et al*. "Accumulation of nuclear and mitochondrial DNA damage in the frontal cortex cells of patients with HIV-associated neurocognitive disorders". *Brain Research* 1458 (2012): 1-11.

41. Kolgiri V., *et al*. "Association of Metabolic Syndrome and Oxidative DNA Damage in HIV/AIDS Patients". *Indian Journal of Clinical Biochemistry* 33.3 (2018): 273-281.

42. El-Amine R., *et al*. "HIV-1 Tat protein induces DNA damage in human peripheral blood B-lymphocytes via mitochondrial ROS production". *Redox Biology* 15 (2018): 97-108.

43. Ramanujam MD. "Free radicals and antioxidants". *Current Status* (2004).

44. Shibutani S., *et al*. "Insertion of specific bases during DNA systhesis past the oxidation-damaged base 8-oxodG". *Nature* 349 (1991): 431-434.

45. Aukrust P., *et al*. "Impaired base excision repair and accumulation of oxidative base lesions in CD4+ T cells of HIV-infected patients". *Blood* 105.12 (2005): 4730-4735.

46. Kern P., *et al*. "Serum neopterin. Screening test to exclude transfusion hazards by blood donors with cytomegalovirus infection, AIDS, etc". *Proceedings of the 18th Congress of the International Society of Blood Transfusion, Munich, Germany* (1984): 10.

47. Tsoukas CM and Bernard NF. "Markers predicting progression of human immunodeficiency virus-related disease". *Clinical Microbiology Reviews* 7.1 (1994): 14-28.

48. Fahey JL., *et al*. "The prognostic value of cellular and serologic markers in infection with human immunodeficiency virus type 1". *The New England Journal of Medicine* 322 (1990): 166-172.

49. Chittiprol S., *et al*. "HPA axis activity and neuropathogenesis in HIV-1 clade C infection". *Frontiers in Bioscience* 12 (2007): 1271-1277.

50. Odeniyi IA., *et al*. "Adrenocortical Function in Nigerians With Human Immunodeficiency Virus Infection". *Ghana Medical Journal* 47.4 (2013): 171-177.

Volume 18 Issue 7 July 2022