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RELATIONSHIP BETWEEN COMMON MARKERS OF INFLAMMATION AND RENAL DISEASE AMONG APPARENTLY HEALTHY HIV PATIENTS IN BENIN CITY, NIGERIA.

Godwin Aigbedo Aikpitanyi-Iduitua[1], Nosakhare Lawrence Idemudia[2,4*], Rosemary Osamede Aikpitanyi-Iduitua[3] and Richard Omoregie[2,4]

[1]Department of Education, Medical Laboratory Science Council of Nigeria, Abuja, Nigeria, [2]Medical Microbiology Division, Medical Laboratory Services, University of Benin Teaching Hospital, Benin City, Nigeria, [3]Department of Physiology, School of Basic Medical Sciences, University of Benin, Benin City, Nigeria and [4]School of Medical Laboratory Sciences, University of Benin Teaching Hospital, Benin City, Nigeria.

*Corresponding Author: Email - lawnosa@gmail.com; Phone number - +2348039258854

ABSTRACT

Renal impairment is one of the frequent complications of HIV infection. The relationships between some common markers of inflammation and chronic kidney disease (CKD) have recently been investigated but not in HIV patients. Therefore, this study aims to determine the relationship between these markers of inflammation and renal disease among apparently healthy HIV patients in Benin City, Nigeria. Blood samples were collected and used to estimate the levels of some inflammatory markers (such as Albumin, CD4 count, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and systemic immune-inflammatory index (SII)) and some biochemical parameters such as electrolytes, urea, creatinine and estimated glomerular filtration rate (eGFR) among 173 participants comprising 81 HIV patients on Highly Active Antiretroviral Therapy (HAART), 44 HAART-naïve HIV patients attending out-patients clinics in the University of Benin Teaching Hospital, Benin City and 48 non-HIV individuals (Controls). All participants were asymptomatic. Healthy control subjects had significantly ($p<0.05$) higher haematocrit and haemoglobin concentration than their HIV-positive counterparts The MCH, MCV, and MCHC values of HIV patients on HAART were significantly higher than those of their HAART-naive counterparts and healthy control subjects ($p<0.05$). There was no significant difference ($p>0.05$) in total white blood cell count, neutrophil counts, lymphocyte counts, platelet counts, mean platelet volume, neutrophil-lymphocyte ratio and systemic immune-inflammatory index. HAART-naïve HIV patients had significantly higher NLR, PLR and SII ($P<0.05$) and significantly lower CD4 count and albumin ($P<0.0001$) than other study groups. The eGFR of HIV patients on HAART were markedly higher than those of HAART-naïve HIV patients ($p<0.05$) and healthy controls ($p<0.01$). The prevalence of CKD was 9.09%, 8.64% and 0% among HAART-naïve HIV patients and HIV patients on HAART and non-HIV subjects, respectively. A significant negative correlation was observed between some inflammatory markers (NLR, PLR and SII) and eGFR among HAART-naïve HIV patients. This study underscores inflammation as a possible cause of renal failure among asymptomatic HAART-naïve HIV patients.

Keywords: Chronic Kidney Disease; HIV infection, HAART, Inflammation, Asymptomatic

INTRODUCTION

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Human Immunodeficiency Virus (HIV) causes an inflammatory disease that impacts every organ and system in the body either directly or by making the host more vulnerable to opportunistic infections with the lungs, brain, heart, stomach, kidney, skin, and lymphoid tissues being the most often impacted organs.[1] The burden of chronic renal disease is a global public health phenomenon with more effects in developing countries, and it has become one of the frequent complications of HIV infection, occurring in 3.5 – 48.5%, and a leading cause of death in AIDS patients.[2],[3]

Numerous studies have demonstrated that HIV as an inflammatory disease can impair the kidneys directly or indirectly, causing thrombotic microangiopathy, immunological complex kidney disease, and HIV-associated nephropathy.[4]-[7] Furthermore, prolonged antiretroviral therapy (ART) use or the presence of opportunistic infections and other diseases resulting from HIV immunosuppression might cause renal impairment in HIV patients.[8] In a healthy state, the kidneys support immunological homeostasis. In contrast, immune system elements play a significant role in chronic kidney disease and mediate many acute types of renal disease. An immune system that is out of balance may directly or indirectly affect the kidneys.[9] HIV, like many other infections, including systemic autoimmune disorders, involves immune complex accumulation in the glomerulus.[10] Under this phenomenon, several antibodies are gathered around their target antigen. Due to their sizes, these complexes frequently collect in the glomerulus and become stuck within different glomerular filtration barrier compartments based on their charge. Complex complexes may occasionally form when a target antigen external to the kidney becomes trapped within the glomerular basement membrane because of its relatively small size and positive charge. Similarly, apoptotic cell nucleosomes from HIV pathogenesis may become entrapped in the negatively charged glomerular basement membrane.[11]

The gold standard for determining renal function is to measure glomerular filtration rate (GFR) using an exogenous agent; however, these methods are either expensive or may take too long to make initial dosing recommendations in the context of an acute illness, like the use of antibiotics for an infection unlike the requirement for 24-hour urine collection, so they are not frequently used in standard clinical practice.[12] Also, serum creatinine, the most straightforward and common clinical marker for determining renal function, is commonly influenced by age, gender, weight, and muscle mass.[13] This has necessitated the development of different methods for estimating GFR (eGFR) and using endogenous biomarkers for renal assessment, especially in HIV care in resource-limited settings. Some common inflammatory indicators and their relationship to the progression of CKD have been explored.[14]-[16] However, to our knowledge, there is a paucity of data on this in HIV patients. Therefore, this study aims to determine the relationship between inflammation and renal disease surrogate markers among apparently healthy HIV patients in Benin City, Nigeria.

MATERIALS AND METHODS

Study population

One hundred and twenty-five HIV patients were recruited for the study at the University of Benin Teaching Hospital in Benin City, Edo State, Nigeria. Of the 125 HIV patients, 81 had previously begun treatment with Highly Active Antiretroviral Therapy (HAART), whereas the remaining 44 were yet to begin treatment and were classified as HAART-naive. The study also included 48 participants who were HIV seronegative and apparently healthy individuals. All HIV patients were asymptomatic out-patients attending HIV clinics in the University of Benin Teaching Hospital, Benin City, Nigeria, without signs and symptoms of any infection or diseases, and were not on any medication other than

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HAART (for those on HAART), while their HIV seronegative counterparts were from the surrounding community. Informed consent was obtained from all participants before specimen collection. The Ethical Committee of Edo State Ministry of Health, Benin City, Nigeria, approved the protocol for this study.

Sample collection and processing

Six millilitres (6ml) of blood sample was aseptically drawn from each of the participants by venipuncture; 3ml of the blood sample was dispensed into Ethylene diamine tetra-acetic acid (EDTA) anticoagulant container and mixed properly to avoid clotting which was used for full blood count and CD4 analysis while the remaining 3ml was dispensed into a plain container and allowed to clot. Serum was separated from the clotted blood sample in the plain container and used for biochemical analysis.

Full Blood Count Analysis

Full blood count (complete blood count) was determined with the EDTA blood sample using a haematology auto-analyser (Sysmex K2IN, Sysmex Corporation, Kobe, Japan) following the manufacturer's instructions.

Inflammatory Markers

Some basic inflammatory markers such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and systemic immune-inflammatory index (SII) were calculated from the obtained parameter of the Full Blood Count as previously described by Idemudia *et al*. and Zhang *et al*.[17],[18] Briefly, NLR was calculated as the ratio of the neutrophils count to lymphocyte counts; PLR was calculated as the ratio of the platelets counts to lymphocyte counts; and the SII was defined as: SII = neutrophil x platelet/lymphocyte.

CD_4 Cell Count Estimation

Flow cytometry was used for the CD4 cell count estimation using the Partec Cyflow Counter II® (Partec, Gmbh, Germany) following the manufacturer's instructions. Briefly, 20 µl of whole blood was placed in a Partec tube, and 20 µl of CD4+ T cell monoclonal antibodies was added. The mixture was then incubated in the dark for 15 minutes at room temperature, after which 800µl of buffer was added. The tube was then placed in the flow cytometer for counting, and the CD4+ T cells value was obtained from a programmed computer connected to the instrument.

Biochemical Analysis

Sera samples were used to determine the following biochemical parameters – Albumin, urea, creatinine, bicarbonate and chloride using Selectra ProS chemistry auto analyzer® (Vital Scientific Inc., Germany) following the manufacturer's instructions while sodium and potassium were analysed using Audicom AC 9800 ISE® (ion selective electrode) analyser following the manufacturer's instructions.

Estimation of the Glomerular Filtration Rate (eGFR)

Estimated GFR was determined using the CKD-EPI creatinine equation as previously described by Mula-Abed *et al*.[19] with an eGFR online calculator available at: https://ukidney.com/nephrology-resources/egfr-calculator. Patients with values <60ml/min.1.73m^2 were regarded to have CKD.

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Statistical analysis

The non-parametric data were analysed with Chi (X^2) and the parametric data were analysed with ANOVA and correlation using the statistical software INSTAT® (Graph Pad Inc., La Jolla, CA, USA).

RESULTS

There were significantly (p=0.021) more males in the healthy control population (58.33%) compared with the HIV patients – HAART-naïve, 40.91% and those on HAART, 24.69%). The healthy controls were younger (30.36±10.07 years) than HAART-naïve HIV patients (40.68±9.63 years; p<0.001) as well as those on HAART (41.19±11.57 years; p<0.001).

The outcome of laboratory tests obtained in this study is summarised in Figures 1 and 2 below. Healthy control subjects had significantly (p<0.05) higher haematocrit and haemoglobin concentrations than their HIV-positive counterparts (Fig 1a and 1b). The MCH, MCV and MCHC (Fig 1c – 1e) values of HIV patients on HAART were significantly higher than those of their HAART-naive counterparts and healthy control subjects (p<0.05). There was no significant difference (p>0.05) in total white blood cell count, neutrophil counts, lymphocyte counts, platelet counts, mean platelet volume, neutrophil-lymphocyte ratio and systemic immune-inflammatory index (Fig 1f – 1k, 1m). Platelet-lymphocyte ratio (Fig 1l) was significantly higher among HAART-naïve HIV patients compared with healthy controls (p<0.05), whereas CD4 counts and albumin levels were significantly lower in HAART-naïve HIV patients than HIV patients on HAART and healthy controls (P,0.001) (fig 1o and 1p). Serum creatinine and sodium levels were significantly lower in HIV patients on HAART than in HAART-naïve and non-HIV patients (Fig. 2 a&b). Bicarbonate levels were significantly higher in the control group than in the other group of participants, whereas chloride levels were the opposite as it was substantially lower in the control group than in HAART-naïve HIV patients and HIV patients on HAART (Fig. 2 d and e). Although there was no significant difference in potassium levels among the study groups, urea levels were significantly higher in HAART-naïve HIV patients than in non-HIV patients (Fig. 2c and 2f, respectively).

The eGFR for the study subjects, as shown in Figure 3, reveal that eGFR of HIV patients on HAART were significantly higher than those of HAART-naïve HIV patients (p<0.05) and Healthy controls (p<0.01) (Fig 3).

The study also examined the prevalence of chronic kidney disease (CKD) using the cut-off value from the eGFR. Although 9.09% of the HAART-naïve HIV patients had CKD, there was no significant difference in the prevalence of CKD among the study groups (p=0.1043) (Table 1).

The correlation of eGFR with the studied markers of inflammation and some biochemical parameters reveals that there was a significant negative correlation between eGFR and NLR, PLR, SII, urea and creatinine amongst HAART-naïve HIV patients whereas, in HIV patients on HAART, only urea and creatinine were observed to have significant negative correlations. Among healthy controls, CD4 count and creatinine significantly negatively correlated with eGFR (Table 2).

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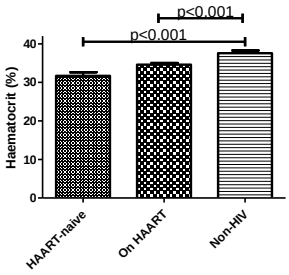

Fig 1a: Haematocrit values of participants

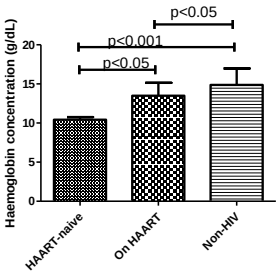

Fig 1b: Haemoglobin concentration of participants

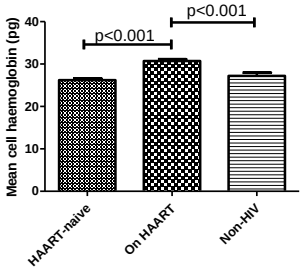

Fig 1c: Mean cell haemoglobin of participants

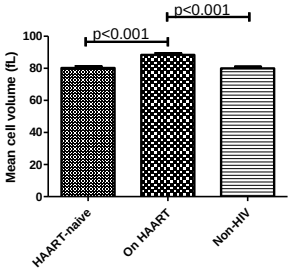

Fig 1d: Mean Cell Volume of participants

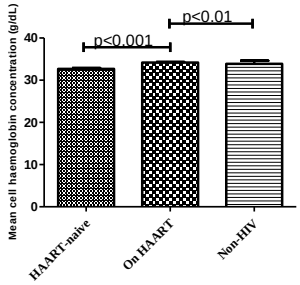

Fig 1e: Mean Cell Haemoglobin Concentration of participants

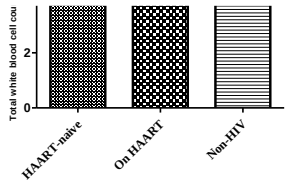

Fig 1f: Total white blood cell count of participants

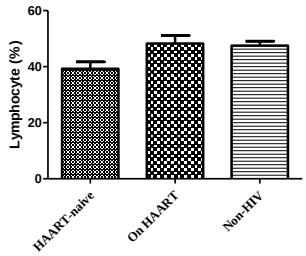

Fig 1g: Lymphocyte count of participants

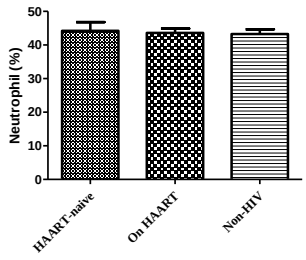

Fig 1h: Neutrophil count of participants

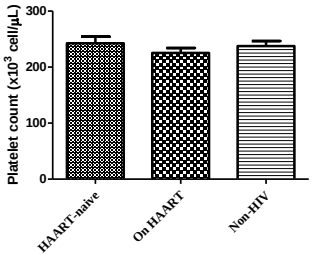

Fig 1i: Platelet count of participants

Fig 1: The levels of haematological parameters and markers of inflammation a

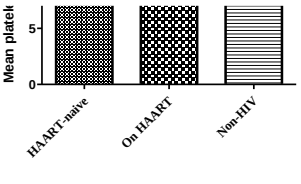

Fig 1j: Mean platelet volume of participants

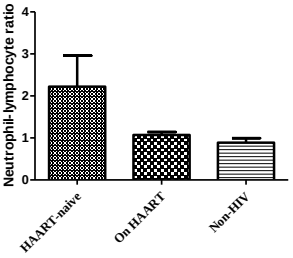

Fig 1k: NLR of participants

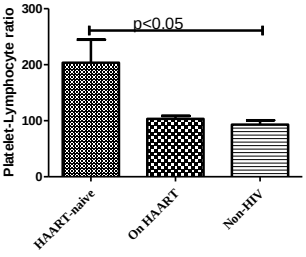

Fig 1l: Platelet-lymphocyte ratio of participants

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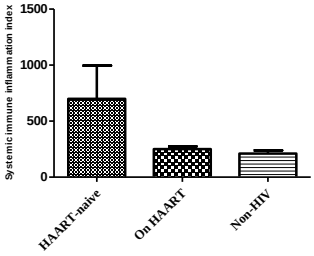

Fig 1m: Systemic immune inflammatory index of participants

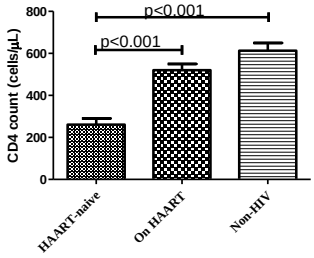

Fig 1o: CD4 count of participants

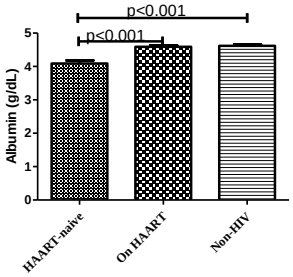

Fig 1p: Albumin levels of participants

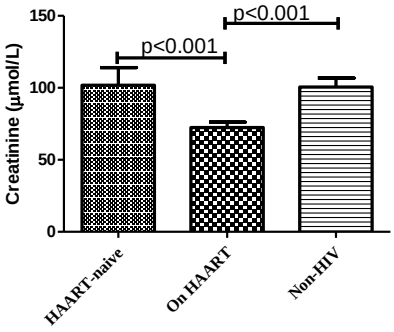

Fig 2a: Creatinine levels of participants

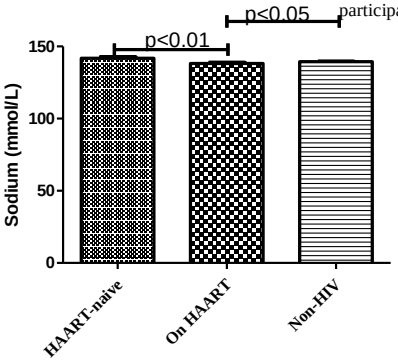

Fig 2b: Sodium levels of participants

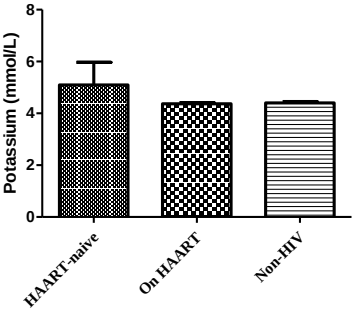

Fig 2c: Potassium levels of participants

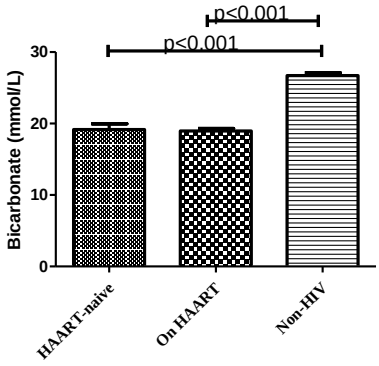

Fig 2d: Bicarbonate levels of participants

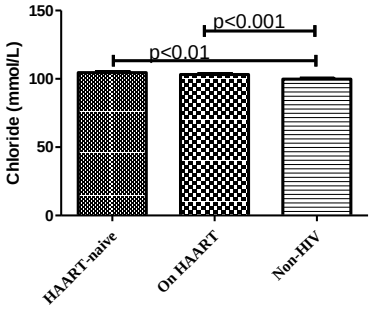

Fig 2e: Chloride levels of participants

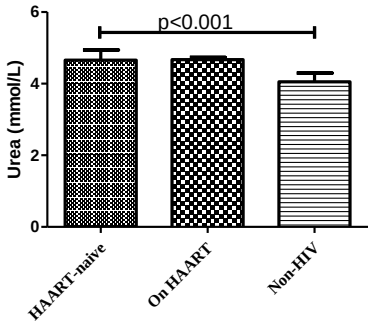

Fig 2f: Urea levels of participants

Fig 2: The levels of Electrolytes, urea and creatinine amongst study participants

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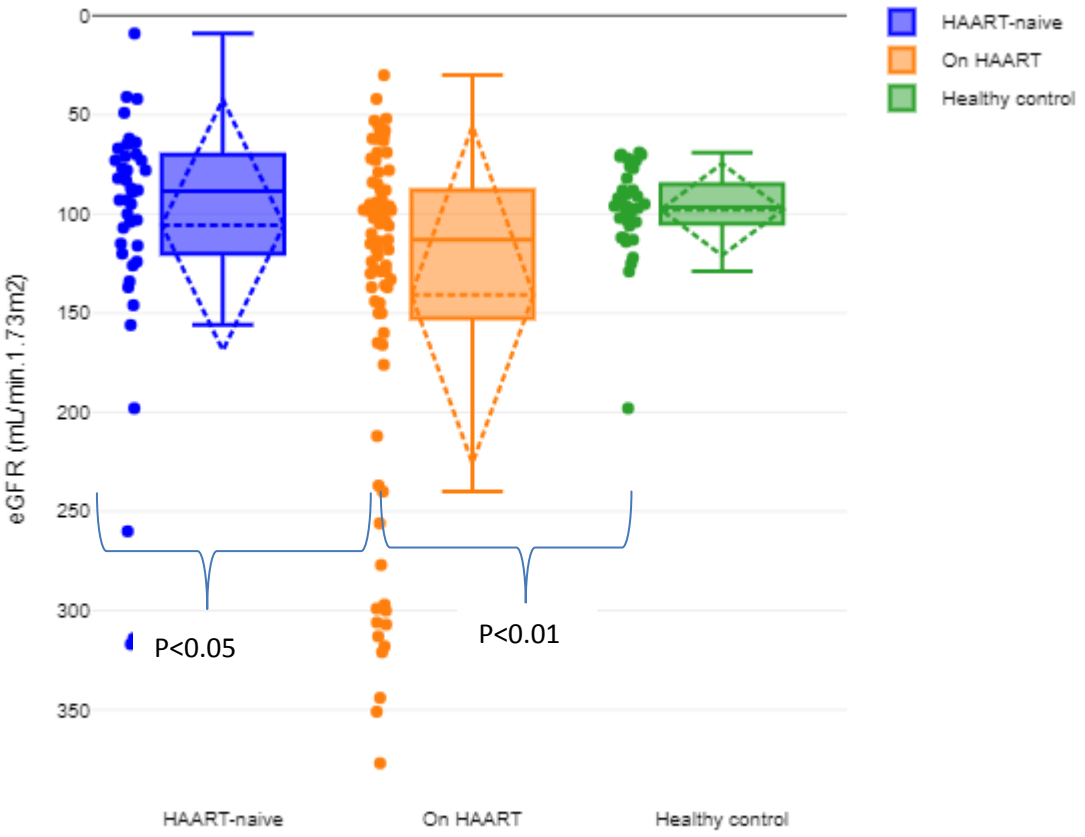

Fig 3: Box and whisker plot of eGFR values among the study subjects (Box and Whisker plot was generated using an online tool available at: https://www.statskingdom.com/advanced-boxplot-maker.html)

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Table 1: Prevalence of chronic kidney disease

Participants	No. tested	No. with CKD (%)
HAART-naïve	44	4 (9.09)
On HAART	81	7 (8.64)
Healthy control	48	0 (0.00)

p= 0.1043

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Table 2: Correlation of eGFR with markers of inflammation and some biochemical parameters

Parameters	HAART-naïve (n= 44)	ON HAART (n= 81)	Healthy Control (n= 48)
Platelet count ($x10^3/\mu L$)	r=-0.2190 (p>0.05)	r=0.1364(p>0.05)	r=-0.1997 (p>0.05)
Mean platelet volume (fL)	r=0.0131 (p>0.05)	r=-0.1396 (p>0.05)	r=0.0359 (p>0.05)
Neutrophil-lymphocyte ratio	r=-0.3202 (p<0.05)*	r=-0.0266 (p>0.05)	r=-0.0347 (p>0.05)
Platelet-lymphocyte ratio	r=-0.3412 (p<0.05)*	r=-0.0302 (p>0.05)	r=-0.0656 (p>0.05)
Systemic immune-inflammation index	r=-0.305 (p<0.05)*	r=0.0463 (p>0.05)	r=-0.0886 (p>0.05)
CD4 count (cells/µL)	r=0.0585 (p>0.05)	r=0.1121 (p>0.05)	r=-0.2957 (p<0.05)*
Albumin (g/dL)	r=0.0125 (p>0.05)	r=0.0195 (p>0.05)	r=0.2515 (p>0.05)
Urea (mmol/L)	r=-0.4331 (p<0.005)*	r=-0.2195 (p<0.05)*	r=0.2767 (p>0.05)
Creatinine (µmol/L)	r=-0.5263 (p<0.001)*	r=-0.7873 (p<0.001)*	r=-0.7796 (p<0.001)*

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DISCUSSION

In this study, there was an observed significantly higher haematocrit and haemoglobin concentration levels in the healthy control group compared to the other groups; this finding agrees with previous reports.[20],[21] Anaemia is believed to be a significant prognostic indicator of HIV disease progression, and anaemia in HIV infection has a variety of root causes varying from the death of red blood cells (hemolysis) or inefficient generation of red blood cells; loss of blood as a result of gastrointestinal lesions arising from opportunistic infections or neoplastic illness; vitamin B12, folate, or iron deficiency as well as immune dysregulation during HIV infection.[22] This study also showed that the haemoglobin concentration of HIV patients on-HAART is significantly higher than that of HAART-naïve HIV patients. This agrees with the findings of Dengue *et al*.[23] which reported that HAART treatment helps reduce the prevalence of anaemia since it suppresses viral replication, thereby reducing HIV viral burden. The observed significantly higher mean cell volume (MCV), mean cell haemoglobin concentration (MCHC), and lymphocyte percentage count in HIV patients on-HAART in this study also agrees with some previous reports.[24],[25] The significant increase in MCV, MCHC and lymphocytes is an indication that the HAART regimen in HIV patients is effective in improving the quality of life of HIV patients and reducing the incidence of anaemia, which is one of the primary adverse outcomes of HIV infection especially as elevated MCV has been previously reported to be associated with the use of zidovudine (AZT) or stavudine (d4T).[25]

Low albumin levels in HIV-infected patients has been linked to increased mortality and a quick transition to AIDS, and albumin has been reported to be a measure of inflammation.[26],[27] Also, it has been reported that GFR and renal function are both affected by low serum albumin levels.[28] In this study, HAART-naive HIV patients' serum albumin levels were shown to be considerably lower than those of HAART-treated HIV patients and non-HIV participants. This would suggest that HIV patients who have never used HAART are more likely to experience renal failure than those on HAART. Although there is no significant correlation between eGFR and albumin amongst all the study groups, reports have shown that starting HAART considerably raises serum albumin levels which may have accounted for the higher albumin level in HIV patients on HAART in this study.[29] The finding that HAART-naïve HIV patients had significantly lower CD4 count than HIV patients on HAART and non-HIV subjects agree with previous reports.[20],[21],[27] It implies that the HAART regime reduces inflammation in HIV patients.

Elevated MCV could be associated with the use

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of zidovudine (AZT) or stavudine (d4T)

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Elevated MCV could be associated with the use

HIV is known to be an inflammatory disease and causes chronic inflammation. The significantly higher levels of NLR, PLR and SII in HAART-naïve HIV patients in this study confirm this. However, there is a paucity of data comparing these markers among our study groups especially relating it to CKD. NLR, PLR, and SII are biomarkers capable of predicting systemic inflammation. They have recently gained interest because they are widely available markers that can be calculated from simple blood counts and show prognostic significance for several diseases and outcomes, including chronic kidney disease.[16],[30] Also, looking at the significantly lower eGFR, in HAART-naïve HIV patients and the higher prevalence of CKD in this group, it follows that the high inflammation resulting from HIV infection has a significant impact in causing CKD. The significant negative correlation between eGFR and these markers, alongside urea and creatinine in HAART-naïve HIV patients observed in this study, further confirms the fact that HIV infection causes inflammation which can lead to chronic kidney disease. Also, the fact that numerous studies have shown that starting HAART for HIV patients with CKD results in an overall improvement in renal function backs the findings in this study, where there was a higher eGFR in HIV patients on HAART and no correlation between the studied inflammatory markers with eGFR in HIV patients on HAART.[2],[31]

Our study had limitations, including the small sample size from a single site. In the future, it is advised to do a prospective, randomised study that entails tracking the long-term outcome. Another drawback is that the research did not collect data on the risk variables for

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CKD. Moreso, we could not modify the models to account for the timing of immunosuppression, bone marrow condition, or the use of other drugs.

In conclusion, this study has shown a relationship between some common markers of inflammation and renal disease in HIV infection and that this inflammation and renal impairment is more in HAART-naïve HIV patients as effective HAART usage is known to decrease adverse outcomes in HIV infection, including renal impairment.

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