

Prevalence of Renal Dysfunction and Its Relationship to CD4 and TNF Alpha of HIV Positive Individuals on Anti-retroviral Therapy in Port Harcourt

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Original Research Article

ABSTRACT

Background: Despite the success of anti-retroviral drugs, renal impairment remains one of the most significant complications of HIV. This study aimed to evaluate the prevalence of renal impairment and its association with age, gender, CD4 and TNF alpha of HIV positives in the University of Port Harcourt Teaching Hospital (UPTH).

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Materials and Methods: This hospital-based, cross-sectional study recruited 397 HIV positive patients on Anti-retroviral therapy for at least 6 months in the UPTH HIV clinic between June and August 2016. These patients were randomly selected from a cluster of patients attending the HIV clinic in UPTH. Using patient's folders, age and gender were obtained while blood samples were collected for TNF and CD4 analysis. Estimated glomerular filtration rate was calculated using a modification of diet in Renal Disease –MDRD formula

Results: Prevalence of renal impairment was estimated at 12.7% based on MDRD equation. Females recorded the significantly high prevalence of renal dysfunction at 11.84%. CD4 57.45 ± 15.33 Cells/ μ l and TNF 38.51 ± 22.40 pg/ml were significantly low in patients with renal dysfunction. EGFR correlated negatively with CD4 and TNF alpha.

Conclusion: The prevalence of renal dysfunction was low in this study. Reduced serum TNF alpha level and CD4 count are associated with renal dysfunction. Therefore, age and CD4 may be considered as the predictors of renal dysfunction. Also, female patients in this study may be at risk of renal dysfunction.

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1. INTRODUCTION

Human immunodeficiency virus (HIV) is a major public health problem all over the world, and if left untreated, devastating health outcomes could result due to the HIV – induced deficiencies [1].

Anti-retroviral therapy has helped to curb deaths caused by HIV and AIDS, but in this era non-AIDS related complications like the chronic kidney disease (CKD) over time have become important. The frequency of renal dysfunction may be increased by drug-induced renal toxicity, opportunistic infection [2] and inflammatory response regulated by cytokines.

The advancement of Anti-retroviral drugs (ARTs) has significantly improved the quality of life of HIV positives and reduced the progression of HIV to AIDS. Unfortunately, some anti-retroviral drugs are capable of causing renal damage. Tenofovir (TDF), a potent nucleotide reverse transcriptase inhibitor is used in HIV treatment and management. But one of its side effects is renal damage, which may occur due to the elimination of Tenofovir in the body by renal clearance and mostly glomerular filtration [3]. Tubular necrosis has been observed in proven cases of TDF nephrotoxicity [4]. This may be the result of proximal tubular injury since TDF is actively transported to renal proximal tubule cells [3].

Consistent monitoring and early detection of renal dysfunction in HIV – positive patients are important for medication dose and prognosis. WHO recommends monitoring of renal function vitals in every six months for patients on Tenofovir [5].

CD4 cells are very important biomarkers in monitoring and management of HIV. Their role in orchestrating other immune cells also makes them vital cells in the immune system. Cd4 cells acts as key elements during inflammation [6]. They infiltrate the glomeruli causing proteinuria and initiating kidney injury. This injury, in turn, initiates an inflammatory response. Although the pathological process involved in progressive interstitial injury and renal dysfunction is not clear, some studies have highlighted that renal dysfunction correlates with the degree of injury and interstitial disease [7]. According to Markovic [12], an interstitial disease is usually associated with inflammatory cell infiltration. These cells comprise T Lymphocytes (CD4 and CD8) and macrophages. Yiping-Wang et al., [8] suggested that CD4 cells have a protective role against the progression of renal dysfunction and that depletion of CD4 cells in mice promotes glomerular and interstitial injury. CD4 cell count less than 200 is a poor prognostic index in HIV positive patients with renal dysfunction [9].

Cytokines are soluble proteins produced by different cells found in sites of local injury exposed to an inflammatory environment [10]. Various cytokines are released by both leucocytes and renal tubular cells when the kidney is injured, and these cytokines are vital components of both the initiation and extension of inflammation in renal dysfunction [11]. Pro-inflammatory cytokines and chemokines are increased in kidney injury [12].TNF alpha is a pro-inflammatory cytokine and an important mediator of inflammatory tissue damage. The inhibition of TNF alpha confers protection from further deterioration in the kidney [13]. TNF

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alpha acts in synergy with IL-17 to induce Chemokine mRNA and to produce protein in mesangial cells. These further enhance the recruitment of renal leucocytes at inflammation sites [14].

During HIV infection, kidney damage is caused by the infection of podocytes and renal epithelial cells by the virus [15]. The mechanism by which HIV infects these cells has been in debate since these cells do not possess the CD4 molecule which is the major receptor needed for HIV entry. However, a study showed that TNF alpha might be a possible mediator in facilitating viral entry into the DNA of renal epithelial cells [16]. Although the present pathological model for renal dysfunction in HIV is that renal epithelial cells when infected produce viral transcripts that result to a renal lesion in genetically predisposed people [17].

Although the risk of renal dysfunction in Sub-Saharan Africa is high, the association between gender, CD4 and cytokines have been relatively understudied, particularly, the relationship between pro-inflammatory cytokine and renal dysfunction. For this reason, this study tried to explore the relationship between makers of renal dysfunction (using eGFR), pro-inflammation (using TNF alpha) and immunological status (using CD4). The study also aimed to profile the different stages of CKD in this present population and its relationship with immune cells. The study, therefore, hypothesise that there will be a relationship between renal function, TNF alpha and CD4 count.

2. MATERIALS AND METHODS

2.1 Study Design and Area

This cross-sectional study was conducted on HIV positive patients on antiretroviral therapy for at least 6 months. Recruitment was carried out from a cluster of patients visiting the Outpatient Clinic of the University of Port Harcourt (UPH) between June and August 2016. The UPH Outpatient Clinic is a regional referral centre located in Port Harcourt, capital of the Rivers State in the South-South region of Nigeria. Multi-stage sampling was used to account for randomness and reduce bias. Since the patients in this location already formed a clustered sample, random sampling was used to recruit patients into the study.

2.2 Study Population and Ethical Clearance

Patients that met the following criteria were recruited into the study:

- ≥18 years of age;
- HIV-positive individuals on antiretroviral therapy for at least 6 months;
- Mentally fit and able to give an informed consent.
- Patients on any form of herbal treatment, less than 18 years and unable to give consent were excluded from the study.

The study was conducted following the ethical principles of the Declaration of Helsinki. The protocol for this study was approved by the University Teaching Hospital Ethical Board (UPH Teaching Hospital Ethical Board, Ref UPTH/ADM/90/SII/VOLX/523) and the University of Port Harcourt Ethical Committee, Ref UPH/R&D/REC/04) before commencement.

2.3 Data Collection

The study recruited 397 participants who were on HAART for at least 6 months and registered at the UPTH anti-retroviral (ART) clinic. Using a well-validated questionnaire, data on age, gender, and other characteristics were obtained from participants.

2.4 Biochemical Determinations

Venous blood was drawn from fasting patients. The CD4 count was measured using a Partec CyFlow Counter (Partec GmbH, Görlitz, Germany), plasma creatinine was done using kits obtained from Randox and following their protocol while tumour necrosis factor-alpha (TNF-alpha) was analysed using kits obtained from UCItech. The glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease study equation. [18] The definition of Chronic kidney disease (CKD) included all individuals with markers of kidney damage or those with an eGFR of less than 60 mL/min/1.73m² on at least 2 occasions 90 days apart (with or without markers of kidney damage). CKD was classified based on the eGFR as Stage 1 with normal or high GFR (GFR > 90 mL/min); Stage 2 Mild CKD (GFR = 60-89 mL/min); Stage 3A Moderate CKD (GFR = 45-59 mL/min); Stage 3B Moderate CKD (GFR = 30-44 mL/min); Stage 4 Severe CKD (GFR = 15-29

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mL/min); and Stage 5 End Stage CKD (GFR <15 mL/min).

Furthermore, the immunological status of participants was classified based on the World Health Organization. [19]. Interim WHO clinical staging of HIV, CD4 levels in relation to the severity of immunosuppression Not significant immunosuppression >500/mm³ Mild immunosuppression 350 –499/mm³ Advanced immunosuppression 200–349/mm³ Severe immunosuppression.

2.5 Data Analysis and Interpretation

Analysis of the data gathered from the study was done using the Statistical Package for the Social Sciences (SPSS) version 20 software program (IBM Corporation, USA). Descriptive and inferential statistics were used to analyse data. Frequency, percentages, mean and standard deviation were used to describe the data while independent t-test, multiple regressions and Pearson's correlation were used to draw inferences on the results and were presented using tables and charts.

2.6 Ethical Considerations

Participants who agreed to join the study signed a consent form and were informed about the need to join the study. Total confidentiality was maintained to protect the integrity of the data

obtained and also protect the participants in the study. Approval to carry out the study was given by both the Hospital ethical board and the university ethical board. Research team discussed the aims and objective of the study with participants. Results were treated as very confidential.

3. RESULTS

3.1 Demographics and Percentage of CD4 and CKD Stages in Participants

The demographics obtained from the study showed that there were more participants within the age range of 28 – 38 years. The participants within age greater than 58 were the least represented. Majority of the participants were Christians and hailed from the south- south region of the country. A higher percentage of the participants were females, though men were adequately represented. The participants in the study were mostly literate with the majority of them being secondary school graduates.

Results also showed that participants with normal CD4 count (CD4 > 500) were 38.4%. Participants with mild immunosuppression (CD4 count: 350 –499/mm³), advanced immunosuppression (CD4 count: 200–349/mm³) and severe immunosuppression (CD4 count: <200) were 27.7%, 14.4% and 23.2% CD4 respectively. (Table 1).

Table 1. Demographics and clinical characteristics of study participants

Variable	Category	Frequency	Percent
Age Distribution	18 – 27	40	10.1
	28 -37	172	43.3
	38 -47	107	27.0
	48 – 57	54	13.6
	58 and above	19	4.8
Sex	Male	116	29.2
	Female	281	70.8
CD4 count (Cells/ μ l)	>500	138	34.8
	350 – 490	110	27.7
	200 – 349	57	14.4
	<200	92	23.2
CKD Normal	Stage1 >90 ml/min/1.73m ²	171	43.1
	Stage2 (60-89 ml/min/1.73m ²)	172	43.3
Renal dysfunction	Stage 3 (30-59 ml/min/1.73m ²)	45	11.3
Renal dysfunction	Stage 4 (15-29 ml/min/1.73m ²)	5	1.3

n=397

Results expressed as Frequency and percentages

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Furthermore, estimated glomerular filtration rate (eGFR) was used to **categorise** patients into stages 1, 2, 3, and 4. From the study, normal renal function was observed in 86.4% of participants. The percentages of participants in the different stages used in **categorising** participants were: eGFR>90 ml/min/1.73m² 43.1%, eGFR between 60 – 89 ml/min/1.73m² was 43.1% (stage 2), 30-59 ml/min/1.73m² (stage 3) and 15 – 29 ml/min/1.73m² (stage 4) were 11.3 and 1.3 % respectively (Table 1). From these results prevalence of renal dysfunction (Renal dysfunction eGFR< 60) was 12.6%.

3.2 Characteristics of Participants Using Renal Dysfunction and Normal Renal Function Categories

Results showed that participants within the age ranges of 28-37 and 38-47 had the most

significant renal dysfunction percentages. It was further revealed that the renal dysfunction observed in the female population was 12 times more than that obtained in the male population. The CD4 count and TNF alpha levels in patients with renal dysfunction **were** significantly lower when compared to that of patients with Normal eGFR (Table 2).

3.3 Duration and Regimen of HAART in Study Participants

Duration and regimen of HAART in the study showed that 47% of the patients have been on therapy for more than 6 years. The least participant in the study had been on therapy for at least one year (Table 3). Majority of the participants were on **Zidovudine**, Lamivudine and Nevirapine, while others were on Tenofovir, Lamivudine and Nevirapine combinations.

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Table 2. Characteristics of participants using Renal dysfunction and Normal Renal function categories

	Renal dysfunction (GFR < 60)		Normal renal function (GFR≥ 60)		
Variables	Frequency	Percentage	Frequency	Percentage	p-value
Age					
18-27	5	1.51	33	8.56	0.005
28-37	14	3.78	158	40.05	
38-47	16	4.28	90	22.92	
48-57	6	1.76	47	12.09	
>58	4	1.26	15	3.78	
Gender					
Female	47	11.84	66	16.62	0.005
Male	4	1.01	280	70.52	
	Renal dysfunction (GFR < 60)		Normal renal function (GFR≥ 60)		P-value
Mean CD4	57.45±15.33		387.36±122.95		0.0001
Mean TNFalpha	38.51±22.40		67.57±31.15		0.0001

n=397

Results expressed as mean ± standard deviation

Table 3. Duration and regimen of HAART in study participants

		Frequency	Percent
Duration of HAART	1 year	40	10.1
	2 years	38	9.6
	3 years	35	8.8
	4 years	39	9.8
	5 years	55	13.9
	6 years	190	47.9
	Total	397	100.0
HAART REGIMEN	Zidovudine+Lamivudine+Nevirapine	330	83.1
	Tenofovir+Lamivudine+Nevirapine	67	16.9
	Total	397	100.0

Table 4. Correlation between eGFR and study variables

	Duration	Regimen	TNF	AGE 0	Sex	CD4	eGFR
EGFR Pearson Correlation	-.087	.060	-.172**	.134**	-.761**	-.870**	1
Sig. (2-tailed)	.090	.247	.018	.009	.000	.000	
TNF Pearson Correlation	.110*	.057	1	.006	-.070	-.177**	.122*
Sig. (2-tailed)	.031	.273		.910	.169	.000	.018
CD4 Pearson Correlation	.057	-.029	-.177**	-.084	.694**	1	.845**
Sig. (2-tailed)	.265	.580	.000	.098	.000		.000
N	397	397	397	397	397	397	397

The relationship between renal dysfunction and study variables was analysed using correlation to test for association. eGFR was negatively correlated with CD4, sex and duration of HAART, but was positively correlated with TNF alpha and age. Also, CD4 was negatively correlated with TNF alpha levels (Table 5).

Results from logistic regression showed that age and CD4 could be used as predictors for renal function.

Multiple regression analysis was done to predict renal dysfunction from gender, age, CD4

and TNF. Age and CD4 statistically significantly predicted renal dysfunction, $F(4,393) = 682.502$, $p < 0.0005$, $R^2 = .89$. Age and CD4 added statistical significance to the prediction, $p < 0.05$.

Fig. 1 shows the mean eGFR of female and male participants. The mean value of female participants was 87.42 ± 22.28 , while that of male participants was 148.26 ± 25.62 . The lower T-bars found in the female box correspond to values lower than the normal (GFR < 60), but the lower limit in the male population sits at a value above normal (GFR ≥ 60).

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Table 5. Showing multiple regression values

Model coefficients	Unstandardised coefficients	Std. error	Sig.
(Constant)	44.596	6.699	.000
AGE 0	.155	.070	.028
CD4(visit 0)	.147	.005	.000
TNF	-.011	.007	.131
Sex distribution	-2.547	2.395	.288

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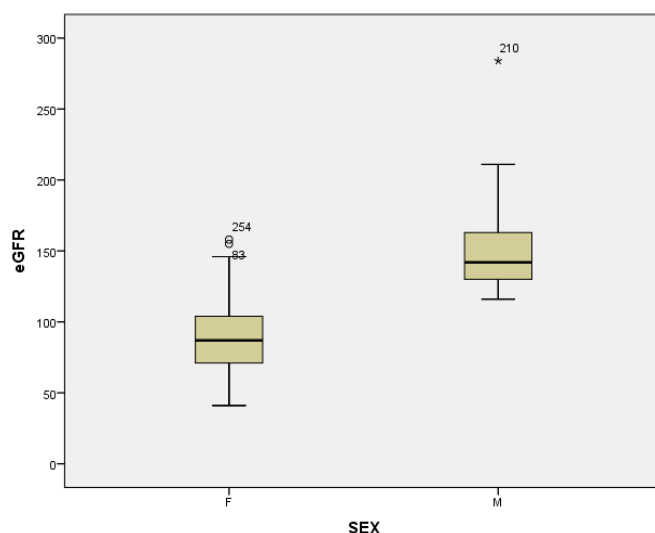


Fig. 1. Showing distribution of eGFR in female and male population

4. DISCUSSION

One of the most frequently occurring complications of HIV infection is kidney disease, and renal dysfunction may be encountered at any stage of HIV infection, ranging from electrolyte imbalance to end-stage renal disease (ESRD).

In this study, the prevalence of renal dysfunction was 12.6 %. This corroborates with Nishijima et al., [20] in Japan, who had a prevalence of 13% in their study. The result of 12% was lower than the 22.9% obtained by Anyabolu et al., [21] in Owerri, South-East Nigeria and 53.3% prevalence observed by Okafor and Unuigbo [22] in Benin city South-South of Nigeria.

These findings corroborate with other findings [23,24,25]. Renal dysfunction was also detected in a portion of the population with decreased CD4. The findings show that HIV, ART and other drugs used to treat opportunistic infections may have nephrotoxicity effects in Nigerian HIV positives [25, 26, 27]. The findings from this study also corroborate with other studies showing that low CD4 count is a risk factor for renal dysfunction. Studies by Emem et al., [28] and Szczech et al., [29] corroborate with the significantly low CD4 count obtained from subjects with renal dysfunction in this study. The study also showed an association between age and sex. Patients between the ages of 28 – 47 had a higher prevalence of renal dysfunction while females also had significantly low eGFR. These findings are similar to the findings of Agbaji et al., [30] in Jos, Nigeria, and they found that the older the age, the greater the likelihood of renal dysfunction and females are more likely to develop renal dysfunction. But the findings in this study are dissimilar to those obtained from Krawczyk et al., [31] who reported that younger and male patients are predictors of renal dysfunction. Findings of the present study may have been different because of the difference in characteristics between study populations, and this study had a higher female to male ratio. The present study also showed that female patients on ART had significantly lower e-GFR when compared to male patients.

Studies have shown that HIV renal damage observed is caused by changes in the production of cytokines during HIV infection [32]. This study showed a decline in TNF alpha production in patients with renal dysfunction, and CD4 count less than 500.

The current study also is one of the few showing the relationship between plasma levels of TNF alpha and eGFR in Nigeria. TNF alpha values in renal impaired patients were significantly lower than those with normal renal function. The study also found that TNF alpha was decreased in patients with renal dysfunction. It also showed that there was an inverse correlation between renal dysfunction and serum TNF alpha. The results are similar to Gupta et al., [33], who found a negative correlation between TNF alpha and renal dysfunction.

The reduced production of TNF alpha by patients with renal dysfunction could be a resultant effect of the patients being immuno-compromised due to low CD4. The TNF alpha values of normal patients are consistent with those obtained by Robinson et al., [34], but TNF alpha of patients with renal impairment are lower than those from their study.

The CD4 count observed in this study is also consistent with findings which have shown that HIV associated nephropathy (HIVAN) is common in blacks, [25, 28]. Multiple regression analysis showed that age and CD4 might be the possible predictors of renal dysfunction.

It is also interesting to note that, although HIV associated renal impairment is a frequent occurrence, not much has been done in the different tribes in Nigeria and other parts of Africa. The current findings showed a prevalence of 12.6% which differ from those obtained by Emem et al., [23] in Nigeria and Uganda [35]. The rate of renal impairment obtained from this study also corroborates with those found in Tanzania (2). Furthermore, the rate of renal impairment observed in this study may be related to the concern of WHO in using Tenofovir or lamivudine, both require adjustment of doses concerning renal impairment. Tenofovir can cause irreversible renal toxicity to the renal tubular [36].

5. LIMITATIONS

The study has some limitations. First, some confounding variables (e.g. nutrition) relating to the quality of life may bias the results. Secondly, the cross-sectional nature of the study may not give a full insight; hence there is the need for a more comprehensive cohort study. Thirdly, no histopathological and proteinuria data was available for analysis. Finally, the study was underpowered, hence could not study the

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full impact of the antiretroviral drugs independently.

6. CONCLUSION

The present study found a low prevalence of renal dysfunction among participants. The study also found a negative association between renal dysfunction and both TNF alpha and CD4. Furthermore, a decrease in serum Tumor necrosis factor alpha and decreased CD4 count was strongly associated with a decline in renal function.

DISCLAIMER

This paper is based on the preliminary dataset. Readers are requested to consider this paper as preliminary research article, as authors wanted to publish the initial data as early as possible. Authors are aware that detailed statistical analysis is required to get a scientifically established conclusion. Readers are requested to use the conclusion of this paper judiciously as statistical analysis is absent. Authors also recommend detailed statistical analysis for similar future studies.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s)

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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