

**Prevalence of Renal dysfunction and its relationship to CD4 and
TNF alpha of HIV positive individuals on Anti-retroviral
Therapy in Port Harcourt.**

Abstract

Background: Despite the success of anti-retroviral drugs, renal impairment still 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 University of Port Harcourt Teaching Hospital (UPTH).

Materials and methods: This hospital-based, cross sectional study recruited 397 HIV positive patients on Anti-retroviral therapy for at least 6 months in UPTH HIV clinic between June and August 2016. The 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 modification of diet in Renal Disease –MDRD formula

Results: Prevalence of renal impairment was estimated at 12.7% based on MDRD equation. Females recorded significantly high prevalence of renal dysfunction 11.84%. CD4 57.45 ± 15.33 Cells/ μ l and TNF alpha 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. Age and CD4 maybe predictors of renal dysfunction. Also female patients in this study may be at risk of renal dysfunction.

1. Introduction

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

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

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

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

46 CD4 cells are very important biomarkers in monitoring and management of HIV. Their role
47 in orchestrating other immune cells also makes them vital cells in the immune system. Cd4
48 cells are also key elements during inflammation [6]. CD4 cells infiltrate the glomeruli thereby
49 causing proteinuria and initiating injury in the kidney. This injury, in turn, initiates an
50 inflammatory response. Although the pathological process involved in progressive interstitial
51 injury and renal dysfunction is not clear, some studies have highlighted that renal dysfunction

52 correlates with the degree of injury and interstitial disease.[7]. According to Markovic, an
53 interstitial disease is usually associated with inflammatory cell infiltration. These cells
54 comprise T Lymphocytes (CD4 and CD8) and macrophages. Yiping-Wang et al.,[8]
55 suggested that CD4 cells have a protective role against the progression of renal dysfunction
56 and that depletion of CD4 cells in mice promotes glomerular and interstitial injury. CD4 cell
57 count less than 200 is a poor prognostic index in HIV positive patients with renal
58 dysfunction[9].

59 Cytokines are soluble proteins produced by different cells found in sites of local injury
60 exposed to an inflammatory environment [10]. Different cytokines are released by both
61 leucocytes and renal tubular cells when the kidney is injured, these cytokines are vital
62 components of both the initiation and extension of inflammation in renal dysfunction
63 [11]. Pro-inflammatory cytokines and chemokines are increased in the event of injury in the
64 kidney[12]. TNF alpha is a pro-inflammatory cytokine and an important mediator of
65 inflammatory tissue damage. The inhibition of TNF alpha confers protection from further
66 damage in the kidney [13]. TNF alpha acts in synergy with IL-17 to induce Chemokine
67 mRNA and production of protein in mesangial cells, these further enhance the recruitment of
68 renal leucocytes to sites of inflammation [14].

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

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

84 **2. Materials and methods**

85 **2.1 Study design and area**

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

94 **2.2 Study population and Ethical clearance**

95 Patients that met the following criteria were recruited into the study.

96 ≥ 18 years of age;

97 HIV-positive individuals on antiretroviral therapy for at least 6 months;

98 Mentally fit and able to give informed consent.

99 Patients on any form of herbal treatment, less than 18 years and unable to give consent were
100 excluded from the study.

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

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107 **2.3 Data collection**

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

111 **2.4 Biochemical determinations**

112 Venous blood was drawn from fasting patients, CD4 count was measured using a Partec
113 CyFlow Counter (Partec GmbH, Görlitz, Germany), plasma creatinine was done using kits
114 obtained from Randox and following their protocol while tumour necrosis factor-alpha
115 (TNF-alpha) was analysed using Kits obtained from UCItech. The estimated glomerular
116 filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease study
117 equation. [18] The definition of Chronic kidney disease (CKD) included all individuals with
118 markers of kidney damage or those with an eGFR of less than 60 mL/min/1.73m² on at least
119 2 occasions 90 days apart (with or without markers of kidney damage). CKD was classified
120 based on the eGFR as Stage 1 with normal or high GFR (GFR > 90 mL/min); Stage 2 Mild
121 CKD (GFR = 60-89 mL/min); Stage 3A Moderate CKD (GFR = 45-59 mL/min); Stage 3B

122 Moderate CKD (GFR = 30-44 mL/min); Stage 4 Severe CKD (GFR = 15-29 mL/min); and
123 Stage 5 End Stage CKD (GFR <15 mL/min).

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

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132 **2.3 Data analysis and interpretation**

133 Analysis of the data gotten from the study was done using statistical package for the social
134 sciences (SPSS) version 20 software program (IBM Corporation, USA). Descriptive and
135 inferential statistics was used to analyze data. Frequency, percentages, mean and standard
136 deviation were used to describe the data while independent t-test, multiple regressions and
137 Pearson's correlation were used to draw inferences on the results were presented using tables
138 and charts.

139 **2.4 Ethical considerations**

140 Participants who agreed to join the study signed a consent form and were informed on the
141 need to join the study. Total confidentiality was maintained to protect the integrity of the data
142 obtained and also protect the participants in the study. Approval to carry out the study was
143 given by both the Hospital ethical board and university ethical board. Research team

discussed the aims and objective of the study with participants. Results were treated as very confidential.

3. Results

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/μl)	>500	138	34.8
	350 – 490	110	27.7
	200 – 349	57	14.4
	<200	92	23.2
CKD Normal	Stage1 >90 ml/min/1.73m²	171	43.1
	Stage2 (60-89 ml/min/1.73m²)	172	43.3
Renal dysfunction	Stage 3 (30-59 ml/min/1.73m²)	45	11.3
Renal dysfunction	Stage 4 (15-29 ml/min/1.73m²)	5	1.3

n=397

Results expressed as Frequency and percentages

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. Most of the participants in the present study were Christians and mostly from the south south region of the country. A greater percentage of the participants were females, though men were adequately represented. The participants in the study were mostly literate with 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 350 –499/mm³, advanced immunosuppression 200–349/mm³ and severe immunosuppression 27.7%, 14.4% and 23.2% CD4 respectively. (Table 1).

Furthermore, estimated glomerular filtration rate (eGFR) was used to categorize 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 categorizing Participants was: $eGFR > 90$ 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%.

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183 population. The CD4 count and TNF alpha levels in patients with renal dysfunction was

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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

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.

Table 4: Correlation between eGFR and study Variables

	Duration	Regimen	TNF	AGE 0	Sex	CD4	eGFR
EGFR	-.087	.060	-.172**	.134**	-.761**	-.870**	1
Pearson Correlation							
Sig. (2-tailed)	.090	.247	.018	.009	.000	.000	

TNF	.110 [*]	.057	1	.006	-.070	-.177 ^{**}	.122 [*]
Pearson							
Correlation							
Sig. (2-tailed)	.031	.273		.910	.169	.000	.018
CD4	.057	-.029	-.177 ^{**}	-.084	.694 ^{**}	1	.845 ^{**}
Pearson							
Correlation							
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).

Table 5: Showing multiple regression values

ModelCoefficients	Unstandardized 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

Results from logistic regression showed that age and CD4 can 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 statistically significantly to the prediction, $p< 0.05$.

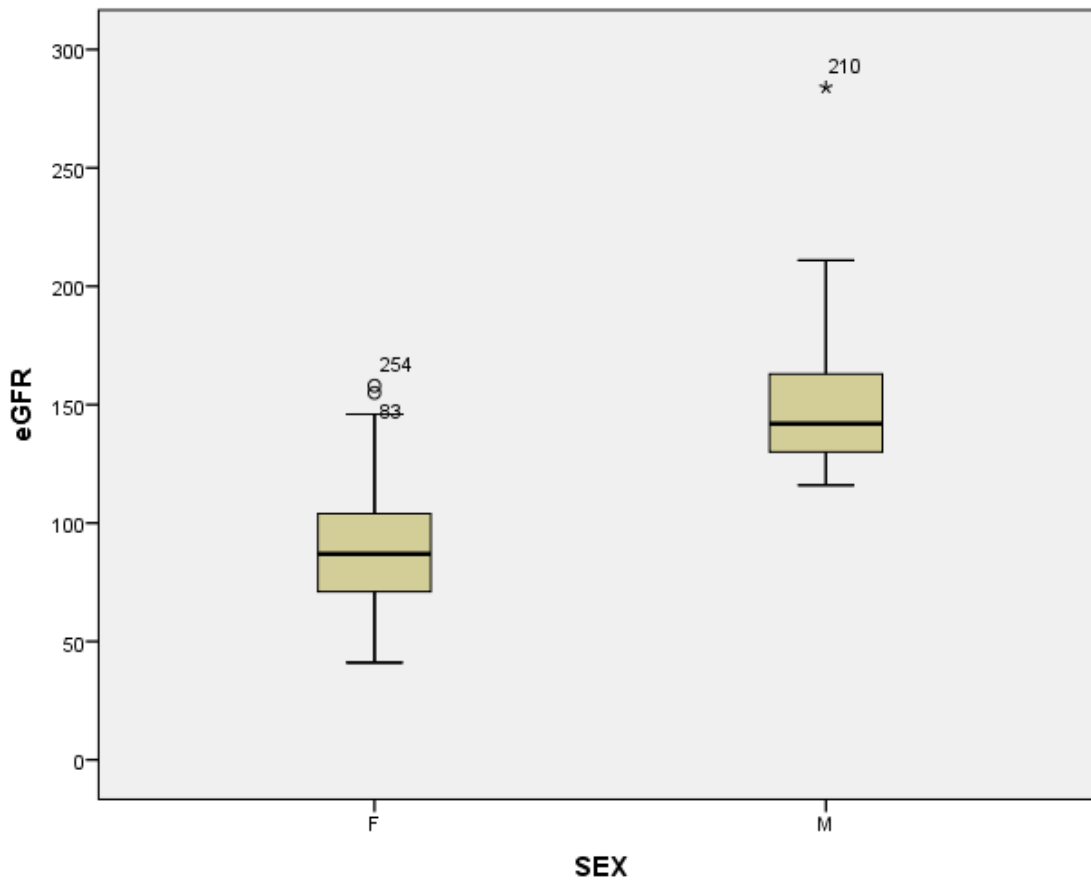


Fig 1: showing distribution of eGFR in female and male population

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 normal ($GFR < 60$), but the lower limit in the male population sits at a value above normal ($GFR \geq 60$).

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234 **4. Discussion**

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

238 In this study the prevalence of renal dysfunction was 12.6 %. This corroborates with [20] in
239 Japan, who had a prevalence of 13% in their study. The result of 12% was lower than the
240 22.9% obtained by [21] in Owerri South-East Nigeria and 53.3% prevalence observed by [22]
241 in Benin city South-South of Nigeria.

242 These findings corroborate with findings from [23][24][25]. Renal dysfunction was also
243 detected in a portion of the population with decreased CD4. The findings show HIV, ART
244 and other drugs used to treat opportunistic infections may have nephrotoxicity effects in
245 Nigerian HIV positives [25][26][27]. The findings from this study also corroborate with other
246 studies showing that low CD4 count was a risk factor for renal dysfunction. Studies by [28]
247 and [29] corroborate with the significantly low CD4 count obtained from subjects with renal
248 dysfunction in this study. The study also showed an association between age and sex. Patients
249 between the ages of 28 – 47 had higher prevalence of renal dysfunction while females also
250 had significantly low eGFR. These findings are similar to findings by [30] in Jos, Nigeria,
251 they found that the older the age, the greater the likelihood of renal dysfunction and that
252 females were more likely to develop renal dysfunction. But the findings in this study are
253 dissimilar to those obtained from [31] who reported that younger and male patients are

254 predictors of renal dysfunction. Our findings may have been different because of difference
255 in characteristics between study populations, this study had higher female to male ratio. The
256 present study also showed that female patients on ART had significantly lower e-GFR when
257 compared to male patients.

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

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

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

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

275 It is also interesting to note that, although HIV associated renal impairment is a frequent
276 occurrence, not much has been done in the different tribes in Nigeria and other parts of

Africa. Our findings showed a prevalence of 12.6% which differ from those obtained by[23]in Nigeria and in 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 in relation to renal impairment. Tenofovir can cause irreversible renal toxicity to the renal tubular[36].

Limitations

Our study has some limitations. First, some confounding variables (e.g. nutrition) relating to the quality of life may bias our results. Secondly, the cross-sectional nature of the study may not give a full insight, hence 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 full impact of the antiretroviral drugs independently.

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, decrease in serum Tumor necrosis factor alpha and decreased CD4 count was strongly associated with a decline in renal function.

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