

Original Research Article**Prevalence of Renal dysfunction and its relationship with CD4 and TNF alpha of HIV patients 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 patients in University of Port Harcourt Teaching Hospital.

Materials and methods: This hospital based study cross sectional study recruited 397 HIV positive patients on Anti-retroviral therapy for more than 3 years 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 55.9% based on MDRD equation. Females a recorded significantly low values for eGFR 87.62 ± 22.26 ml/min/ 1.73m^2 , CD4 293.24 ± 146.76 Cells/ μl and TNF alpha 52.27 ± 45.97 pg/ml compared to male counterparts with eGFR 148.68 ± 25.63 ml/min/ 1.73m^2 , CD4 count 711.36 ± 164.94 Cells/ μl and TNF alpha 92.67 ± 15.29 pg/ml. EGFR correlated positively with sex and CD4 but was inversely correlated with age and TNF alpha.

Conclusion: Female patients in this study had higher burden of CKD. Also serum TNF alpha level was reduced with reduced CD4 count in female patients



29 **1. Introduction**

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

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

36 Consistent monitoring and early detection of renal dysfunction in HIV – positive patients are
37 important for medication dose and prognosis. WHO recommends monitoring of renal
38 function vitals every six months for patients on Tenofovir (3)

39 Although the risk of renal dysfunction in Sub-Saharan Africa is high, the association between
40 gender, CD4 and cytokines have been relatively understudied, particularly, the relationship
41 between pro inflammatory cytokine and renal dysfunction. For this reason this study tries to
42 explore the relationship between makers of renal dysfunction (using eGFR), pro
43 inflammation (using TNF alpha) and immunological status (using CD4), the study also
44 aimed to profile the different stages of CKD in this present population, profiled the
45 immunological status of . We therefore hypothesize that there will be a relationship between
46 renal function, TNF alpha and CD4 count.

47 **2. Materials and methods**

48 **2.1 Study design and area**

49 An institution based cross sectional study was carried out at the University of Port Harcourt
50 Teaching Hospital (UPTH) in Port Harcourt the capital of Rivers state in Nigeria, the
51 Hospital acts as a referral center for hospitals in the South- South region of Nigeria.

52 2.2 Data collection technique and Study participants

53 The study recruited 375 participants who were on HAART for at least 6 months and
 54 registered at UPTH anti-retroviral (ART) clinic. A questionnaire was used to collect age
 55 gender and other characteristics from participants. Blood sample was collected by a medical
 56 laboratory scientist into an EDTA collection bottle and plain bottle. The EDTA blood was
 57 used to analyze for CD4 count using a Partec Cytoflow counter FMC system (Partec GmbH,
 58 2006 Germany) at the department of hematology UPTH, the blood sample in the plain bottles
 59 was separated after spinning with a centrifuge for fifteen minutes and the serum collected for
 60 Tumor necrosis factor alpha (TNF alpha) analysis in the department of chemical pathology in
 61 UPTH. Results were entered into a work sheet and computer and protected for
 62 confidentiality.

63 The estimated glomerular filtration rate (eGFR) was estimated using the Modification of Diet
 64 in Renal Disease study equation (4).

65 Chronic kidney disease (CKD) was defined as $GFR < 60 \text{ ml/min/1.73m}^2$. For this study
 66 kidney outcome was defined as CKD stages 2 ($60 - 89 \text{ ml/min/1.73m}^2$), 3 ($30 - 59$
 67 ml/min/1.73m^2) and 4 ($15 - 29 \text{ ml/min/1.73m}^2$).

68 Furthermore, immunological status of participants was classified based on CD4 counts into
 69 normal ($>500 \text{ cells/}\mu\text{l}$), (350 - 499  (200-349 $\text{cells/}\mu\text{l}$), immunological failure (<200
 70 $\text{cells/}\mu\text{l}$).

71 2.3 Data analysis and interpretation

72 Data analysis was done using statistical package for the social sciences (SPSS) version 20
 73 software program (IBM Corporation, USA). Descriptive statistics was done using frequency

percentages mean and standard deviation, inferential statistics was done using ANOVA, Pearson's correlation was also done and results presented using tables.

2.4 Ethical considerations

Data were collected after ethical clearance was given obtained from the University of Port Harcourt Teaching Hospital ethical board with ref number UPH/R&D/REC/04. A consent form was given to prospective participants after discussing the aims and objective of the study. Results were treated as very confidential.

3. Result

Table 1: Demographics and percentage of CD4 and CKD stages in 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 (Cells/μl)	count >500	138	34.8
	350 – 490	110	27.7
	200 – 349	57	14.4

	<200	92	23.2
CKD stage	Stage1 >90 ml/min/1.73m²	171	43.1
	Stage2 (60-89 ml/min/1.73m²)	172	43.3
	Stage 3 (30-59 ml/min/1.73m²)	45	11.3
	Stage 4 (15-29 ml/min/1.73m²)	5	1.3

83 **n=397**

84 **Results expressed as Frequency and percentages**

85

86 **Demographics and percentage of CD4 and CKD stages in participants**

87  demographics obtained from the study showed that more participants were within the age
88 range of 28 – 38 years (43%) while the least were participants in the > 58 years group with
89 4.8%. Female participants in the study comprised of 70.8% while the male participants were
90 29.2%. (Table 1).

91 Results also showed that participants in the category of CD4 > 500 were 38.4%. Participants
92 with CD4 < 500 (immuno-compromised) was 61.6%, this percentage was spread in 3
93 categories, CD4 350 – 490, 200 – 349 and < 200. Participants in the category of <200
94 (immune failure) were 23.2% (Table 1).

95 Furthermore estimated glomerular filtration rate (eGFR) was used to categorize patients into
96 stages 1, 2, 3, and 4. Participants with eGFR >90 ml/min/1.73m² were 43.1%, participants
97 with eGFR between 60 – 89 ml/min/1.73m² were 43.1% (stage 2), participants with values
98 between 30-59 ml/min/1.73m² (stage 3) and 15 – 29 ml/min/1.73m² (stage 4) were 11.3 and
99 1.3 % respectively (Table 1).

100

101 **Table 2: Mean values of CD4, TNF alpha eGFR in male and female distribution.**

	CD4(cells/ μ L)	TNF alpha (pg/ml)	eGFR ml/min/1.73m ²
Male	711.36 $\pm$ 164.94	92.67 $\pm$ 15.29	148.68 $\pm$ 25.63
Female	293.24 $\pm$ 146.76*	52.27 $\pm$ 45.97*	87.62 $\pm$ 22.26*

102 **n=397**

103 **Results expressed as mean $\pm$ standard deviation**

104 **Superscript* shows significant differences between groups**

105 **Mean values of CD4, TNF alpha eGFR in male and female distribution.**

106 The mean values of CD4, TNF alpha and eGFR in the male and female groups of the study
 107 were analysed, the results showed significant differences ($p < 0.05$) between male and female
 108 values. Female participants had significantly lower CD4 293.24 $\pm$ 146.76 in females against
 109 711.36 $\pm$ 164.94 found in male. TNF alpha in females was also significantly higher
 110 92.67 $\pm$ 15.29pg/ml in males against 52.27 $\pm$ 45.97 pg/ml in females. Estimated GFR was also
 111 significantly lower in females 87.62 $\pm$ 22.26 ml/min/1.73m² against 148.68 $\pm$ 25.63
 112 ml/min/1.73m² in male(Table 2).

113 **Table 3: Mean values of CD4, TNF alpha eGFR in different age groups.**

Age	CD4(cells/ μ L)	TNF(PG/ML)	eGFR ml/min/1.73m ²
18 – 27	433.13 $\pm$ 268.39	72.67 $\pm$ 15.03	102.13 $\pm$ 30.92
28 – 37	374.53 $\pm$ 216.24	59.04 $\pm$ 16.52	99.53 $\pm$ 32.58
38 – 47	449.81 $\pm$ 265.33	75.27 $\pm$ 12.65	109.26 $\pm$ 39.26
48 – 57	424.61 $\pm$ 227.89	59.09 $\pm$ 6.87	106.79 $\pm$ 35.65

>58 years 472.21±283.81 64,86±7.87 119.11±47.48

n=397

Results expressed as mean ± standard deviation

Superscript* shows significant differences between groups

CD4 count, TNF alpha and eGFR comparison in different age groups.

The CD4 count 374.53±216.24 observed in the 28-37 years age group was significantly lower than those in other groups and highest in participants >58 years (Table 3). Participants in the age bracket of 28 – 37 also had significantly lower TNF alpha values 59.04±16.52 when compared to other age groups, this was also the same for the eGFR values, participants within 28-37 years also had significantly lower eGFR value 99.53±32.58 when compared to other age groups.(Table3).

Table 4: CD4 count, TNF alpha and eGFR of patients in different CD4 stages of participants

CD4 stages	CD4(cells/μL)	TNF alpha(pg/ml)	eGFR ml/min/1.73m ²
>500 (Stage 1)	679.82±167.74	89.12±14.42	144.61±25.58
350 – 490 (Stage 2)	409.85±43.82	55.84±4.89	103.63±10.77
200 – 349 (Stage 3)	269.56±45.78	56.60±5.93	82.89±4.81
<200 (Stage 4)	115.82±48.27	40.92±27.62	62.97±10.48

CD4 count, TNF alpha and eGFR of patients in different CD4 stages of participants

129 The different CD4 stages were used as a category to compare CD4, TNF and eGFR.
 130 Participants with CD4 greater than 500 stage had significantly higher CD4 679.82 ± 167.74 ,
 131 TNF alpha 89.12 ± 14.42 and eGFR 144.61 ± 25.58 when compared to other CD4 stages.
 132 Results also showed that participants with CD4 < 200 had significantly lower Cd4 count,
 133 serum TNF alpha levels and eGFR values: 115.82 ± 48.27 , 40.92 ± 27.62 and 62.97 ± 10.48
 134 respectively. Results further showed chronic kidney disease when CD4count was lower than
 135 300 (Table 4) 

136 **Table 5: CD4 count, TNF alpha and eGFR of patients in different CKD stages**

CD4 stages	CD4(cells/ μ L)	TNF alpha(pg/ml)	eGFR ml/min/ $1.73m^2$
Stage1 >90 ml/min/ $1.73m^2$	623.76 ± 150.97	82.43 ± 12.01	137.92 ± 26.36
Stage2 (60-89 ml/min/ $1.73m^2$)	292.58 ± 94.94	52.62 ± 50.29	87.10 ± 12.38
Stage 3 (30-59 ml/min/ $1.73m^2$)	87.31 ± 22.76	39.68 ± 25.90	56.89 ± 7.04
Stage 4 (15-29 ml/min/ $1.73m^2$)	27.60 ± 7.89	37.33 ± 18.90	43.60 ± 2.61

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138 **CD4 count, TNF alpha and eGFR of patients in different CKD stages**

139 Participants in Stage1 (>90 ml/min/ $1.73m^2$) group of the study showed significantly higher
 140 CD4, TNF and eGFR, values were 623.76 ± 150.97 , 82.43 ± 12.01 and 137.92 ± 26.36
 141 respectively. Participants in stage 4 CKD showed reduced CD4 (27.60 ± 7.89), TNF alpha
 142 (37.33 ± 18.90) and eGFR with mean value of 43.60 ± 2.61 (Table 6).

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146 **Table 6: Correlation between variable**



		AGE	Sex	CD4	eGFR	TNF
AGE	Pearson Correlation	1	-.148**	-.059	-.067	.003
	Sig. (2-tailed)		.003	.244	.187	.955
Sex distribution	Pearson Correlation	-.148**	1	.696**	.625**	-.197**
	Sig. (2-tailed)	.003		.000	.000	.000
CD4	Pearson Correlation	-.059	.696**	1	.844**	-.190**
	Sig. (2-tailed)	.244	.000		.000	.001
	N	392	397	397	393	319
eGFR	Pearson Correlation	-.067	.625**	.844**	1	-.172**
	Sig. (2-tailed)	.187	.000	.000		.002
TNF alpha	Pearson Correlation	.003	-.197**	-.190**	-.172**	1
	Sig. (2-tailed)	.955	.000	.001	.002	

** . Correlation is significant at the 0.01 level (2-tailed).

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148 Correlation values showed that TNF was positively correlated with eGFR, CD4 and sex
 149 (Table 6). Also CD4 was inversely correlated with sex, eGFR and TNF, while eGFR was
 150 inversely correlated with sex, Cd4 and (eGFR Table 6).

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153 4. Discussion

154 The present study shows that female patients on ART have significantly lower eGFR hen
155 compared to male patients. There is a decline in renal function as CD 4 count decreases and
156 in this study there it was observed that patients with CD4 count between 200 – 349 and less
157 CD4 less than 200 showed a decrease in renal function.

158 It was also observed that patients greater than 58 years presented good renal function, also all
159 other age groups used for this study showed renal function > 90 .

160 These findings corroborate with findings from(5), (6), (7) A decline in eGFR in the range of
161 stages 3 and 5 CKD was also detected in a portion of the population with decreased CD4, the
162 findings show HIV, ART and pther drugs used to treat opportunistic infections may have
163 nephrotoxicity effects in Nigerian HIV patients. This finding is consistent with those obtained
164 by (7), (8), (9).

165 Studies have shown that HIV renal damage observed is a caused by changes in production of
166 cytokines during HIV infection (10). This study showed a decline in TNF alpha production
167 in patients with CKD stages 3 and 4, and CD4 count less than 500 (immuno-comprised
168 patients).

169 The current study also is one of the few showing the relationship between plasma levels of
170 TNF alpha and eGFR. TNF alpha values in female patients were significantly lower than
171 those in the male, it was also noticed that TNF alpha levels in the age grades 28-37 and 48-47
172 was lowest, further more TNF alpha levels of patients with CD4 lower than 500 (immuno-
173 comprised patients) was also lower when compared to patients with CD4 greater than 500,
174 finally patients with CKD values in stages 2, 3 and 4 was significantly lower when compared
175 to patients in stage 1. This reduced production of TNF alpha by patients in stages 2, 3 and 4

could be a resultant effect of the patients been immuno-compromised tumor necrosis factor alpha correlated inversely with CD4 count and eGFR in this study. the TNF alpha values of normal patients is consist with those gotten by (11), But TNF alpha of patients with renal impairment was 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, (7), (12)

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. Our findings showed CKD frequency of 43.3%, 11.3% and 1.3% for CKD stages 2,3 and 4 respectively. This finding is similar those obtained by (5) in Nigeria: in Uganda (13). The high rate of renal impairment gotten from this study also corroborates with those gotten from Tanzania (2). Furthermore, the high 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 (14)

Limitations

Our study has some limitations. First some hidden variables cofounding relating to 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 histopatological data was available for analysis. Finally, the study was underpowered hence could not study the full impact of the antiretroviral drugs independently.

199 **Conclusion**

200 The present study found that ART is associated with both improvement and worsening of
 201 renal function as time goes by. Also, decline in eGFR was still found in treated patients.
 202 Furthermore, decrease in serum Tumor necrosis factor alpha and decreased CD4 count was
 203 strongly associated with a decline in renal function. Female gender is also a risk factor and
 204 contributes to continuous decline in renal function.

205 **References.**

- 206 1. Brooks GF, Carroll KC, Butel JS, Morse SA, Mietzner TA. Medical Microbiology.
 207 Jawetz, Melnick and Adelbergs [Internet]. 27th ed. Newyork: McGraw Hill
 208 Professiona; 2010 [cited 2018 Mar 19]. 406–407. p. Available from:
 209 [https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=Brooks+GF%2C+Carro](https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=Brooks+GF%2C+Carro+ll+KC%2C+Butel+JS%2C+Morse+SA%2C+Mietzner+TA.+Jawetz%2C+Melnick%2C+%26+Adelberg's+Medical+Microbiology.+25th+ed.+New+York%3A+McGraw-Hill%3B+2010.+pp.+406–407.&btnG=#)
 210 [ll+KC%2C+Butel+JS%2C+Morse+SA%2C+Mietzner+TA.+Jawetz%2C+Melnick%2](https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=Brooks+GF%2C+Carro+ll+KC%2C+Butel+JS%2C+Morse+SA%2C+Mietzner+TA.+Jawetz%2C+Melnick%2C+%26+Adelberg's+Medical+Microbiology.+25th+ed.+New+York%3A+McGraw-Hill%3B+2010.+pp.+406–407.&btnG=#)
 211 [C+%26+Adelberg's+Medical+Microbiology.+25th+ed.+New+York%3A+McGraw-](https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=Brooks+GF%2C+Carro+ll+KC%2C+Butel+JS%2C+Morse+SA%2C+Mietzner+TA.+Jawetz%2C+Melnick%2C+%26+Adelberg's+Medical+Microbiology.+25th+ed.+New+York%3A+McGraw-Hill%3B+2010.+pp.+406–407.&btnG=#)
 212 [Hill%3B+2010.+pp.+406–407.&btnG=#](https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=Brooks+GF%2C+Carro+ll+KC%2C+Butel+JS%2C+Morse+SA%2C+Mietzner+TA.+Jawetz%2C+Melnick%2C+%26+Adelberg's+Medical+Microbiology.+25th+ed.+New+York%3A+McGraw-Hill%3B+2010.+pp.+406–407.&btnG=#)
- 213 2. Msango L, Downs J, ... SK-A (London, 2011 undefined. Renal dysfunction among
 214 HIV-infected patients starting antiretroviral therapy in Mwanza, Tanzania.
 215 ncbi.nlm.nih.gov [Internet]. [cited 2018 Mar 19]; Available from:
 216 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3631352/>
- 217 3. Gupta S, Eustace J, ... JW-CI, 2005 undefined. Guidelines for the management of
 218 chronic kidney disease in HIV-infected patients: recommendations of the HIV
 219 Medicine Association of the Infectious Diseases. academic.oup.com [Internet]. [cited
 220 2018 Mar 19]; Available from: [https://academic.oup.com/cid/article-](https://academic.oup.com/cid/article-abstract/40/11/1559/442353)
 221 [abstract/40/11/1559/442353](https://academic.oup.com/cid/article-abstract/40/11/1559/442353)
- 222 4. Levey A, Bosch J, Lewis J, Rogers N, Roth D. A simplified equation to predict
 223 glomerular filtration rate from serum creatinine. 2000 [cited 2018 Mar 19]; Available
 224 from: <http://en.journals.sid.ir/ViewPaper.aspx?ID=240721>
- 225 5. Emem CP, Arogundade F, Sanusi A, Adelusola K, Wokoma F, Akinsola A. Renal
 226 disease in HIV-seropositive patients in Nigeria: an assessment of prevalence, clinical
 227 features and risk factors. Nephrol Dial Transplant [Internet]. 2007 Oct 30 [cited 2018
 228 Mar 19];23(2):741–6. Available from: [https://academic.oup.com/ndt/article-](https://academic.oup.com/ndt/article-lookup/doi/10.1093/ndt/gfm836)
 229 [lookup/doi/10.1093/ndt/gfm836](https://academic.oup.com/ndt/article-lookup/doi/10.1093/ndt/gfm836)
- 230 6. Cailhol J, Nkurunziza B, Izzedine H, Nindagiye E, Munyana L, Baramperanye E, et al.
 231 Prevalence of chronic kidney disease among people living with HIV/AIDS in Burundi:
 232 a cross-sectional study. BMC Nephrol [Internet]. 2011 Dec 24 [cited 2018 Mar
 233 19];12(1):40. Available from:
 234 <http://bmcnephrol.biomedcentral.com/articles/10.1186/1471-2369-12-40>
- 235 7. Adedeji TA, Adedeji NO, Adebisi SA, Idowu AA, Fawale MB, Jimoh KA. Prevalence

- 236 and Pattern of Chronic Kidney Disease in Antiretroviral-Naïve Patients with
237 HIV/AIDS. *J Int Assoc Provid AIDS Care* [Internet]. 2015 Sep 26 [cited 2018 Mar
238 19];14(5):434–40. Available from:
239 <http://journals.sagepub.com/doi/10.1177/2325957415587570>
- 240 8. Kimmel P, ... AF-C-K, 1993 undefined. Viral DNA in microdissected renal biopsy
241 tissue from HIV infected patients with nephrotic syndrome. *kidneyinternational-*
242 *online.org* [Internet]. [cited 2018 Mar 19]; Available from:
243 [http://www.kidneyinternational-online.org/article/S0085-2538\(15\)58070-8/abstract](http://www.kidneyinternational-online.org/article/S0085-2538(15)58070-8/abstract)
- 244 9. Klotman PE. HIV-associated nephropathy. *Kidney Int* [Internet]. 1999 [cited 2018 Mar
245 19];56:1161–76. Available from: [http://www.kidneyinternational-](http://www.kidneyinternational-online.org/article/S0085-2538(15)46400-2/pdf)
246 [online.org/article/S0085-2538\(15\)46400-2/pdf](http://www.kidneyinternational-online.org/article/S0085-2538(15)46400-2/pdf)
- 247 10. Kopp J, international CW-K, 2003 undefined. HIV-associated nephropathy in African
248 Americans1. *kidneyinternational-online.org* [Internet]. [cited 2018 Mar 19]; Available
249 from: [http://www.kidneyinternational-online.org/article/S0085-2538\(15\)49182-](http://www.kidneyinternational-online.org/article/S0085-2538(15)49182-3/abstract)
250 [3/abstract](http://www.kidneyinternational-online.org/article/S0085-2538(15)49182-3/abstract)
- 251 11. Robinson O, Obianime A, Aprioku J, Tamuno I. Immunological and Hematological
252 Profile of HIV Patients on Anti-retroviral Therapy in Port Harcourt, Rivers State,
253 Nigeria. *journalrepository.org* [Internet]. [cited 2018 Mar 19]; Available from:
254 http://www.journalrepository.org/media/journals/IBRR_28/2017/Sep/Robinson742017
255 [IBRR36037_p.pdf](http://www.journalrepository.org/media/journals/IBRR_28/2017/Sep/Robinson742017)
- 256 12. Emem C, Arogundade F, ... AS-ND, 2007 undefined. Renal disease in HIV-
257 seropositive patients in Nigeria: an assessment of prevalence, clinical features and risk
258 factors. *academic.oup.com* [Internet]. [cited 2018 Mar 19]; Available from:
259 <https://academic.oup.com/ndt/article-abstract/23/2/741/1854126>
- 260 13. Peters P, Moore D, ... JM-K, 2008 undefined. Antiretroviral therapy improves renal
261 function among HIV-infected Ugandans. *kidneyinternational-online.org* [Internet].
262 [cited 2018 Mar 19]; Available from: [http://www.kidneyinternational-](http://www.kidneyinternational-online.org/article/S0085-2538(15)53428-5/abstract)
263 [online.org/article/S0085-2538\(15\)53428-5/abstract](http://www.kidneyinternational-online.org/article/S0085-2538(15)53428-5/abstract)
- 264 14. Karras A, Lafaurie M, Furco A, Bourgarit A, Droz D, Sereni D, et al.
265 Tenofovir-Related Nephrotoxicity in Human Immunodeficiency Virus–Infected
266 Patients: Three Cases of Renal Failure, Fanconi Syndrome, and Nephrogenic Diabetes
267 Insipidus. *Clin Infect Dis* [Internet]. 2003 Apr 15 [cited 2018 Mar 19];36(8):1070–3.
268 Available from: <https://academic.oup.com/cid/article-lookup/doi/10.1086/368314>