Journal of Infection (2013) **67**, 43—50

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# High prevalence of renal dysfunction and association with risk of death amongst HIV-infected Ghanaians

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Accepted 12 March 2013
Available online 28 March 2013

**KEYWORDS**
HIV;
Kidney;
Renal;
Africa;
Antiretroviral therapy

**Summary** *Objectives:* To determine the prevalence of HIV-associated renal dysfunction (RD), identify risk factors for RD and explore the association between baseline renal function and mortality in an HIV-infected population in Ghana.
*Methods:* Creatinine clearance (CrCl) or estimated glomerular filtration rate (eGFR) was calculated in patients attending an HIV clinic between 2004 and 2011 using Cockcroft-Gault, MDRD and CKD-EPI formulae. Logistic regression analysis was used to identify risk factors associated with RD and Kaplan—Meier/Cox proportional regression analyses to explore associations between baseline CrCl/eGFR and subsequent mortality.
*Results:* In 3137 patients starting antiretroviral therapy (ART) the frequency (95%-CI) of RD, defined by CrCl <60 ml/min/1.73 $m^2$ using Cockroft-Gault formula was 38.8% (37.1—40.5%). RD prevalence in a sub-population of 238 patients, including proteinuria in the definition, was 15.3% (10.3—22.1%) in ART-treated and 43.6% (34.0—53.7%) in ART-naïve patients. RD at baseline was associated with increasing age, low CD4 counts, advanced WHO stage and female gender. Cox proportional hazard analysis identified an increased hazard of death with decreasing CrCl, HR 1.46 (1.31—1.63) for each tertile lower than CrCl of 90 ml/min/1.73 $m^2$.
*Conclusions:* RD is very common in HIV-infected ART-naïve Ghanaians, and associated with increased risk of mortality. Screening and monitoring of RD is important in this setting, particularly as tenofovir use increases.


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0163-4453/$36 
http://dx.doi.org/10.1016/j.jinf.2013.03.008

## Introduction

HIV infection is associated with an increased risk of chronic kidney disease (CKD) and when untreated, HIV-related kidney disease can rapidly progress to end stage renal disease (ESRD) with an associated increased risk of mortality.[1–3] HIV-associated nephropathy (HIVAN), characterised histologically by focal segmental glomerulosclerosis with glomerular collapse and commonly manifesting as persistent proteinuria, is the most common HIV-related renal pathology in Sub-Saharan Africa.[4,5] Studies from the USA suggest there is a higher prevalence of CKD among the African-American population (largely of West African descent) compared to the Caucasian population.[6] Genetic associations exploring this risk have recently identified higher frequencies of recessive polymorphisms in the MYH9 gene and the neighbouring APOL1 gene, both located on chromosome 22q13 locus, which predispose to an increased risk for HIVAN and idiopathic focal segmental glomerulosclerosis.[7,8] Although data is scarce, in the few studies conducted to date, the prevalence of HIV-related CKD among West Africans[4] appear to be higher compared with those from East and Southern Africa.[9–11] One reason why the prevalence of renal impairment has varied between studies is because the definition of renal disease has varied, with different methods employed ranging from estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCl), urine dipstick measurements and renal biopsies for histology.

Similar to the situation in most countries in Sub-Saharan Africa, antiretroviral therapy (ART) has been rolled out in Ghana since 2004. In this treatment program, first-line ART is composed of a backbone of 2 nucleotide reverse inhibitors (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) according to WHO guidelines. There is growing evidence that ART is associated with reduced incidence of HIV-related CKD, decreased proteinuria and slowing of progression to ESRD,[10,12,13] however various antiretroviral drugs have themselves been associated with renal impairment.[14–16] Given the disparities in the reported prevalences of HIV-related renal impairment, the paucity of data on the associations between baseline renal function and the risk of death and the increasing use of tenofovir and protease inhibitors across Sub-Saharan Africa, further studies are needed to address these questions.

We have approached this study by calculating CrCl/eGFRs using the three widely accepted formulae in a large cohort of HIV-infected Ghanaian initiating ART to determine the prevalence and risk factors for renal impairment. This was followed by a cross-sectional study where proteinuria as well as CrCl was assessed in ART-naïve patients and patients on long-term ART. Finally, the association between baseline renal impairment on mortality after initiating ART was assessed.

## Patients and methods

### Patients and data

This was an observational single-centre study involving a retrospective analysis of all HIV-infected patients who started ART from January 2004 to December 2010, and a cross-sectional analysis of individuals attending the HIV clinic from May 2010 to January 2011 who were screened at random for renal disease. This study was conducted at the Komfo Anokye Teaching Hospital (KATH) in Kumasi, Ghana. Approval for the study was given by the Committee on Human Research Publications and Ethics at KATH. Data was collected from the case notes of patients with data censored on December 31st, 2011. Demographic, medical and laboratory data at the date of initiation of ART was collected from case notes. Laboratory data collected was CD4 counts and serum creatinine, which is normally only tested prior to ART initiation and rarely afterwards. HIV viral loads were not routinely performed. Upon initiating ART clinical outcomes such as death and loss to follow-up were recorded for each patient. Participants in the cross-sectional study were eligible if they were $\geq$18 years and were able to give informed consent. Serum creatinine was measured at the point of recruitment and urinalysis was performed using reagent strips (Multistix, Siemens Healthcare Diagnostics Inc). Individuals with known causes of renal impairment or who had urinary tract infections confirmed by a positive urine culture were excluded. To further define the level and characteristics of proteinuria in individuals with proteinuria (defined as $\geq$1 + protein on urinalysis), urine protein:creatinine ratios (uPCR) and urine albumin:creatinine ratios (uACR) were calculated. A uPCR >45 mg/mmol was considered significant. Whenever possible, repeat urinalysis was performed after 4 weeks to confirm persistent proteinuria. As urinalysis was not routine practice in the clinic, CKD was defined only by low CrCl/eGFR in the Retrospective Cohort.

### Classification of HIV-related renal disease

Serum creatinine was used to determine CrCl using the using the Cockroft-Gault,[17] and eGFR using the MDRD[18] and CKD-EPI[19] formulae. For the Retrospective Cohort CKD was defined as CrCl/eGFR <60 ml/min/1.73 $m^2$; for the Cross-sectional Cohort CKD was defined as either CrCl <60 ml/min/1.73 $m^2$, or proteinuria $\geq$1 + (confirmed by uPCR > 45 mg/mmol) on urinalysis.

### Statistical analysis

Demographic, clinical characteristics, and laboratory features were compared using the Mann–Whitney's *U*-test or student's *t*-test for continuous non-parametric and parametric data (respectively), and chi-squared tests for discrete variables; medians between more than 2 groups were compared using the Kruskal Wallis test. Bland–Altman plots and Kappa statistics were used to assess agreement between the 3 formulae for CrCl/eGFR. Bland–Altman plots of agreement between CrCl/eGFRs calculated using the three formulae were performed and the biases of estimates with the standard deviation and 95% limits of the bias presented. In assessing the inter-rater agreement between the 3 formulae for stages of renal impairment, the Cohen kappa statistic $\kappa$-value with the standard error as well as a linearly weighted Fleiss' kappa values were reported. Factors associated with renal impairment were explored in the Retrospective Cohort using multiple logistic regression analysis while Kaplan–Meier plots and Cox proportional regression analysis were used

to examine the associations between CrCl/eGFR and risk of mortality on ART. In survival analysis, patients lost to follow-up were censored to the last clinic visit. Statistical analyses were performed using the GraphPad Prism 4 and Cox proportional hazards regressions were performed using SPSS version 17.

## Results

### Baseline demographic and laboratory characteristics of study participants

Baseline characteristics of patients in the two cohorts studies are shown in Table 1. In the Retrospective Cohort, of 4039 patients who initiated ART between 2004 and 2010, 3137 had a baseline creatinine measurement with 3130 having sufficient data to calculate eGFR by MDRD and CK-EPI formulae and 3054 sufficient to calculate CrCl using the Cockcroft-Gault formula (Table 2). Baseline demographic and laboratory characteristics of the patients without creatinine results did not differ significantly from those with creatinine measurements (data not shown). Only 2 patients received tenofovir, whilst 1% received either ritonavir-boosted lopinavir or nelfinavir. In the Cross-sectional Cohort, of 261 patients randomly screened, 23 were excluded due to know risk factors for CKD, and 144 were taking ART for a median of 39.2 months (range, 22.1–62.7 months). Only 3 patients received tenofovir, whilst 5 received either ritonavir-boosted lopinavir or nelfinavir. ART-naïve patients in this cohort included both patients with low CD4 counts (72% < 350 cells/mm$^3$) or late stage disease, who started ART shortly after screening, and those with higher CD4 counts.

### Calculating CrCl/eGFR to assess of renal impairment among HIV-infected patients at baseline

Using the Bland–Altman plots, it was evident that when compared with both the MDRD and CKD-EPI formulae, the Cockroft-Gault gave a negative bias in the CrCl/eGFR.

**Table 1** Baseline characteristics of two study populations.[a]

| | Retrospective Cohort, $n = 3137$ | Cross-sectional Cohort: ART naïve, $n = 94$ | Cross-sectional Cohort: on ART, $n = 144$ | $p$-Value[f] |
|---|---|---|---|---|
| Age (years) (IQR) | 38 (32–45) | 38 (32–45) | 40 (36–45) | 0.0095 |
| Gender: female, *n* (%) | 2114 (67) | 68 (72) | 104 (72) | 0.03 |
| BMI (IQR), kg/m$^2$ | 20.3 (17.6–22.7) | 20.0 (18.2–22.6) | 22.7 (20.0–26.9) | <0.0001 |
| WHO clinical stage,[b] *n* (%) | | | | |
| 1 | 200 (6) | 7 (7) | 3 (2) | <0.0001 |
| 2 | 397 (13) | 22 (23) | 18 (13) | |
| 3 | 1706 (54) | 33 (35) | 66 (46) | |
| 4 | 521 (17) | 12 (13) | 8 (6) | |
| NRTI combination, *n* (%) | | | | |
| Stavudine/lamivudine | 1629 (52) | – | 30 (21) | <0.0001 |
| Zidovudine/lamivudine | 1494 (48) | – | 111 (78) | |
| NNRTI base, *n* (%) | | | | |
| Efavirenz | 1848 (59) | – | 87 (60) | 0.47 |
| Nevirapine | 1256 (40) | – | 52 (36) | |
| CD4 count/mm$^3$ (IQR) | 133 (49–217) | 212 (96–332) | 419 (329–584) | <0.0001 |
| Serum creatinine/μmol/l (IQR) | 86.6 (70.7–106.1) | 63 (48–83.8) | 65 (51.8–73.3) | <0.0001 |
| CrCl[c] (ml/min/1.73 m$^2$) (IQR) | 66.0 (50.0–86.0) | 86.9 (66.9–116.9) | 94.1 (75.4–125.7) | 0.39 |
| CrCl < 60 ml/min/1.73 m$^2$, *n* (%) | 1186 (38.8) | 20 (21.3) | 12 (8.3) | <0.0001 |
| eGFR-MDRD[d] (ml/min/1.73 m$^2$) (IQR) | 91.0 (70.0–118.0) | 99.1 (86.9–116.8) | 104.7 (85.7–115.1) | 0.42 |
| eGFR < 60 ml/min/1.73 m$^2$-MDRD, *n* (%) | 429 (13.7) | 9 (9.6) | 40 (27.7) | <0.0001 |
| Proteinuria,[e] *n* (%) | Not done | 31 (32.9) | 11 (9.6) | <0.0001 |
| Renal impairment[e] | 1186 (38.8) | 41 (43.6) | 22 (15.3) | <0.0001 |

Median values used. IQR, interquartile range. ART, anti-retroviral therapy; BMI, body mass index.

[a] At initiation of ART in the Retrospective Cohort, and at screening in the Cross-sectional Cohort.

[b] Missing values for 313 in the Retrospective Cohort, 49 in the on-ART and 20 in the ART-naïve Cross-sectional Cohorts.

[c] Creatinine clearance calculated using Cockcroft Gault equation.

[d] Estimated glomerular filtration rate calculated by the MDRD formula.

[e] Proteinuria defined as urinary protein/creatinine ratio >45 mg/mmol; renal impairment defined as CrCl/eGRF <60 ml/min/1.73 m$^2$ or proteinuria (only defined by CrCl < 60 ml/min/1.73 m$^2$ in the Retrospective Cohort).

[f] Comparison between on-ART and ART-naïve groups within the Cross-sectional Cohort using Mann Whitney *U* test or Chi squared test.

**Table 2** Frequency of stages of renal impairment in the Retrospective Cohort by creatinine clearance or estimated glomerular filtration rate using Cockroft-Gault, MDRD and CKD-EPI formulae.

| Stage of renal impairment | Frequency (%) by Cockcroft-Gault | Frequency (%) by MDRD | Frequency (%) by CKD-EPI | κ statistic, (95% CI), weighted κ CG vs MDRD | κ statistic, (95% CI), weighted κ CG vs CKD-EPI | κ statistic (95% CI); weighted κ CKD-EPI vs MDRD |
|---|---|---|---|---|---|---|
| **Stage 1** $>$ 90 ml/min/1.73 m$^2$ | 693 (22.7) | 1636 (52.3) | 1696 (54.2) | 0.23 (0.21—0.26); | 0.22 (0.20—0.25); | 0.94 (0.93—0.95); |
| **Stage 2** 60—89 ml/min/1.73 m$^2$ | 1175 (38.5) | 1065 (34.0) | 1000 (31.9) | 0.418 | 0.410 | 0.959 |
| **Stage 3A** 45—59 ml/min/1.73 m$^2$ | 644 (21.1) | 241 (7.7) | 231 (7.4) | | | |
| **Stage 3B** 30—44 ml/min/1.73 m$^2$ | 368 (12.0) | 92 (2.9) | 106 (3.4) | | | |
| **Stage 4** 15—29 ml/min/1.73 m$^2$ | 130 (4.3) | 62 (2.0) | 61 (1.9) | | | |
| **Stage 5** $<$ 15 ml/min/1.73 m$^2$ | 44 (1.4) | 34 (1.1) | 36 (1.2) | | | |
| **Total** | 3054 | 3130 | 3130 | 3054 | 3054 | 3130 |

However the difference between eGFR by MDRD and CKD-EPI was 2.9 $\pm$ 14.5 ml/min/1.73 m$^2$ with the two formulae diverging at eGFRs above 125 ml/min/1.73 m$^2$. Consequently, there was very good agreement between stages of renal impairment using eGFR calculated by MDRD and CKD-EPI with a κ-value (95% CI) of 0.94 (0.93—0.95) and a weighted κ-value of 0.96. Bland—Altman's plots exploring the agreement between stages of renal impairment estimated using the Cockcroft-Gault and either the MDRD or CKD-EPI showed fair degrees of agreements with κ-values 0.23 and 0.22 respectively and moderate agreements in linearly weighted kappa (Table 2).

## Prevalence and risk factors for HIV-related renal impairment

In the Retrospective Cohort, the frequencies (95% CI) of renal impairment, determined solely by CrCl/eGFR $<$60 ml/min/1.73 m$^2$ using the Cockroft-Gault, MDRD and CKD-EPI formulae were 38.8% (37.1—40.5%), 13.7% (12.6—15.0%) and 13.9% (12.7—15.1%) respectively, while the frequencies of severe renal impairment with CrCl/eGFR $<$30 ml/min were 5.7% (4.9—6.6%), 3.1% (2.5—3.7%) and 3.1% (2.6—3.8%) respectively (Table 2). Given that none of these formulae has been validated for use in HIV-infected patients, results of analysis of the risk factors for HIV-related renal impairment were conducted using all 3 formulae but only those for Cockroft-Gault and the CKD-EPI are shown (Table 3). On adjusted analysis, risk factors associated with CrCl $<$60 ml/min/1.73 m$^2$ calculated using the Cockroft-Gault formula were age, female gender, CD4 count at baseline and advanced WHO clinical stages of HIV disease. However using CKD-EPI, only increasing age was significantly associated with the risk of developing HIV-related renal impairment. In a similar analysis, severe renal impairment with CrCl $<$30 ml/min/1.73 m$^2$ calculated

**Table 3** Baseline risk factors associated with creatinine clearance or estimated glomerular filtration rate $<$60 ml/min/1.73 m$^2$.

| | CrCl by Cockroft-Gault formula | | | | eGFR by CKD-EPI | | | |
|---|---|---|---|---|---|---|---|---|
| | Unadjusted OR (95% CI) | *p*-Value | Adjusted OR (95% CI) | *p*-Value | Unadjusted OR (95% CI) | *p*-Value | Adjusted OR (95% CI) | *p*-Value |
| Age/10-year higher | 1.93 (1.77—2.11) | 0.00 | 2.08 (1.90—2.29) | 0.00 | 1.60 (1.44—1.79) | 0.00 | 1.59 (1.42—1.77) | 0.00 |
| Male gender | 0.68 (0.58—0.81) | 0.00 | 0.49 (0.40—0.58) | 0.00 | 0.90 (0.71—1.14) | 0.39 | — | — |
| CD4/every 50 cells higher | 0.97 (0.93—1.00) | 0.07 | 0.95 (0.91—0.99) | 0.016 | 0.98 (0.93—1.03) | 0.48 | — | — |
| WHO stage/1 stage higher | 1.35 (1.22—1.50) | 0.00 | 1.35 (1.20—1.51) | 0.00 | 1.06 (0.92—1.23) | 0.38 | — | — |
| Hypertension | 2.25 (1.28—3.95) | 0.047 | 1.18 (0.62—2.24) | 0.62 | 2.66 (1.45—4.90) | 0.002 | 1.32 (0.65—2.68) | 0.44 |
| Diabetes mellitus | 2.03 (0.89—4.64) | 0.09 | 1.28 (0.45—3.67) | 0.64 | 3.91 (1.70—9.00) | 0.003 | 2.05 (0.70—6.00) | 0.19 |
| Hypertension & diabetes mellitus | 7.79 (0.91—66.76) | 0.06 | 3.95 (0.32—48.75) | 0.28 | 12.93 (2.36—70.84) | 0.003 | 3.81 (0.46—31.92) | 0.22 |

using Cockroft-Gault was significantly associated with increasing age, low CD4 counts, advanced WHO clinical stages and having a diagnosis of hypertension at baseline. Using the CKD-EPI formula, the only factor associated significantly with severe renal impairment was a low CD4 count at baseline with marginal but non-significant associations between increasing age and WHO clinical stage (data not shown).

In the Cross-sectional Cohort the overall prevalence (95% CI) of renal impairment, as defined by CrCl <60 ml/min/1.73 $m^2$ (Cockcroft-Gault) or proteinuria, was 26.5% (21.3–32.4%). There was a significantly higher frequency of renal impairment in the ART-naïve group 43.6% (34.0–53.7%) compared to the ART-treated group of 15.3% (10.3–22.1%), $p$ <0.001 (Table 1). Nearly 75% of ART-naïve patients' CKD was defined solely by proteinuria. Analysis of 6 individuals with relatively high proteinuria (uPCR > 100 mg/mmol) showed half had uACR <30 mg/mmol, suggesting a possible tubular (rather than glomerular) aetiology for their renal dysfunction. None of these patients were taking tenofovir.

### Association between baseline renal impairment and mortality after starting cART

The median (IQR) duration of follow of patients in the Retrospective Cohort was 30 (12–54) months. At closure of data for analysis 2197 (72%) were still alive, 623 (20%) were lost-to-follow-up and 234 were dead (8%). The causes of death for 188 (80%) of patients were ascertained from medical records and death certificates, of which 4 deaths were recorded as due to end-stage renal disease. It was not possible to ascertain what proportion of patients lost to follow up had died, however a recent audit conducted in the HIV clinic suggested nearly two thirds of all patients lost to follow up over a similar time period had died. The outcomes of patients according to baseline CrCl are presented in Table 4 showing that there was a graded risk of attrition, defined as death or loss-to-follow-up, with decreasing CrCl. In a Kaplan Meier analysis there was a significant trend towards increased mortality according to decreasing stage of CKD defined by CrCl, log rank test $p$ <0.001 (Fig. 1). In a multivariate Cox proportional hazard analysis with adjustment for gender, age, baseline CD4 counts, WHO clinical stage, NRTI backbone and NNRTI, there was also a significantly higher mortality with an CrCl/eGFR <60 ml/min/1.73 $m^2$ using either the Cockroft-Gault formula (Table 5), the CKD-EPI or MDRD formulae (data not shown), with an adjusted HR of 1.46 (95% CI 1.31–1.63) for each tertile lower than an CrCl/eGFR of 90 ml/min/1.73 $m^2$. Other factors independently associated with the risk of death were male gender, lower CD4 counts at initiation of ART, advanced WHO clinical stages and initiating therapy with a stavudine-containing NRTI backbone.

## Discussion

We have assessed the prevalence of and risk factors for renal impairment, associations with mortality and utility of three formulae to measure CrCl/eGFR among HIV-infected Ghanaian. We found a high frequency of renal impairment (39%), defined solely by CrCl <60 ml/min using the Cockroft-Gault formula, in a large retrospectively-defined cohort of patients starting ART, and 26.5% in a smaller cross-sectional cohort, defined by both reduced CrCl and proteinuria. Risk factors associated with renal impairment included increasing age, female gender, lower baseline CD4 counts and advanced clinical stages of HIV disease. Finally, we showed there is a gradient of increased risk of mortality according to baseline CrCl amongst this West African cohort after initiating ART.

Our finding of 39% of patients initiating therapy having renal dysfunction (defined only by CrCl <60 ml/min/1.73 $m^2$, using Cockcroft-Gault) and 5.7% severe renal dysfunction (CrCl < 30 ml/min/1.73 $m^2$), is substantially more than the respective prevalences found in other Sub-Saharan African populations, using the same definition.[9,10,20–22] Furthermore when including proteinuria as a definition, the prevalence of renal impairment was considerably higher (44%) in our ART-naïve than ART-treated population (15%). This is broadly consistent with studies indicating frequencies between 38% and 45% amongst Nigerian,[4] Tanzanian[20] and Burundian[21] (mostly ART-naïve) patients, where renal impairment was defined more often by proteinuria than low CrCl/eGFR. Given the relative scarcity of other causes of renal dysfunction identified, our data suggests that HIV-associated renal impairment is more common in Ghana than in most other developing and developed countries. The implications of this in terms of progression to CKD, associated morbidity and mortality, and whether progression to

**Table 4** Vital status at censoring of patients according to creatinine clearance (Cockroft-Gault formula) at start of cART.

| Stage of renal impairment | Estimated glomerular filtration rate (ml/min/1.73 $m^2$) | Alive *n* (%) | Death *n* (%) | Lost-to-follow up *n* (%) | Composite of death and loss to follow-up. *n* (%) |
|---|---|---|---|---|---|
| Stage 1, $n$ = 315 | >90 | 263 (83.5) | 14 (4.4) | 38 (12.1) | 52 (16.5) |
| Stage 2, $n$ = 943 | 60–89 | 726 (77.0) | 69 (7.3) | 148 (15.7) | 217 (23.0) |
| Stage 3A, $n$ = 845 | 45–59 | 578 (68.4) | 71 (8.4) | 196 (23.2) | 267 (31.6) |
| Stage 3B, $n$ = 654 | 30–44 | 452 (69.1) | 49 (7.5) | 153 (23.4) | 202 (30.9) |
| Stage 4, $n$ = 240 | 15–29 | 141 (58.8) | 28 (11.7) | 71 (29.6) | 99 (41.3) |
| Stage 5, $n$ = 57 | <15 | 37 (64.9) | 3 (5.3) | 17 (29.8) | 20 (35.1) |
| Total, $n$ = 3054 | | 2197 | 234 | 623 | 857 |

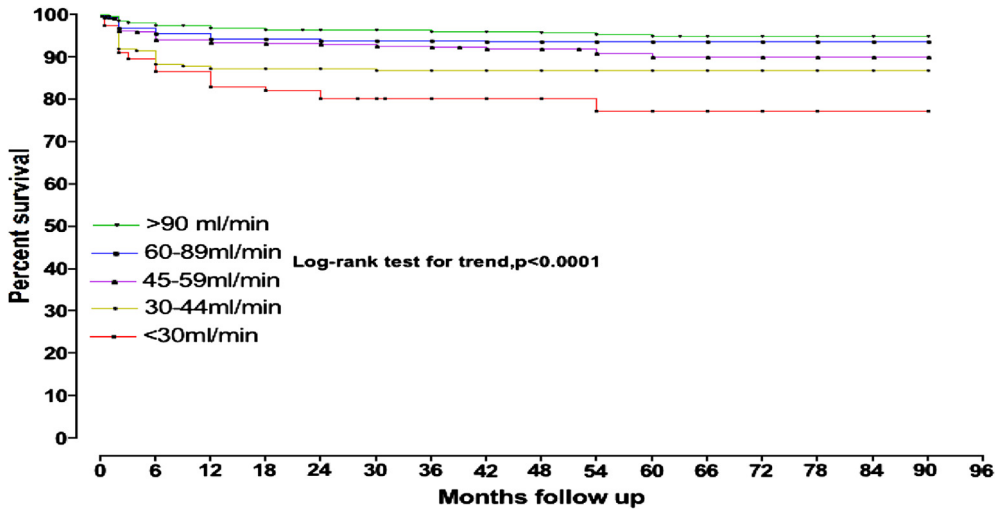


**Figure 1** Kaplan–Meier analysis for risk of death according to baseline creatinine clearance using the Cockcroft-Gault formula.

end-stage renal disease can be arrested through earlier ART or other interventions are not clear, and further studies are needed to determine the long-term outcomes in patients with evidence of renal impairment prior to starting ART. However given the frequency of renal impairment in ART-naïve patients there is a strong case for introducing routine urinalysis for all patients newly-diagnosed with HIV infection, and monitoring creatinine in patients identified with renal dysfunction, which should be feasible in this setting. As ACE-inhibitor therapy has been suggested in addition to ART in patients with persistent and significant proteinuria and/or hypertension,[5] further studies to assess potential benefits of ACE inhibitors are warranted in West Africa.

The risk factors associated with renal dysfunction amongst Ghanaian patients were female gender, increasing age, advanced stage of HIV disease and lower baseline CD4 counts. Whilst increasing age and low CD4 counts have been associated with increased risk of renal dysfunction in a number of studies,[23–25] it was of interest that female gender was identified as an independent risk factor for renal dysfunction, as has been found in three other African studies.[20–22] Our observation that the risk of death among

**Table 5** Cox proportional hazard analysis for mortality on ART according to creatinine clearance (by Cockroft-Gault formula) and other factors at baseline.

| Variable | Unadjusted HR | *p*-Value | Adjusted HR | *p*-Value |
|---|---|---|---|---|
| CrCl | | | | |
| >90 ml/min/1.73 $m^2$ | 1.00 | | 1.00 | |
| 60–89 ml/min/1.73 $m^2$ | 1.34 (0.86–2.10) | 0.19 | 1.29 (0.83–2.03) | 0.26 |
| 45–59 ml/min/1.73 $m^2$ | 2.14 (1.35–3.38) | 0.0012 | 1.95 (1.21–3.12) | 0.0057 |
| 30–44 ml/min/1.73 $m^2$ | 3.41 (2.13–5.44) | 0.0000 | 2.55 (1.55–4.17) | 0.0002 |
| <30 ml/min/1.73 $m^2$ | 5.75 (3.45–9.59) | 0.0000 | 4.08 (2.34–7.11) | 0.0000 |
| Gender | | | | |
| Male | 1.61 (1.23–2.10) | 0.0004 | 1.58 (1.19–2.10) | 0.0016 |
| Female | 1.00 | | 1.00 | |
| Age | | | | |
| <40 years | 1.08 (0.83–1.41) | 0.56 | – | – |
| ≥40 years | 1.00 | | – | – |
| WHO stage | | | | |
| Each stage higher | 1.90 (1.55–2.31) | 0.0000 | 1.53 (1.24–1.88) | 0.0001 |
| Baseline CD4 count | | | | |
| Each 50 cells higher | 0.71 (0.66–0.78) | 0.0000 | 0.77 (0.70–0.83) | 0.0000 |
| NRTI backbone | | | | |
| D4T plus 3TC | 2.10 (1.59–2.78) | 0.0000 | 1.57 (1.18–2.08) | 0.0020 |
| AZT plus 3TC | 1.00 | | 1.00 | |
| NNRTI | | | | |
| Nevirapine | 0.70 (0.53–0.92) | 0.01 | 0.92 (0.68–1.23) | 0.56 |
| Efavirenz | 1.00 | | 1.00 | |

the retrospectively-defined cohort increased with decreasing baseline CrCl and was independently predicted by baseline CD4 counts and clinical stage is again consistent with other studies. The finding that patients with baseline CrCl $<30$ ml/min/1.73 $m^2$ had a roughly four-fold increased (adjusted) risk of death compared to those without renal impairment is similar to recent data from a large UK cohort[26] and illustrates the importance of renal impairment as an independent predictor of poor outcome in HIV infection. Also of note was the observation that stavudine was independently associated with an increased risk of death and loss-to-follow up. Since testing of creatinine was rarely repeated in this population after starting ART, and stavudine dose adjustments very rarely seen in those with reduced CrCl, it is possible that stavudine toxicity contributed to a proportion of deaths. Stavudine is now being replaced by tenofovir in the Ghanaian ART programme, however given the high prevalence of renal impairment among this cohort, replacement by tenofovir should be approached with caution. Although the DART study has provided some reassuring data on the safety of tenofovir among Africans,[10] further long-term data is needed to assess its safety in HIV-infected populations with increased susceptibility to CKD, as appears may be the case in West Africa.

We compared the CrCl/eGFRs using the 3 widely used formulae for estimating GFR. It was clear, as found in many other studies, that the proportion of patients classified as having Stage 3–5 CKD was substantially greater using the Cockcroft-Gault formula as compared the MDRD and CKD-EPI formulae. As we did not undertake any direct measurements of creatinine clearance, we cannot determine whether the Cockcroft-Gault formula overestimated Stage 3–5 CKD or the MDRD/CKD-EPI formulae underestimated it. It is however of interest that a recent study which included GFR estimation in a very similar Ashanti population in Ghana suggested a closer correlation with CrCl calculated by the Cockcroft-Gault formula than eGFR by the other formulae in the age groups relevant to our clinic population.[27] Given that many of the patients had low body weights at initiation of ART, as is common in patients presenting with advanced HIV infection, it is possible that one advantage of the Cockcroft-Gault formula is to take account of this, rather than assuming a standard lean body mass, as is the case for the other formulae. Nonetheless, further work is needed to define formulae which estimate GFR more accurately in HIV-infected African populations.

Our study has a number of limitations. Baseline creatinines were rarely repeated when high in patients starting ART, and it is possible some patients had acute, rather than chronic renal dysfunction, making it difficult to conclude there was a high prevalence of CKD. Conversely, using CrCl/eGFR without analysis of urine proteinuria may well have underestimated the prevalence of renal disease in the Retrospective Cohort and may have prevented identification of further risk factors associated with CKD. In summary we have shown that HIV-related renal dysfunction is very common among untreated Ghanaian HIV-infected patients and independently predicts subsequent mortality. Routine screening of all HIV-infected patients before and during ART is needed to detect renal impairment and prioritise those identified for ART.

## Acknowledgements

This study received financial support from the South Tees Infectious Diseases Research Fund and via a HIV Research Trust Scholarship to FSS. We are grateful to the nurses and patients at KATH for assistance with this study.

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