ORIGINAL RESEARCH ARTICLE

# The prevalence of renal impairment among adults with early HIV disease in Blantyre, Malawi

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**Summary:** We determined the prevalence of renal impairment and possible HIV-associated nephropathy (HIVAN) in adults with World Health Organization (WHO) stages I or II HIV, presenting to the antiretroviral therapy (ART) clinic in a central hospital in Malawi. We enrolled 526 ART-naïve subjects, 67% women, median age 34 (17–73) years and mean CD4 count 305 (3–993) cells/μL. Blood pressure, weight, urine dipstick and microscopy, CD4 cell count and serum creatinine were measured. Creatinine clearance (CrCL) was estimated using the Cockcroft–Gault equation. Possible HIVAN was diagnosed based on levels of proteinuria and CrCl. In all, 23.3% had proteinuria (≥1+). 57.4% had reduced CrCl (<90 mL/minute): 18.8% had moderate (CrCl 30–59 mL/minute) and 2.2% severe (CrCl <30 mL/minute) renal dysfunction. Extrapolating from renal biopsy studies that confirmed HIVAN, the proportion of patients with HIVAN in our clinic ranges from 1.8–21.2%. We conclude that renal impairment was common, though rarely severe, among HIV-infected adults with clinically non-advanced HIV disease. Renal dysfunction has been demonstrated to be a risk factor for (early) mortality. These results are relevant for ART programmes, such as those in Malawi, where renal function is not routinely assessed.

**Keywords:** renal insufficiency, HIV, HIV-associated nephropathy, glomerular filtration rate, epidemiology, Malawi

## BACKGROUND

Renal impairment is an important co-morbidity of HIV, whether due to direct effects of HIV in the kidney (e.g. HIV-associated nephropathy [HIVAN]), or due to factors related to HIV such as opportunistic infections (e.g. tuberculosis) or drug toxicity (e.g. tenofovir [TDF]). Renal impairment is more common in HIV patients of African origin than among HIV patients of Caucasian origin[1] and has been shown to be an important predictor of early mortality in patients starting antiretroviral therapy (ART) in western settings and in Africa.[2]

The prevalence rates of renal impairment in cohort studies of HIV-positive subjects have varied depending on the clinical status of the patients and the definition of renal impairment used. Moderate or severe renal dysfunction (creatinine clearance [CrCl] <60 mL/minute) was present in 26.5% of 25,779 Zambian patients[2] and 14.4% of 2189 patients in KwaZulu-Natal.[3] In both studies, the patients were ART-naïve and severely immunosuppressed, with mean CD4 counts 148 and 119 cells/μL, respectively. In a cohort of ART-naïve Kenyan patients with less severe immunosuppression (mean CD4 389 cells/μL), 11.5% of 373 patients had an CrCl of <60 mL/minute.[4]

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HIVAN is a World Health Organization (WHO) clinical stage IV condition, making patients eligible for ART irrespective of their CD4 count. ART is the main effective treatment for this condition, which otherwise leads to end-stage renal failure.[5] Identification of HIVAN and other forms of renal impairment is important in patients in all clinical stages of HIV disease; however, it is crucial in those with clinical stage I and II, since these patients might not otherwise be identified to be in urgent need of ART. Heavy proteinuria, particularly if coupled with renal dysfunction, may identify up to 27% of those with HIVAN.[5] HIVAN was the most common histological finding in HIV-positive patients with varying degrees of persistent proteinuria, including microalbuminuria, in KwaZulu-Natal[6] and Soweto.[7] The gold standard for the diagnosis of HIVAN is renal biopsy, but this is not available in most settings where ART scale up is underway. Proteinuria could be detected without expensive and technically advanced laboratory methods; however, proteinuria may not be a valid screening test for chronic kidney disease in HIV-infected patients.[3]

The aim of this study was to prospectively screen patients with early HIV disease on first referral to an ART clinic for renal impairment and to determine the prevalence of possible HIVAN, since this might be the only indication for ART therapy. Renal impairment and possible HIVAN were identified by finding a reduced CrCl and by detecting proteinuria on urine analysis.

## METHODS

### Study design, population and setting

A prospective, cross-sectional survey was conducted at the ART clinic at Queen Elizabeth Central Hospital in Blantyre, Malawi, from April 2009 to July 2009. This large clinic provides primary to tertiary ART care to an urban and suburban population of around 700,000 persons. At the time of the study some 7000 patients were enrolled on ART. We recruited consecutive newly-referred patients, aged 18 years and over, not yet on ART, who were in WHO clinical stages I or II.[8] As far as we could ascertain, all patients were stable without major illnesses at the time of screening for kidney disease.

### Study procedures

Patients completed a questionnaire to document demographic characteristics and factors relevant for renal disease such as previously diagnosed hypertension or diabetes mellitus. Blood pressure, weight and height were measured and the presence of ankle oedema was assessed. WHO clinical stage was abstracted from the patients' health passport, a patient-kept booklet widely used in Malawi to document personal clinical records. CD4 T-cell count (FACSCount, Becton Dickinson, San Jose, CA, USA) and serum creatinine (Nova 1 Autoanalyser, Nova Biomedical Corporation, Waltham, MA, USA) were measured. Urine dipstick for glucose, blood, protein, nitrites and leukocytes was performed (U11, Shenzhen Mindray Bio-medical Electronics Co, Shenzhen, China). We defined proteinuria as $\geq 1+$ on a semi-quantitative scale from 0 to $4+$ [3,4] and heavy proteinuria as $\geq 2+$. Urine microscopy was carried out on a midstream urine sample to document the presence of bacterial infection, *Schistosomiasis haematobium* ova, *Trichomonas vaginalis* and casts. None of the samples were cultured. Ten-millilitre samples of urine were centrifuged for five minutes at 2000 rpm and then 0.5 mL of the resuspended sediment was examined microscopically. The numbers of epithelial cells and granular casts seen per low-powered field ($\times 10$) were counted.

### Measurement of renal function

None of the equations to estimate the glomerular filtration rate (GFR) have been validated for the Malawian population, and there is much debate about the most appropriate method to use.[9] We calculated CrCl by the Cockcroft–Gault (C–G) and Modification of Diet in Renal Disease (MDRD) equations; however, unless indicated, only the results calculated by the C–G equation are presented. We used guidelines from the USA National Kidney Foundation's Kidney Disease Outcome Quality Initiative to categorize renal insufficiency.[10] Creatinine clearance of at least 90 mL/minute was considered normal. Individuals with a creatinine clearance of 60–89 mL/minute were categorized as mild renal insufficiency, 30–59 mL/minute as moderate, and less than 30 mL/minute as severe insufficiency.

### Diagnosis of suspected HIVAN

In HIV-infected patients HIVAN may be indicated by the presence of persistent proteinuria in the absence of other causes of proteinuria.[7,11] In our study, proteinuria was screened for at a single point in time so persistence could not be determined. We did exclude other causes of proteinuria (urinary infections [presence of *Schistosoma* ova, *T. vaginalis*, nitrite and/or bacteria in the urine sample], diabetes and hypertension) and no subjects were assumed to have active tuberculosis (TB), which can cause proteinuria, as they were in WHO stages I and II. For the purpose of this study, we used four different sets of criteria to diagnose (possible) HIVAN: any proteinuria ($\geq 1+$); heavy proteinuria ($\geq 2+$); any proteinuria ($\geq 1+$) in conjunction with renal dysfunction (estimated GFR by the C–G equation [CrCl] $\leq 60$ mL/minute) and heavy proteinuria ($\geq 2+$) in conjunction with renal dysfunction (CrCl $\leq 60$ mL/minute) and the absence of any alternative cause for renal dysfunction or proteinuria.

### Statistical and ethical considerations

We used Pearson's chi-square test and Student's *t*-test to analyse categorical and continuous data, respectively. Since CrCl was not normally distributed we used the Mann-Whitney U test to compare the CrCl between men and women and persons with and without proteinuria. To determine factors associated with moderate and severe renal impairment and with proteinuria, we performed logistic regression analyses. We included factors with a *P* value $\leq 0.1$ in the univariate analyses as co-variates in the models. Additionally, we included a previous diagnosis of hypertension in the moderate and severe renal impairment model because of the biological importance of this factor. We calculated adjusted odds ratios (ORs) and obtained *P* values based on the Wald test. SPSS software (version 12, SPSS Inc, Chicago, IL, USA) was used for all analyses. The study was approved by the College of Medicine Research and Ethical Committee and written informed consent was obtained from all participants.

## RESULTS

Of 533 persons enrolled in the study, seven were excluded because of creatinine results that were judged to be laboratory errors. Therefore, 526 persons were included in the analysis, for which urine results were available in 519. There was a preponderance of women (66.5%) similar to the ART patient population in our clinic. The mean age was 34.3 years (standard deviation [SD] 9.3; range 17–73). The mean CD4 count was 305 cells/μL (SD 190; range 3–993). Although all patients were in WHO clinical stage I (60.3%) or stage II (39.7%), in fact 63.8% had a CD4 count of $<350$ cells/μL, 41.9% had $<250$ cells/μL, and 14.5% $<100$ cells/μL. Documentation of a previous diagnosis of hypertension was found in 6.1% and of diabetes mellitus in 0.6% of patients. Most patients (53.8%) reported one or more urinary symptoms (frequency, change of appearance of urine and dysuria). A systolic blood pressure above 140 mmHg was found in 6.1%, and a diastolic pressure above 95 mmHg in 3.6%. Proteinuria (1+ or more on dipstick) was present in 23.3%. The median creatinine was 80 μmol/L (range 9–433). In 21.6% of the patients we found a creatinine level above the upper level of the reference range (106 μmol/L). The median CrCl was 84.5 mL/minute. A reduced CrCl ($<90$ mL/minute) was found in 57.4% of the subjects, of whom 36.4% had mild (CrCl 60–89 mL/minute), 18.8% moderate (CrCl 30–59 mL/minute) and 2.2% severe renal impairment

(CrCl <30 mL/minute). The median CrCl of patients with proteinuria was similar to those without (81.9 versus 85.0 mL/minute, respectively; $P = 0.49$). Men were older on average, had a higher body weight, more advanced immune suppression and a lower CrCl (Table 1). CrCl values determined with the MDRD method were generally higher and a lower prevalence of renal insufficiency was recorded: CrCl-mdrd median 109 mL/min; prevalence CrCl-mdrd <60 mL/minute = 10.6%.

Higher age, lower weight, lower CD4 count, a previous diagnosis of hypertension, the absence of oedema and the presence of proteinuria were associated with moderate to severe renal impairment (as indicated by CrCl) in univariate analyses. However, only higher age (OR 1.07 95% confidence interval [CI] 1.04–1.10) and lower weight (OR 0.92 95% CI 0.90–0.95) remained independent risk factors for moderate to severe renal impairment in the logistic regression analysis (Table 2).

Factors that were associated with proteinuria in univariate analyses were lower age and weight, lower CD4 count, WHO stage, presence of granular casts and lower systolic and diastolic blood pressures. In the logistic regression analysis, lower age (OR 0.96, 95% CI 0.93–0.98), lower CD4 count (OR 0.998, 95% CI 0.997–0.999), presence of granular casts (OR 3.65, 95% CI 1.79–7.44) and previous diagnosis of hypertension (OR 3.10, 95% CI 1.22–7.90) were independent risk factors for proteinuria (Table 3).

### Diagnosis of suspected HIVAN

After exclusion of subjects with a previous diagnosis of diabetes (or current glycosuria), hypertension and possible urinary infections (defined as a potentially infective organism seen on microscopy, or nitrite positive), proteinuria (≥1+) was present in 88 out of the remaining 415 patients (21.2%), heavy proteinuria (≥2+) in 29 (7.0%), proteinuria (≥1+) with CrCl <60 mL/minute in 22 (5.3%) and proteinuria (≥2+) with CrCl ≤60 mL/minute in 8 (1.8%).

The majority of subjects with proteinuria (≥1+) (69/88) had a CD4 count <350 cells/μL and therefore would have started ART on the basis of the new WHO recommendations. However, in the group with heavy proteinuria, there were five subjects (17.2%) with CD4 >350 cells/μL, one of whom also had a CrCl <60 mL/minute, in whom ART was not started.

## DISCUSSION

Renal impairment, based on a single CrCl measurement, was very common among Malawian HIV-infected adults with clinically non-advanced HIV disease: 19% had moderate and 2% severe renal impairment. Our study excluded subjects with clinical stages III and IV HIV and we would expect even higher rates of renal impairment in those patients since HIVAN, other diseases that affect the kidneys and the use of nephrotoxic drugs are more common with advancing HIV infection. Our figures are comparable with other studies from our region, in which levels of moderately to severe renal dysfunction ranging from 11.5 to 26.5% were found.[2–4]

In the public health approach to ART scale up[12] that takes place in Malawi and throughout sub-Saharan Africa, screening for renal impairment prior to starting ART does not routinely take place and would not be feasible within the current service delivery framework. Most ART prescribing facilities in Malawi do not have laboratory support, and even if it was available

Table 1 **Patient characteristics by gender**

| | Male | | Female | | |
|---|---|---|---|---|---|
| | ***n*** | **Value** | ***n*** | **Value** | ***P* value** |
| Gender | 176 | 33.5% | 349 | 66.5% | |
| Mean age (years) | 176 | 36.6 | 349 | 33.1 | <0.001 |
| Mean weight (kg) [SD] | 176 | 57.2 [7.9] | 349 | 54.5 [9.3] | 0.001 |
| Mean CD4 (cells/μL) [SD] | 173 | 251 [179] | 338 | 333 [190] | <0.001 |
| **CD4 > 499** | 173 | 6.9% | 338 | 18.0% | |
| 350–499 | 173 | 18.5% | 338 | 23.7% | |
| 200–349 | 173 | 31.2% | 338 | 30.8% | |
| 100–199 | 173 | 20.2% | 338 | 17.5% | |
| 0–99 | 173 | 23.1% | 338 | 10.1% | <0.001 |
| WHO HIV stage I | 171 | 58.8% | 345 | 61.2% | 0.61 |
| Previous hypertension diagnosis | 174 | 4.0% | 348 | 7.2% | 0.16 |
| Presence of oedema | 176 | 5.1% | 349 | 2.3% | 0.09 |
| Any urinary symptom* | 176 | 54.0% | 349 | 53.6% | 0.93 |
| Mean systolic BP† | 176 | 113.2 | 349 | 114.2 | 0.54 |
| Mean diastolic BP | 176 | 72.6 | 349 | 72.8 | 0.86 |
| **Renal Function** | | | | | |
| Proteinuria ≥1+‡ | 174 | 24.1% | 345 | 22.9% | 0.75 |
| Median CrCl | 170 | 79.5 | 339 | 86.4 | 0.004 |
| CrCl > 89 [95% CI] | 170 | 35.3% [28–42] | 339 | 46.3% [41–52] | |
| CrCl 60–89 | 170 | 41.2% [34–49] | 339 | 33.9% [29–39] | |
| CrCl 30–59 | 170 | 21.8% [16–28] | 339 | 17.4% [13–21] | |
| CrCl < 30 | 170 | 1.8% [0–4] | 339 | 2.4% [0–4] | 0.10 |
| **Urine microscopy** | | | | | |
| Presence of granular casts | 171 | 12.3% | 340 | 6.5% | 0.03 |
| *Schistosoma* ova | 172 | 3.5% | 341 | 1.5% | 0.14 |
| *Trichomonas vaginalis* | 173 | 3.4% | 341 | 8.9% | 0.02 |

SD = standard deviation; WHO = World Health Organization; BP = blood pressure; CrCl = creatinine clearance by Cockcroft–Gault method

*Change in frequency, volume, colour and/or experiencing pain

†Based on a single measurement

‡ ≥ 30 mg/dL

Table 2 **Factors associated with moderate to severe renal impairment**

| | CrCl ≥60 mL/minute (*n* = 402) Value | CrCl <60 mL/minute (*n* = 107) Value | *P* value | Multivariate analysis AOR (95% CI) | *P* value |
|---|---|---|---|---|---|
| Female gender | 67.7% | 62.6% | 0.33 | | |
| Mean age (years) [SD] | 33.5 [8.4] | 38.1 [11.0] | <0.001 | 1.07 (1.04–1.10) | <0.001 |
| Mean weight (kg) [SD] | 56.4 [9.1] | 51.8 [7.5] | <0.001 | 0.92 (0.90–0.95) | <0.001 |
| Mean CD4 (cells/μL) [SD] | 312 [191] | 273 [183] | 0.06 | 1.00 (0.99–1.00) | 0.55 |
| **CD4 > 499** | 15.3% | 9.5% | | | |
| 350–499 | 23.1% | 17.1% | | | |
| 200–349 | 30.7% | 31.4% | | | |
| 100–199 | 16.8% | 25.7% | | | |
| 0–99 | 14.1% | 16.2% | 0.13 | | |
| WHO HIV Stage I | 60.4% | 62.1% | 0.74 | | |
| Previous hypertension diagnosis | 5.5% | 9.4% | 0.14 | 2.23 (0.89–5.62) | 0.09 |
| Previous diabetes mellitus diagnosis | 0.8% | 0.0% | 0.37 | | |
| Presence of oedema | 4.2% | 0.0% | 0.03 | 0.00 (0.00–) | 0.99 |
| Any urinary symptom* | 53.7% | 50.5% | 0.55 | | |
| Mean systolic BP† | 114.0 | 114.6 | 0.77 | | |
| Mean diastolic BP | 72.9 | 72.3 | 0.63 | | |
| Proteinuria ≥1+‡ | 21.4% | 31.4% | 0.03 | 1.60 (0.93–2.74) | 0.09 |
| **Urine microscopy** | | | | | |
| Presence of granular casts | 7.4% | 12.4% | 0.11 | | |
| *Schistosoma* ova | 2.5% | 1.0% | 0.32 | | |
| Haematuria§ | 25.2% | 19.4% | 0.22 | | |

AOR = adjusted odds ratio; CI = confidence interval; SD = standard deviation; WHO = World Health Organization; BP = blood pressure; CrCl = creatinine clearance by Cockcroft–Gault method

*Change in frequency, volume, colour and/or experiencing pain

†Based on a single measurement

‡ ≥ 30 mg/dL

§ > 5 red blood cells/high power field

the additional cost would negatively impact on the number of patients who could potentially treated with ART. However, there are several reasons why screening to identify patients with renal impairment may improve outcomes. First, clinicians can apply more intensive follow-up for these patients who are at high risk for early mortality on ART.[2] Second, doses of stavudine and lamivudine, which are part of first-line ART regimens in Malawi and many countries in Africa, should be reduced when the GFR is <50 mL/minute.[13] Failure to institute dose reductions of ART on the basis of renal function may contribute

Table 3 **Factors associated with significant proteinuria**

| | No proteinuria (*n* = 398) Value | ≥1+ proteinuria (*n* = 121) Value | *P* value | Multivariate analysis AOR (95% CIs) | *P* value |
|---|---|---|---|---|---|
| Female gender | 66.8% | 65.3% | 0.75 | | |
| Mean age (years) [SD] | 34.9 [9.3] | 32.3 [8.9] | 0.007 | 0.96 (0.93–0.98) | 0.002 |
| Mean weight (kg) [SD] | 56.0 [8.9] | 53.3 [8.9] | 0.003 | 0.98 (0.96–1.01) | 0.19 |
| Mean CD4 (cells/μL) [SD] | 323 [192] | 252 [172] | <0.001 | 0.998 (0.997–0.999) | 0.004 |
| **CD4 >499** | 16.1% | 8.4% | | | |
| 350–499 | 24.1% | 15.1% | | | |
| 200–349 | 31.1% | 31.9% | | | |
| 100–199 | 16.6% | 23.5% | | | |
| 0–99 | 12.2% | 21.0% | 0.006 | | |
| WHO HIV Stage I | 62.1% | 50.1% | 0.02 | 0.73 (0.46–1.16) | 0.18 |
| Previous hypertension diagnosis | 5.3% | 9.1% | 0.13 | 3.10 (1.22–7.90) | 0.02 |
| Previous diabetes mellitus diagnosis | 0.5% | 0.8% | 0.68 | | |
| Presence of oedema | 3.0% | 4.1% | 0.55 | | |
| Any urinary symptom* | 53.0% | 55.4% | 0.65 | | |
| Mean systolic BP [SD]† | 115 [17] | 110 [19] | 0.005 | 0.99 (0.97–1.01) | 0.34 |
| Mean diastolic BP [SD] | 74 [12] | 71 [13] | 0.02 | 1.00 (0.97–1.03) | 0.83 |
| Mean CrCl (mL/minute) [SD] | 95 [60] | 95 [70] | 0.94 | | |
| **CrCL ≥90** | 43.1% | 41.5% | | | |
| 60–89 | 38.2% | 30.5% | | | |
| 30–59 | 16.6% | 25.4% | | | |
| > 30 | 2.1% | 2.5% | 0.15 | | |
| **Urine microscopy** | | | | | |
| Presence of granular casts | 4.9% | 20.3% | <0.001 | 3.65 (1.79–7.44) | <0.001 |
| *Schistosoma* ova | 2.0% | 2.5% | 0.75 | | |

AOR = adjusted odds ratio; CI = confidence interval; SD = standard deviation; WHO = World Health Organization; BP = blood pressure; CrCl = creatinine clearance by Cockcroft–Gault method

*Change in frequency, volume, colour, and/or experiencing pain

†Based on a single measurement

to the high rates of toxicity, particularly of stavudine, that are observed in African ART programmes.[14] Thirdly, knowledge of levels of renal impairment will be relevant if tenofovir is to be widely introduced in first-line regimens in Africa, following recent WHO recommendations.[15] Tenofovir is potentially nephrotoxic and this risk increases with pre-existing renal impairment.[16] Fourth, clinicians in busy ART clinics will less easily overlook HIVAN as a criterion to start ART in patients who have no other manifestations of HIV. This would be particularly relevant where CD4 counts cannot be routinely measured. Finally, patients with HIV and renal impairment may benefit from management of their renal problem, for example treatment with angiotensin-converting enzyme inhibitors; at present such patients are missing out on this treatment.

Independent predictors of moderate to severe renal impairment (CrCl $<60$ mL/minute) were higher age and lower body weight. This corresponds with findings from other studies from sub-Saharan Africa in which wasting syndrome, low body mass index, higher age, severe immunosuppression (CD4 $<100$ cells/$\mu$L) and WHO stages III and IV HIV were identified as factors associated with renal impairment.[2–4]

The use of the C–G equation to estimate GFR affected our estimates of the prevalence of renal impairment. No CrCl method has been validated in the Malawi population. We chose the C–G method based on observations in populations similar to ours;[17] however, very low creatinine values in some subjects led to implausibly high CrCl calculations. A study on lean Africans from Ghana suggested that other formulae may be more appropriate.[9]

Significant proteinuria was present in 23.3% in our population. Lower age, lower CD4 count, presence of granular casts and a previous diagnosis of hypertension were independent risk factors for significant proteinuria; however, proteinuria was only associated with CrCl in univariate analysis. Franey *et al.*[3] also noted that proteinuria had a poor predictive value for renal dysfunction. This may be due to factors leading to false-positive results such as urinary tract infection (UTI) and sexually transmitted infection (STI), significant dehydration, fever or intercurrent illness, and also the relative insensitivity of dipstick testing leading to false-negative results in those with low-grade microalbuminuria. The absence of an association between the degree of dipstick protein positivity and CrCl may also be related to the fact that urine dipsticks are poor in discerning the severity of proteinuria. Detection of lower levels of proteinuria and greater sensitivity and specificity require measurement of the microalbumin-to-creatinine ratio, which is elaborative, expensive and less likely to be available in resource poor settings. Thus, proteinuria measured with urine dipsticks may not be a useful tool to identify clinically important reductions of the GFR in HIV-infected persons.

Persistent proteinuria in HIV-positive subjects may indicate HIVAN, and renal biopsy studies from South Africa found HIVAN on renal histology in 27–83% of biopsies from patients with persistent proteinuria.[5–7] In our study the association of proteinuria with low CD4 cell count may also suggest that HIVAN was a contributory cause of proteinuria in some subjects. Our data are insufficiently robust to determine the prevalence of HIVAN reliably and further study, in particular with clarification of the diagnosis by renal biopsy, will be needed to elucidate the full impact of HIVAN in Malawi.

We aimed to determine whether there were many subjects who had an indication for ART purely on the basis of identification of possible HIVAN. When using different sets of criteria for suspected HIVAN, we found that between 1.8% and 21.2% had a diagnosis of possible HIVAN and in these patients this was the only *clinical* indication to start ART as they were in WHO clinical stage I or II. However, of these, the majority had CD4 cell counts $<350$ cells/$\mu$L, so would have been identified to start ART anyway on the basis of their CD4 count. Of patients in WHO clinical stages I and II, 1.2–4.6% had a CD4 $>350$ cells/$\mu$L and were eligible to start ART only on the basis of identification of possible HIVAN. However, it should be noted that, although CD4 counting was available in our hospital, it is not available in the majority of ART clinics in Malawi, where clinical triaging must still occur.

UTIs were uncommon in our patients. The most common pathogen was *T. vaginalis* and a few had schistosomiasis. Our ability to diagnose bacterial infections was limited; samples were not specifically collected to detect bacterial urinary tract infection and only nine subjects had positive nitrite on urine dipstick testing. This is in contrast to a South African study of ART-naïve patients with an average CD4 count of 130 cells/$\mu$L, where 49% of those with microalbuminuria had an infection, particularly TB (50%), bacterial UTI (37%) and STI (7%).[11] Proteinuria was also associated with TB in a study from Kenya.[4] We did not look for this association as we did not anticipate cases of active TB in our study population, by virtue of the exclusion of clinical stages III and IV. Cases of undiagnosed TB may have been included inadvertently however, given the limitations of clinical review in the routine setting that took place before enrolment in the study.

A further limitation of our study is that both creatinine and proteinuria were measured at a single point in time; therefore, we may have included short term, reversible causes of renal impairment. Finally, our observations are from an urban/peri-urban population at a central hospital and extrapolation of our findings to other populations must be done with care.

In conclusion, we have found a high rate of renal impairment in Malawian adults with early HIV disease (WHO clinical stages I and II). We have demonstrated that possible cases of HIVAN who are otherwise asymptomatic would not be identified in the absence of screening for renal impairment and as a result may miss out on receiving ART, especially if CD4 counting is unavailable. Our findings support that it is desirable that the CrCl is determined at the start of ART; however, the cost involved has to compete with expenditures for many other priorities to improve ART programmes in sub-Saharan Africa.

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