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Renal Dysfunction among HIV-Infected Patients Starting Antiretroviral Therapy in Mwanza, Tanzania

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Abstract

Objective—HIV-related renal dysfunction is associated with high mortality. Data on the prevalence of renal dysfunction among HIV-infected outpatients starting antiretroviral therapy (ART) in sub-Saharan Africa is limited. Recent recommendations to include the nephrotoxic drug tenofovir in first-line ART regimens make clarification of this issue urgent.

Methods—We screened for renal dysfunction by measuring serum creatinine, proteinuria, and microalbuminuria in HIV-positive outpatients initiating ART in Mwanza, Tanzania. We excluded patients with preexisting renal disease, hypertension, diabetes, or Hepatitis C virus co-infection. Estimated glomerular filtration rates (eGFRs) were calculated by Cockroft-Gault and Modification of Diet in Renal Disease (MDRD) equations.

Results—Only 129 (36%) of 355 enrolled patients had normal eGFRs (Grade 0 or 1) above 90 ml/min/1.73m^2. Grade 2 renal dysfunction (eGFR between 60 and 89 ml/min/1.73m^2) was present in 137 patients (38.6%), and 87 patients (25%) had Grade 3 dysfunction (eGFR between 30 and 59 ml/min/1.73m^2). Microalbuminuria and proteinuria were detected in 72% and 36% of patients, respectively. Factors predictive of renal dysfunction in multivariate analysis included female gender (OR 3.0, 95% confidence interval (CI) [1.8–5.1], p<0.0001), Body Mass Index (BMI) <18.5 (OR 2.3 [1.3–4.1], p=0.004), CD4+ T-cell count <200 cells/mm^3 (OR 2.3 [1.1–4.8], p=0.04), and World Health Organization (WHO) clinical stage II or above (OR 1.6 [1.2–2.3], p=0.001).

Conclusions—Renal dysfunction was highly prevalent in this population of HIV-positive outpatients initiating first ART in Tanzania. This highlights the critical and underappreciated need to monitor renal function in HIV-positive patients in sub-Saharan Africa, particularly given the increasing use of tenofovir in first-line ART.

Keywords

renal dysfunction; HIV; antiretroviral therapy; sub-Saharan Africa

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Conflicts of Interest: None.

INTRODUCTION

HIV infection and HIV-induced inflammation can cause chronic kidney disease (CKD), which is associated with increased mortality [1,2]. The occurrence of renal dysfunction in the HIV-infected population may be further increased by drug-induced renal toxicity, opportunistic infections, and comorbid diseases including hypertension, diabetes, and Hepatitis C. With the inclusion of tenofovir in first-line antiretroviral therapy (ART) regimens recommended by the World Health Organization (WHO), risk for renal dysfunction in HIV-positive patients may continue to rise.

Early diagnosis and regular monitoring for renal dysfunction in HIV-positive patients is essential for prognosis, medication dosing, and treatment. The risk of undiagnosed HIV-associated renal dysfunction is worrisome in resource-limited settings where routine laboratory testing is often not available. The WHO recommends assessing creatinine clearance (CrCl) for patients at initiation of tenofovir and every six months "if feasible," though inability to test does not preclude tenofovir use [3]. In high-resource countries, renal monitoring is recommended at HIV diagnosis and at least yearly thereafter for patients with CKD risk factors including African ethnicity, CD4+ T-cell (CD4) count <200 cells/mm^3, or plasma viral load >4000 copies/mL [4–6]. In sub-Saharan Africa, screening may be even more urgent because many patients have all of these risk factors, often first presenting for care when they already have low CD4 counts and high viral loads.

Despite the high risk for renal dysfunction among HIV-infected patients from sub-Saharan Africa, it has been studied relatively infrequently in this population. In particular, the prevalence of microalbuminuria, which has recently been associated with increased mortality [7] has received little attention. For this reason, we explored markers of renal dysfunction as measured by serum creatinine, eGFR, proteinuria, and microalbuminuria in a cohort of Tanzanian outpatients initiating ART.

METHODS

Trial Design and Study Participants

This cross-sectional study was conducted in the outpatient HIV clinic at Bugando Medical Centre in Mwanza, Tanzania between November 2009 and February 2010. Bugando is the regional referral hospital that serves approximately 13 million people in the Lake Victoria region of northwest Tanzania. Over 4000 outpatients are currently on ART at Bugando's HIV clinic.

Patients who were at least 18 years old, were antiretroviral therapy naïve, and had been referred for counseling to initiate ART were consecutively invited to participate. Patients with risk factors for renal disease including Hepatitis B or C virus co-infections, hypertension, hyperglycemia, pregnancy, or febrile illness were excluded. Patients who provided written informed consent underwent structured interviews, physical examinations, and laboratory testing. This study was approved by the joint research ethics committee of Bugando Medical Centre and Weill-Bugando University College of Health Sciences and by Weill-Cornell Medical College's Institutional Review Board.

Clinical and Laboratory Assessment

Physical examinations included two blood pressure readings and height and weight measurements for body mass index (BMI) calculations. Random blood glucose was measured by fingerstick. Patients with glucose levels higher than 7.0mmol/L (126mg/dL) were excluded.

Urine samples were measured for proteinuria using urine dipstick Multistix™ (Bayer, Germany) and for microalbuminuria using Micral-TestB immunoassay (Boehringer-Mannheim, Germany). Proteinuria was reported as negative, 1+ (30 mg/dL), 2+ (100 mg/dL), 3+ (300 mg/dL), or 4+ (1000 mg/dL). Microalbuminuria was reported as negative, 20 mg/L, 50 mg/L, and 100 mg/L. A reading of 20 mg/L or higher was considered positive, in accordance with the manufacturer's recommendations.

Blood samples were analyzed for Hepatitis B surface antigen and Hepatitis C antibody by One-Step Ultra rapid chromatographic and Hepatitis C Virus Rapid Test Strip immunoassays, respectively (Acon Laboratories, California). Serum creatinine and hemoglobin are routinely measured for patients initiating ART. We calculated eGFRs using the Cockroft-Gault (CG) and the Modification of Diet in Renal Disease (MDRD) formulae, and normalized the CG result for body surface area so that results of both equations were in units of ml/min/m^2, as previously described [8].

Renal dysfunction was graded from 0 to 5 according to the National Kidney Foundation guidelines (Table 1) [9].

Statistical Analysis

Data were analyzed using STATA 11 (College Station, Texas). Continuous data were described as means (± standard deviations (SD)) and compared by student t-test. Categorical data were described as proportions and analyzed using Chi-squared or Fisher's exact test. Univariate followed by multivariate logistic regression analyses were performed using Pearson's correlation coefficient to determine predictors of eGFR <60 ml/min/1.73m^2.

RESULTS

Patient Characteristic

Of 418 HIV-infected patients starting ART at Bugando, 355 (85%) were eligible and provided informed consent. Sixty-three patients were excluded for the following reasons: Hepatitis B co-infection (30), pregnancy (15), febrile illness (9), lost to follow-up (4), hypertension (3), and Hepatitis C co-infection (2). Patients were 65% female, with a mean age ±SD of 36.1 ±7.9 years. The mean BMI was 21.3 ±3.8 kg/m^2, and the mean CD4 count was 141 ±90 cells/mm^3.

Prevalence of Markers of Renal Dysfunction

In this population without known preexisting renal disease or risk factors aside from HIV infection, 85.6% of patients (304/355) had evidence of renal dysfunction as defined by an eGFR <90 ml/min/1.73m^2 or an eGFR >90 ml/min/1.73m^2 with proteinuria or microalbuminuria (Table 1). If we conservatively consider only patients with eGFRs <90 ml/min/1.73m^2, renal dysfunction affected 63.7% (226/355). Overall, 137 (38.6%) had eGFRs of 60–89 ml/min/1.73m^2, and 87 (24.5%) had eGFRs of 30–59 ml/min/1.73m^2. The prevalence of microalbuminuria was 72.1%, and 36.3% had proteinuria. Microalbuminuria was significantly more common in women (75.3% versus 65.3%, p=0.047), but not in patients with BMIs <18.5 kg/m^2 (67.1% versus 73.3%, p=0.30).

Predictors of Moderate to Severe Renal Dysfunction

By both univariate and multivariate analysis, significant predictors of moderate or severe renal dysfunction (eGFR <60 ml/min/1.73m^2) included: female gender, BMI <18.5 kg/m^2, CD4 count <200 cells/mm^3, and symptomatic HIV infection (WHO Stage II, III, or IV disease) (Table 2). Age and clinical signs including wasting, flank pain, edema, and anemia were not predictive of renal dysfunction.

Assessment of CG and MDRD Equations

We also calculated eGFR by MDRD equation, which has been adapted for use in North American populations, including African-Americans. The prevalence of abnormal eGFR <90 ml/min/1.73m^2 remained approximately 60% regardless of which equation was used (Table 1).

DISCUSSION

Over 80% of HIV-infected patients starting ART in our setting in Tanzania had evidence of renal dysfunction, with reduced eGFR in over 60% of patients screened. These patients had no known preexisting renal disease or risk factors for renal dysfunction aside from HIV infection. These high rates of renal dysfunction were confirmed by the finding that over 70% of patients had detectable microalbuminuria. To the best of our knowledge this is the first large HIV-positive African cohort in which microalbuminuria, often the first marker of renal disease, has been measured in all study participants. The finding that renal dysfunction may be present in the majority of HIV-infected outpatients initiating ART has important ramifications given the increasingly-widespread use of tenofovir, a first-line agent recommended by the WHO with known renal toxicity.

Our data suggest that the low eGFRs that we observed reflect true renal disease because patients with lower eGFRs were also more likely to have microalbuminuria. A single measurement showing microalbuminuria has recently been associated with increased mortality in HIV-infected women [7]. We observed mostly mild to moderate microalbuminuria (20–50 mg/dL), rather than overt proteinuria (>100 mg/dL). This may reflect early-stage, rather than advanced, renal dysfunction. Factors highly predictive of renal dysfunction included female gender and BMI <18.5 kg/m^2, in addition to previously-described risk factors of low CD4 count and advanced WHO clinical stage [10,11]. Microalbuminuria was also more common among women, supporting our finding that female gender is associated renal dysfunction.

The 25% prevalence of at least moderate renal dysfunction (eGFR <60 ml/min/1.73m^2) in our cohort is among the highest reported from sub-Saharan Africa. In a cohort of Ugandan outpatients initiating ART, the prevalence was 42% [12]. Rates have been lower in other HIV-positive, ART-naïve outpatients in sub-Saharan countries: 8% in Zambia [13], 7% in the DART study (Uganda/Zimbabwe) [10], and 12% in Kenya [11]. Aside from the Kenyan study in which patients had less-advanced disease, patients in the other studies had mean BMIs and CD4 counts comparable to or lower than ours, and gender distributions were similar.

Our study was conducted in the Lake Victoria region, where both *Schistosoma haematobium* and *mansoni* are endemic. Schistosomiasis is associated with cystitis, obstructive uropathy, and immune-mediated glomerulonephritis, and may have contributed to the prevalent renal dysfunction we observed. Resources did not permit performance of diagnostic renal biopsies, but HIV-Associated Nephropathy (HIVAN) may also be prevalent in our setting. While not well-studied in sub-Saharan Africa, development of HIVAN may depend on genetic factors and prevalence appears to vary even within countries [14–18] so this could be another explanation for differences between our findings and others'. Depending on etiology, ART may improve or further impair renal function [12,19]. Regardless of etiology, our study reinforces the importance of monitoring renal function before initiating and while using ART in HIV-infected individuals in sub-Saharan Africa.

We observed some variation between GFRs estimated by the CG and MDRD equations, with lower GFRs estimated by CG. This is consistent with other studies from East Africa

[8,11]. It has been suggested that this discrepancy is caused by an MDRD adjustment for black race that is too high for East Africans [8]. The MDRD equation was derived in the United States, where most black patients in the derivation cohort were likely of West African descent. For optimal individual patient management, the discrepancies observed underscore the need for additional studies to clarify which eGFR equation is most accurate in East African populations. From a public health perspective, the high prevalence of renal dysfunction in our patients is notable and consistent regardless of which formula was used.

Clinically, the high rates of renal dysfunction we observed are concerning given the WHO's recommendation to use either tenofovir or lamivudine, both of which require dose adjustment in renal dysfunction, in all four first-line ART regimens [3]. Tenofovir can additionally cause new-onset or worsening renal toxicity due to proximal tubular dysfunction [19–22] which is not always reversible with tenofovir discontinuation [19]. Based on recommendations to adjust doses for CrCl <50 ml/min [3,23–24], 51 (14.4%) of the patients in our cohort would have required lower medication doses. Importantly, only 21 of these 51 patients (41.2%) had serum creatinine levels above our laboratory's the upper limit of normal (>139 mmol/L) and would have had abnormal renal function identified without calculation of eGFR.

In conclusion, we observed high rates of eGFR impairment in our population of HIV-positive outpatients initiating ART and our findings were corroborated by high rates of microalbuminuria. These results highlight the importance of screening for abnormal eGFR, not merely measuring creatinine, in African HIV-infected patients prior to the initiation of ART for proper dosing of antiretroviral medications. Longitudinal studies are ongoing in our cohort to monitor renal function after ART initiation, to identify other potential contributory factors for renal disease, and to correlate eGFR with true creatinine clearance.

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Table 1

Markers of Renal Dysfunction in HIV-Infected Patients Starting ART.

Characteristic	Number (n= 355)	%
Microalbuminuria (mg/dL)		
Negative	99	27.9
20	138	38.9
50	109	30.7
100	9	2.5
Proteinuria (mg/dL)		
Negative	226	63.7
1+ (30)	117	32.9
2+ (100)	10	2.8
3+ (300)	2	0.6
4+ (1000)	0	0
eGFR by adjusted CG equation (ml/min/1.73m^2)		
≥ 90	129	36.3
60–89	137	38.6
30–59	87	24.5
15–29	2	0.6
< 15	0	0
Rates of Renal Dysfunction by CG Equation		
Stage 0 (increased risk only)	51	14.4
Stage 1 (eGFR ≥ 90 with proteinuria)	78	22.0
Stage 2 (eGFR 60–89)	137	38.6
Stage 3 (eGFR 30–59)	87	24.5
Stage 4 (eGFR 15–29)	2	0.6
Stage 5 (eGFR <15)	0	0
Rates of Renal Dysfunction by MDRD Equation		
Stage 0	69	19.4
Stage 1	110	31.0
Stage 2	115	32.4
Stage 3	61	17.2
Stage 4	0	0
Stage 5	0	0

Table 2

Univariate and Multivariate Analysis of Predictors of Renal Dysfunction among HIV-infected Patients Starting ART (n=355).

	Univariate Analysis			Multivariate Analysis		
Variable	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**p-value**
Female gender	3.0	0.18–0.52	0.0001	3.0	1.8–5.1	<0.001
BMI <18.5	2.4	1.4–4.2	0.001	2.3	1.3–4.1	0.004
CD4+ count <200	0.47	0.22–0.99	0.46	2.3	1.1–4.8	0.04
WHO Clinical Stage (II–IV)	5.2	0.94–13	0.001	1.6	1.2–2.3	0.001