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Original Article

Renal disease in an antiretroviral-naïve HIV-infected outpatient population in Western Kenya

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Abstract

Background. Several commonly used antiretrovirals (ARVs) require dose adjustments to prevent toxicities in the presence of renal insufficiency. Because no prospective studies of the prevalence or risk factors for kidney disease in stable outpatient human immunodeficiency virus (HIV)-infected indigenous African populations have been published to date, it is not known if already scarce resources should be allocated to detect renal dysfunction, in those without risk factors for kidney disease, prior to initiation of increasingly available antiretrovirals in developing countries.

Methods. A cross-sectional study to determine the prevalence of and risk factors for renal disease in a cohort of medically stable, HIV-infected, antiretroviral-naïve adults, without diabetes or hypertension, presenting to an HIV clinic in western Kenya.

Results. Of 373 patients with complete data, renal insufficiency (CrCl <60 ml/min) was identified in 43 (11.5%) [18 (4.8%) had a CrCl <50 ml/min]. Despite high correlation coefficients between the three renal function estimating equations used, when compared to creatinine clearance as calculated by Cockcroft–Gault, lower rates of moderate to severe renal insufficiency were identified by the Modification of Diet in Renal Disease equations. Proteinuria, defined as a urine dipstick protein of equal to or greater than 1+, was detected in only 23 subjects (6.2%).

Conclusions. Renal insufficiency is not uncommon, even in stable patients without diabetes or hypertension. Conversely, proteinuria was unexpectedly infrequent in this population. Utilizing resources to assess renal function prior to initiation of antiretrovirals in order to identify those likely to benefit from dosage adjustment is justified.

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Introduction

Although the Infectious Disease Society of America (IDSA) HIV Renal Guidelines [1] recommend determining baseline renal function prior to initiation of antiretrovirals (ARVs), due to resource constraints many programs in sub-Saharan Africa initiate treatment without this assessment. In the U.S. and Europe, renal disease as a complication of human immunodeficiency virus (HIV) infection disproportionately impacts individuals of African descent [2,3], with HIV-associated nephropathy (HIVAN) being the most commonly detected pathology. Although HIVAN has been documented in indigenous African patients, little is known about the prevalence or risk factors for renal disease in this population [4,5]. As HIV treatment programs ramp-up in sub-Saharan Africa, data on the prevalence of kidney disease are necessary in order to prioritize resources and ensure patient safety.

To gather data on renal function in an HIV-infected East African population without previously documented risk factors for renal insufficiency, we performed a prospective cross-sectional study of the prevalence of and factors associated with, renal insufficiency and proteinuria in medically stable antiretroviral-naïve patients attending an outpatient HIV-treatment clinic in western Kenya.

Methods

Study design

This cross-sectional study was approved by the Institutional Review Bodies at Indiana University School of Medicine and Moi University School of Medicine.

Study population and setting

The study was conducted at the Academic Model for the Prevention and Treatment of HIV/AIDS (AMPATH) clinic at Moi Teaching and Referral Hospital, in Eldoret, Kenya. Details of the AMPATH program are described elsewhere [6]. Patients presenting to the clinic were eligible for enrolment if they were at least 18 years of age, HIV-infected, antiretroviral-naïve and able to provide informed consent. Because we believe that individuals with conditions known to be highly associated with kidney disease (e.g. sickle cell disease; acute infection; pregnancy; previously diagnosed diabetes, marked hypertension, or renal disease) should always have renal function measured [1], such individuals were excluded.

Study procedures

Participants underwent a structured health history and physical examination. Information on HIV associated conditions and WHO staging was abstracted from the patient's AMPATH initial visit form [6]. At enrollment, blood pressure, weight and height were documented and CD4+ T-cell count (Roche Monitor 1.5 test kit; Becton-Dickinson FACS Count), haemoglobin, haematocrit, albumin, blood urea nitrogen, creatinine (fixed time kinetic assay by Human) and glucose were measured. A urine dip stick for protein (Chemstrip 4, Roche) was also performed. Data were entered into an MS-ACCESS Database (Microsoft Corporation, Redmond WA).

Measurements of renal function

Although the IDSA Renal Guidelines state that the Modification of Diet in Renal Disease (MDRD) equation may be used for staging of renal disease, they do not advocate it as the basis for ARV dosing [1]. These guidelines recommend the Cockcroft–Gault equation as the basis for dosage modification [1]. As there is no validated renal function estimating equation for an East African population, renal function was estimated using three equations derived in North America, namely the Cockcroft–Gault equation [7] for estimating creatinine clearance (CrCl) and the full [8] and abbreviated [9] Modification of Diet in Renal Disease (MDRD) equations for estimating glomerular filtration rate (GFR). As per convention, the upper limit for both CrCl and GFR were set at 200 [10].

Statistical analysis

Renal function and proteinuria (a known marker of renal disease) were the dependent variables of interest. We dichotomized renal function into renal insufficiency (CrCl <60 ml/min: the threshold for moderate renal disease) and relatively normal renal function (CrCl ≥ 60 ml/min)[1]. For the analyses of renal insufficiency, weight, gender and age were excluded as independent variables because they are components of the estimating equations. To analyse the association between each dependent variable and categorical and continuous independent variables, a Chi-square test (or Fisher's exact test) and a two-sample *t*-test were used, respectively. Any variables with a *P*-value of ≤ 0.20 in univariate analysis were included in the multiple logistic regression models. Multivariable models for renal function estimated by the MDRD equations were not constructed because of the failure to find more than one significant factor on univariate analysis. All analyses were conducted in SAS v9.12.

Results

Subject characteristics

Between May 2004 and November 2005, a total of 389 study subjects were enrolled (Table 1). The sample was predominantly female (67.9%) with a mean age of 35 years. The mean weights and body mass indices (BMI) were 61.1 kg and 62.9 kg and 22.3 kg/m^2 and 20.6 kg/m^2 for women and men, respectively. The mean CD4 count of the population was 391 cells/mm^3

Table 1. Demographic and clinical characteristics of the study cohort

Subject characteristics	
Total number	389
Demographics	
Mean age (range)	35.0 (19–60)
Female gender (%)	264 (67.9)
Mode of HIV acquisition [number, (%)]	
Heterosexual	341 (87%)
Unknown	41 (10.5%)
Blood transfusion	2 (0.5%)
Other	5 (1.3%)
Injection drug use	0(0%)
Clinical measures [mean (range)]	
Weight (kg)	61.7 (33–110)
Mean systolic BP, mmHg (range)	104.7 (80–140)
Mean CD4 count, cells/mm^3 ($n=384$)	391 (1–1215)
Mean hemoglobin (g/dL) ($n=378$)	12.97 (4.4–20)
Mean glucose (mg/dL)($n=374$)	86.6 (27–504)
Mean albumin (g/dL) ($n=333$)	4.3 (2.0–8.3)
Renal function [mean, (range)]	
Mean creatinine (mg/dL) ($n=373$)	0.96 (0.21–2.72)
Mean BUN (mg/dL) ($n=359$)	6.2 (1.96–18.21)
Mean CrCl (Cockcroft-Gault), mL/min ($n=373$)	90 (31–200)
Mean GFR (full MDRD), mL/min/1.73 m^2($n=332$)	116 (40–200)
Mean GFR (Abb MDRD), mL/min/1.73 m^2 ($n=373$)	103 (29–200)
Proteinuria [number, (%)]	23 (5.91%)
Family history of renal disease [No (%)]	26 (6.9)
History of OI [No (%)]	
Tuberculosis	50 (12.9)
Pneumocystis pneumonia	6 (1.6)
Recurrent pneumonia	3 (0.8)
Herpes zoster	23 (5.9)
Severe bacterial infection	36 (9.3)
History of other disease [No (%)]	
Wasting syndrome	15 (3.9)
Weight loss < 10%	43 (11.1)
Chronic diarrhea	2 (0.5)
Mucocutaneous manifestations	39 (9.8)
Lymphadenopathy	7 (1.8)
Recurrent upper respiratory infection	3 (0.8)

(range 1–1215) with 16.7% and 5.2% having a CD4 count less than 200 and 100 cells/mm^3, respectively. Twenty-five individuals had blood glucoses greater than 126 mg/dl (four of which were greater than 200 mg/dl). A minority of subjects (6.9%) had a family history of renal disease; a personal history of tuberculosis was reported in 50 subjects (12.9%).

Renal function

For the 373 individuals with complete data, the mean CrCl was 90ml/min (range 30 –200ml/min). CrCl <60 ml/min was identified in 43 (11.5%) subjects with 18 (4.8%) having a CrCl <50 ml/min. High correlation coefficients were found among the three estimating equations: 0.83 for Cockcroft–Gault *vs* full MDRD, 0.84 for Cockcroft–Gault *vs* abbreviated MDRD and 0.96 for full MDRD *vs* abbreviated MDRD. When compared to the Cockcroft–Gault estimation, lower rates of renal insufficiency were identified by the MDRD and the abbreviated MDRD, 2.1% and 4.8%, respectively. Due to the high correlation between the two MDRD equations, only the full MDRD was used for subsequent analyses.

Proteinuria, defined as a urine dipstick protein of equal to or greater than 1+, was detected in only 23 subjects (6.2%).

Factors associated with reduced renal function and proteinuria

Table 2 lists the patient characteristics included in our univariable analysis of risk factors for renal dysfunction in the study population. Factors found to be significantly associated with renal insufficiency, in univariable analysis, as estimated by Cockcroft–Gault include lower absolute CD4 count, CD4 < 100 cells/mm^3, CD4 < 200 cells/mm^3, lower haemoglobin, proteinuria, wasting syndrome and lower systolic blood pressure (Table 2). In the multivariate analysis, only lower haemoglobin [OR 0.79 (0.69–0.91), $P = 0.001$] and wasting syndrome [OR 4.17 (1.15–15.11), $P = 0.03$] continued to be significantly associated with a CrCl <60 ml/min while proteinuria trended towards a significant association with CrCL < 60 ml/min [OR 2.9 (0.96–8.78), $P = 0.06$].

Factors significantly associated with proteinuria on univariate analysis (data not shown) included lower weight, lower absolute CD4 count, lower haemoglobin, history of tuberculosis, and presence of renal insufficiency. Only a history of tuberculosis [OR 3.0 (1.02–8.96), $P = 0.04$] remained significantly associated with proteinuria on multivariate analysis.

Discussion

In this cohort of stable HIV-infected Kenyan outpatients, we found that 11.5% had a CrCl less than 60 ml/min and 4.8% less than 50 ml/min. Using the estimates of renal function provided by the application of the Cockcroft–Gault equation to our study population, approximately 5% of our patients would have required dosage adjustment of the nucleoside analogue components of the ARVs used in the Kenyan primary regimen (stavudine and lamivudine) and an additional 6.5% would require careful monitoring due to reduced renal function. As access to antiretroviral therapy and in particular to tenofovir expands in sub-Saharan Africa, identification of renal insufficiency in these individuals will be imperative prior to consideration of a regimen containing this drug [11]. Failure to adjust ARV dosages appropriately in such patients could potentially increase the risk of drug toxicities, namely neuropathy, lipodystrophy, and Fanconi Syndrome [1].

Table 2. Univariate associations between clinical characteristics and calculated renal function

	Cockcroft–Gault			Full MDRD		
	<60 ($n = 43$)	≥60 ($n = 330$)	*P*-value	<60 ($n = 7$)	≥60 ($n = 325$)	*P*-value
Mean systolic BP, mmHg [mean, (SD)]	100.2 (10.4)	105.0 (10.5)	0.005*	104.3 (11.3)	104.1 (10.7)	0.945
Mean CD4 cells/mm^3 [mean, (SD)]	310.9 (243.9)	400.5 (211.5)	0.01*	259.9 (233)	396.7 (222.1)	0.108
CD4 < 200 cells/mm^3 [No., (%)]	13 (30.2)	49 (14.8)	0.01*	4 (57.1)	55 (16.9)	0.006*
CD4 < 100 cells/mm^3 [No., (%)]	7 (16.3)	13 (3.9)	< 0.001*	1 (14.3)	19 (5.9)	0.353
Mean Hgb g/dl [mean, (SD)]	11.5 (2.1)	13.2 (2.4)	<0.001*	11.5 (1.9)	13 (2.5)[f]	0.106
Mean glucose mg/dl [mean, (SD)]	82.9 (27.0)	86.5 (34.2)[a]	0.674	91.89 (43.2)	84.7 (34.2)	0.626
Proteinuria [No., (%)]	6 (13.9)	13 (3.9)	0.005*	1 (14.3)	17 (5.2)	0.295
Family history of renal disease [No., (%)]	3 (7.7)[b]	22 (6.8)[c]	0.834	1 (14.3)	21 (6.7)[f]	0.429
TB [No., (%)]	9 (20.9)	37 (11.2)[d]	0.069	1 (14.3)	40 (12.4)[g]	0.877
Zoster [No., (%)]	9 (20.9)	19 (5.8)[e]	0.369	0 (0)	22 (6.8)[h]	0.475
Severe bacterial infection [No., (%)]	4 (9.3)	31 (9.4)	0.985	2 (28.6)	33 (10.2)	0.116
Wasting syndrome [No., (%)]	6 (13.9)	8 (2.4)	<0.001*	0 (0)	14 (4.3)	0.575
Weight loss <10% [No., (%)]	7 (16.3)	35 (10.6)	0.268	1 (14.3)	41 (12.6)	0.895
Mucocutaneous manifestations [No., (%)]	5 (11.6)	32 (9.7)	0.69	1 (14.3)	34 (10.5)	0.744

Superscripts denote the number of participants for which data were available [a]320; [b]39; [c]324; [d]329; [e]328; [f]315; [g]324; [h]323.
Values designated with an asterisk indicate *P*-values ≤.05.

While we developed a multivariable model that identified wasting syndrome, and presence of ≥1+ dipstick measured proteinuria as risk factors for reduced creatinine clearance, only 27.9% of subjects with CrCL < 60 ml/min had one or both of these risk factors. While this percentage would be considered too small to recommend limiting serum creatinine testing to individuals with only proteinuria and/or wasting if resources for such testing were routinely available, such an approach could be helpful if limited resources precluded routine tests for reduced renal function.

The prevalence of HIVAN in black Americans during the HAART era has ranged from 3.5% in an ambulatory cohort [12] to 12% in an autopsy series in the mid 1990's [13]. Although no population-based study of renal biopsies has been performed in a Western HIV-infected cohort, the available biopsy series data suggest that 45–60% of chronic kidney disease in HIV infected individuals from the United States is attributed to HIV-associated nephropathy (HIVAN) [14–16]. In these regions, HIVAN is almost exclusively found in blacks (a population predominately of West African descent). HIVAN is known to be highly correlated with higher HIV RNA levels and proteinuria [2,17]. Given the prevalence of proteinuria in Western cohorts of 14–32%, we had anticipated comparable, if not higher rates in this East African cohort, instead we found a much lower prevalence [18,19]. Although it is possible that this finding is the result of selection bias (only stable outpatients were included in our study), we hypothesize that proteinuria and the predilection to HIVAN is specifically associated with a genetic milieu more common in individuals of West African descent rather than East. This hypothesis is strengthened by a recent study of an Ethiopian immigrant cohort attending an Israeli clinic [20] in which a low rate of proteinuria and no clinically diagnosed cases of HIVAN were detected. It is possible however, that environmental factors may also contribute to the epidemiology of renal disease burden in HIV-infected patients of African descent. These findings indicate a need for further study of renal epidemiology in HIV-infected populations, in order to identify potential genetic as well as environmental factors associated with kidney disease. It is noteworthy that the Cockcroft–Gault equation suggested a prevalence of renal insufficiency two to four times higher than that estimated by the MDRD equations. This is likely due to the incorporation of weight as a variable in the Cockcroft–Gault equation but not the MDRD equations. As our cohort has a lower average weight than the population from which Crockcroft–Gault was derived, its validity in this population is questioned [8]. The Cockcroft–Gault and MDRD (full and abbreviated) equations are commonly used in resource-rich settings for clinical purposes such as drug dosing and disease staging. However, with regard to the validity of using the Cockcroft–Gault and MDRD equations in our study population, it is important to understand that neither of these tests has been validated in HIV-infected persons or East African populations. Furthermore, the MDRD equation has not been validated in patients without chronic kidney disease and thus may underestimate GFR in such patients [21]. While we excluded individuals from our study who were known to be acutely ill, we were unable to confidently distinguish between those with chronic kidney disease from those who may have had acute renal insufficiency. In addition, estimates of GFR and creatinine clearance can be profoundly affected by diet, protein intake, medications, circulating cortisol levels and muscle wasting, factors which our study did not explore. As such, whether or not any of the three estimating equations is appropriate for this population can only be answered with studies utilizing more direct measures of renal function such as iothalamate clearance or 24 h urine collections for creatinine clearance. In order to address these issues a study using more direct measurements of renal function in a cohort of HIV-infected Kenyans is under development.

Other limitations of this study include the absence of viral load data; as such, we were unable to correlate renal function with HIV viral burden. In addition, our study used a cross-sectional study design with a single measurement of serum creatinine and dipstick measurement of urinary protein. As the study was performed in a resource-poor setting we were unable to perform more expensive, albeit more accurate testing methods to measure renal function and proteinuria. As such, there is potential for misclassification bias with respect to estimating renal function and determining the true prevalence of proteinuria. In this study we were most interested in assessing the use of renal function testing in a population of HIV-infected patients without identifiable risks for renal disease because we believe that individuals with other conditions known to be highly associated with kidney disease should always have renal function measured [1]. The use of these restrictive study eligibility requirements may have resulted in a relatively healthy cohort effect, which would underestimate the actual prevalence of reduced GFR in the HIV-infected population residing in this region. Furthermore, as we enrolled only patients at a single institution in East Africa it would be difficult to generalize our findings to other international treatment settings. Finally, we did not attempt to determine the causes of renal dysfunction in our study population. Limited studies performed in HIV-infected, sub-Saharan African patients with microalbuminuria or proteinuria without known risks for renal disease other than HIV-infection, have identified HIVAN as the most common biopsy-proven diagnosis [4,5]. Membranoproliferative nephropathy, interstitial nephritis and membranous nephropathy have also been reported [4,5]. Future longitudinal evaluations that include assessments of the causes of renal disease are necessary in order to determine the natural history of renal disease in HIV-infected sub-Saharan African populations and to verify the effects of kidney disease on clinical outcomes.

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Conflict of interest statement. None declared.

(See related article by Cohen and Kimmel HIV-associated renal diseases in Africa—a desperate need for additional study: an editorial for 'Renal Disease in an Antiretroviral Naïve HIV-infected Outpatient Population in Western Kenya'. *Nephrol Dial Transplant* 2007; 22: 2116–2119.)

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