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Decreased Kidney Function in a Community-based Cohort of HIV-Infected and HIV-Negative Individuals in Rakai, Uganda

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Abstract

Background—High prevalences of reduced glomerular filtration rate (GFR) have been reported from HIV-infected individuals in sub-Saharan Africa when initiating antiretroviral therapy. However little is known about natural history HIV-related kidney disease or about background rates of reduced GFR in HIV-negative individuals in this region.

Methods—We estimated GFR from first and last available stored serum samples from 1202 HIV-infected and 664 age-matched and sex-matched HIV-negative individuals in a community-based cohort of HIV-infected and HIV-negative individuals in Rakai, Uganda, between 1994 and 2003. We assessed the prevalence and incidence of mildly (60–89 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) and moderately (<60 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) reduced GFR using standard analytical methods.

Results—At baseline, 8.4% of HIV-infected and 4.7% of HIV-negative individuals had mildly or moderately reduced GFR ($P = 0.002$). During follow-up, the rates of decline to a lower GFR category were of 32.4 and 20.3 per 1000 person-years in HIV-infected and HIV-negative subjects, respectively ($P = 0.019$).

Conclusions—In an unselected community sample of HIV-infected individuals followed in Rakai, Uganda, before the availability of antiretroviral therapy, the prevalence of decreased GFR and the incidence of a decline in GFR category during follow-up were both significantly higher in HIV-infected subjects compared with HIV-negative subjects, although moderately reduced GFR was uncommon.

Keywords

Africa; chronic kidney disease; cohort study; HIV infection; Uganda

INTRODUCTION

In the industrialized countries, African ancestry is a strong risk factor for HIV-related chronic kidney disease (CKD) and end-stage renal disease.[1,2] Because approximately two-thirds of the global burden of HIV infection is borne by sub-Saharan Africa, it is important to characterize

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the epidemiology of HIV-related CKD in this region of the world. Recent studies from sub-Saharan Africa have reported high prevalences of decreased glomerular filtration rate (GFR) among HIV-infected individuals initiating antiretroviral therapy (ART), with between 7% and 20% of individuals having a GFR <60 mL·min^{-1}·1.73 m^{-2}.[3–6] However, individuals selected for the early roll-out of ART may not be representative of HIV-infected individuals in the general population, and rates of reduced GFR in comparable HIV-negative individuals have not been described. The objective of our study was to determine the prevalence and incidence of reduced GFR in HIV-infected and HIV-negative participants followed before the availability of ART in a community-based cohort in Rakai, Uganda.

METHODS

The Rakai Community Cohort Study (RCCS) was established in 1994 and has been described previously.[7] The RCCS enrolled all consenting individuals aged 15–49 years residing in every household in 50 Rakai District communities (approximately 16,000 persons of whom 12% were HIV infected). RCCS survey workers conducted follow-up surveys with the complete population at 10-month to 14-month intervals. Demographic and behavioral information and venous blood samples were attained at all visits. Blood was tested for HIV infection and sera were stored at −70°C.

We selected a random sample of HIV-infected participants who were enrolled in 1994 and were believed to have stored sera available from ≥2 study visits. We randomly selected a sample of HIV-negative participants from the same communities who were age and sex frequency matched to the HIV-infected subjects. For each participant, we measured creatinine concentration from the first and last available sera using a rate-based enzymatic assay from Roche Diagnostics, which was calibrated using isotope dilution mass spectrometry traceable standards. GFR was estimated using the abbreviated modification of diet in renal disease (MDRD) equation.[8] We defined GFR categories according to the National Kidney Foundation guidelines,[9] with normal, mildly reduced, and moderately reduced GFR corresponding to >90, 60–89, and <60 ml·min^{-1}·1.73 m^{-2}, respectively.

We selected a sample size of 1240 HIV-infected and 620 HIV-negative subjects to have greater than 90% power to detect a 5% difference in prevalence of reduced GFR between the groups, assuming a prevalence of 5% in HIV-negative subjects and 10% of sera being unavailable. We oversampled HIV-infected participants to assess changes in GFR with greater precision in this group. We used the Fisher exact test and the Wilcoxon rank sum test for categorical and continuous variables, respectively, and log-binomial regression[10] to calculate unadjusted and adjusted prevalence ratios of mildly and moderately reduced GFR. We used person-time analysis and Poisson regression models to assess incidence rate ratios (IRR) of transition from a higher to a lower GFR category. The institutional review boards of the Uganda Virus Research Institute's Science and Ethics Committee, the Uganda National Council for Science and Technology, and collaborating institutions in the United States (Johns Hopkins University and Columbia University) approved this research.

RESULTS

Among 1960 participants selected from the database, 1866 (95%) had at least 1 serum sample for creatinine measurement: 1202 were HIV infected and 664 were HIV negative (Table 1). HIV-negative and HIV-infected participants did not differ by sex; however, HIV-infected individuals were statistically significantly older, despite frequency matching by age (5-year categories). The average baseline serum creatinine concentration was significantly higher and the average GFR was significantly lower in HIV-infected compared with HIV-negative participants (Table 1). The proportions of individuals with mild or moderately decreased GFR

at baseline were significantly greater in HIV-infected than in HIV-negative subjects (Table 1, $P = 0.002$). Adjusting for age and sex, the prevalence of mild or moderately reduced GFR was significantly higher in HIV-infected subjects than in HIV-negative subjects [prevalence ratio: 1.61, 95% confidence interval (CI): 1.09 to 2.38].

Among 1866 included in the study, 1345 (72%) had serum samples available from 2 study visits; and of these, 491 were HIV negative at both time points and 854 were HIV positive at baseline. The median time between first and last GFR measurement was 5.3 years (interquartile range: 1.8–7.1) for HIV-negative and 2.6 years (interquartile range: 1.5–1.8) for HIV-infected participants ($P < 0.001$). The mortality rate was significantly higher among HIV-infected than HIV-negative participants (34.5 vs. 7.3 deaths per 1000 person-years, respectively, $P < 0.001$). During follow-up, 130 participants declined to a lower GFR category (either to mildly or moderately reduced GFR), corresponding to incidence rates of 20.3 and 32.4 per 1000 person-years in HIV-negative and HIV-infected subjects, respectively ($P = 0.011$, Table 2). In univariate analyses, age above the median was significantly associated with decline to a lower GFR category (IRR: 2.05, 95% CI: 1.43 to 2.92), whereas male sex was not significantly associated (IRR: 0.89, 95% CI: 0.62 to 1.29). In a model adjusted for age and sex, HIV infection remained significantly associated with a decrease in GFR category during follow-up (Table 2). Only 15 subjects declined to moderately reduced GFR, corresponding to incidence rates 1.3 and 4.6 per 1000 in HIV-negative and HIV-infected subjects, respectively ($P = 0.052$, Table 2).

DISCUSSION

CKD is a common sequela of HIV infection or its treatment. Concern has rightly been raised about an epidemic of HIV-associated CKD in sub-Saharan Africa given the overlap of high HIV prevalence and putative increased susceptibility to HIV-related CKD.[11] This study provides empirical GFR data from randomly selected HIV-infected and HIV-uninfected individuals in a representative rural community-based cohort, followed in the pre-ART era. Our study contributes to existing knowledge about HIV-related CKD in 2 ways. First, to date, most information on HIV-related CKD in Africa has come from individuals with clinically advanced HIV disease, whereas our study includes a community-based sample of HIV-infected individuals. Second, ours is among the first studies to simultaneously estimate rates of CKD in comparable HIV-negative individuals, important contextual information that is rare in sub-Saharan Africa.[12] We found that the prevalence of decreased GFR at enrollment was 61% higher (95% CI: 9% to 138%) and the incidence of GFR category decline during follow-up was 52% higher (95% CI: 6% to 118%) in HIV-infected compared with HIV-uninfected participants.

Intriguingly, we found a substantially lower burden of decreased GFR in HIV-infected individuals than has been reported in other African studies. For example, programs in Uganda, Zimbabwe, Kenya, and Zambia[3–6] reported prevalences of moderately decreased GFR (MDRD estimates) between 3.1% and 12%, compared with 0.7% in our study. A high CKD prevalence has also been reported from Nigeria.[13] The prevalence of moderately decreased GFR in HIV-infected individuals in Rakai was also lower than prevalences that have been reported in HIV-infected persons in Western Europe (4.7%)[14] and New York City (5.9%).[15] Additionally, the incidence of moderately decreased GFR among HIV-infected individuals in Rakai with GFR >60 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ at baseline was lower than that reported in cohort of HIV-infected African Americans followed in Baltimore,[16] 4.6 versus 12.5 per 1000 person-years, respectively.

Three factors may contribute to the lower burden of decreased GFR in our study compared with others. First, the MDRD equation, which was derived in industrialized settings and does

not incorporate weight data, may overestimate GFR in populations where the average weight and dietary protein intake is substantially lower than in industrialized countries. Although this factor may explain the differences in CKD estimates between the Rakai cohort and studies in developed countries, it is less likely to explain the lower rate of CKD that we found compared with HIV-infected individuals in other African settings. Second, the design of the Rakai cohort ensures that HIV-infected individuals are representative of the spectrum of HIV disease stage in the community. In contrast, other reports from African settings were restricted to HIV-infected individuals who were selected to start ART or were seeking treatment,[3–6] and thus may have had more advanced HIV disease than HIV-infected persons in our cohort. Third, the HIV-infected subjects in our study were substantially younger (median age 30 years) than HIV-infected persons in other published studies (mean or median age range 35–39 years).[3–6] Taken together, these findings imply that the prevalence of reduced GFR, although fairly low in a representative sample of HIV-infected individuals in a sub-Saharan African community setting, increases substantially with age or as HIV disease progresses. This concurs with data from industrialized countries showing that HIV-associated nephropathy generally manifests at CD4 cell counts below 100 cell per square millimeter.[17]

Our study was limited by a lack of detailed clinical information about participants. In particular, the lack of weight data precluded us from accounting for baseline weight or weight changes in GFR estimates. For this reason, we could not use the Cockcroft-Gault formula for creatinine clearance, which requires weight.[18] We also did not have information on comorbid conditions, such as hypertension and diabetes. However, we anticipate that the contribution of these conditions to CKD was small because the average age of participants was only 30 years. Additionally, urine samples, which would have permitted us to assess proteinuria, were not collected in the cohort. Finally, we did not have data on CD4 cell counts or HIV RNA levels in the HIV-infected participants. The Rakai cohort was originally established to monitor HIV prevalence and incidence and to test specific interventions to reduce HIV incidence in the communities, and detailed clinical information was not obtained from participants.[7,19,20]

Our study has implications for future work in this area. First, research is needed on cost-effective screening tests (eg, proteinuria) to identify individuals who may benefit from ART to prevent kidney function decline even if other criteria for ART are not met. Second, our study underscores the need to develop GFR estimating equations in African populations that are based on gold-standard GFR measures, such as iohexol clearance. Prior studies in Africa have demonstrated the Cockcroft-Gault equation identifies approximately twice as many individuals as having clinically reduced GFR compared with using the MDRD equation.[3,5] However, the degree to which these equations may be underestimating or overestimating kidney function in this population is unknown.

In conclusion, in an unselected community sample of HIV-infected individuals followed in Rakai, Uganda, before the availability of ART, we found a relatively low burden of overtly decreased GFR compared with previously published studies. However, the prevalence of decreased GFR and the incidence of a decline in GFR category during follow-up were both significantly higher in HIV-infected subjects compared with HIV-negative subjects.

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TABLE 1

Baseline Characteristics from HIV-Negative and HIV-Infected Participants Enrolled in a Community Cohort Study in 1994, Rakai, Uganda

Characteristics	HIV Negative (n = 664)	HIV Infected (n = 1202)	*P*
Female, n (%)	407 (61.3)	777 (64.6)	0.16
Age (yrs), median (IQR)	28 (24–35)	30 (25–36)	0.0002
Serum creatinine concentration (mg/dL), median (IQR)	0.7 (0.6–0.8)	0.7 (0.6–0.8)	0.029
GFR ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$), median (IQR)	127(116–156)	136 (107–152)	<0.0001
GFR category, n (%)			
$\geq 90 ml \cdot min^{-1} \cdot 1.73\ m^{-2}$	633 (95.3)	1101 (91.6)	0.002
60–89 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$	31 (4.7)	93 (7.7)	
<60 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$	0	8 (0.7)	

IQR, interquartile range.

TABLE 2

Incidence of Decrease in GFR Category According to HIV Status, Rakai, Uganda

Event	Number	Person-Years	Rate* (95% CI)	Age-Adjusted and Sex-Adjusted IRR (95% CI)
Mildly or moderately reduced GFR†				
HIV negative	46	2258	20.3 (15.3 to 27.2)	1.0
HIV infected	84	2583	32.4 (26.3 to 40.3)	1.52(1.06 to 2.18)
Moderately reduced GFR				
HIV negative	3	2258	1.3 (0.4 to 4.1)	1.0
HIV infected	12	2583	4.6 (2.6 to 8.2)	3.44 (0.97 to 12.23)

*Rate per 1000 person-years.

†New onset of mildly reduced (60–89 ml·min^{-1}·1.73 m^{-2}) or moderately reduced (<60 ml·min^{-1}·1.73 m^{-2}) GFR.