Kidney function and the risk of cardiovascular events in HIV-1-infected patients

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Objective: Cardiovascular events (CVEs) are a significant cause of mortality in HIV/AIDS patients. The objective is to determine the correlation between kidney function and the risk of CVEs in the HIV-infected population.

Design: Nested, matched, case–control study design was employed.

Methods: We performed a single-center study of 315 HIV-infected patients (63 patients who had CVEs and 252 controls). Estimated glomerular filtration rate (eGFR), calculated by the Chronic Kidney Disease Epidemiology Collaboration formula and the Modification of Diet in Renal Disease equation, and proteinuria were the primary exposures of interest.

Results: Mean eGFR was significantly lower in the patients compared with controls (68.4 vs. 103.2 ml/min per 1.73 m^2, $P < 0.001$ by Chronic Kidney Disease Epidemiology Collaboration formula and 69.0 vs. 103.1 ml/min per 1.73 m^2, $P < 0.001$ by Modification of Diet in Renal Disease equation). In univariate analysis, an eGFR of less than 60 ml/min per 1.73 m^2 was associated with a 15.9-fold increased odds of a CVE compared with an eGFR of at least 60 ml/min per 1.73 m^2 ($P < 0.001$). In multivariate analysis, a 10 ml/min per 1.73 m^2 decrease in eGFR was associated with a 20% increased odds of a CVE (odds ratio 1.2, 95% confidence interval 1.1–1.4). The prevalence of proteinuria in the patients was approximately twice that of controls (51 vs. 25%, $P < 0.001$). Proteinuria was associated with CVEs both in univariate and multivariate analyses (odds ratio 3.6, 95% confidence interval 1.9–7.0 and odds ratio 2.2, 95% confidence interval 1.1–4.8, respectively). Traditional cardiovascular risk factors, such as history of previous CVEs, diabetes mellitus, and dyslipidemia, along with low CD4 cell counts were also found as significant predictors of risk of CVEs.

Conclusion: Our study shows a significant independent association between decreased kidney function and increased risk of CVE in HIV-1-infected patients.

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Introduction

There were about 571 378 people living with HIV/AIDS in the United States at the end of 2007, with 42 655 (21.1 per 100 000 population) new cases reported in that year [1]. With the introduction of HAART, the proportion of deaths due to infectious causes in HIV/AIDS patients has declined from 80 to 43.6%, and a higher proportion of deaths has been attributed to noninfectious causes, with cardiovascular disease (CVD) causing 21.8% of deaths in

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the HAART era compared with 8.4% of deaths in the pre-HAART era [2].

In HIV-infected patients, contributors to CVD may include traditional cardiovascular risk factors (e.g., age, sex, diabetes, hypertension, cigarette smoking, and hypercholesterolemia), direct or indirect effects of HIV infection itself (including inflammation and immune activation), or adverse effects of HIV therapy (which may be partially mediated by changes in traditional risk factors) [3–6]. In non-HIV-infected persons, an extensive body of literature demonstrates strong associations between reduced estimated glomerular filtration rate (eGFR) or proteinuria and subsequent cardiovascular events and mortality [7–10]. Despite the fact that chronic kidney disease (CKD) is highly prevalent in HIV-infected patients in the United States [11,12], the potential contribution of CKD to CVD risk has been little studied and underappreciated. For example, in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study [13], a large prospective cohort study of cardiovascular events in HIV-infected persons living in developed countries, data regarding eGFR and proteinuria were not obtained. Similarly, in the Strategies for Management of Anti-Retroviral Therapy (SMART) study [14], data on renal function were not provided in an analysis in which the association of antiretroviral agents with cardiovascular events was assessed.

Using a nested case–control design, we evaluated the association between markers of kidney disease (eGFR and proteinuria) and cardiovascular events in a well characterized cohort of HIV-infected individuals in Baltimore, Maryland.

Methods

Setting and cohort

The Johns Hopkins HIV Clinic in Baltimore, Maryland, provides care to a large number of HIV-infected individuals in the region. The Johns Hopkins Clinical Cohort includes data from over 6000 participants who have received primary care in the clinic from 1990 onward. Information from clinical records was reviewed and abstracted by trained technicians onto structured data collection forms, and then entered into a relational database. The clinic medical records, the main hospital medical records, and various institutional computerized databases (e.g., laboratory, radiology, pathology, and hospital discharge summaries) were abstracted. Comprehensive demographic, clinical, laboratory, pharmaceutical, and psychosocial data were collected at times corresponding to enrollment in the clinic and at 6-month intervals thereafter. In 1998, information regarding possible cardiovascular events (coronary artery disease and stroke) was added to routine data abstraction procedures. The study protocol was approved by the Johns Hopkins Medicine Institutional Review Board, and participants provided written, informed consent.

Participant selection

One investigator (E.G.) reviewed the medical records of participants who were identified in the cohort database as having sustained a cardiovascular event. To be included as a case in the present analysis, participants had to meet established criteria for myocardial infarction (MI) [15] or cerebrovascular accident. MI was defined as a documented increase in cardiac biomarkers in combination with supporting symptoms, electrocardiogram findings, or cardiac imaging; sudden death accompanied by symptoms suggestive of cardiac ischemia or compatible electrocardiographic or angiographic findings; or pathologic findings of acute myocardial ischemia. Cerebrovascular accident was defined as a focal neurological deficit lasting for more than 24 h or imaging evidence of an acute, clinically relevant ischemic brain lesion that was associated with rapidly vanishing symptoms. Individuals with MI or cerebrovascular accident were excluded from the analysis if the clinical history suggested that metastatic or primary cancer, vasculitis, drug overdose, interventional procedures, or infection (e.g., toxoplasmosis or septic embolization) were likely to have caused the event. Controls (four per study participant) were randomly selected from the cohort population using incidence density sampling, with replacement, excluding individuals with any history of cardiovascular event. Controls were matched with patients by sex, race (black or nonblack), and age (5-year intervals). Individuals who sustained multiple events during the observation period were included in the analysis only once at the earliest event.

Definitions

Laboratory values for patients and their matched controls were those closest in time but not after the event date for patients and the matching date for controls. GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) formula [16] and the four-variable Modification of Diet in Renal Disease (MDRD) Study equation [17] using serum creatinine, age, race, and sex. MDRD estimates that exceeded 200 ml/min per $1.73\,m^2$ were truncated at that value. The modified National Kidney Foundation classification of CKD was used for GFR categorization: at least 90 ml/min per $1.73\,m^2$ (stage 1), 60–89 ml/min per $1.73\,m^2$ (stage 2), 30–59 ml/min per $1.73\,m^2$ (stage 3), 15–29 ml/min per $1.73\,m^2$ (stage 4), and less than 15 ml/min per $1.73\,m^2$ (stage 5). Stages 3, 4, and 5 of CKD were combined due to small numbers of individuals in these strata. Proteinuria was defined as urine dipstick reading of at least above 1+.

Diabetes mellitus was defined as prior diagnosis of diabetes mellitus, prior/current treatment for diabetes

mellitus, or fasting plasma glucose of more than 126 mg/dl (7.0 mmol/l) or random plasma glucose of more than 200 mg/dl (11.1 mmol/l). Hypertension was defined as previous hypertension diagnosis, blood pressure greater than or equal to 140 mmHg systolic or 90 mmHg diastolic on at least two occasions, or use of antihypertensive pharmacological therapy [18]. Individuals were considered to have a history of CVD if there was a compelling history of possible MI or stroke not meeting the diagnostic criteria, peripheral arterial disease, angina, or intervention for coronary artery disease prior to the observation period. Family history was defined as CVD in male first-degree relative of less than 55 years of age or in a female first-degree relative of less than 65 years of age [19]. Dyslipidemia [19] was defined as total cholesterol of more than 200 mg/dl, high-density lipoprotein (HDL) cholesterol of less than 40 mg/dl, serum triglycerides of more than 150 mg/dl, or low-density lipoprotein (LDL) cholesterol higher than the corrected goals determined by the risk factors on random blood lipid estimation. The major risk factors that modify LDL goals were smoking, hypertension, low HDL cholesterol (<40 mg/dl), and family history. HDL cholesterol of more than 60 mg/dl removes one risk factor from the total count. The corrected LDL goals were less than 100 mg/dl for coronary heart disease and coronary heart disease risk equivalents (diabetes mellitus), less than 130 mg/dl for multiple (more than two) risk factors, and less than 160 mg/dl for zero to one risk factor. Both current and previous cigarette smokers were included as smokers. A BMI of more than 30 kg/m^2 was defined as obesity [20]. All the above-mentioned comorbidities were estimated from records closest in time but not after the match date. Participants were included as HAART users if they had any exposure in the 60 days preceding the match date, similarly for the different subgroups of HAART drugs. Certain drugs, such as didanosine and abacavir, which were shown to be associated with cardiovascular events in prior studies [13,14], were also analyzed separately. Statin users were those who had used any statin drug for at least 6 months immediately prior to the match date.

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between explanatory variables and cardiovascular events were estimated using conditional logistic regression models for matched sets. *P* values below 0.05 were considered to be statistically significant. Estimates for the associations between the primary explanatory variables of interest (eGFR and proteinuria) were adjusted in multivariate models that included potential confounding covariates that were statistically significant in univariate analysis. Statistical analysis was performed using STATA version 10 software package (STATA Inc., College Station, Texas, USA).

Results

A total of 117 participants were identified in the Johns Hopkins HIV Clinical Cohort as possibly sustaining a cardiovascular event between 1998 and 2008. Of these, 39 participants were found to have an alternative diagnosis and 15 participants had possible events, but diagnostic criteria were not met or supporting data were unavailable, leaving 63 patients who were included in the analysis. A total of 252 matched controls were selected for the 63 patients.

Baseline characteristics

The baseline characteristics of patients and controls are presented in Table 1. Patients and controls were closely matched by race, sex, and age, and these covariates were not considered further in the analysis. The patients and controls were significantly different in the severity of HIV infection. The CD4 cell counts in the two groups were significantly different with 49.2% of patients having a CD4 cell count of less than 200 cells/μl as compared with 24.6% of controls ($P < 0.001$). Also, a greater proportion of patients (38.7%) had an HIV-1 RNA concentration of more than 50 000 copies/ml as compared with controls (20.1%) ($P = 0.007$). The patients and controls were not significantly different in the HIV transmission category. Patients who experienced cardiovascular events were more likely to be diabetic (31.8 vs. 11.1%, $P < 0.001$), hypertensive (63.5 vs. 36.5%, $P < 0.001$), dyslipidemic (71.4 vs. 48%, $P = 0.001$), and to have a previous history of a cardiovascular event (41.3 vs. 6.7%, $P < 0.001$). There was no statistically significant difference in the prevalence of obesity, cigarette smoking, family history of CVD, or HAART use in the two groups. However, exposure to statins was different, being present in 21% of patients compared with 8.5% of controls ($P = 0.004$).

Kidney function and cardiovascular events

The kidney function of study participants is shown in Table 2. The mean serum creatinine (in mg/dl) was significantly higher in patients as opposed to controls (2.4 vs. 1.1, $P < 0.001$). Using the CKD-Epi formula, the mean eGFR was significantly higher in controls (103.2 ± 27.6 ml/min per 1.73 m^2) than in patients (68.4 ± 41.7 ml/min per 1.73 m^2) ($P < 0.001$). With an eGFR of more than 90 ml/min per 1.73 m^2 as a reference, eGFR of 60–89 ml/min per 1.73 m^2 was associated with an OR of 3.9 ($P = 0.002$) and an eGFR of less than 60 ml/min per 1.73 m^2 with an OR of 15.9 ($P < 0.001$). When potential confounders in the relationship between eGFR and cardiac events, including diabetes mellitus, hypertension, previous cardiac events, dyslipidemia, HIV viral load, and CD4 cell count, were added to the model, an eGFR of 60–89 ml/min per 1.73 m^2 was associated with an OR of 1.8 ($P = 0.175$) and an eGFR of less than 60 ml/min per 1.73 m^2 with an OR of 6.4 ($P < 0.001$) as compared with an eGFR of more than 90 ml/min per 1.73 m^2. Use of the MDRD formula to derive eGFR estimates produced similar results. The

Table 1. Baseline characteristics of participants.

Variables	Patients ($n=63$)	Controls ($n=252$)	P
Demographic data			
Age* [years, mean (SD)]	49.5 (10)	49.5 (9.5)	NA
Men*, *n* (%)	40 (63.5)	160 (63.5)	NA
Black*, *n* (%)	53 (84.1)	212 (84.1)	NA
Transmission category†, *n* (%)			
Homo/bisexual	8 (12.7)	56 (22.2)	0.105
Heterosexual	33 (52.4)	138 (54.8)	0.732
IDU	29 (46)	121 (48)	0.909
Transfusion	4 (6.3)	20 (7.9)	0.386
HIV status, *n* (%)			
CD4 cell count (cells/μl)			<0.001
Median (IQR)	216 (84–425)	375 (210–559)	
<200	31 (49.2)	62 (24.6)	
201–350	13 (20.6)	55 (21.8)	
>350	19 (30.2)	135 (53.6)	
HIV-1 RNA (copies/ml)			0.007
Median (IQR)	6374 (75–96826)	750 (52–22131)‡	
<1000	26 (41.9)	126 (50.6)	
1001–50 000	12 (19.4)	73 (29.3)	
>50 000	24 (38.7)	50 (20.1)	
Cardiovascular risk factors, *n* (%)			
Obesity	13 (20.6)§	41 (16.3)‖	0.777
Smoking	53 (84.1)	189 (75)¶	0.248
Diabetes	20 (31.8)	28 (11.1)	<0.001
Dyslipidemia	45 (71.4)§	121 (48)‡	0.001
Hypertension	40 (63.5)	92 (36.5)	<0.001
Family history	10 (15.9)**	34 (13.5)††	0.242
Previous cardiovascular events	26 (41.3)‡	17 (6.7)	<0.001
Medications, *n* (%)			
Use of HAART	32 (50.8)	124 (49.2)	0.822
PI	17 (27.4)	52 (21.0)	0.275
NRTI	32 (51.6)	113 (45.6)	0.393
NNRTI	11 (17.5)	61 (24.2)	0.254
Abacavir	9 (14.3)	52 (20.6)	0.254
Didanosine	2 (3.2)	12 (4.8)	0.585
Statins	13 (21.0)‡	21 (8.5)¶	0.004

IQR, interquartile range; NA, not applicable; NNRTI, nonnucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; SD, standard deviation.
*Matched in patient and control.
†Transmission categories not additive, as many patients had multiple risk factors for HIV acquisition.
‡Information missing in three patients.
§Information missing in one patient.
‖Information missing in 40 patients.
¶Information missing in eight patients.
**Information missing in 20 patients.
††Information missing in 38 patients.

presence of proteinuria was also found to be significantly different between patients (51%) and controls (25%) and was associated with an OR of 3.6 ($P<0.001$), which remained significant in multivariate analysis (OR 2.2, $P=0.038$). When a composite variable was created that included both eGFR (CKD-Epi) and proteinuria, it was found that participants with an eGFR of less than 60 ml/min per 1.73 m^2 and proteinuria had a 41-fold increased odds as compared with participants with an eGFR of at least 90 ml/min per 1.73 m^2 and no proteinuria (OR 41.4, $P<0.001$). This association remained highly statistically significant in adjusted analysis and with use of the MDRD GFR estimates. However, the CIs were wide in this composite analysis.

In univariate analysis (Table 3), eGFR (CKD-Epi) was found to be a significant predictor of cardiac events with an OR of 1.3 (95% CI 1.2–1.5) per 10 ml/min per 1.73 m^2 decrease in value (Table 3). A similar correlation was also demonstrated using the GFR estimates derived using the MDRD formula (OR 1.3, 95% CI 1.2–1.4). A locally weighted regression and smoothing plot demonstrates a linear increase in CVD risk as eGFR declined from normal values (~120 ml/min per 1.73 m^2) (Fig. 1). Other factors found to be significantly associated with cardiovascular events included prior cardiovascular event, diabetes mellitus, hypertension, dyslipidemia, statin use, CD4 cell count of more than 350 cells/μl, and HIV RNA plasma concentration of more than 50 000 copies/ml.

Table 2. Kidney function of study participants using estimated glomerular filtration rate as a categorical variable.

	Patients ($n=63$)	Controls ($n=252$)	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Serum creatinine (mg/dl)*				<0.001		
Mean (SD)	2.4 (2.9)	1.1 (1.4)	–	–	–	–
Median (IQR)	1.2 (0.9–2.5)	0.8 (0.7–1)	–	–	–	–
eGFR (by CKD-Epi formula, ml/min per 1.73 m^2)*,†						
Mean (SD)	68.4 (41.7)	103.2 (27.6)	–	<0.001	–	–
Median (IQR)	65 (33–105)	109 (92–123)	–	<0.001	–	–
>90	21 (33.3)	192 (76.5)	1 (ref)	–	1 (ref)	
60–89	13 (20.6)	39 (15.5)	3.9 (1.7–9.1)	0.002	1.8 (0.7–4.7)	0.175
<60	29 (46)	20 (8)	15.9 (6.7–37.5)	<0.001	6.4 (2.6–15.6)	<0.001
eGFR (by MDRD, ml/min per 1.73 m^2)*,†						
Mean (SD)	69 (45.8)	103.1 (32.5)		<0.001		
Median (IQR)	62 (32–99)	105 (86–124)		<0.001		
>90	19 (30.2)	181 (72.1)	1 (ref)	–	1 (ref)	–
60–89	15 (23.8)	48 (19.1)	3.3 (1.5–7.3)	0.003	1.8 (0.8–4.3)	0.175
<60	29 (46)	22 (8.8)	12.8 (5.7–28.6)	<0.001	5 (2.1–11.8)	<0.001
Proteinuria‡						
Absent/trace	25 (39.7)	158 (62.7)	1 (ref)	–	1 (ref)	–
Present	32 (51)	63 (25)	3.6 (1.9–7)	<0.001	2.2 (1.1–4.8)	0.038
eGFR and proteinuria (by CKD-Epi formula, ml/min per 1.73 m^2)†						
eGFR ≥ 90 without proteinuria	14 (41.2)	127 (51.2)	1 (ref)	–	1 (ref)	–
eGFR < 60 with proteinuria	22 (34.9)	12 (4.8)	41.4 (5.5–312.1)	<0.001	28.5 (2–400.1)	0.013
eGFR and proteinuria (by MDRD, ml/min per 1.73 m^2)†						
eGFR ≥ 90 without proteinuria	13 (20.6)	120 (48.4)	1 (ref)	–	1 (ref)	–
eGFR < 60 with proteinuria	22 (34.9)	14 (5.6)	18.5 (4.2–80.9)	<0.001	10.7 (1.6–69.5)	0.013

CKD-Epi, Chronic Kidney Disease Epidemiology Collaboration; CI, confidence interval; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease; OR, odds ratio; SD, standard deviation.
*Information missing in one control.
†Adjusted for diabetes, hypertension, previous events, CD4 cell counts and HIV viral load, and dyslipidemia.
‡Information missing in six patients and 30 controls.

Table 3. Univariate and multivariate analyses for odds of cardiac events using estimated glomerular filtration rate as a continuous variable.

	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI) (model 1)	*P*	Adjusted odds ratio (95% CI) (model 2)	*P*
eGFR value* (CKD-Epi formula, ml/min per 1.73 m^2)	1.3 (1.2–1.5)	<0.001	1.2 (1.1–1.4)	0.009		
eGFR value* (MDRD formula, ml/min per 1.73 m^2)	1.3 (1.2–1.4)	<0.001	–	–	1.2 (1.1–1.5)	0.004
Proteinuria	3.6 (1.9–7)	<0.001	2.9 (0.9–9)	0.070	2.7 (0.8–8.9)	0.101
Diabetes	4.4 (2.1–9.3)	0.010	3.6 (0.9–15.3)	0.077	5.9 (1.1–29.1)	0.037
Hypertension	3.3 (1.8–6.2)	0.001	1.3 (0.5–3.9)	0.593	1.9 (0.6–6.1)	0.253
Obesity	1.1 (0.6–2.3)	0.31	–	–	–	–
Previous cardiac event	13.7 (5.6–33.6)	<0.001	29.8 (6.1–145.7)	<0.001	91.3 (11.7–711.7)	<0.001
Family history	1.9 (0.8–4.7)	0.149	–	–	–	–
Dyslipidemia	3.6 (1.8–7.1)	<0.001	4.1 (1.1–14.9)	0.034	2.9 (0.8–10.5)	0.108
Statin use	3.6 (1.5–8.7)	0.005	–	–	–	–
Any HAART use	1.1 (0.6–1.9)	0.857	–	–	–	–
NRTI use	1.2 (0.7–2.2)	0.479	–	–	–	–
PI use	1.4 (0.9–2.3)	0.197	–	–	–	–
NNRTI use	0.6 (0.3–1.3)	0.209	–	–	–	–
Abacavir use	0.6 (0.2–1.4)	0.215	–	–	–	–
Didanosine use	0.6 (0.1–3.1)	0.574	–	–	–	–
CD4 cell count (cells/μl)						
>350	1 (ref)	–	1 (ref)	–	1 (ref)	–
201–350	1.5 (0.7–3.2)	0.332	0.4 (0.1–1.7)	0.227	0.5 (0.1–2.1)	0.308
<200	3.4 (1.8–6.6)	<0.001	2.3 (0.8–7.1)	0.141	4.8 (1.3–18.2)	0.019
HIV-1 RNA (copies/ml)						
<1000	1 (ref)	–	1 (ref)	–	1 (ref)	–
1001–50 000	0.8 (0.4–1.8)	0.639	2 (0.5–7.3)	0.293	2.4 (0.6–9.5)	0.201
>50 000	2.4 (1.2–4.6)	0.011	1.5 (0.3–6.5)	0.596	1.7 (0.3–8.7)	0.551

Model 1 analyzed eGFR according to the CKD-Epi equation and model 2 according to the MDRD GFR estimation formula. CKD-Epi, Chronic Kidney Disease Epidemiology Collaboration; CI, confidence interval; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor.
*OR for every 10 ml/min per 1.73 m^2 fall in eGFR.

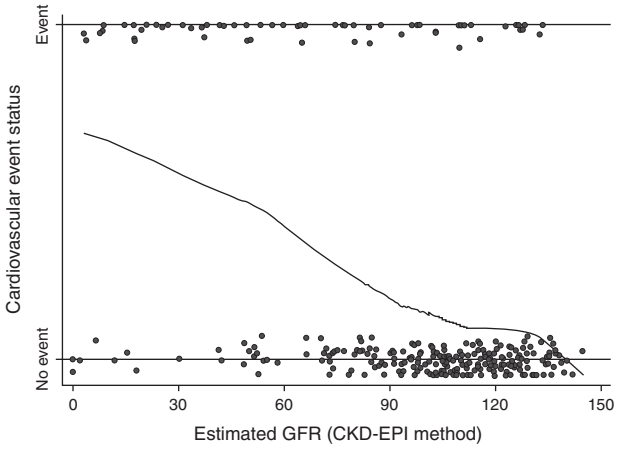

Fig. 1. Relationship between estimated glomerular filtration rate and cardiovascular event status in a nested, matched, case–control study of HIV-infected individuals. The points correspond to individual patients. The curve, generated by a locally weighted regression smoothing function, represents cardiovascular disease risk according to estimated GFR. CKD-Epi, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate.

Family history of CVD, obesity, and HAART use was not found to be significantly associated with cardiovascular events.

When potential confounders in the relationship between eGFR and cardiac events, such as diabetes mellitus, hypertension, previous cardiac events, dyslipidemia, HIV-1 RNA concentration, and CD4 cell count, were adjusted for (Table 3), the OR for every 10 units/ml/min per 1.73 m^2 decrease in eGFR (CKD-Epi) (model 1) remained almost unchanged with an OR of 1.2 ($P = 0.009$). In another multivariate model using eGFR (MDRD) (model 2), identical results were obtained (OR 1.2, $P = 0.004$).

In multivariate models, lower eGFR remained significantly associated with cardiovascular events (Table 3), whether GFR was estimated with the CKD-Epi formula (model 1) or the MDRD formula (model 2). Other factors that remained significantly associated with cardiovascular events included history of previous cardiac events, diabetes, dyslipidemia, and CD4 cell count of less than 200 cells/μl, although results were not consistent in the two models. However, proteinuria, hypertension, and HIV-1 RNA plasma concentration were not significantly associated with cardiovascular events, after adjustment for other factors in these models.

Discussion

In an HIV clinic-based population, decreasing eGFR was associated with a significantly increased risk of cardiovascular events independent of traditional cardiovascular risk factors and HAART. Whereas an eGFR of 60–89 ml/min per 1.73 m^2 was associated with a marginally increased risk, which became nonstatistically significant after adjustment for other factors, an eGFR of less than 60 ml/min per 1.73 m^2 was associated with a significant five-fold to six-fold increase in odds of cardiovascular events. The association between GFR and CVD events was similar whether GFR was estimated with the MDRD or CKD-Epi equations. Consistent with other studies in the general population, proteinuria was also a significant independent predictor of CVD in this group of patients and, as shown in Table 2, individuals with both proteinuria and an eGFR of less than 60 ml/min per 1.73 m^2 were at markedly increased risk for cardiovascular events. However, proteinuria was not found to be a significant predictor of cardiovascular events in the continuous eGFR model, possibly suggesting an eGFR-dependent additive effect of proteinuria, which amplifies the risk when associated with low eGFR, but not contributing significantly when associated with small changes in eGFR.

Our study highlights the existence of a strong link between kidney function and CVD risk in HIV-infected individuals, an association that is at least as strong, if not stronger, than that reported in the general population. This finding is important because the prevalence of kidney disease has been found to be three-fold to five-fold higher in HIV-infected than in HIV-negative persons [2,21] and because indicators of reduced GFR or kidney damage (e.g., albuminuria) have often been omitted in large multisite studies [13,14] addressing risk factors for cardiovascular events in HIV-infected persons. The strength of the association we found is notable because only relatively crude measures of kidney disease were available to us in this retrospective study. Equation-based estimates of GFR are inaccurate at higher levels of kidney function [22]. In our analysis, we included GFR estimated by both the widely used MDRD equation [16] and the recently published CKD-Epi equation [17], the latter of which is designed to function better in a population that does not predominantly have kidney disease.

Other traditional factors found to be significantly associated with cardiovascular events in our analysis include diabetes mellitus, hypertension, previous cardiovascular events, dyslipidemia, statin use, CD4 cell counts, and HIV-1 RNA concentration. The higher odds for a cardiovascular event associated with statin use could be accounted for by associated dyslipidemia and poor lipid level control achieved with statin therapy in HIV patients as opposed to non-HIV population [23–25]. The significant risk associated with hypertension and higher HIV-1 RNA viral loads on univariate analysis was not found on multivariate analysis, suggesting an overlap of causal pathway with the other variables. Family history

was not found to be a significant risk factor in this study. However, it is possible that family history of cardiovascular events was not rigorously collected in this HIV-based cohort. We found no significant associations between cardiovascular events and HAART use, individual drug class use, or abacavir or didanosine use, as have been found in other studies [13,14,26]. However, our study was not sufficiently powered to detect effect sizes in the range found in prior studies of associations between antiretroviral drug use and cardiovascular events.

Many mechanisms have been proposed for the cardiovascular risk in kidney disease. Renal insufficiency is known to be associated with elevated levels of apolipoprotein B [27], fibrinogen [27], homocysteine [27], C-reactive protein [27], and other inflammatory and procoagulant biomarkers [28], and decreased apolipoprotein A1 [27]. Anemia associated with decreased erythropoietin production in CKD also contributes to cardiovascular risk by causing elevated levels of markers of endothelial activation and left ventricular hypertrophy [29–31]. Secondary hyperparathyroidism associated with CKD is also known to be an independent risk factor for cardiovascular events [32]. Hypercalcemia and hyperphosphatemia play a major role in the occurrence of vascular calcification in patients with CKD, together with endocrine disturbances including vitamin D, fibroblast growth factor-23, and klotho [33].

There has been much interest in studying cardiovascular risk factors, morbidity, and mortality in HIV-1-infected patients. Traditional CVD risk factors [4,5], lower CD4 cell counts [4], and duration of nucleoside reverse transcriptase inhibitor (NRTI) [4] and protease inhibitor [5] use have been reported to be associated with cardiovascular events. Traditional risk factors, inflammatory effects of HIV, and the metabolic complications of antiretroviral therapy [34] are hypothesized to underlie the pathophysiology of CVDs in HIV patients. No previous study has correlated kidney function with cardiovascular events in HIV patients. In 2004, Go *et al.* [7] performed a longitudinal study in 1 120 295 non-HIV-infected adults and observed a graded increase in cardiovascular events with decreasing GFR. Using more than 60 ml/min per 1.73 m^2 as a reference, the study demonstrated increasing OR for any cardiovascular event with worsening stages of CKD.

This study has several limitations. A single measurement of serum creatinine prior to the event might not be an accurate measurement of kidney function. Neither the MDRD nor the CKD-Epi study equations are validated in the HIV-1-infected population. The sample size of our study was small, limiting our ability to detect potentially clinically important associations. Proteinuria was determined by a semi-quantitative measure of urine protein concentration (dipstick), which is inferior to quantitative measures such as protein-to-creatinine ratio from a random or 24-h sample [35]. Additionally, data on proteinuria were not complete, as urinalyses, unlike serum creatinine measurements, were not routinely performed in this cohort. Other potential confounders that were not accounted for include diet, physical activity, duration of HIV infection, duration of and adherence to HAART medication, and severity of comorbidities such as diabetes mellitus and hypertension. HAART drugs other than abacavir and didanosine were analyzed only within their subgroups and not as individual drugs. Lipoatrophy, a known complication of HAART therapy, could not be distinctly defined and adjusted for. Abnormalities in the individual components of lipid profile were not analyzed separately for effect on cardiovascular events. All current and previous smokers were considered together, and quantification of total exposure was not attempted. Considering the population differences and the hospital-based nature of the study, the results may not be generalizable to all HIV cohorts. Nevertheless, our study lays the groundwork for future prospective studies that involve a larger sample size to further explore the potential role of kidney function on CVD in HIV-1-infected individuals.

Conclusion

We found an independent association between decreasing GFR and the risk of cardiovascular events in HIV-1-infected patients. This risk was prominent at an eGFR below 60 ml/min per 1.73 m^2. Similarly, the presence of proteinuria in this study was an independent predictor of cardiovascular events in addition to the traditional risk factors, and its effect was amplified by low GFR. Our findings require further confirmation but suggest the potential value of early screening and treatment of CKD in HIV-1-infected patients, particularly those with other cardiovascular risk factors.

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