Mild renal impairment is associated with calcified plaque parameters assessed by computed tomography angiography in people living with HIV

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Objective: To investigate the association of mild renal impairment and coronary plaque in people living with HIV (PLHIV).

Methods: PLHIV and non-HIV controls with serum creatinine less than 1.5 mg/dl were investigated. Estimated glomerular filtration rate (eGFR) (calculated by CKD-EPI formula) was related to coronary plaque indices obtained by CT angiography.

Results: One hundred and eighty-four PLHIV [HIV viral load, 49 (47,49) copies/ml, $CD4^+$ cell count, median 536 (370, 770) cells/μl, duration HIV, 15 ± 7 years] and 72 HIV-negative controls without known cardiovascular disease (CVD) were studied. The two groups were well matched for traditional CVD risk factors. Serum creatinine (0.9 ± 0.2 vs. 0.9 ± 0.2 mg/dl, $P = 0.96$) and eGFR (96 ± 22 vs. 96 ± 24 ml/min per 1.73 m^2, $P = 0.99$) were similar between PLHIV and non-HIV, respectively. In PLHIV, eGFR inversely related to total severity of coronary plaque score ($r = -0.27$, $P = 0.002$), total coronary segments with plaque ($r = -0.21$, $P = 0.005$), calcified plaque segments ($r = -0.15$, $P = 0.045$), and Agatston score ($r = -0.21$, $P = 0.006$). Adjusting for total Framingham point score, BMI, and HIV parameters, eGFR remained significantly associated with calcified plaque and Agatston score in PLHIV. In HIV negative controls, eGFR did not correlate with calcified plaque ($r = -0.20$, $P = 0.10$) or Agatston score ($r = -0.13$, $P = 0.29$). Among PLHIV, those with eGFR less than 90 ml/min per 1.73 m^2 demonstrated increased total severity of coronary plaque score compared with those with eGFR greater than or equal to 90, $P = 0.02$. This relationship was stronger in PLHIV than the non-HIV group.

Conclusion: Our data highlight a robust relationship between subclinical renal impairment and coronary artery disease among PLHIV. Further research is needed to understand the relationship between mild renal impairment and CVD in HIV.

Introduction

Cardiovascular disease (CVD) is increased among HIV-infected patients [1], which is because of traditional and nontraditional factors [2]. Among traditional risk factors, renal disease is increased among HIV-infected patients [3]. Prior studies have demonstrated that kidney disease is associated with CVD among non-HIV patients [4–6], but little is known about the relationship between chronic kidney disease (CKD) and CVD in HIV. Also, kidney disease in HIV is often subclinical in nature [7], and only one study, to our knowledge, has investigated whether

subclinical, mild renal impairment relates to coronary artery disease in HIV patients using only Agatston score [8]. To extend these findings, we used computed tomography (CT) angiography to investigate the relationship of moderate changes in estimated glomerular filtration rate (eGFR) to calcified and noncalcified plaque parameters, in PLHIV and HIV negative participants.

Method

Study design

This study reports on new analyses from a previously performed observational study of HIV-infected men and women and well matched non-HIV control participants to assess coronary plaque [9]. Participants between 18 and 65 years of age and with BMI $20-35 \, \text{kg/m}^2$ were recruited from Boston community centers and infectious disease clinics. One hundred and eighty-four men and women with chronic HIV infection [>5 years; 66% men, median age 48 (43,53) years] and seventy-two non-HIV controls [58% men, median age 47 (43,50) years] were enrolled as a comparison group. Controls were selected to be similar in age and sex, and from the same neighborhoods and health clinics as the HIV participants. Participants from both groups with known cardiac disease, arrhythmias, valvular disease, congestive heart failure or symptoms consistent with angina were excluded. In addition, participants with creatinine greater than 1.5 mg/dl were excluded to reduce the risk of contrast nephropathy. Participants with an acute illness of any type were also excluded. Finally, participants with contraindication to beta blockers and nitroglycerin were excluded. Cardiovascular risk was determined using total Framingham point score and 10-year Framingham CVD risk score. The 2013 ACC/AHA risk scoring algorithm was not used as the data were collected prior to the introduction of this scoring system, which can only score those 40 years and older, and would thus be inappropriate for this study. All participants provided informed consent prior to enrollment. The previous study was approved by the institutional review boards of Massachusetts General Hospital and Massachusetts Institute of Technology.

Coronary plaque measurement

Agatston calcium score was calculated using the non-contrast CT images by standardized techniques [9]. Coronary CT imaging was performed using a 64-slice CT scanner (Sensation 64; Siemens Medical Solutions) as previously described [9]. Assessment of coronary atherosclerotic plaque, including number of total coronary segments with plaque, coronary segments with calcified plaque, and coronary segments with noncalcified plaque were determined by a consensus reading between two investigators, including a cardiologist and a radiologist with significant experience in the interpretation of coronary CT. Total severity of coronary plaque score was determined by the sum of severity plaque score at each segment, which was based on plaque size assessed qualitatively by the cardiac imaging specialists at each individual coronary segment. A scoring system for total severity of coronary plaque was established using a numerical scale from zero to three. The system was defined as: 0, no plaque; 1, mild; 1.5, mild to moderate; 2, moderate; 2.5, moderate to severe; and 3, severe coronary plaque. Physicians analyzing the scans were blinded to the participants' clinical history or HIV status.

Metabolic, biochemical, and immunologic parameters

Total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, glucose, hemoglobin A1c (HbA1c), and creatinine were determined using standard techniques. The Chronic-Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation was used to calculate eGFR. $CD4^+$ and $CD8^+$ T-cell counts were assessed by flow cytometry. HIV viral load was determined by ultrasensitive real-time PCR (lower limit of detection 50 copies/ml). HIV testing was performed by chemiluminometric immunoassay and confirmed by western blot.

Statistical analysis

Normality of distribution was determined using the Shapiro−Wilks test. Continuous and normally distributed variables were analyzed using Student's t-test for two group comparisons and were presented as mean ± SEM. Nonnormally distributed variables were analyzed using Wilcoxon rank sum test for two group comparisons and were presented as median (IQR). Categorical variables were presented as proportions. Pearson correlation coefficient was used to assess relationships with eGFR and total severity of coronary plaque score, total coronary segments with plaque, coronary segments with calcified plaque, coronary segments with noncalcified plaque and Agatston score within the HIV and non-HIV groups. Total severity of coronary plaque score was presented as mean ± SEM when stratifying participants based on eGFR less than 90. Multivariable regression analysis was used to assess the relationship of eGFR to coronary plaque parameters and Agatston score within the HIV group and HIV negative controls, controlling for traditional CVD risk factors and duration of HIV diagnosis, viral load, $CD4^+$ cell count, and protease inhibitor, tenofovir disoproxil (TDF), abacavir and efavirenz in the HIV group. Statistical significance was defined as P value less than 0.05. Statistical analyses were performed using SAS JMP (version 11.0; SAS Institute, Cary, North Carolina, USA).

Results

Demographics and clinical parameters

PLHIV and HIV negative controls were well matched for age, sex, race, and ethnicity (Table 1). There was no

Table 1. Baseline demographics and clinical parameters.

	HIV negative controls ($n = 72$)	PLHIV ($n = 184$)	P value
Demographics			
Age (years)	47 (43–50)	48 (43–53)	0.11
Sex (men %)	58	66	0.27
Race (%)			0.30
Black	36	36	
White	53	55	
Asian	4	0.6	
More than 1 race	6	6	
Hispanic	7	11	0.36
Current tobacco (use %)	40	43	0.72
Metabolic parameters			
History of hypertension (%)	17	22	0.36
History of DM (%)	7	11	0.40
Total Framingham point score	8 ± 5	9 ± 5	0.25
SBP (mmHg)	116 ± 14	119 ± 14	0.18
DBP (mmHg)	76 ± 9	76 ± 9	0.97
BMI (kg/m^2)	28 ± 5	27 ± 5	0.44
Waist circumference (cm)	97 ± 16	97 ± 14	0.91
HbA1c (%)	5.5 (5.3–5.8)	5.5 (5.2–5.8)	0.36
Total cholesterol (mg/dl)	178 (158–207)	175 (154–205)	0.70
LDL (mg/dl)	105 (89–128)	98 (78–122)	0.16
HDL (mg/dl)	49 (42–63)	50 (40–62)	0.58
Triglycerides, mg/dl	84 (62–125)	95 (75–162)	0.009
Statin duration, years; use (%)	0 (0,0); (4)	0 [0,0]; (14)	0.16
Creatinine (mg/dl)	0.9 ± 0.2	0.9 ± 0.2	0.96
eGFR (ml/min/1.73 m^2)	96 ± 24	96 ± 22	0.99
Coronary plaque parameters			
Total coronary segments with plaque	1.4 ± 2.2	1.9 ± 2.7	0.15
Total severity of coronary plaque score	1.6 ± 3.0	2.5 ± 4.1	0.09
Coronary segments with calcified plaque	0.35 ± 0.84	0.26 ± 0.85	0.47
Coronary segments with noncalcified plaque	0.44 ± 1.2	0.91 ± 1.5	0.01
Agatston score	31 ± 79	32 ± 105	0.92
HIV Parameters			
Duration of HIV diagnosis (years)		15 ± 7	
HIV viral load (copies/ml)		49 (47–49)	
CD4+ cell count (cells/µl)		536 (370–770)	
Undetectable HIV viral load (%)		78	
Current PI use (%)		48	
Current NRTI use (%)		81	
Current NNRTI use (%)		32	
Current integrase inhibitor use (%)		12	
Current TDF use (%)		70	
Current abacavir use (%)		14	
Current raltegravir use (%)		12	
Current efavirenz use (%)		28	

DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; NRTI, nucleoside/nucleotide reverse transcriptase inhibitors; NNRTI, nonnucleoside reverse transcriptase inhibitors; PI, protease inhibitors; TDF, tenofovir disoproxil. Data reported as mean ± standard deviation, median (interquartile range), or percentage.

significant difference in current tobacco use, hypertension, diabetes, and total Framingham point score between PLHIV and HIV negative controls. Clinical parameters (including SBP and DBP, and BMI) were not significantly different between the two groups. There were no significant differences in HbA1c, total cholesterol, LDL, and HDL levels. As expected, triglycerides were higher in PLHIV compared with HIV negative controls. Statin use was not different between the groups. There was no significant difference in serum creatinine levels between PLHIV and HIV negative controls (0.9 ± 0.2 and 0.9 ± 0.2 mg/dl, $P = 0.96$, respectively). eGFR was also similar between PLHIV and HIV negative controls, 96 ± 22 vs. 96 ± 24 ml/min per 1.73 m^2, $P = 0.99$, respectively. The PLHIV group had a duration of HIV infection of 15 ± 7 years, and HIV viral load was 49 [47,49] copies/ml. Seventy-eight percent of PLHIV had undetectable viral load. The median CD4$^+$ cell count was 536 [370,770] cells/µl. Seventy percent of PLHIV were on tenofovir disoproxil, 14% were on abacavir, and 28% were on efavirenz at the time of the study. Calcified plaque parameters and Agatston score were similar between HIV and non-HIV groups, whereas noncalcified plaque was increased in PLHIV (Table 1).

Table 2. Correlation of estimated glomerular filtration rate with traditional cardiovascular risk factors in people living with HIV and HIV negative controls.

	HIV negative (*r*)	*P* value	PLHIV (*r*)	*P* value
SBP (mmHg)	0.023	0.85	−0.18	0.03
DBP (mmHg)	0.023	0.85	−0.12	0.11
HA1c (%)	0.14	0.26	0.06	0.37
Total cholesterol (mg/dl)	0.10	0.43	−0.004	0.96
HDL (mg/dl)	0.25	0.03	−0.01	0.87
LDL (mg/dl)	−0.02	0.88	0.07	0.37
Triglycerides (mg/dl)	0.0003	1.0	−0.12	0.15
Statin use	−0.07	0.60	−0.12	0.46
Total Framingham point score	−0.07	0.54	−0.17	0.02
10-year Framingham CVD risk score[a]	−0.33	0.006	−0.19	0.01
Duration of HIV diagnosis (years)			−0.14	0.07
CD4+ cell count (cells/μl)			0.22	0.004
HIV viral load (copies/ml)			−0.05	0.54

[a]Spearman coefficient is reported for 10-year Framingham cardiovascular (CVD) risk score. HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Correlation between estimated glomerular filtration rate and traditional cardiovascular risk factors

In PLHIV, eGFR was correlated with SBP ($r = -0.18$, $P = 0.03$), CD4+ cell count ($r = 0.22$, $P = 0.004$), total Framingham point score ($r = -0.17$, $P = 0.02$), and 10-year Framingham CVD risk score ($\rho = -0.19$, $P = 0.01$) and was inversely related to duration of HIV infection ($r = -0.14$, $P = 0.07$; Table 2). In HIV negative controls, HDL ($r = 0.25$, $P = 0.03$) and 10-year Framingham CVD risk score ($\rho = -0.33$, $P = 0.006$) were significantly associated with eGFR. There was no correlation between eGFR and HbA1c, DBP, total cholesterol, LDL, triglycerides, or statin use in either group.

Relationship of estimated glomerular filtration rate to antiretroviral therapy use among HIV-infected participants

eGFR was lower among participants receiving protease inhibitors and TDF treatments. PLHIV on efavirenz had significantly higher eGFR (Supplemental Table 1, http://links.lww.com/QAD/B376). There was no significant correlation between eGFR and nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), abacavir, or raltegravir.

Correlation between creatinine and estimated glomerular filtration rate with coronary plaque type in people living with HIV and HIV negative controls

In PLHIV, eGFR was inversely and significantly related to total severity of coronary plaque score, total coronary segments with plaque, number of coronary segments with calcified plaque, and Agatston score (Table 3). In contrast, eGFR did not correlate with coronary segments with noncalcified plaque in PLHIV. In the HIV negative group, directionally similar but less robust relationships were seen relating eGFR to plaque parameters. The relationship was the strongest between eGFR and number of coronary segments with calcified plaque, which trended toward significance. Creatinine related significantly to multiple plaque parameters in PLHIV, but these relationships were less robust than with eGFR (Table 3). The same was seen among the non-HIV group.

We stratified eGFR to indicate normal and impaired renal function, defined by eGFR less than 90 ml/min per 1.73 m^2. PLHIV with eGFR less than 90 ml/min per 1.73 m^2, had significantly higher total severity of coronary plaque score compared with PLHIV with eGFR greater than or equal to 90 ml/min per 1.73 m^2, 3.46 ± 4.98 and 1.73 ± 3.07, $P = 0.02$, respectively (Fig. 1). Among

Table 3. Correlation between serum creatinine and estimated glomerular filtration rate and coronary plaque type in people living with HIV and HIV negative controls.

	HIV negative				PLHIV			
	Creatinine		eGFR		Creatinine		eGFR	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
Total severity of coronary plaque score	0.02	0.90	−0.11	0.44	0.21	0.01	−0.27	0.002
Total coronary segments with plaque	−0.02	0.88	−0.14	0.25	0.15	0.049	−0.21	0.005
Coronary segments with calcified plaque	0.007	0.96	−0.20	0.10	0.16	0.03	−0.15	0.045
Coronary segments with noncalcified plaque	−0.10	0.41	0.07	0.60	0.12	0.30	−0.10	0.36
Agatston score	−0.06	0.62	−0.13	0.29	0.20	0.02	−0.21	0.006

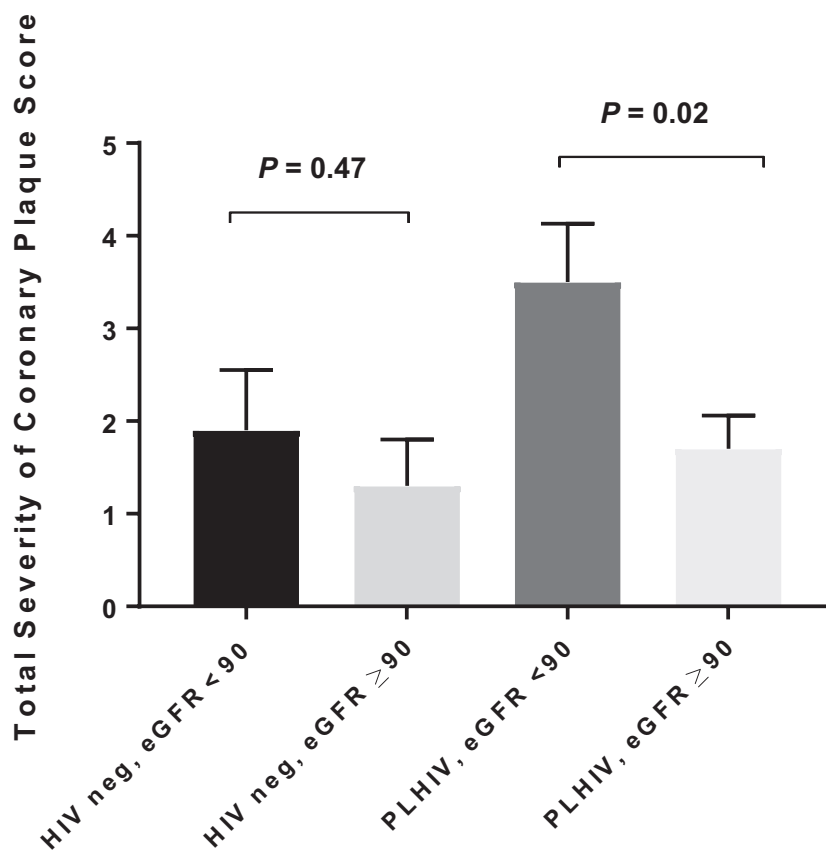eGFR, estimated glomerular filtration rate; PLHIV, people living with HIV.

Fig. 1. Total severity of coronary plaque score in people living with HIV and HIV negative controls with estimated glomerular filtration rate at least 90 and less than 90 ml/min per 1.73 m². In the HIV negative group, 27 participants had eGFR less than 90 and 29 had eGFR at least 90 ml/min per 1.73 m². In PLHIV, 62 participants had eGFR less than 90 ml/min per 1.73 m² and 71 had eGFR at least 90 ml/min per 1.73 m². Data reported as mean ± SEM. eGFR, estimated glomerular filtration rate.

HIV-negative controls, the difference in total severity of plaque score was less comparing participants with eGFR less than 90 ml/min per 1.73 m² and participants with eGFR greater or equal to 90 min per 1.73 m², and did not reach statistical significance (Fig. 1).

Multivariable regression modeling to evaluate the effect of estimated glomerular filtration rate on Agatston score and coronary plaque types

To evaluate whether the observed correlation between eGFR and coronary plaque types was independent of traditional CVD risk and HIV-specific risk factors, we performed multivariable regression analysis controlling for total Framingham point score, BMI, duration of HIV diagnosis, $CD4^+$ cell count, HIV viral load, protease inhibitors, TDF, abacavir, and efavirenz use (Table 4). After adjusting for the above potential covariates, eGFR remained significantly correlated with coronary segments with calcified plaques ($\beta = -0.009$, $P = 0.01$) and Agatston score ($\beta = -0.97$, $P = 0.02$). In the model, TDF tended to be associated with total coronary segments with plaque, coronary segments with calcified plaque, and Agatston score. HIV viral load was also

significantly and independently related to total coronary segments with plaque and Agatston score. The overall model was reasonably robust and highly significant, for example, explaining over 55% of the variability for Agatston score, a parameter often obtained clinically. We did not control for race or sex as that was included in the calculation of eGFR. Sensitivity analyses controlling for statin use showed similar results. Among HIV negative controls, eGFR tended to relate to coronary segments with calcified plaque, controlling for traditional CVD risk scores and BMI (Supplemental Table 2, http://links.lww.com/QAD/B376).

Discussion

Here for the first time, we show that mild subclinical renal impairment in PLHIV is independently correlated with coronary plaque assessed using CT angiography. Both creatinine and more strongly eGFR significantly correlated with critical indices of overall coronary plaque severity, including total severity of coronary plaque, total coronary segments with plaque, as well as calcium-specific indices including coronary segments with

Table 4. Correlation between estimated glomerular filtration rate and Agatston score and coronary plaque after adjusting for traditional and nontraditional cardiovascular risk factors in people living with HIV.

	Total severity of coronary plaque score ($R^2 = 0.22$, $P = 0.008$)		Total coronary segments with plaque ($R^2 = 0.23$, $P = 0.0002$)		Coronary segments with calcified plaque ($R^2 = 0.16$, $P = 0.012$)		Coronary segments with non-calcified plaque ($R^2 = 0.08$, $P = 0.34$)		Agatston score ($R^2 = 0.31$, $P < 0.0001$)	
	β	P	β	P	β	P	β	P	β	P
Total Framingham point score	0.17	0.02	0.12	0.007	0.04	0.01	0.03	0.30	4.30	0.02
eGFR (ml/min per 1.73 m^2)	−0.02	0.35	−0.01	0.20	−0.009	0.01	−0.0008	0.88	−0.97	0.02
BMI	−0.06	0.42	−0.04	0.40	0.01	0.53	0.007	0.77	−2.2	0.23
Duration of HIV	0.14	0.03	0.04	0.21	−0.02	0.11	0.03	0.13	0.56	0.69
CD4$^+$ count	−0.001	0.37	0.0006	0.40	0.0002	0.48	0.0003	0.50	0.03	0.32
HIV viral load	0.0001	0.70	0.0006	0.004	0.00009	0.26	−0.00007	0.60	0.05	<0.0001
Current PI use	−0.15	0.76	−0.04	0.90	0.12	0.24	−0.28	0.08	12.86	0.26
Current TDF use	0.68	0.10	0.45	0.06	0.16	0.07	0.17	0.23	19.26	0.06
Current Abacavir use	0.08	0.86	0.05	0.90	0.03	0.77	0.06	0.74	6.19	0.65
Current efavirenz use	−0.38	0.44	−0.18	0.52	0.06	0.57	−0.30	0.08	2.36	0.85

eGFR, estimated glomerular filtration rate; PI, protease inhibitors; TDF, tenofovir disoproxil.

calcified plaque and Agatston score, but not with measures of noncalcified plaque, in PLHIV. The correlation between eGFR and key indices of calcified plaque, including the Agatston score, remained significant after multivariable regression analysis adjusting for total Framingham point score, BMI, CD4$^+$ cell count, HIV viral load, duration of HIV diagnosis, and protease inhibitor, TDF, abacavir, and efavirenz use, suggesting a strong independent association, even among this group, chosen to exclude those with overt renal disease. These data provide further supporting evidence that mild subclinical renal disease, often common in HIV, may have important consequences for the development of coronary artery disease in this population.

In studies performed in the general population, CKD is associated with higher rates of CVD events [6,10,11]. Moreover, the most common cause of mortality and morbidity in individuals with CKD is CVD rather than progression to ESRD [5]. Traditional risk factors such as hypertension, diabetes, and obesity play an intricate role in both CVD and CKD. In CKD, nontraditional risk factors such as albuminuria, disorders of mineral metabolism, oxidative stress, and inflammation have been shown to be associated with increased risk of CVD events [4,12,13]. Furthermore, carotid artery studies in the general population have shown that individuals with CKD have significantly increased calcification and alteration in plaque composition and vulnerability for plaque rupture [14,15]. In one study, carotid intima−media thickness was inversely correlated with eGFR [15]. Bundy et al. [4] showed that lower eGFR was significantly associated with coronary artery calcification in non-HIV participants in the Chronic Renal Insufficiency Cohort (CRIC) study.

In contrast, there is sparse literature evaluating the relationship of CKD to CVD events and no data, to our knowledge, assessing the relationship of overt or subclinical CKD to coronary artery disease indices assessing detailed measures of plaque obtained using CT angiography in HIV. In the D:A:D study, PLHIV and increased predicted risk for CKD (eGFR < 60 ml/min per 1.73 m^2) were shown to have higher CVD event rates [16,17]. In contrast to clinical CKD, subclinical CKD is more common in HIV [18]. In this regard, Roy et al. [8] demonstrated a relationship of eGFR to CAC score, among those with minimal changes in eGFR in the MACS cohort, but did not assess detailed indices of plaque by CTA and was thus unable to differentiate relationships of eGFR to specific plaque characteristics and plaque parameters including noncalcified plaque. We now extend the prior findings of Roy et al., demonstrating significant differences in coronary plaque severity at a higher eGFR threshold of 90 ml/min per 1.73 m^2 and clear associations to detailed coronary plaque parameters across a range of eGFR consistent with subclinical disease. Assessing carotid intima−media thickness (cIMT), Serrano-Villar et al. [19] demonstrated an association between mild renal impairment defined as eGFR less than 90 ml/min and subclinical atherosclerosis in PLHIV but did not assess coronary plaque. Unlike these prior studies, we include women and show a more robust relationship between eGFR and plaque among HIV than non-HIV participants.

In the current study, we relate eGFR using the well accepted CKD-EPI formula, which accounts for race and sex, to measures of calcified and noncalcified coronary plaque in HIV-infected participants without a known history of CVD. Here, we demonstrate that mild renal impairment is significantly correlated with calcified plaque parameters, but not to noncalcified plaque parameters in PLHIV. This relationship to calcified but not to noncalcified plaque has not previously been compared in PLHIV. Calcified plaque is thought to relate

to traditional CVD risk factors, whereas noncalcified plaque to other factors including immune activation in HIV [9,20,21]. Calcified plaque, more representative of traditional risk factors, is an important predictor of CVD events among non-HIV participants [22,23]. Such data is not yet available in PLHIV, but the ongoing REPRIEVE study will assess differential relationships of calcified and noncalcified plaque as well as eGFR to CVD events in HIV (NCT#02344290). Our finding suggests that early onset of subtle renal impairment can contribute to the development of calcified plaque in PLHIV. Importantly, we control for total Framingham point score, a global index of traditional CVD risk, and demonstrate persistent, independent associations of eGFR to coronary plaque and overall plaque burden, highlighting the independent effects of eGFR apart from other risk factors. Potential mechanisms by which subclinical renal disease and atherosclerosis are associated are likely multifactorial. Traditional risk factors such as age, sex, race, diabetes, hypertension, tobacco use and increased chronic inflammation from HIV alone can contribute to CKD and atherosclerotic disease [7,20,24–26]. Furthermore, HIV-related complications such as lipodystrophy and metabolic syndrome are also known to contribute to CVD [27–29]. Importantly, there may be a heightened interaction between mild renal impairment, immune and inflammatory factors, which drive increased coronary plaque in HIV. Indeed, in the current study, we show that HIV viral load is highly related to calcified plaque parameters consistent with prior data [18], suggesting that both traditional risk factors, including eGFR and nontraditional immune factors contribute to calcified plaque in this population.

Prior studies also suggest an association of antiretroviral therapy to CVD in PLHIV [30]. Older protease inhibitor-containing ART have been associated with increased risk of CVD [31,32]. However, there remain conflicting reports of the association of older NRTIs including abacavir and CVD risk and event rates [30,33–35]. There was no difference in eGFR between abacavir and nonabacavir users. Certain protease inhibitors and TDF-containing ARTs are well known to cause renal impairment [36]. Specifically, TDF has been well established as a nephrotoxic drug [37]. In this study, we show differences in eGFR among participants using protease inhibitors, TDF, and efavirenz. Importantly, controlling for the use of protease inhibitors, TDF, abacavir, and efavirenz, confirms an independent association of subtle renal disease and calcified coronary plaque. Indeed, overall severity of plaque was much greater above and below the eGFR threshold of $90\,\mathrm{ml}/\mathrm{min}$ per $1.73\,\mathrm{m}^2$ in the HIV compared with the non-HIV group. These differences were not because of the fact of any differences in calcified plaque indices or eGFR between the groups. Further studies are needed to confirm this potentially important observation and assess the mechanisms of such an effect.

HIV negative controls were included in the current analysis, and demonstrate generally similar, but less robust associations between coronary plaque and eGFR. It is unknown why subtle renal impairment relates more strongly to plaque in HIV patients. HIV and non-HIV groups may differ in the biological mechanisms of plaque formation. Alterations in kidney function resulting from virological factors may contribute to immune activation and other mechanisms of advanced plaque formation [38,39]. Future research is needed to further elaborate on this issue.

This study has a number of strengths but also some important limitations. The data are cross-sectional and thus we cannot assess the relationship of subtle changes in eGFR and plaque over time or the threshold or development of significant plaque. Moreover, as the cohort excluded participants with overt renal disease, we did not assess potential mechanistic covariates, such as calcium, phosphate, albuminuria and FGF-23. Nonetheless, we do show a novel association of subtle renal impairment with coronary plaque, assessed using the CTA technique. Moreover, our study points out potential differences with simultaneously assessed non-HIV participants of similar race, ethnicity, sex, and with overall similar CVD risk and renal function. Our finding demonstrates the clinical significance of early assessment of renal function in PLHIV, which may presage development of advanced coronary atherosclerosis. Future studies are needed to assess whether such mild impairment in renal function is associated with CVD events in PLHIV and importantly, whether early treatment of mild renal impairment with ACEI or ARB will prevent events or improve coronary plaque indices. Additionally, aggressive management of diabetes, hypertension, hyperlipidemia including life style changes may be particularly warranted in such patients.

Our data highlight a robust relationship between subclinical renal impairment and overall coronary artery disease burden among PLHIV. This finding emphasizes the importance of identifying renal disease in the early stages and that potential intervention with medical therapy and referral to nephrologist may be needed in such patients. Further research is needed to understand the interplay between renal impairment and cardiovascular disease in HIV and clinical impact of this relationship in HIV.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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