Association between mild chronic kidney disease and coronary artery disease in persons living with and without HIV in Uganda.

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Abstract

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Background

Severe chronic kidney disease (CKD), associated with HIV, is a risk factor for coronary artery disease (CAD). However, the impact of the more common, subclinical form of kidney disease in people living with HIV (PLWH) on CAD risk is less understood. Using non-invasive computed tomography angiography (CTA), we aim to determine if an association exists between mild CKD and plaque parameters indicative of CAD in persons living with and without HIV, in a sub-Saharan African population.

Methods

This cross-sectional analysis stems from the Ugandan sTudy of HIV effects on the Myocardium and Atherosclerosis (mUTIMA) study. mUTIMA compared 100 PLWH on stable antiretroviral therapy (ART) and 100 matched non-HIV participants, all aged over 45 with ≥1 cardiovascular disease risk factor. For 165 of these participants with available CTA data, we performed multivariable Tobit regression to examine the association between the mild CKD parameters, estimated glomerular filtration rate (eGFR) (≥60-<90mL/min/1.73 m^2), and albumin creatinine

ratio (ACR) (>30mg/g), with detectable CAD. CAD was assessed using segment involvement score (SIS) (>0), segment stenosis score (SSS) (≥3), or coronary artery calcium (CAC) (>0).

Results

Our findings indicate that in PLWH, lower eGFR values are associated with increased SIS (coefficient: 3.31, 95% CI: 0.41 to 6.21, p = 0.03), and increased SSS (coefficient: 5.95, 95% CI: 0.54 to 11.36, p = 0.03). The association with SIS, but not SSS, remained significant after adjusting for age, gender, and 10-year ASCVD score (coefficient: 2.58, 95% CI: 0.10 to 5.06, p = 0.04). There was no association among people not living with HIV.

Conclusion

Mild to moderately low eGFR is associated with increased CAD plaque parameters. Estimation of renal function by relatively simple methods like eGFR monitoring therefore may be a valuable tool for cardiovascular risk assessment among PLWH in addition to that provided by traditional risk factors. The observed association also highlights the need for early integrated cardiovascular and renal care in this population.

Keywords: Mild chronic kidney disease, Coronary artery disease, Coronary CT angiography.

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Introduction.

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality worldwide, affecting both the general population and specific vulnerable groups, such as people living with HIV (PLWH). PLWH have heightened cardiovascular risk, attributable to both traditional risk factors and HIV-specific factors, such as chronic inflammation and immune activation (1,2). Additionally, chronic kidney disease (CKD), which can be assessed by estimated glomerular filtration rate (eGFR) and albumin creatinine ratio (ACR), plays a pivotal role in the pathogenesis of coronary artery disease (CAD) (3–5). Evidence suggests that HIV-related nephropathy and traditional renal risk factors collectively contribute to the development of coronary artery disease in this population (6). However, the association between early mild CKD and subclinical CAD remains less investigated.

The use of non-invasive computed tomography angiography (CTA) imaging allows for robust and accurate assessment of CAD including qualitative, semi-quantitative, or quantitative plaque parameters and has emerged as an excellent gatekeeper for invasive angiography (7–9). Coronary artery calcium scores (CAC) via the Agatston method serve as markers of calcific plaque burden and cardiovascular risk. The segment involvement score (SIS) on CTA tallies segments with any obstructive or non-obstructive plaque and has been shown to be a strong, independent predictor of cardiovascular events (10). The segment stenosis score (SSS) provides a good estimate of plaque burden by incorporating weighting factors for stenosis severity.

While a few studies have investigated the link between mild CKD and CAD using only the Agatston score (4,11), the full extent of the relationship between mild reduction in estimated glomerular filtration rate (eGFR) and various plaque parameters in PLWH and HIV-negative participants have not been thoroughly explored. In our study, we aim to fill this knowledge gap by utilizing CTA to assess not only the CAC but also the SIS and SSS in both PLWH and HIV-negative individuals. This comprehensive approach will allow for a more complete understanding of the association between renal function and subclinical coronary artery disease, providing crucial insights for a sub-Saharan African population.

Methods

Study design and population.

This is a cross-sectional secondary analysis of an observational cohort study. The **U**gandan s**T**udy of H**I**V effects on the **M**yocardium and **A**therosclerosis (mUTIMA) study is an observational study of men and women living with HIV and matched non-HIV participants. A total of 100 PLWH were recruited from the Joint Clinical Research Centre (JCRC) in Kampala; they were age- (+/-3 years) and sex-matched 1:1 with 100 participants who were HIV-uninfected and recruited from internal medicine clinics in Kampala. Participants had to be over 45 years of age, have CTA data available, and have at least one of these CVD risk factors: hypertension, low high-density lipoprotein cholesterol (HDL), high low-density lipoprotein cholesterol (LDL), diabetes mellitus, smoking, or a family history of early CAD. PLWH had to have been on a stable antiretroviral therapy (ART) regimen for over 6 months, with no changes in their regimen within 12 weeks of enrolment. Participants with a history of known CAD, peripheral artery disease, ischemic stroke, uncontrolled chronic inflammatory conditions, pregnancy, use of chemotherapy or immunomodulating agents (except low-dose aspirin), or an eGFR less than 60 mL/min/1.73 m^2,

were excluded to avoid the potential risk of contrast nephropathy. Findings and methods from the baseline examination of the cohort have been previously published (12–14). For this analysis, we selected 165 participants with available CTA data. The reasons for missing angiography (total N=35) were: eGFR<60 (N=9); other technical reason (e.g. tachycardia; N=13); images not available for research read (N=5); poor quality (N=6); and cardiac CT not performed (N=2) (15).

Clinical procedures

Enrollment

Baseline data were collected via a standardized questionnaire asking about socio-demographic characteristics, smoking status, and clinical parameters by medical history and blood and urine specimen were obtained at enrollment. A history of diabetes and hypertension was self-reported or inferred if the patient was on medication for the condition. For PLWH data regarding time since diagnosis, current and nadir $CD4^+$ counts, ART regimen and duration of ART was obtained from their medical charts. HIV RNA was not routinely measured in clinical practice at the time of the study. HIV-uninfected controls were confirmed negative by a rapid HIV test (Determine HIV-1/2: Abbot/Alere, Chicago IL).

Laboratory procedures

Total cholesterol, HDL, LDL, triglycerides, and creatinine were measured at the JCRC clinical laboratory after a 12-hour fast (COBAS Integra: Roche Diagnostics), Basel, Switzerland. The JCRC is a national reference laboratory in Uganda and maintains the College of American Pathologists (CAP) accreditation.

Albumin and creatinine concentrations were measured from spot urine specimens. Urine albumin excretion was estimated using the ACR and calculated by dividing the spot urine albumin

concentration by the spot urine creatinine concentration (16–18). The eGFR (CKD-EPI) provides the most accurate estimates of glomerular filtration rate when compared with gold-standard clearance measurements (19–21) and appears most predictive of clinical out-comes (22–24). The eGFR was determined using the CKD-EPI 2021 formula, which has been recently redesigned to eliminate the inclusion of the race coefficient (25). For our study, 5 participants with eGFR <60 mL/min/1.73m^2 were reclassified as cases as the CKD-EPI 2021 formula gives a lower calculated value compared to the previously accredited CKD-EPI 2009 formula which was utilized at recruitment of study participants. Ten-year risk of atherosclerotic cardiovascular disease (ASCVD score) was calculated using the pulled-cohort equation for "Other" race (26).

CT Scanning and Analysis Procedures

Details of the CT scanning procedures have been described previously (15). Briefly, in preparation for cardiovascular imaging, participants received 100mg of oral metoprolol 2 hours prior with another 50mg dose 30mins prior if the heart rate remained >60 beats per minute and then IV contrast injection unless contraindicated. CT scanning equipment included 128-slice Siemens Somatom multi-detector CT at Nsambya St. Francis Hospital in Kampala. A single expert reader who was unaware of participant characteristics and HIV serostatus analyzed the images in batch offline. The acquisition and analysis protocols of the images were designed following the guidelines of the Society of Cardiovascular Computed Tomography (27). The reader utilized axial images, multi-planar reconstructions, and maximum intensity projections to evaluate the size, composition, and presence of coronary plaque, as well as the degree of luminal narrowing stenosis in all assessable coronary segments. SIS was defined as the total number of diseased segments. SSS was calculated using a luminal obstruction weight for that segment (x1 if <25% obstruction, x2 if 25–50%, x3 if 50–70%, x4 if 70–99% and x5 if totally occluded), giving a maximum possible

SSS of 90 for an 18-segment model. A few segments were either absent or not able to be evaluated due to artefacts. Given the low disease prevalence and the limited non-evaluable segments per participant, these segments were assumed to be normal for the analysis. Calcified lesions were defined as having ≥6 pixels with density >130 Hounsfield units and total CAC score was calculated using the Agatston method(28). Presence of CAD was defined as SIS >0, SSS ≥3 or CAC >0.

Statistical Analysis

The study population was characterized in terms of demographic characteristics, HIV characteristics and cardiovascular risk factors by eGFR and ACR. Descriptive statistics were presented as counts and proportions for categorical variables, and median and interquartile range for continuous variables. The Wilcoxon rank-sum test was employed to assess the association between eGFR and ACR stratified by HIV status. Tobit regression analysis was used to investigate the associations between outcomes SIS, SSS and CAC with renal function, as measured by eGFR and ACR, stratified by HIV status while censoring data at the lower limit. The category eGFR ≥90 mL/min/1.73m^2 and ACR < 30mg/g were used as reference groups in their respective models. The cut-offs were selected due to their clinical significance, with eGFR ≥90 mL/min/1.73m2 representing normal renal function and ACR < 30mg/g denoting normal ACR levels. Coefficients with 95% confidence intervals (CI) and p-values were calculated for each variable. Adjusted models controlled for age, gender, and 10-year atherosclerotic cardiovascular disease (ASCVD) score. We chose Tobit regression analysis as it is provides a suitable approach for analyzing the relationships between predictors and censored outcomes. We chose Tobit regression analysis over standard regression methods due to its capacity to handle censored data, and its suitability for investigating associations even when outcomes, exhibit an excess of zeros, which is particularly relevant given the low prevalence of CAD in our study population.

As a secondary analysis, we performed multivariable modified Poisson regression analysis. The association between renal function and dichotomized coronary plaque parameters was presented as prevalence ratios (PR) with 95% CI. Prevalence ratios are more straight-forward to interpret and allows our results to be compared to similar prior analyses. Age, sex and ASCVD score were similarly included for adjustment in multivariable models. The analysis was stratified by HIV status. Statistical significance was defined as P value <0.05. Missingness for most variables was low at <3% and treated as random. Participants with missing data were excluded from all models. Statistical analyses were performed using R statistical software (R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Human subjects' approval

The individuals who agreed to participate in the parent study were asked to sign a written consent form and were subsequently enrolled in the study. The parent study was approved by the Institutional Review Boards (IRB) at University Hospitals of Cleveland (Cleveland, Ohio, USA) and the JCRC (Kampala, Uganda). Further regulatory approval was obtained from the Uganda National Council for Science and Technology. The University of Washington IRB made a determination of exemption for this secondary analysis of a deidentified dataset.

Results

Baseline Characteristics and Clinical Parameters:

Baseline characteristics and clinical parameters of the participants with reduced eGFR (<90 mL/min/1.73 m^2, n = 65) and those with normal eGFR (≥ 90 mL/min/1.73 m^2, n = 100) are summarized in Table 1. The eGFR <90 mL/min/1.73 m^2 group had a median age of 59 (IQR:

54.0 to 63.0) years, while the control group had a median age of 56 (IQR: 52.6 to 60.3) years. Gender distribution differed, with 30.8% males in the reduced eGFR group and 42% males in the control group. Patient groups were largely similar in terms of prevalence and duration of diabetes and hypertension, smoking tobacco use, statin use, hypertension medication use, cardiovascular risk factors such as LDL, HDL and Waist: Hip ratio, years living with HIV, current Tenofovir difumarate (TDF) usage, duration of ART usage and HIV viral load suppression. The median duration of HIV infection and antiretroviral therapy (ART) was similar between the reduced eGFR group (14.0 &12.8, respectively) and the control group (13.9 & 12.6, respectively). The majority of participants in both groups had HIV viral load suppression, indicating effective management of HIV infection. The baseline characteristics of participants with ACR ≥30 mg/gm (albuminuria) versus those with ACR 30 mg/gm (normal albumin excretion) are presented in Supplementary Table 1.

Comparison of albumin creatinine ratio (ACR) and eGFR Levels by HIV status

Figure 1a and 1b illustrate distribution of ACR and eGFR stratifies by HIV status. There were no significant differences in ACR and eGFR levels between the PLWH and HIV-negative participants in this study (p-value=0.12).

Univariable and Multivariable Regression Modeling to Evaluate the Effect of eGFR and ACR on SIS, SSS and CAC.

Among PLWH, a significant association was observed between eGFR and some coronary plaque parameters. Low eGFR values were associated with increased SIS scores in people living with HIV (Table 2a) (coef: 3.31; 95% CI: 0.41 to 6.21, p = 0.03), and this association remained significant after adjusting for age, gender, and 10-year ASCVD score (coef: 2.58; 95% CI: 0.10

to 5.06, p = 0.04). Low eGFR was associated with SSS in the adjusted (Table 2b) (Coef: 5.95, 95% CI: 0.54 to 11.36, p = 0.03) analysis, although this result was slightly attenuated and no longer significant after adjustment (Coef: 4.60, 95% CI: -0.05 to 9.25, p = 0.05). Among PLWH, eGFR demonstrates a non-significant positive association with CAC in adjusted models (Coef: 85.36; 95% CI: -174.80 to 345.52) as presented on Table 2c.

Among HIV-negative individuals, both unadjusted and adjusted analyses did not reveal statistically significant associations between eGFR and SSS, SIS and CAC scores (Tables 2a-c). No significant associations were found between ACR and coronary plaque parameters among either PLWH or controls.

Discussion

This study demonstrated that among PLWH, lower eGFR values were associated with increased coronary plaque parameters SIS and SSS. Secondly, SIS remained significant after multivariable regression analysis adjusting for age, sex and 10- year ASCVD score. These findings suggest that low eGFR may be a strong indicator of early CAD even among those without overt renal disease. These findings have clinical implications, as plaque development and progression are key factors in the pathogenesis of cardiovascular disease, which is a significant concern in the management of PLWH.

It is increasingly apparent that individuals with CKD are more likely to die of cardiovascular disease than to progress to end stage renal disease (28,29). CKD contributes to accelerated atherosclerosis through various mechanisms, such as endothelial dysfunction, inflammation, oxidative stress, and dyslipidemia, all of which increase the risk of CVD events. In the context of HIV infection, these factors are further exacerbated due to chronic inflammation, immune

dysregulations and monocyte activation, contributing to endothelial dysfunction and a pro-atherogenic state(31). Notably, this association is seen in a substantial number of studies which have focused on participants with moderate to severely impaired renal function. Rostand et al. reported that 73% of hemodialysis patients had significant coronary stenosis of more than 50% (32). Additionally among individuals with end-stage renal disease, CAC is highly prevalent, progresses rapidly, and is associated with an increased risk of death(33,34). In a community-based study of people without clinical cardiovascular disease, the Multi-Ethnic Study of Atherosclerosis recruiting participants with an eGFR of <60 ml/min/1.73 m^2, participants with prevalent CAD had lower estimated GFR, and a modestly greater ACR (35). Our study advances this understanding by addressing a critical gap—evaluating mild CKD and subclinical CAD among PLWH and HIV-negative individuals. Most of the studies looking at mild CKD have been done in western countries (36,37). To our knowledge, this is the first study assessing mild CKD and subclinical CAD in PLWH and HIV-negative persons in sub-Saharan Africa.

Recent evidence indicates that evaluating the degree of stenosis and extent of atherosclerosis, regardless of calcified plaque, offers better predictive capabilities for cardiac events compared to calcium scoring and traditional risk scores (38). Metkus et al (39) as part of the MACS study cohort showed that among men with CAC scores of zero, HIV infection was associated with an increased prevalence of noncalcified coronary plaque independent of traditional cardiovascular risk factors. These finding suggests that independent CAC scanning may underestimate plaque burden. Our study demonstrated a significant association between eGFR for two important non-calcified plaque scores, SSS and more strongly the SIS. Consistently with the findings of our study, a study among PLWH in Boston reported that mild to moderate eGFR was inversely

related to total severity of coronary plaque score (β=-0.27, P=0.002), total coronary segments with plaque (β=−.21, P=0.005) (36).

While the correlation of prevalence of calcified plaque with mild CKD lacked statistically significance, the CAC score demonstrated a positive association with eGFR. A relatively large study, Multicenter AIDS Cohort Study (MACS) found this association significant (11). Quantification of coronary arterial calcification (CAC) provides prognostic information beyond identification of traditional CV risk factors (40,41). Higher coronary calcium scores are associated with higher prevalence, more diffuse and greater extent of CAD in patients with CKD. Calcified plaque is believed to be associated with traditional cardiovascular disease (CVD) risk factors, while noncalcified plaque is linked to other factors, including immune activation in individuals with HIV. In our study we also found significant associations between markers of CKD and CAD only in PLWH. This could be because HIV infection is associated with chronic inflammation and immune activation, even when the virus is well-controlled with ART (42). This could potentially amplify the development and progression of CKD and coronary plaque making the influence of CKD on CAD more pronounced in our analysis. In a relatively large Dutch study by Joosen et al (43) in non-HIV participants, coronary plaque prevalence was higher in patients with mild CKD (OR 1.83, 95%CI 1.52–2.21) compared to patients with normal renal function (P<0.001) and plaques with >70% luminal stenosis was found significantly more often in patients with mild CKD compared with normal renal function (P<0.01). We were possibly not powered to achieve this association for both groups.

The absence of significant differences in ACR and plaques parameters between PLWH and HIV-negative individuals is intriguing and warrants further exploration. While ACR is a valuable marker of kidney damage, its association with CAD may be limited. In contrast, previously

reported findings from a much larger HIV positive patient population (Defilippis et al., 6814 patients (37) showed significant independent association between high ACR levels and increased prevalence and calcification of coronary artery plaque. However, a smaller study by Jassal et al (44) in a community based cohort did not demonstrate an association between albuminuria and CAC. Our current findings suggest that, at least in this study population, ACR may not be associated with CAD, regardless of HIV status. It is also important to note that the size of our study population may have limited our ability to detect this correlation effectively.

The strengths of our study are the robust design that includes a participant cohort, encompassing both PLWH and non-HIV participants with matched characteristics. Additionally, we used advanced imaging techniques to assess coronary plaque parameters which is less researched, especially in the African population. We used a newer and more precise CKD-EPI 2021 formula to calculate eGFR which removes the ethnic coefficient thereby addressing potential biases related to race.

Limitations of our study are the small sample size and low prevalence of CAD in this population, which may limit the power to detect significant associations. Another limitation is our study design which excluded participants with an eGFR of <60mL/min/1.73m^2 which could introduce bias by disproportionately excluding sicker HIV-positive individuals, potentially masking significant associations and distort health comparisons between the groups. Additionally, a degree of variability is inherent in visual estimation qualitative techniques used to categorize SSS and SIS, although this method of interpretation is also used in clinical practice and has been used in all prior coronary CTA prognosis articles published to date. The study is cross-sectional in nature and identified associations cannot be used to assign causality and as with all observational studies, we cannot rule out the possibility of residual confounding.

Despite these limitations, this pilot study is a valuable step forward. Future prospective and interventional studies to understand the differential impact of eGFR and ACR on various plaque parameters may be pivotal in shaping evidence-based approaches that target the specific cardiovascular risks and management strategies.

Conclusion

In conclusion, even mild chronic kidney disease is associated with coronary artery disease in PLWH, which underscores the importance of comprehensive healthcare strategies tailored to address the intricacies of this unique population. Our study adds to the growing list evidence that a holistic approach to HIV management encompassing not just traditional risk factors but also assessment and monitoring of early renal health.

Tables & Figures.

Table 1: Baseline characteristics and clinical parameters stratified by estimated glomerular filtration rate (eGFR)

	eGFR < 90 (n=65) **n (%) or median (IQR)**	**eGFR ≥ 90 (n=100)** **n (%) or median (IQR)**
Demographics		
Age, years	59.0 (54.0 to 63.0)	56.0 (52.6 to 60.3)
Gender, male,	20 (30.8)	42 (42)
Medical history		
History of hypertension,	58 (89.2)	86 (86.0)
History of DM,	20 (30.8)	32 (32.0)
History of MI	0 (0)	0(0)
History of Stroke	3 (4.6)	0 (0.0)
Duration of diabetes in years	6.5 (3.1 to 9.5)	7.7 (5.5 to 13.9)

Duration of HTN in years	5.5 (4.3 to 9.0)	6.3 (3.6 to 13.4)
Cardiovascular Risk Factors		
Systolic BP, mmHg	151.0 (135.0 to 174.0)	146.5 (129.8 to 168.2)
Diastolic BP. mmHg	89.0 (82.0 to 100.0)	89.0 (80.0 to 99.0)
BMI, kg/m2	30.1 (25.3 to 33.9)	28.4 (25.1 to 32.8)
Waist: hip ratio	0.89 (0.85 to 0.94)	0.91 (0.86 to 0.95)
10-year ASCVD score	8.6 (5.1 to 13.3)	6.7 (3.4 to 12.3)
Total cholesterol, mg/dL	209.2 (180.2 to 234.6)	192.4 (168.7 to 231.2)
LDL, mg/dL	134.0 (108.4 to 163.1)	127.4 (107.9 to 151.7)
HDL, mg/dL	54.3 (43.8 to 67.9)	53.9 (43.4 to 65.2)
Any BP medication	48 (73.8)	70 (70.0)
CCB	38 (58.5)	61 (61.0)
ACEi/ARB	30 (46.2)	34 (34.0)
β Blocker	12 (18.5)	17 (17.0)
Statin	5 (7.7)	7 (7.0)
Current smoker	3 (4.6)	5 (5.0)
Aspirin	13 (20.0)	13 (13.0)
HIV Characteristics		
Living with HIV	29 (44.6)	49 (49.0)
Nadir CD4+ count (cells/mm^3)	142.5 (66.2 to 232.5)	169.5 (67.2 to 284.8)
Current CD4+ count (cells/mm^3)	581.0(430.2 to 745.5)	537.0 (409.0 to 654.5)
HIV duration, years	14.0 (12.0 to 16.5)	13.9 (11.5 to 15.4)
ART duration, years	12.8 (8.6 to 13.9)	12.6 (8.6 to 14.0)

HIV viral load suppressed	27(93.1)	48(98.0)
VL not suppressed	2 (6.9)	1(2.0)
Current Protease inhibitor	23 (79.3)	41(83.7)
Current Tenofovir	15(51.7)	22(44.9)

Tobit regression models- Relationship between eGFR, ACR, and coronary plaque parameters in PLHIV and HIV negative controls.

Table 2

a) Tobit regression model for segment involvement score (SIS)

Variable	**HIV negative (n=87)**			**HIV positive (n=78)**		
	Coefficient	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**
eGFR <90 (unadj)	-0.07	-2.39; 2.25	0.9535	3.31	0.41; 6.21	**0.0252**
eGFR <90 (adj)	-0.22	-2.27; 1.83	0.8327	2.58	0.10; 5.06	**0.0411**
ACR≥30 (unadj)	0.54	-1.70;2.78	0.6356	-1.27	-4.44; 1.90	0.4323
ACR≥30 (Adj)	0.40	-1.63;2.44	0.6975	-0.74	-3.55; 2.08	0.6074

unadj – Unadjusted
adj –Adjusted for age, gender and 10-year ASCVD score.
The category with eGFR ≥ 90 was used as the reference group.
The category with ACR <30 was used as the reference group.

b) Tobit regression model for segment stenosis score (SSS).

Variable	HIV negative (n=87)			HIV positive (n=78)		
	Coefficient	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**
eGFR<90 (unadj)	0.36	-3.96; 4.68	0.8701	5.95	0.54; 11.36	**0.0310**
eGFR<90 (adj)	0.11	-3.73; 3.95	0.9545	4.60	-0.05; 9.25	0.0527
ACR≥30(unadj)	0.74	-3.56;5.04	0.7356	-2.25	-8.31; 3.81	0.4674
ACR≥30 (Adj)	0.41	-3.48; 4.30	0.8369	-1.28	-6.62; 4.05	0.6373

unadj – Unadjusted
adj – Adjusted for age, gender and 10-year ASCVD score.
The category with eGFR ≥ 90 was used as the reference group.
The category with ACR <30 was used as the reference group.

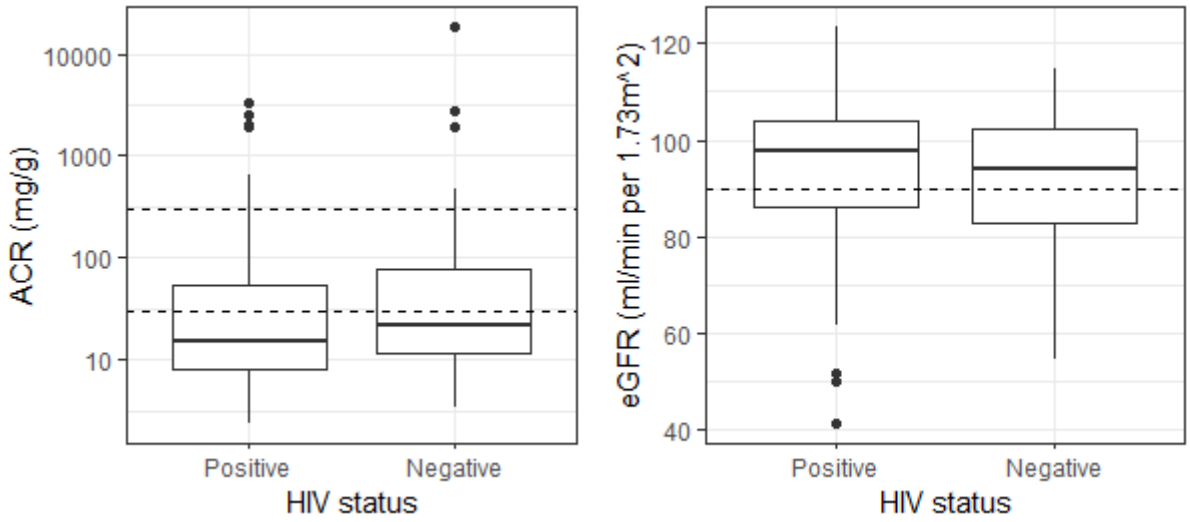
c) Tobit regression model for coronary artery calcium (CAC) score.

Variable	HIV negative (n=87)			HIV positive (n=78)		
	Coefficient	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**
eGFR<90(unadj)	75.61	-155.76; 306.97	0.5219	144.36	-129.24; 417.96	0.3011
eGFR<90 (adj)	58.92	-165.63; 283.48	0.6070	85.36	-174.80; 345.52	0.5202
ACR≥30 (unadj)	45.75	-188.99; 280.50	0.7025	1.01	-0.08; 2.11	0.0696
ACR≥30 (Adj)	39.83	-188.01; 267.68	0.7319	-86.15	-391.18; 218.87	0.5799

unadj – Unadjusted
adj –Adjusted for age, gender and 10-year ASCVD score.
The category with eGFR ≥ 90 was used as the reference group.
The category with ACR <30 was used as the reference group.

Figure 1: Comparison of [A] albumin to creatinine ratio (ACR) and [B] estimated glomerular filtration rate (eGFR) by HIV status

[A] **[B]**



	HIV+ (n=78)	**HIV- (n=87)**	**P- value***
ACR, Median (IQR)	15.1 (8.2 to 55.2)	21.7 (11.4 to 78.6)	0.1206

	HIV+ (n=78)	**HIV- (n=87)**	**P- value***
eGFR, Median (IQR)	97.6 (86.2 to 104.0)	94.0 (82.7 to 102.1)	0.2433

***Wilcoxon rank sum**

Supplementary tables

Table S1- Baseline characteristics and clinical parameters stratified by albumin creatinine ratio (ACR).

	ACR ≥ 30 (n=64)	**ACR < 30 (n= 93)**
Demographics		
Age, years	55.5 (53.8 to 60.3)	57.0 (52.0 to 63.0)
Gender, male,	21 (32.8)	36 (38.7)
Medical history		

History of hypertension,	57 (89.1)	81 (87.1)
History of DM,	23 (35.9)	27 (29.0)
History of MI	0 (0)	0 (0)
History of Stroke	2(3.1)	1 (1.1)
Duration of diabetes	7.2 (3.3 to 12.0)	7.0 (5.5 to 14.0)
Duration of HTN	5.9 (3.7 to 13.3)	6.3 (4.4 to 10.7)
Cardiovascular Risk Factors		
Systolic BP, mmHg	151.5 (134.5 to 173.2)	146.0 (130.0 to 162.0)
Diastolic BP. mmHg	91.0 (82.8 to 101.2)	88.0 (78.0 to 98.0)
BMI, kg/m2	29.4 (25.4 to 32.9)	28.8 (25.4 to 33.9)
Waist: hip ratio	0.89 (0.84 to 0.94)	0.90 (0.86 to 0.95)
10-year ASCVD score	8.0 (4.9 to 13.1)	7.2 (3.4 to 12.5)
Total cholesterol, mg/dL	202.9 (176.9 to 227.9)	196.9 (172.3 to 234.6)
LDL, mg/dL	126.0 (107.5 to 153.0)	132.6 (107.8 to 166.8)
HDL, mg/dL	51.4 (42.7 to 61.1)	54.4 (44.8 to 67.2)
Any BP medication	46 (71.9)	65 (69.9)
CCB	39 (60.9)	54 (58.1)
ACEi/ARB	27 (42.2)	34 (36.6)
β Blocker	11 (17.4)	18 (19.4)
Statin	1 (1.6)	10 (10.8)
Current smoker	4 (6.3)	4 (4.3)

Aspirin	9 (14.1)	15(16.1)
HIV Characteristics		
Living with HIV	23 (35.9)	47 (50.5)
Nadir CD4+ count (cells/mm^3)	135.0 (37.8 to 251.8)	180.0 (96.0 to 264.0)
Current CD4+ count (cells/mm^3)	547.0 (465.5 to 775.2)	542.0 (403.5 to 656.2)
HIV duration, years	13.9 (11.7 to 14.5)	14.0 (11.5 to 15.9)
ART duration, years	13.4 (11.4 to 14.1)	11.4 (8,2 to 14.0)
HIV viral load suppressed	21(91.3)	46(97.9)
VL not suppressed	2(8.7)	1(2.1)
Current Protease inhibitor	18(78.3)	38(80.9)
Current Tenofovir	41(56.5)	23(44.7)

Table S2: Relationship between eGFR, ACR and coronary plaque parameters in PLHIV and HIV-negative controls.

a) Modified multivariable Poisson regression model for SIS.

Variable	**HIV negative (n=87)**			**HIV positive (n=78)**		
	PR	**95% CI**	**p-value**	**PR**	**95% CI**	**p-value**
eGFR<90 (unadj)	0.76	0.36; 1.59	0.4606	2.96	0.95; 9.24	0.0622
eGFR<90	0.74	0.39; 1.42	0.3687	2.44	0.77; 7.74	0.1299

(adj)						
ACR≥30 (unadj)	1.46	0.72; 2.96	0.2967	0.88	0.25; 3.08	0.8362
ACR≥30 (Adj)	1.43	0.77; 2.67	0.2611	1.12	0.31; 4.01	0.8582

unadj – Unadjusted
adj – Adjusted for 10- year ASCVD, age, sex.
The category with eGFR ≥ 90 was used as the reference group.
The category with ACR <30 was used as the reference group.

Overall- For SIS

Variable	**Overall**			
	N	**PR**	**95% CI**	**p-value**
eGFR<90 (unadj)	165	1.21	0.67; 2.21	0.5259
eGFR<90 (adj)	165	1.08	0.63; 1.87	0.7713
ACR≥30 (unadj)	157	1.37	0.75; 2.50	0.3096
ACR≥30 (Adj)	157	1.42	0.82; 2.45	0.2141

unadj – Unadjusted
adj –Adjusted for age, gender and 10-year ASCVD score.
The category with eGFR ≥ 90 was used as the reference group.
The category with eGFR ≥ 90 was used as the reference group.
The category with ACR <30 was used as the reference group.

b) Multivariable modified Poisson regression for SSS (dichotomized as less than 3 or greater than or equals to 3)

Variable	HIV negative (n=87)			HIV positive (n=78)		
	PR	95% CI	p-value	PR	95% CI	p-value
eGFR<90 (unadj)	1.42	0.44;4.52	0.5575	2.82	0.73;10.92	0.1344
eGFR<90 (adj)	1.55	0.56;4.29	0.3983	1.94	0.48;7.83	0.3515
ACR≥30 (unadj)	1.12	0.35;3.60	0.8466	-	-	-
ACR≥30 (Adj)	1.11	0.37;3.33	0.8546	-	-	-

unadj – Unadjusted
adj –Adjusted for age, gender and 10-year ASCVD score.
The category with eGFR ≥ 90 was used as the reference group.
The category with ACR <30 was used as the reference group.

Overall- SSS

Variable	Overall			
	N	PR	95% CI	p-value
eGFR<90 (unadj)	165	1.92	0.80;4.62	0.1433
eGFR<90 (adj)	165	1.73	0.79;3.81	0.1709
ACR≥30 (unadj)	157	0.57	0.19;1.71	0.3178
ACR≥30 (Adj)	157	0.62	0.26;1.47	0.2762

unadj – Unadjusted
adj –Adjusted for age, gender and 10-year ASCVD score.
The category with eGFR ≥ 90 was used as the reference group.
The category with ACR <30 was used as the reference group.

c) Multivariable modified Poisson regression for CAC.

Variable	HIV negative (n=87)			HIV positive (n=78)		
	PR	**95% CI**	**p-value**	**PR**	**95% CI**	**p-value**
eGFR<90 (unadj)	0.94	0.43;2.07	0.8867	2.32	0.81;6.63	0.1171
eGFR<90 (adj)	0.91	0.45; 1.85	0.7992	1.90	0.66;5.46	0.2344
ACR≥30 (unadj)	1.68	0.76;3.71	0.1962	0.75	0.22;2.56	0.6464
ACR≥30 (Adj)	1.68	0.83;3.42	0.1488	0.89	0.26; 3.12	0.8617

unadj – Unadjusted
adj –Adjusted for age, gender and 10-year ASCVD score.
The category with eGFR ≥ 90 was used as the reference group.
The category with ACR <30 was used as the reference group.

Overall- For CAC

Variable	Overall			
	N	**PR**	**95% CI**	**p-value**
eGFR<90 (unadj)	164	1.34	0.72;2.50	0.3500
eGFR<90 (adj)	164	1.19	0.67;2.13	0.5509

ACR≥30 (unadj)	156	1.45	0.66; 3.21	0.3534
ACR>≥ (Adj)	156	1.39	0.77;2.51	0.2714

unadj – Unadjusted
adj –Adjusted for age, gender and 10-year ASCVD score.
The category with eGFR ≥ 90 was used as the reference group.
The category with ACR <30 was used as the reference group.

Table S3- Tobit regression model- Overall

a) Tobit regression- Overall (SIS)

Variable	**Overall**			
	N	**MD**	**95% CI**	**p-value**
eGFR<90 (unadj)	165	1.26	-0.53; 3.05	0.1670
eGFR<90 (adj)	165	0.93	-0.64; 2.50	0.2465
ACR≥30 (unadj)	157	0.15	-1.63; 1.93	0.8685
ACR≥30 (Adj)	157	0.05	-1.56; 1.66	0.9484

MD = mean difference
unadj – Unadjusted
adj –Adjusted for age, gender and 10-year ASCVD score.
The category with eGFR ≥ 90 was used as the reference group.
The category with ACR <30 was used as the reference group.

b) Tobit regression- overall (SSS)

Variable	Overall			
	N	**MD**	**95% CI**	**p-value**
eGFR<90 (unadj)	165	2.53	-0.79; 5.85	0.1350
eGFR<90 (adj)	165	1.94	-1.00; 4.87	0.1955
ACR≥30 (unadj)	157	0.15	-3.26;3.56	0.9332
ACR≥30 (Adj)	157	`-0.12	-3.19; 2.95	0.9383

MD- mean difference
unadj – Unadjusted
adj –Adjusted for age, gender and 10-year ASCVD score.
The category with eGFR ≥ 90 was used as the reference group.
The category with ACR <30 was used as the reference group.

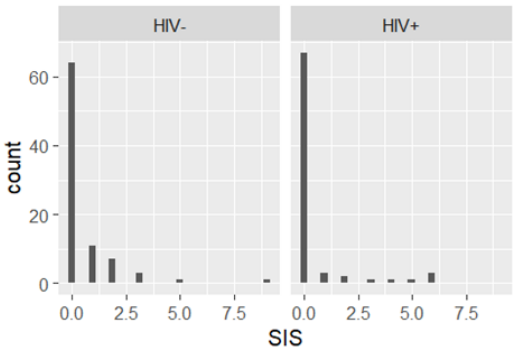
c) Tobit regression- Overall (CAC)

Variable	Overall			
	N	**MD**	**95% CI**	**p-value**
eGFR<90 (unadj)	164	102.94	-73.34; 279.21	0.2524
eGFR<90 (adj)	164	69.72	-100.82; 240.25	0.4230
ACR ≥30 (unadj)	156	-1.4	-185.50; 182.62	0.9878
ACR≥30 (Adj)	156	-9.38	-186.43; 167.68	0.9173

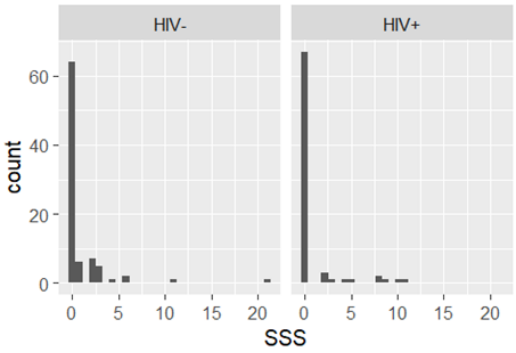
MD- mean difference
unadj – Unadjusted
adj –Adjusted for age, gender and 10-year ASCVD score.
The category with eGFR ≥ 90 was used as the reference group.
The category with ACR <30 was used as the reference group.

Figure S1: Comparison of the distribution of [A] SIS, [B] SSS, and [C] CAC scores among people living with HIV and HIV-uninfected study participants

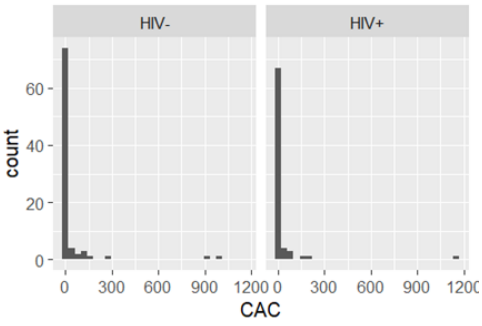
[A]



[B]



[C]



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