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The association between systemic inflammation and albuminuria among people living with HIV

A cross-sectional study from Botswana

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Abstract

Treated human immunodeficiency virus (HIV) is associated with persistent systemic inflammation, even after many years of sustained viral suppression following initiation of antiretroviral therapy (ART). Albuminuria is common among people living with HIV (PLWH), but the impact of persistent systemic inflammation on outcome of albuminuria is not well understood. Thawed serum samples from PLWH who participated in an albuminuria prevalence study in Gaborone, Botswana, between January 2020 and March 2022, were selected randomly for a cross-sectional study of the link between inflammation and albuminuria. Systemic inflammation (interleukin [IL] 1β, IL 6, and soluble cluster of differentiation-163 [sCD163]) was assessed using enzyme linked immunosorbent assay, and albuminuria was reported as urinary albumin–creatinine ratio (ACR) (mg/g), as obtained from the parent study. The association between systemic inflammation and albuminuria was first explored by ACR quartiles, graphically using simple linear models, and then using general additive models for the adjusted analysis. The study population comprised 715 ART treated PLWH, with a mean age of 49.9 (SD 10.7) years, median HIV disease duration of 13.5 (IQR 8.7–16.7) years, and 398/715 (55.7%) were male. The relationship between log transformed ACR and sCD163 was linear, with regression coefficient β = 0.10, *P*-value = .02 but was nonlinear for log transformed IL-1β and IL-6, β = 0.10, *P* -value = .82 and β = -0.04, *P*-value = .36, respectively. In the final adjusted general additive models, sCD163 was not associated with ACR, *P*-value = .137. IL-1β, IL-6, and sCD163 were not associated with ACR among ART treated PLWH. Novel strategies to identify inflammatory pathways that may promote albuminuria among PLWH should consider other innovative and sensitive markers of both systemic and organ specific inflammation.

Abbreviations: ACR = albumin–creatinine ratio, ART = antiretroviral therapy, CRP = c-reactive protein, GAM = generalized additive model, HIV = human immunodeficiency virus, IL = interleukin, PLWH = people living with HIV, sCD163 = soluble cluster of differentiation-163.

Keywords: Africa, albuminuria, Botswana, human immuno-deficiency virus, inflammation

1. Background and rationale

Treated human immunodeficiency virus (HIV) infection is associated with a chronic systemic inflammatory state.[1] In several studies, persistent inflammation despite sustained HIV viral suppression following the use of antiretroviral therapy (ART) has been linked to cardiovascular disease,[2,3] neurocognitive impairment,[4,5] and malignancies.[6,7] Despite this, the impact of inflammation on kidney function is not well understood in high burden HIV settings such as Botswana.

Botswana has one of the highest HIV prevalence rates globally.[8] Previous studies have demonstrated that living with HIV is associated with excess systemic inflammation. For example, in our cross-sectional study of 208 people living with HIV (PLWH) and treated with ART versus 224 adults who were not living with HIV, soluble cluster of differentiation-163 (sCD163)

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was significantly higher among PLWH compared to people without HIV.[9] In addition, chronically elevated IL-6 among ART-treated adults in Botswana was associated with all-cause mortality.[10]

While the association between systemic inflammation and end-organ dysfunction such as albuminuria has not been studied in Botswana and many other African countries, there is some preliminary evidence of the impact of inflammation on albuminuria from studies conducted elsewhere. For example, both IL-6 and tumor necrosis factor-alpha ,[11,12] were associated with elevated urine albumin-to-creatinine ratio in the general population while elevated c-reactive protein (CRP)[13] and nonclassical (CD14low/+CD166) monocytes[14] were associated with higher albuminuria as defined by elevated urine albumin-to-creatinine ratio among ART-treated PLWH. However, these associations have not been studied among ART-treated Black Africans living with HIV.

In the current cross-sectional study, we aim to study the relationship between systemic inflammation (IL-1 beta [β], IL-6 plus soluble CD163) and a one-time assessment of albuminuria among virally suppressed PLWH who participated in a larger albuminuria prevalence study. Our hypothesis is that there will be a dose-response relationship between inflammation and albuminuria (where higher inflammatory status will be associated with higher albuminuria).

2. Methods

2.1. Study design and setting

This is a serum/plasma analysis of stored samples from a completed cross-sectional observational study of albuminuria, which was conducted in Gaborone, Botswana, between January 2020 and March 2022 at the largest HIV clinic in the city (Princess Marina Hospital Infectious Disease Care Clinic) and 3 additional satellite HIV clinics across the city. Choosing this mix of clinics was considered to be representative of the cohort of PLWH in urban and peri-urban Botswana.

At the baseline study visit, which coincided with scheduled HIV clinic services, participants who provided written consent to participate had their demographic and clinical details abstracted by trained research assistants into electronic data collection forms designed by the investigators. At the same visit, urine and blood samples were collected and stored for future studies at the Botswana-Harvard Health Partnership Laboratory. All participant details were stored in REDCap©, and these were linked to the stored urine and plasma/serum samples using Senait© laboratory information management system.

2.2. Study population and sampling

Participants had to initially be part of a cohort of randomly selected attendees for HIV clinic services across the 4 study sites. Inclusion criteria in the main albuminuria prevalence study included being on ART for 6 months or more and being 21 years of age or older, while exclusion criteria included recent activity or exposure to factors that may result in elevated albuminuria (e.g., intense exercise, fever, known or suspected myositis). A random sample of 715 samples was selected from the frozen repository to form the analysis population for the current study.

2.3. Ethical approval

This study was approved by the University of Botswana Institutional Review Board and the Botswana Ministry of Health Human Research and Development Committee, HPDME 13/18/1. All study activities were conducted according to the Helsinki declaration.

2.4. Clinical data collection

Study clinical data were abstracted from an investigator-designed data collection form in REDCap©. Age, sex, medical comorbidities (diabetes mellitus, hypertension, chronic kidney disease, dyslipidemia, etc), use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and other hypertensive drugs (e.g., beta-blockers and calcium channel blockers), were collected from the main study. Additionally, right-arm systolic and diastolic blood pressure measurements (taken in triplicate) were abstracted from the main study data collection form. Finally, albuminuria, measured as ACR, in mg/g, was already available from the main study.

2.5. Laboratory measurements

As noted above, ACR measurements were already available from the parent "albuminuria prevalence study." Inflammation assessment was done among 715 participants who had sufficient stored serum/plasma in our biorepository. Frozen serum samples were thawed at Botswana-Harvard HIV Reference Laboratory, Gaborone, Botswana and serum IL-1β and IL-6 in pg/mL were measured using the R&D Systems© ELISA Kit (sandwich enzyme linked immune-sorbent assay) following the manufacturer's instructions (R&D Systems, Inc., Minneapolis). The level of sCD163 (ng/mL) was measured using a sandwich enzyme linked immune-sorbent assay (Trillium Diagnostics©, Bangor) as per the manufacturer's instructions.

Our selection of IL-1β, IL-6, and sCD163 was based on their well-established roles in the pathogenesis of HIV-associated comorbidities, particularly kidney dysfunction and albuminuria. IL-6 is a key pro-inflammatory cytokine involved in endothelial activation and tissue injury (processes integral to the development of albuminuria).[15–17] IL-1β also contributes to inflammatory signaling pathways associated with vascular and renal damage.

sCD163 was included for its specificity in capturing monocyte/macrophage-driven immune activation in HIV. Elevated sCD163 levels have been independently associated with renal disease progression in PLWH.[18] While high-sensitivity CRP is a recognized marker of chronic low-grade inflammation, our laboratory only has the capacity to perform standard CRP testing, which is more reflective of acute inflammation. Moreover, high-sensitivity-CRP is downstream of cytokines like IL-6 and IL-1β and may offer limited specificity in the context of chronic HIV-associated immune activation.[19]

2.6. Covariates

The main exposures were serum biomarkers of inflammation, and the outcome of interest was albuminuria, represented as albumin–creatinine ratio. The main potential confounders of interest for this study were age and sex.

2.7. Statistical analysis

The baseline characteristics of the study population were presented for the entire population and then separately by sex. Demographic details were presented as proportions (%) if they were categorical while continuous variables were presented as means (standard deviation) if they were normally distributed or as median (interquartile range) if they were non-normally distributed. Additionally, all variables that were skewed were log transformed.

Baseline variables were compared between sex groups using a 2 sample *t* test or nonparametric Kruskal–Wallis test, as appropriate based on the distribution of the continuous variables. The relationship between serum inflammatory markers and ACR as a continuous variable was first explored using simple linear regression for each marker separately and plotted for visual graphical assessment. If the relationship between each inflammatory marker

and ACR was not consistently linear for each of the 3 biomarkers, then a bivariate generalized additive model (GAM) was presented for each serum inflammatory marker. The initial adjusted GAM, adjusted for sex and age only, included serum inflammatory markers that had a *P*-value equal to or <.2 in the bivariate GAM. The final adjusted GAM then included common comorbidities like central obesity, clinical diagnosis of hypertension and diastolic blood pressure at time of enrollment. A *P*-value of .05 or lower was considered statistically significant in all analyses. In sensitivity analysis, we re ran the GAM using non-log transformed data, and compared model fitness parameters for the 2 GAM models. Finally, we assessed for possible effect modification by key comorbidities (central obesity and diagnosis of hypertension). All analyses were done using the R statistical package©, version 4.1.0.

3. Results

3.1. Demographic characteristics of participants

Among the 715 participants with available serum/plasma, the median age was 50 (IQR 43–57) years and 398/715 were male (55.7%). Hypertension was the most prevalent comorbidity, n = 212 (29.7%). The rest of the baseline characteristics are shown below in Table 1 for the entire study population, and then compared by sex group.

3.2. Association between serum inflammatory markers and ACR

The relationship between each inflammatory marker and ACR is depicted in Fig. 1.

3.3. Unadjusted and adjusted general additive model to assess the association between serum inflammatory markers and ACR

As shown in Table 2, while sCD163 met the criteria to be further assessed in the initial and fully adjusted analysis, none of the serum markers of inflammation were associated with ACR in the final adjusted GAM . See Tables S1 and S2, Supplemental Digital Content, https://links.lww.com/MD/P602 in the appendix showing the similar GAM results using non log transformed data, and then model fit parameters for the 2 GAM analysis respectively. Model fitness parameters show that using log transformed data performed better than using skewed data. Additionally, there was no effect modification by clinical comorbidity (central obesity, clinical diagnosis of hypertension and diastolic blood pressure), see Table S3, Supplemental Digital Content, https://links.lww.com/MD/P602.

4. Discussion

Among 715 ART treated PLWH in Botswana, serum markers of systemic inflammation, represented by IL-1β, IL-6, and sCD163, were not associated with albuminuria measured as a one-time calculated ACR. Additionally, there was a limited impact of systemic inflammation on ACR when assessed including comorbidities.

Our study included an older cohort of PLWH with a mean age of 50 years old. This cohort represents aging PLWH who are at high risk for noncommunicable diseases, including but not limited to persistent inflammation. There was no statistically significant relationship between serum inflammatory markers and ACR in the final adjusted models (even after adjusting for sex, given several statistically significant differences by sex group in the study population baseline demographics). While previous studies have examined the relationship between inflammatory biomarkers and kidney injury among PLWH, our study addresses a significant gap by focusing on a well-characterized cohort of ART-treated, virologically suppressed individuals in sub-Saharan Africa. To our knowledge, this is the first study in Botswana, and among the very few in Africa, that examines associations between IL-1β, IL-6, and sCD163 and albuminuria in this population, given the high burden of HIV and CKD in sub-Saharan Africa.[20–22]

IL-1β is increased in different anatomic compartments during treated chronic HIV disease and it is associated with chronic immune activation.[23] In ART treated chronic HIV disease,

Table 1

Demographic characteristics of study population, overall and then according to sex group.

Variable	Overall N = 715 (100%)	Male n = 398 (55.7%)	Female n = 317 (44.3%)	*P*-value
Age, mean (SD)	49.9 (10.7)	49.9 (11.3)	49.9 (9.77)	.97
HIV disease duration (years), median (IQR)	13.5 (8.70–16.7)	11.6 (6.73–15.7)	15.1 (11.6–17.3)	<.001
ART duration (years), median (IQR)	12.1 (7.64–15.7)	10.6 (5.95–14.8)	13.7 (9.26–16.5)	<.001
Current mean CD4 count, median (IQR)	557.0 (439.0–771.5)	520.5 (390.5–692.3)	662.0 (519.0–843.0)	<.001
Hypertension, n (%)	212 (29.7%)	89 (22.4%)	123 (38.8%)	<.001
Other conditions, n (%)	39 (5.5%)	17 (4.3%)	22 (6.9%)	.16
Systolic BP (mm Hg), median (IQR)	124.5 (115.0–137.0)	125.5 (115.5–138.0)	124.0 (114.5–135.0)	.09
Diastolic BP (mm Hg), median (IQR)	82.8 (74.0–90.5)	82.5 (72.5–90.5)	83.0 (76.0–91.0)	.25
Obesity*	405 (56.6%)	135 (33.9%)	270 (85.2%)	<.001
ACEi/ARB, n (%)	131 (18.3%)	50 (12.6%)	81 (25.6%)	<.001
Other BP medication, n (%)	199 (27.8%)	86 (21.6%)	113 (35.6%)	<.001
ACR (mg/g), median (IQR)	8.94 (4.34–25.3)	7.70 (3.76–25.0)	10.1 (5.13–25.4)	.006
IL-1β (ng/mL), median (IQR)	7.37 (5.11–11.3)	7.77 (4.94–12.1)	6.88 (5.37–10.0)	.039
IL-6 (ng/mL), median (IQR)	12.1 (7.53–28.5)	12.4 (7.70–31.7)	11.6 (7.23–25.4)	.19
sCD163 (ng/mL), median (IQR)	267.0 (152.7–373.4)	237.8 (139.2–349.7)	306.9 (193.2–400.6)	<.001

ACEi/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, ACR = albumin–creatinine ratio, ART = antiretroviral therapy, BP = blood pressure, HIV = human immunodeficiency virus.
*Based on waist-hip ratio >0.90 for men and >0.85 for women.

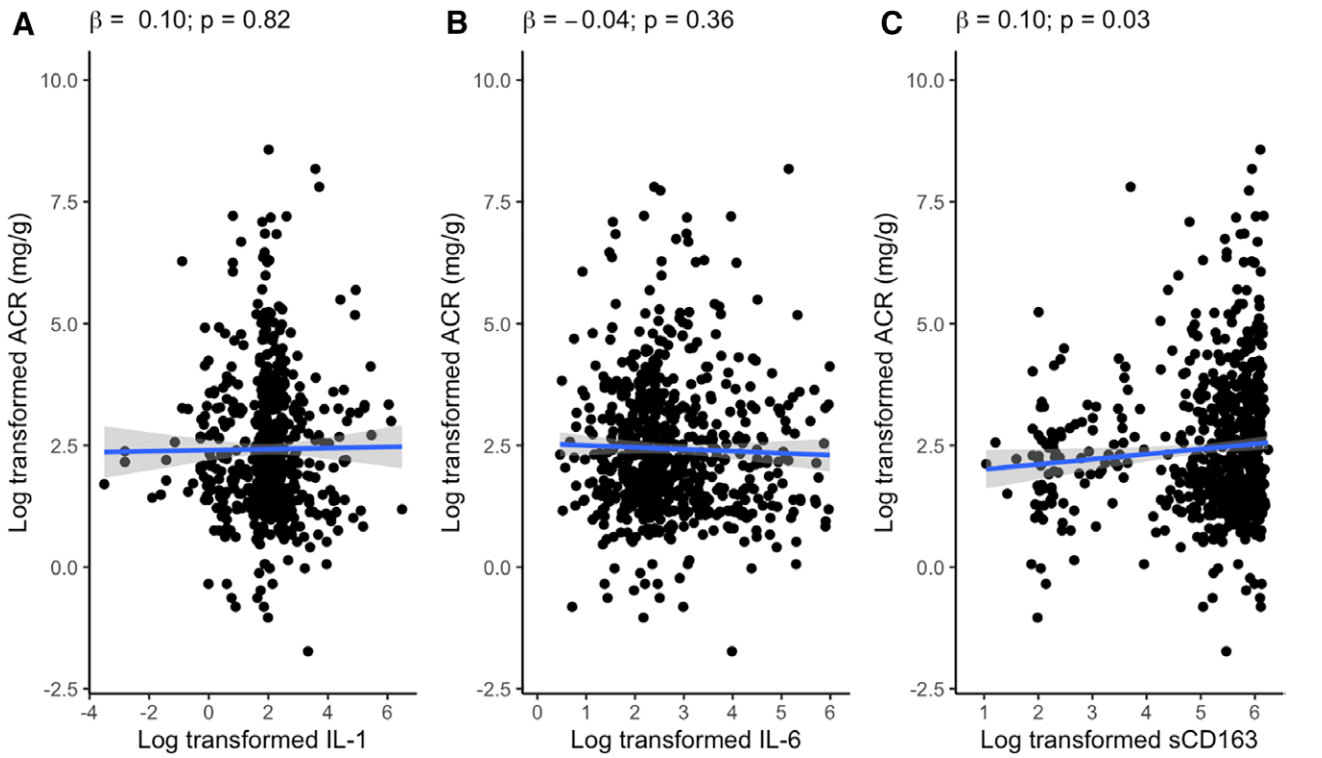

Figure 1. Scatter plots showing the association between log-transformed serum inflammatory markers and log-transformed ACR as a continuous variable. The solid line represents the best-fit values for the linear regression, bending around 0 indicating no obvious pattern between the biomarker and ACR measures. ACR = albumin–creatinine ratio, IL-1 = interleukin-1, IL-6 = interleukin-6, sCD163 = soluble cluster of differentiation 163.

Table 2

Unadjusted and adjusted general additive model analysis of the association between inflammatory markers and albumin–creatinine ratio .

	Unadjusted GAM analysis		Adjusted GAM analysis*	
	Effective degrees of freedom	*P* value	Effective degrees of freedom	*P* value
Log_IL-1β (ng/mL)	1	0.819	N/A	N/A
Log_IL-6 (ng/mL)	1	0.362	N/A	N/A
Log_sCD163 (ng/mL)†	2.69	0.107	2.56	.137

GAM = generalized additive model, IL-1 = interleukin-1, IL-6 = interleukin-16, sCD163 = soluble cluster of differentiation 163.

*Adjusted for age and sex.

†Criteria for including in the multivariate model at $P \leq .1$ as significant.

elevated IL-1β has been associated with end-organ dysfunction such as progressive decline in lung function[24] and atherosclerosis among PLWH.[25] These pleiotropic effects of chronically elevated IL-1β among PLWH have not been studied in relation to ACR in sub-Saharan Africa. We did not find an association between IL-1 and ACR in our study. Other newer studies of the association between IL-1 and ACR suggest that the serum omentin 1 to IL-1 ratio was a better predictor of albuminuria among people with diabetes mellitus.[26] In summary, while IL-1β may be associated with some, but not all, organ impairment among PLWH, it was not associated with ACR in Botswana. Sensitive urinary inflammatory markers may be another way to better understand the role of IL-1β associated immune activation on albuminuria among PLWH.

We did not detect an association between serum IL-6 and albuminuria even though there is evidence of an association between serum IL-6 and albuminuria in other patient populations. In a large study of adults in the general population (Framingham Offspring cohort in the USA), serum IL-6 was associated with higher quartile ACR.[11] Small mechanistic studies of multiplex bead array of serum biomarkers of inflammation among adults with type 2 diabetes mellitus revealed that circulating IL-6 was associated with albuminuria if estimated glomerular filtration rate was on the decline.[27] So, while we did not find an association between circulating (serum) IL-6 and albuminuria in our cohort, it remains unknown for now if IL-6 may be associated with albuminuria among PLWH with lower estimated glomerular filtration rate similar to people with type 2 diabetes mellitus- something we did not evaluate in the current study. Of note, in a study of urinary IL-6 (and not serum as we did), urinary IL-6 was associated with albuminuria in a cohort of children with sickle cell disease.[28] In the same study,[28] urinary IL-6 above the 50th percentile predicted persistence of albuminuria. Among adults with known type 2 diabetes mellitus, increased urinary IL-6 was associated with the highest ACR quartile.[29] In summary, the current study indicates that exploration of the relationship between IL-6 and albuminuria may require larger studies and a focus on urinary inflammatory markers, among other innovative ways of assessing clinical correlates of IL-6 among PLWH.

The macrophage activation marker, sCD163, has been associated with end organ dysfunction such as nonalcoholic fatty liver disease in the general population[30] and ACR among people with diabetes mellitus.[31] Globally, treated HIV on the other hand is associated with a persistent residual inflammatory state characterized by elevated levels of sCD163, including in Africa.[32] This elevated sCD163 may be associated with subclinical coronary artery disease[33] in some but not all PLWH in Africa.[9] Our study is the first to report that macrophage activation marker, sCD163, was not associated with ACR in Africa. It is possible that elevations in serum sCD163 may not predict the same organ dysfunction across all patient groups as the drivers of immune activation may differ by geographic locality and organ resilience may differ by population due to racial and genetic differences.

For instance, a small study of adults of Chinese descent with lupus nephritis, elevated serum sCD163 correlated with severity of lupus nephritis,[34] thereby underscoring the significance of elevated sCD163 in the kidney-a relationship that we did not detect among ART treated PLWH in our study. Future studies may assess the association between urinary sCD163[35] and ACR among PLWH or consider a more robust design and sampling plan to investigate the relationship between sCD163 and ACR among PLWH.

This exploratory study on the relationship between systemic inflammation and albuminuria had several limitations. Our small sample size and cross-sectional sampling may have limited our ability to fully ascertain the link between serum/systemic inflammation and albuminuria. Albuminuria can vary widely hence one time sampling of albuminuria may have weakened this study's ability to show an association between systemic inflammation and albuminuria. However, it is important to note that emerging data from our setting suggest that albuminuria in PLWH may persist or even progress over time despite long-term ART. For instance, a recently published longitudinal study[36] involving a subset of patients from this cohort, demonstrated progressive albuminuria in PLWH despite virologic suppression and sustained ART. These findings highlight the clinical relevance of even a single elevated ACR measurement, especially in high-risk populations. Further, more sensitive markers of renal specific inflammation such as measuring urinary levels of inflammatory markers including metabolomics or proteomics may have yielded different results or confirmed our current observations. Additionally, other sensitive markers of immune activation such as study of monocytes, instead of serum markers of inflammation, may have been better ways to assess the association between immune activation and albuminuria, if resources were available to conduct such work. In our analysis, we only included those who completed all 3 scheduled study visits- and excluded those who did not attend for repeat albuminuria assessment during scheduled HIV clinic visit. This may have introduced bias if those who completed were different to those who did not complete. We acknowledge that antiretroviral regimen composition, particularly the use of tenofovir-containing regimens, can significantly influence renal outcomes. Due to the lack of detailed data on individual treatment regimens in our dataset we did not stratify our analysis by specific HAART regimens. However, at the time of the study, Botswana national guidelines recommended tenofovir/lamivudine/dolutegravir as the first-line regimen for almost everyone living with HIV.[37] Therefore, we anticipate limited variability in ART regimens across participants. We also acknowledge that immunologic and virologic parameters (such as current and nadir CD4 counts, viral load, and timing of ART initiation) could offer valuable insights into the relationship between systemic inflammation and albuminuria. Unfortunately, these data were not consistently available for our analysis because they can only be derived from patient medical records. Where these records were incomplete, we could not reliably make these assessments. However, Botswana achievement of the USAID 97:97:97 targets prior to and during the study period[38] indicates that the vast majority of participants were virally suppressed. Therefore, viral load variability is unlikely to have significantly influenced albuminuria outcomes in this cohort. Future studies should incorporate longitudinal immunovirological data in albuminuria studies among PLWH.

Lastly, we did not have data on hepatitis B and C virus coinfections, which can potentially influence renal outcomes and systemic inflammation in PLWH. Future studies should include viral hepatitis screening to better understand its contribution to kidney injury and inflammation in this population.

However, our study still provides new knowledge about aspects of immune activation in serum that may not explain albuminuria among PLWH in Africa. It also provides rare and contextually important data on systemic inflammation and kidney dysfunction among ART-treated people living with HIV in Africa, a population that has been historically underrepresented in immunologic and kidney research. While prior studies on IL-1β, IL-6, and sCD163 have largely focused on non-African populations, our findings contribute unique insight into how these markers behave in a well-characterized African cohort. Though the study was conducted in Botswana, the results have broader relevance to Black African populations across sub-Saharan Africa, where similar epidemiologic and treatment patterns exist. Given the paucity of such data in African PLWH, this study serves as an important step toward understanding region- and population-specific drivers of kidney injury in the setting of treated HIV.

In conclusion, elevated markers of systemic inflammation, namely IL-1β, IL-6, and sCD163 were not associated with albuminuria among ART treated PLWH in Botswana. However, limitations in data collection, including one-time ACR measurement, lack of urine-based inflammatory markers, and incomplete clinical information, may have influenced our findings. Future studies should incorporate longitudinal designs, organ-specific biomarkers, and comprehensive clinical data to better elucidate the inflammatory pathways that may promote albuminuria among ART treated PLWH.

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