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Markers of Renal Disease and Function Are Associated with Systemic Inflammation in HIV

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Abstract

Objectives—Both renal disease and systemic inflammation predict non-AIDS events and overall mortality in HIV-infected patients. Here we sought to determine the relationships between renal disease and circulating inflammation markers.

Methods—We performed a secondary analysis of AIDS Clinical Trials Group study A5224s to determine if markers of renal disease [urine protein/creatinine (uPCR); urine albumin/creatinine (uACR); estimated glomerular filtration rate, eGFR, using CKD-EPI creatinine and cystatin C-creatinine] were associated with markers of systemic inflammation [high sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-alpha, soluble receptors of TNF-α (sTNFRI and II), soluble vascular cellular and intercellular adhesion molecules]. We correlated these renal and inflammatory markers prior to antiretroviral initiation and at 96 weeks of therapy.

Results—We found that estimated eGFR (using CKD-EPI cystatin C-creatinine), uPCR, and uACR were significantly correlated with most assessed markers of systemic inflammation prior to antiretroviral initiation. uPCR and eGFR (using CKD-EPI cystatin C-creatinine), but not uACR, remained significantly correlated with most of the assessed inflammatory markers after 96 weeks of ART. Most of these correlations, although statistically significant, were under 0.50. eGFR using

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CKD-EPI creatinine was much less frequently associated with inflammation markers and only significantly correlated with sTNFR1 at Week 0 and with sTNFRI and II at Week 96.

Conclusions—Renal disease and function are associated with systemic inflammation in HIV both before and after ART. Systemic inflammation may partially explain the relationships between proteinuria, albuminuria, and reduced renal function and future adverse outcomes.

Keywords

HIV-1; nephropathy; inflammation; albuminuria; proteinuria

INTRODUCTION

Impaired renal function and markers of renal injury, namely proteinuria and albuminuria, are predictors of new AIDS-defining events (1, 2), cardiovascular disease (3, 4) and all-cause mortality (2, 5–7) in HIV-infected patients both naïve to antiretroviral therapy (ART) and in those subsequently receiving ART. However, the underlying mechanisms for these associations are not clearly identified.

Renal disease in HIV has previously been linked to heightened systemic inflammation and immune activation (8), which, in turn, have been tied to worse clinical outcomes, including lower CD4 cell count restoration with ART (9) and poorer survival (10, 11). Thus, it stands to reason that markers of nephropathy in HIV may be reflective of a greater systemic inflammatory burden. If so, then perhaps estimating renal function and measuring urine protein and albumin would be easily performed tests which may identify those patients at greater risk of future adverse events.

We have previously shown that cystatin C, which has been suggested to be a better marker of renal function compared to creatinine in predicting future outcomes in both the general population (12) and in HIV-infected women (13), is related to systemic inflammation and that reductions in absolute cystatin C levels are related to reductions in markers of inflammation in ACTG 5224s (14).

However, relationships between estimated glomerular filtration rates (eGFR) using the 2012 CKD-EPI creatinine (Cr) and cystatin C-creatinine (CysC-Cr) equations (15) and markers of systemic inflammation have not been previously assessed. In addition, the relationships between markers of renal injury and inflammation and the relationships between these various renal markers with immunologic and virologic responses to ART have also not been examined. As such, we here present the analyses assessing the relationships between eGFR, proteinuria, and albuminuria with inflammation, CD4 cell counts, and HIV-1 RNA levels from ACTG 5224s.

METHODS

Study Design and Procedures

AIDS Clinical Trials Group A5224s was a metabolic substudy of A5202 (ClinicalTrials.gov NCT00118898) in which antiretroviral therapy-naïve study participants were randomized to

four different once-daily antiretroviral regimens (16). We have previously described the methods to measure the markers of inflammation [high sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), soluble receptors of TNF-α (sTNFRI and II), soluble vascular cellular and intercellular adhesion molecules (sVCAM-1 and sICAM-1) (17), renal disease [spot urine protein-creatinine ratio (uPCR) and urine albumin-creatinine ratio (uACR)] (18), and renal function (19) analyzed here.

Study Participants

To be included in the main A5202 trial participants were required to have a screening creatinine clearance by Cockcroft-Gault > 60mL/min. To be included in the substudy A5224s, participants also could not have uncontrolled thyroid disease or American Diabetes Association-defined diabetes mellitus. The human subjects ethics committee at each participating center approved the study protocol, and written informed consent was obtained from all participants in compliance with the human experimentation guidelines of the U.S. Department of Health and Human Services.

Statistical Analysis

Secondary renal study objectives of A5224s were (1) to explore the relationship between changes in inflammatory markers and changes in renal function and urinary markers of renal injury, (2) to explore the relationship between changes in virologic and immunologic markers and changes in renal function and urinary injury markers, and (3) to explore the relationship between baseline levels of renal function and urinary injury markers and changes in virologic and immunologic markers after ART initiation. As we were interested in the associations between these renal and inflammatory markers in general, we do not present analyses dependent on treatment assignment. All analyses were performed using intent-to-treat principles and used all available data regardless of modifications to randomized treatment. Due to the highly skewed distribution of the urine albumin- and protein-to-creatinine ratios, HIV-1 RNA, and the other inflammatory markers, these measures were $\log_{10}$ transformed prior to analysis. Spearman's correlation coefficient was used to assess correlations between continuous variables. Due to the large number of participants with viral suppression below the lower limit of assay detection at week 96, associations between the renal markers and HIV-1 RNA at week 96 were assessed using a two-sample t-test between those who had and did not have values <50 copies/mL. P-values below 0.05 were considered statistically significant, and nominal values are reported without adjustment for multiple comparisons. Analyses were performed using SAS, version 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Participant characteristics

A total of 271 participants enrolled in A5224s. Two participants were subsequently found to be ineligible; thus, 269 were included in the overall analysis population. The disposition of these participants during the trial has been described previously (20). These study participants were primarily men (85%). The study group was comprised of Black non-Hispanics (33%), White non-Hispanics (47%), and Hispanics (16%). The mean (SD) age

was 38 (10) years, CD4 cell count was 236 (165)/μL, HIV-1 RNA level was 4.6 (0.7) $\log_{10}$ copies/mL, eGFR CKD-EPI Cr was 107.1 (17.9) mL/min/1.73, and eGFR CKD-EPI CysC-Cr was 103.2 (17.2) mL/min/1.73^2. The mean (SD) change in CD4 cell count from week 0 to week 96 was 252 (181)/μL.

A smaller subset of 245 participants had data available at week 0 for uPCR and uACR. For these participants, the median (IQR) uPCR was 95 (67–146) mg/g and uACR was 4.75 (3.20–10.00) mg/g. Another subset of 207 participants had both eGFR and HIV-1 RNA levels available at week 96 and were used for the correlations for changes in these parameters with the biomarkers and CD4 counts; of these 207, 181 (87%) achieved an HIV-1 RNA level <50 copies/mL. A separate subset of 207 participants had inflammatory biomarker data available at both weeks 0 and 96 and was used to assess correlations between changes in these markers with changes in renal markers and CD4 cell counts.

Associations between renal function and inflammatory markers

The results at weeks 0 and 96 (and the changes between these two time points) for eGFR (19), the renal injury markers (18), and the inflammatory markers (17) have previously been presented. The correlations between the renal markers and the inflammatory markers at week 0, week 96, and changes from week 0 to week 96 in renal disease and inflammatory markers are shown in Table 1 (correlations between week 0 renal markers and changes in CD4 cell count, HIV-1 RNA levels are not in Table 1 but stated below).

eGFR Cr was inversely and significantly associated only with sTNFRI at weeks 0 and 96 and with sTNFRII at week 96. However, eGFR Cys-Cr was significantly and inversely associated with most of the inflammatory biomarkers, with the strongest correlations with sTNFRI and sTNFRII.

eGFR, using either estimating equation, was not significantly correlated with CD4 cell count at either week 0 or week 96; changes in eGFR were also not significantly correlated with changes in CD4 cell count. eGFR using the CKD-EPI CysC-Cr equation, but not with the CKD-EPI Cr equation, was significantly correlated with HIV-1 RNA at week 0 ($r=-0.16$, $P=0.008$). Neither eGFR estimate was significantly associated with suppressed HIV-1 RNA at week 96. Change in CD4 cell count from weeks 0 to 96 was significantly associated with week 0 eGFR using the CKD-EPI Cr equation ($r=0.16$, $P=0.019$) but not with the CKD-EPI CysC-Cr equation ($r=0.10$; $P=0.13$). Week 0 eGFR using either equation was not associated with achieving an HIV-1 RNA <50 copies/mL at week 96 ($P>0.15$).

Associations between proteinuria and inflammatory markers

uPCR was significantly correlated with all inflammatory markers at week 0 but only significantly correlated with IL-6, sICAM-1, TNF-α, and both TNF receptors at week 96. Change in uPCR was significantly correlated with changes in all inflammatory biomarkers tested.

uPCR was inversely and significantly correlated with CD4 cell count at weeks 0 and 96; uPCR was significantly correlated with HIV-1 RNA at week 0. However, uPCR at neither week 0, week 96, nor changes in uPCR from week 0 to 96 were associated with having an

HIV-1 RNA <50 copies/mL at week 96. Neither Week 0 uPCR nor change in uPCR was correlated with change in CD4 cell count from weeks 0 to 96.

Associations between albuminuria and inflammatory markers

Week 0 uACR was significantly correlated with all week 0 inflammatory markers except for sICAM-1; however, week 96 uACR was not correlated with any inflammatory markers at that time point. Change from weeks 0 to 96 in uACR was most strongly and significantly correlated with changes in both TNF receptors.

Week 0 uACR was not significantly correlated with change in CD4 cell count from weeks 0 to 96 (r=0.10, P=0.16). uACR was inversely and significantly correlated with CD4 cell count at week 0 but not at week 96, although change in uACR from week 0 to 96 was inversely and significantly correlated with change in CD4. uACR and HIV-1 RNA level were significantly correlated at week 0. However, uACR at week 0, week 96, and change in uACR from week 0 to 96 were not associated with achieving a week 96 HIV-1 RNA level <50 copies/mL.

DISCUSSION

The current analysis expand on our previous findings (14) which demonstrated that absolute cystatin C levels as a marker of renal function are associated with inflammation markers. In this current analysis of the A5224s substudy, we found that significant associations between nephropathy and inflammation persist using eGFR as the measure of renal function as well as using proteinuria and albuminuria as markers of renal injury. We found that eGFR, uPCR, and uACR were correlated with most of the circulating markers of inflammation we measured both prior to ART initiation and again after 96 weeks of ART, although these associations were less consistent with uACR and eGFR by CKD-EPI Cr at 96 weeks. Thus, if the purpose of estimating renal function is to identify those HIV-infected patients with greater systemic inflammation, then perhaps the CKD CysC-Cr equation should be preferentially used over the CKD-EPI Cr equation.

The significant correlations between changes in these renal markers and changes in most of the assessed inflammatory markers after almost two years of ART provide further support that inflammation and renal disease are related in HIV. It should be noted, however, that most of these correlations were of modest strength with rho values less than 0.50 (only the correlations between sTNFRI and weeks 0 and 96 eGFR CysC-Cr were greater than 0.50).

The presence of proteinuria (2), albuminuria (6, 21), and reduced renal function (1, 2, 22) prior to ART initiation has been shown in multiple cohorts to be associated with increased mortality in HIV-infected patients. We have previously demonstrated that higher HIV-1 RNA levels are significantly associated with greater proteinuria and that this relationship is not restricted to Blacks (23), the group of patients at highest risk for HIV-associated nephropathy. So it was not surprising that we found that uPCR and uACR were significantly correlated with HIV-1 RNA levels at week 0. The lack of association between these markers and the suppression of HIV-1 RNA to <50copies/mL at week 96 may suggest that any persistent nephropathy at this time point is not due to viremia and may rather be due to other

factors, such as drug-induced nephrotoxicity. In addition, these renal markers were associated with the inflammatory markers hsCRP and IL-6, increased levels of which have previously shown to be associated with overall mortality (24). Thus, systemic inflammation may underlie the relationships between pre-ART renal disease and mortality in HIV found previously in large cohort studies (10, 11).

We were surprised that the pre-ART levels of these renal markers were not associated with response to therapy as measured by change in CD4 cell counts or achieving an HIV-1 RNA level <50 copies/mL. Given that proteinuria is associated with greater CD8+ activation prior to ART initiation (8) and that greater CD8+ activation pre-ART is associated with poorer CD4 cell count recovery with ART (9), we had speculated that greater uPCR would be associated with smaller increases in CD4 counts at 96 weeks. It is possible that perhaps the relatively low levels of proteinuria observed in this study precluded finding a significant relationship with CD4 change or HIV-1 RNA suppression. However, the prevalences of proteinuria and albuminuria in this cohort are similar to those found in other studies of non-diabetic, stable HIV-infected patients and thus are externally valid (25).

Of interest are the differences observed between the correlations with proteinuria and albuminuria and the inflammatory markers in this cohort. uPCR was inversely correlated with several of the inflammatory markers measured at week 96, but uACR was not correlated with any of the inflammatory markers measured. This may be explained by the fact that most urine proteins in treated HIV-infected patients are not albumin, but rather, of tubular origin (26, 27). We suspect that this non-albuminuric fraction may reflect greater levels of systemic markers of inflammation and immune activation, such as β2-microglobulin, that are found in the urine through glomerular filtration in those with HIV (28, 29).

Higher circulating levels of hsCRP and IL-6 have been associated with increased numbers of cardiovascular events in HIV (30), while greater levels of sVCAM-1 and TNF-α have been associated with greater carotid intima media thickness (31). Thus, the significant associations between these systemic inflammatory markers and both proteinuria and reduced eGFR may partly explain the relationships between renal disease and increased risk of cardiovascular disease seen in HIV (3, 5). Interestingly, a recent trial demonstrated that treatment with rosuvastatin compared to placebo reduced both cystatin C levels and markers of inflammation and improved eGFR in patients receiving ART; these results support the link between renal function and inflammation in HIV (32).

Renal function estimated by the CKD-EPI CysC-Cr equation was inversely correlated with all inflammatory markers measured prior to ART and at week 96 of ART (except for hsCRP at this latter time point). Interestingly, eGFR estimated by CKD-EPI Cr did not have this global association with inflammatory markers. We and others have previously found that cystatin C is associated with inflammation (14, 33, 34). Given that that 2012 CKD-EPI CysC-Cr equation may be at least as accurate, and perhaps even marginally more accurate, for estimating GFR than the CKD-EPI Cr equation in HIV-infected patients (35), our results may imply that inflammation may impair renal function and that the CKD-EPI CysC-Cr equation is more likely to detect such impairment. However, this remains speculative as we

did not directly measure GFR in this study and thus could not directly determine if true GFR is related to systemic inflammation.

We acknowledge that our results may not be generalizable to patients with diabetes or to those with pre-treatment creatinine clearance <60 mL/min. However, less than 5% of antiretroviral-naïve patients have renal function lower than this threshold (36), so our study is reasonably representative of most of the HIV-infected population. These analyses were performed without adjustment for multiple comparisons, thereby increasing the possibility of type I errors for falsely detecting associations. However, we believed it was important to examine our results without such adjustment to limit false negative associations that lead us to inadvertently dismiss real biologic mechanisms underlying the association between renal disease and inflammation in HIV (37, 38).

The results from this analysis support a modest link between renal disease and systemic inflammation in HIV. Future studies should be performed to determine if monitoring for lower eGFR by CKD-EPI CysC-Cr and higher uPCR after ART initiation identify those HIV-infected patients at higher risk for non-AIDS events, such as cardiovascular disease, and overall mortality.

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Table 1

Correlations (Spearman Coefficient; P-value) between Renal and Inflammatory Markers at Week 0, Week 96, and Change from Week 0 to Week 96 in A5224s[a]

Variable	CD4	HIV-1 RNA	hsCRP	IL-6	sICAM-1	sVCAM-1	TNF-α	sTNFRI	sTNFRII
eGFR Cr[c]									
Week 0	−0.03;0.67	0.00;0.95	−0.05;0.43	0.00;0.97	0.01;0.93	−0.01;0.84	−0.04;0.51	**−0.25;<0.001**	−0.10;0.12
Week 96	0.01;0.87	;0.67[b]	0.00;0.96	−0.11;0.13	−0.01;0.88	−0.07;0.30	−0.13;0.063	**−0.38:<0.001**	**−0.23;0.001**
Week 0–96 change	−0.07;0.34	;0.78[b]	0.08;0.24	−0.04;0.62	0.05;0.44	0.04;0.62	−0.04;0.56	−0.08;0.25	0.04;0.59
eGFR CysC-Cr[d]									
Week 0	0.09;0.17	**−0.16;0.008**	**−0.20;0.002**	**−0.23;<0.001**	**−0.24;<0.001**	**−0.36;<0.001**	**−0.40;<0.001**	**−0.58;<0.001**	**−0.49;<0.001**
Week 96	0.08;0.25	0.085	−0.07;0.34	**−0.28;<0.001**	**−0.23;0.001**	**−0.27;<0.001**	**−0.37;<0.001**	**−0.61;<0.001**	**−0.49;<0.001**
Week 0–96 change	−0.01;0.94	0.39	0.01;0.87	−0.07;0.34	**−0.23;0.001**	**−0.33;<0.001**	**−0.43;<0.001**	**−0.42;<0.001**	**−0.42;<0.001**
uPCR									
Week 0	**−0.32;<0.001**	**0.24;<0.001**	**0.26;<0.001**	**0.36;<0.001**	**0.18;0.007**	**0.33;<0.001**	**0.32;<0.001**	**0.34;<0.001**	**0.44;<0.001**
Week 96	**−0.17;0.022**	0.17	0.01;0.89	**0.18;0.017**	**0.26;<0.001**	0.13;0.072	**0.18;0.013**	**0.20;0.008**	**0.21;0.004**
Week 0–96 change	−0.06;0.40	0.85	**0.23;0.003**	**0.21;0.007**	**0.20;0.010**	**0.26;0.001**	**0.17;0.036**	**0.29;<0.001**	**0.37;<0.001**
uACR									
Week 0	**−0.33;<0.001**	**0.28;<0.001**	**0.22;0.001**	**0.33;<0.001**	0.10;0.13	**0.26;<0.001**	**0.29;<0.001**	**0.26;<0.001**	**0.37;<0.001**
Week 96	−0.14;0.051	0.75	0.03;0.69	0.12;0.11	0.09;0.22	0.03;0.68	0.09;0.25	0.07;0.32	0.03;0.71
Week 0–96 change	**−0.15;0.044**	0.94	0.07;0.33	0.10;0.21	**0.18;0.021**	**0.26;0.001**	**0.17;0.024**	**0.26;0.001**	**0.32;<0.001**

Abbreviations: eGFR=estimated glomerular filtration rate; Cr=creatinine; CysC=cystatin C; uPCR=urine protein to creatinine ratio; uACR=urine albumin to creatinine ratio; hsCRP=high sensitivity C-reactive protein; IL-6=interleukin-6; sICAM-1=soluble intercellular adhesion molecule-1; sVCAM-1=soluble vascular cell adhesion molecule-1; TNF-α=tumor necrosis factor-alpha; sTNFRI and II=soluble tumor necrosis factor receptors I and II.

[a]Coefficients with P-values <0.05 are bolded. The correlation coefficients listed under Week 0 and Week 96 are for those time points only; the correlation coefficients for Week 0–96 change are for the correlations between changes in both markers (e.g. change in eGFR from week 0–96 with change in CD4 cell count from week 0–96).

[b]For HIV-1 RNA at Week 96 and for HIV-1 RNA Week 0–96 change, only P-values are presented for the two-sample Student t-test comparisons between those with and without a level <50 copies/mL at Week 96.

[c]Estimated in mL/min/1.73^2 using the 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine equation.

[d]Estimated in mL/min/1.73^2 using the 2012 Chronic Kidney Disease Epidemiology Collaboration cystatin C-creatinine equation.