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Proteinuria, CrCl, and Immune Activation in Antiretroviral-Naïve HIV-Infected Subjects

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Abstract

Because both renal disease and immune activation predict progression to AIDS, we evaluated the relationships between dipstick proteinuria ≥1+ [7% of 1012 subjects], CrCl <90mL/min [18% of 1071 subjects], and percentages of peripheral activated CD8 cells (CD8+CD38+HLA-DR+) in antiretroviral-naïve, HIV-infected subjects enrolled into AIDS Clinical Trials Group studies 384 and A5095. Proteinuria, but not CrCl, was associated with higher percentages of CD8+CD38+HLA-DR+ cells [55% vs. 50%; *P*=0.01], with even more pronounced differences in men and among Blacks and Hispanics. Proteinuria may be a surrogate measure of greater immune activation in HIV-infected patients initiating antiretroviral therapy.

Keywords

HIV-1; proteinuria; renal failure; nephropathy; immune activation

Two U.S. based cohort studies of HIV-infected women have demonstrated that proteinuria and renal function are independent predictors of both progression to AIDS [1] and overall mortality [1,2], even when accounting for CD4 cell count, HIV-1 RNA level, history of AIDS, and use of antiretroviral therapies. The mechanism by which these markers of kidney disease are independently associated with poorer outcomes is unknown.

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Increased levels of activated T cells, especially CD8 cells, are independently associated with faster progression to AIDS and death [3]. Immune activation decreases with combination antiretroviral therapy (cART) but generally do not return to levels found in HIV-uninfected individuals [4], suggesting that even treated HIV infection is associated with chronic activation of T cells.

The kidneys are known reservoirs for persistent HIV replication even when peripheral viral load is suppressed with cART [5]. Kidneys in patients with HIV-associated nephropathy have a dense tubulointerstitial inflammatory infiltrate, primarily composed of activated CD4 and CD8 cells, and the amount of the infiltrate appears to correlate with the degree of clinical nephropathy [6]. It has been suggested that HIV-infected renal tubular epithelial cells trigger upregulation of pro-inflammatory genes [7]. This pro-inflammatory renal environment may stimulate increased immune activation in the kidneys which may consequently lead to heightened systemic immune activation. Alternatively, patients with increased systemic immune activation may be prone to having infiltration of activated T cells into the kidneys, thereby leading to proteinuria and reduced renal function.

Therefore, we hypothesized that markers of renal disease, namely dipstick proteinuria and reduced CrCl, are associated with higher levels of peripheral blood activated T cells in antiretroviral-naïve HIV-infected subjects.

Subjects, materials, and methods

A cross-sectional analysis of pre-cART data from subjects participating in AIDS Clinical Trials Group (ACTG) 384 [8] and A5095 [9] was performed. Urine dipstick, serum creatinine, and advanced flow cytometry measurements were available prior to cART initiation in U.S. participants in ACTG 384. Urine dipstick and serum creatinine, but not advanced flow cytometry, were systematically collected prior to cART in A5095. A subset of A5095 subjects who co-enrolled into A5001, the ACTG Longitudinal Linked Randomized Trial [ALLRT], had advanced flow cytometry measured at randomization. Eligibility criteria for ACTG 384 and A5095 were similar, including the requirement for both studies that pre-cART serum creatinine be less than 1.5 times the upper limit of normal at the local laboratory.

Proteinuria was defined by the presence of ≥1+ protein on dipstick. We defined reduced renal function as an estimated CrCl (CrCl) <90mL/min as only 9 subjects had estimated CrCl <60mL/min. We estimated CrCl using the Cockcroft-Gault formula [10] for these analyses, instead of with glomerular filtration rate using the Modification of Diet in Renal Disease formula, as CrCl may be more consistent in predicting HIV disease progression and mortality in antiretroviral-naïve patients (Wools-Kaloustian K, et al.; Abstract 741, 16th Conference on Retroviruses and Opportunistic Infections, 2009). T cell activation was determined by the proportion of CD3+CD8+CD38+HLA-DR+ cells on advanced flow cytometry using standardized methodology in ACTG approved laboratories [11].

Data are presented as medians (interquartile ranges, IQR). Between-group statistical comparisons used either the Wilcoxon rank-sum or Fisher's exact tests, as appropriate. Logistic regression was used to investigate the association between immune activation and ≥1+ dipstick proteinuria or CrCL< 90, after adjusting for potential explanatory variables. Linear correlations between CrCl and immune activation levels were also performed. *P*-values below 0.05 were considered statistically significant.

Results

In the combined ACTG 384 and ACTG A5095 cohorts, 1012 and 1071 subjects had advanced flow cytometry data and either documented urine dipstick protein or serum creatinine, respectively. The characteristics of the study subjects included in the proteinuria analyses are presented in Table 1. The characteristics of those included in the CrCl analyses were nearly identical (data not shown).

In the combined cohort, the percentage of CD8+CD38+HLA-DR+ cells was significantly higher in those with dipstick proteinuria ≥1+ compared to those without proteinuria in the total cohort [55% (44, 69) vs. 50% (37, 61); *P*=0.01, Stratified Wilcoxon Rank Sun]. There were significantly higher proportions of CD8+CD38+HLA-DR+ cells in those with proteinuria compared to those without proteinuria in non-Hispanic Blacks [53% (43, 59) vs. 45% (34, 58)], Hispanics [70% (55, 78) vs. 57% (46, 67)], and men [55% (45, 70) vs. 49% (37, 61)], regardless of race or ethnicity, in the combined cohort. The association between proteinuria and higher proportions of CD8+CD38+HLA-DR+ cells in the total cohort remained significant (*P*<0.01) after adjustment for study group (384 vs. A5095/ALLRT), sex, race, and ethnicity.

The percentage of CD8+CD38+HLA-DR+ cells in those with CrCl <90mL/min was non-significantly higher compared to those with higher CrCl in the overall combined cohort [53% (38, 65) vs. 49% (37, 61); *P*=0.08, Stratified Wilcoxon Rank Sum]. Contrary to the proteinuria analyses, there were no significant associations between higher immune activation and reduced CrCl in subgroups based on race, ethnicity, or sex. There was also no significant correlation between percentage immune activation and CrCl in the total cohort.

There was a notable and statistically significant difference in immune activation levels between the two studies [49% (38, 60) in 384 vs. 53% (37, 64) in A5095/ALLRT; *P*=0.02]. We then focused on the individual study groups, so that the differences between the study cohorts would not be missed. There was a higher percentage of CD8+CD38+HLA-DR+ cells in ACTG 384 study participants with proteinuria compared to those without proteinuria [57% vs. 48%; *P*=0.005]. Characteristics of those with and without proteinuria in ACTG 384 are shown in Table 2. Variables associated with proteinuria or the percentage of CD8+CD38+HLA-DR+ cells in univariable or bivariable analyses were included in the final multivariable models (Table 3). Because of the strong correlation between CD4 cell count and HIV-1 RNA level in ACTG 384, two models were constructed for this study group incorporating each of these variables separately. In both 384 models, the percentage of CD8+CD38+HLA-DR+ cells, lower hemoglobin levels, and being non-Hispanic Black remained significantly associated with proteinuria. CD4 cell count was marginally associated with proteinuria in Model 1, but HIV-1 RNA level was not associated with proteinuria in Model 2.

Table 4 shows the univariable comparisons between those with and without CrCl <90mL/min in ACTG 384. The percentage of CD8+CD38+HLA-DR+ cells was higher in those with reduced CrCl compared to those without reduced renal function (53% vs. 48%; *P*=0.04). Multivariable models assessing the relationship between reduced CrCl and immune activation in ACTG 384 (Table 3) were constructed similarly to those for the proteinuria analyses. However, as age, weight, and sex are already included in the Cockcroft-Gault estimating formula, these variables and body mass index (which also uses weight for its estimation) were not included in the models. Higher immune activation, non-Hispanic Black race, and lower hemoglobin remained significantly associated with CrCl <90mL/min. However, there was no significant correlation between CrCl modeled as a continuous variable and immune activation in this study group.

In the A5095 study group, the percentages of activated CD8 cells were not significantly different in those with and without dipstick proteinuria (Table 2). Using the same co-variates as in the ACTG 384 analyses to assess multivariable predictors of proteinuria, we found that higher HIV-1 RNA levels were significantly associated with proteinuria whereas being non-Hispanic White appeared to be associated with not having proteinuria in A5095/ALLRT. Unlike the ACTG 384 cohort, the percentage of CD8+CD38+HLA-DR+ cells, hemoglobin level, non-Hispanic black race, and CrCl <90mL/min were not associated with proteinuria in the A5095/ALLRT model.

There was also no difference in CD8 immune activation in those with and without reduced renal function in A5095/ALLRT (Table 4). The multivariable predictors of CrCl <90mL/min in A5095/ALLRT are shown in Table 3. Lower CD4 cell counts and smaller height were associated with CrCl <90mL/min in this cohort. Like in the 384 study group, no significant correlation was found between CrCl and immune activation in the A5095/ALLRT study group.

Discussion

In this large cohort of antiretroviral-naïve, HIV-infected subjects about to initiate antiretroviral therapy, we found that dipstick proteinuria, but not CrCl <90mL/min, was significantly associated with a higher percentage of peripheral blood CD8+CD38+HLA-DR+ cells. The absolute difference in median immune activation of 5% between those with and without dipstick proteinuria in the combined cohort has been shown to be significantly associated with poorer CD4 cell count increases after initiation of antiretroviral therapy [12]. There were even larger differences in immune activation in specific subgroups, including non-Hispanic Blacks, Hispanics, and men. The prognostic implications of these findings will require longitudinal analysis in additional studies.

The findings from the current study suggest that nephropathy, as reflected in dipstick proteinuria, may be related to worse clinical outcomes due to increased systemic immune activation. It is tempting to speculate that viral replication in the renal reservoir may lead to increased local and systemic immune activation through persistent inflammatory stimulation [7]. Conversely, higher systemic immune activation, whatever the underlying cause, may somehow induce increased infiltration of activated T cells into the renal interstitium which consequently causes renal damage.

We did not find that CrCl was significantly associated with higher systemic immune activation in the overall cohort, although there did appear to be a significant association in the 384 study group. However, the exclusion of those individuals with more advanced renal dysfunction from these trials may have precluded our ability to detect a relationship between lower CrCl and immune activation.

In light of the recent results from the Strategies for Management of Antiretroviral Therapies (SMART) study [13], in which antiretroviral treatment interruption significantly increased the risk of serious organ dysfunction, the results of the current study may have potential relevance. It has been suggested that increased inflammation due to treatment interruption may result in a greater risk for developing an elevated cystatin C level, another marker of kidney dysfunction [14]. Our results demonstrate that increased systemic immune activation, possibly a result or in conjunction with other inflammatory mediators, may be in the pathway of events leading to renal failure in HIV-infected patients.

The findings presented here were plainly dependent on the study cohort. It is not clear why there were such disparate results based on study cohort. We investigated multiple potentially confounding variables (including region of enrollment, medical infectious/inflammatory

diagnoses, degree of proteinuria; data not shown), but none explained the discrepancies in results. Of course, there may have been unmeasured confounders that affected the results. The results from the A5095 study group may have been affected by the non-random selection of participants who co-enrolled in A5001 and had advanced flow cytometry results available. We must also allow the possibility of chance playing a role in the discrepancies found in our analyses.

Additional limitations include the cross-sectional observational design of this study, which does not allow us to infer causality. Second, the inclusion criteria for the two trials included in our investigation precluded enrollment of those with more severe renal dysfunction. In addition, these results may be applicable only to those patients about to start cART. The single measurement of immune activation and renal disease markers may have led to some misclassification of subjects, especially those whose renal function estimates were near the cutoff of 90mL/min used in these analyses. The use of renal function estimating equations, including the Cockcroft-Gault formula, may not be reliably accurate in relatively normal ranges [15]. Finally, other markers of inflammation (e.g. high sensitivity C-reactive protein, interleukin-6) and quantitative measures of proteinuria and albuminuria may provide greater and more precise insights into the associations between renal disease and immune activation. To overcome these limitations, future studies investigating the relationships between nephropathy and immune function should be longitudinal, include patients with more severe renal dysfunction, and use several and quantitative measurements of proteinuria and kidney function for more accurate categorization.

In summary, we found that dipstick proteinuria, but not estimated CrCl less than 90mL/min, was associated with higher proportions of peripheral blood CD8+CD38+HLA-DR+ cells. However, these findings were driven by the results from the ACTG 384 study group. As such, these findings should be considered hypothesis-generating and should be confirmed in larger prospective studies.

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Table 1

Characteristics of the study subjects in the proteinuria analyses.

Variable	ACTG 384 N=576	ACTG A5095/ALLRT N=436	Total N=1012
Age, yrs	35 (30, 42)	37 (32, 43)	36 (31, 43)
Male n, (%)	472 (82)	375 (86)	846 (84)
Race/ethnicity, n (%)			
Black, non-Hispanic	219 (38)	126 (29)	346 (34)
White, non-Hispanic	265 (46)	205 (47)	472 (47)
Hispanic	81 (14)	96 (22)	176 (17)
CD4 cell count/μL			
Median	275 (100, 452)	244 (109, 374)	262 (103, 425)
<200, n (%)	216 (38)	180 (41)	
Log_{10} HIV-1 RNA/mL	4.95 (4.35, 5.54)	4.75 (4.38, 5.33)	4.85 (4.37, 5.47)
Hemoglobin, g/dL	13.7 (12.5, 14.9)	13.8 (12.5, 14.8)	13.7 (12.5, 14.8)
Hypertension, n (%)	36 (6)	36 (8)	72 (7)
Diabetes mellitus, n (%)	9 (2)	16 (4)	25 (2)
Viral hepatitis B or C co-infection, n (%)	38 (7)	68 (16)	106 (10)
Creatinine clearance, mL/min			
Median	113 (95, 138)	121 (99, 143)	116 (96, 141)
<90, n (%)	104 (18)	72 (17)	176 (18)
Proteinuria, n (%)			
≥1+	39 (7)	34 (8)	73 (7)
≥2+	17 (3)	7 (2)	24 (2)
≥3+	6 (1)	1 (<1)	7 (<1)
%CD8+/CD38+/HLA-DR+	49 (38, 60)	53 (37, 64)	50 (37, 62)

NOTE. All values are presented as median (25^{th} percentile, 75^{th} percentile) unless otherwise specified.

Table 2

Univariable comparisons between those with and without dipstick proteinuria.

	ACTG 384			ACTG A5095/ALLRT		
	Dipstick proteinuria ≥ 1+			Dipstick proteinuria ≥ 1+		
Variable	**Yes N=39 (7%)**	**No N=537 (93%)**	***P***	**Yes N=34 (8%)**	**No N=402 (92%)**	***P***
%CD8+/CD38+/HLA-DR+	57 (45, 69)	48 (37, 60)	0.005	52 (42, 70)	52 (37, 64)	0.42
Age, yrs	36 (32, 41)	35 (30, 43)	0.67	38 (34, 45)	37 (32, 43)	0.22
Sex, no. male (%)	30 (77%)	446 (83%)	0.39	30 (88%)	343 (85%)	0.80
Body mass index, kg/m^2	24.9 (21.9, 29.8)	24.6 (22.1, 27.9)	0.70	24.0 (21.4, 27.1)	24.7 (22.0, 27.6)	0.57
Race/ethnicity, no. (%)			0.056			0.003
Black, non-Hispanic	24 (62%)	195 (36%)		18 (53%)	109 (27%)	
White, non-Hispanic	12 (31%)	257 (48%)		7 (21%)	199 (50%)	
Hispanic	3 (8%)	79 (15%)		8 (24%)	86 (21%)	
CD4 cell count/μL						
Median	164 (37, 264)	288 (117, 460)	0.0002	123 (27, 286)	250 (116, 383)	0.005
<200, no. (%)	25 (64%)	190 (35%)	<0.001	21 (62%)	159 (40%)	0.017
Log_{10} HIV-1 RNA/mL	5.39 (4.78, 5.74)	4.91 (4.33, 5.51)	0.016	5.27 (4.70, 5.75)	4.74 (4.36, 5.30)	0.001
Hemoglobin, g/dL	11.9 (11.1, 13)	13.8 (12.6, 15.0)	<0.001	13.1 (11.3, 14.2)	13.8 (12.5, 14.8)	0.005
Hypertension, no. (%)	3 (8%)	33 (6%)	0.73	4(12%)	32 (8%)	0.51
Diabetes, no. (%)	1 (3%)	8 (1%)	0.47	2 (6%)	14 (3%)	0.36
Viral hepatitis co-infection, no. (%)	4 (11)	34 (6)	0.31	7 (21)	61 (15)	0.46
Creatinine clearance <90mL/min, no. (%)	12 (31%)	92 (17%)	0.05	8 (23%)	64 (16%)	0.24

Note. All values are presented as median (interquartile range) unless otherwise specified.

Table 3

Multivariable predictors of proteinuria and creatinine clearance less than 90mL/min in subjects enrolled in 384 and A5095/ALLRT.

	≥1+ PROTEINURIA					
	ACTG 384 Study Group				ACTG A5095/ALLRT Study Group	
	Model 1[a]		Model 2[b]		Model[c]	
Variable	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
% CD8+/CD38+/HLA-DR+ cells (per 5 percentage points)	1.15 (1.04,1.29)	0.009	1.15 (1.03, 1.28)	0.012	1.03 (0.93, 1.14)	0.78
CD4 (per 10 cells/μL)	0.98 (0.96,1.0)	0.056			--	--
Log_{10} HIV-1 RNA/mL			1.21 (0.81, 1.83)	0.34	2.87 (1.66, 4.95)	0.0001
Hemoglobin (per 5 g/dL)	0.11 (0.03, 0.37)	<0.001	0.083 (0.026, 0.27)	<0.0001		
Black, non-Hispanic[d]	2.37 (1.14, 4.95)	0.021	2.28 (1.08, 4.80)	0.030		
White, non-Hispanic[e]	--	--	--	--	0.22 (0.09, 0.52)	0.0007

	CREATININE CLEARANCE <90mL/min			
	ACTG 384 Study Group[f]		ACTG A5095/ALLRT Study Group[g]	
Variable	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
% CD8+/CD38+/HLA-DR+ cells (per 5 percentage points)	1.08 (1.01, 1.15)	0.024	0.99 (0.92, 1.07)	0.80
Black, non-Hispanic[d]	1.69 (1.10, 2.61)	0.018	--	--
Hemoglobin (per 5 g/dL)	0.45 (0.24, 0.86)	0.015	--	--
CD4 (per 10 cells/μL)	--	--	0.98 (0.97, 1.00)	0.009
Height (per 10cm)	--	--	0.44 (0.32, 0.59)	<0.0001

NOTE. Dashed lines indicate this variable was not significantly associated with either proteinuria or creatinine clearance <90mL/min in univariable or bivariable models and, therefore, was not included in the multivariable models. Other variables considered in either or both of these models included HIV-1 viral load, sex, age, weight, height, body mass index, region of enrollment, history of hypertension, history of diabetes mellitus, history of viral hepatitis co-infection (either hepatitis B or hepatitis C), dipstick proteinuria, and creatinine clearance. OR, odds ratio; CI, confidence interval.

[a] Predicted 80.2% of the variability in proteinuria.

[b] Predicted 79.6% of the variability in proteinuria.

[c] Predicted 71.4% of the variability in proteinuria.

[d] Compared to White, non-Hispanic and Hispanic.

[e] Compared to Black, non-Hispanic and Hispanic.

[f] Model for ACTG 384 predicted 63.1% of the variability in creatinine clearance.

[g] Model for ACTG 5095 predicted 73.0% of the variability in creatinine clearance.

Table 4

Univariable comparisons between those with and without creatinine clearance less than 90mL/min.

	ACTG 384			ACTG A5095/ALLRT		
	Creatinine clearance <90mL/min			Creatinine clearance <90mL/min		
Variable	**Yes N=119 (19%)**	**No N=496 (81%)**	***P***	**Yes N=76 (17%)**	**No N=380 (83%)**	***P***
%CD8+/CD38+/HLA-DR+	53 (38, 64)	48 (37, 59)	0.04	51 (38, 66)	53 (37, 64)	0.82
Age, yrs	42 (36, 51)	35 (29, 41)	<0.01	41 (35, 51)	37 (32, 42)	<0.01
Sex, no. male (%)	93 (78)	414 (83)	0.17	60 (79)	329 (87)	0.09
Weight, kg	64.2 (57.5, 71.4)	76.7 (68.9, 88.3)	<0.01	61.3 (56.6, 68.3)	77.6 (68.5, 86.4)	<0.01
Race/ethnicity, no. (%)						
Black, non-Hispanic	61 (51)	179 (36)	0.01	28 (37)	104 (27)	0.03
White, non-Hispanic	40 (34)	239 (48)		32 (42)	186 (49)	
Hispanic	15 (13)	69 (14)		12 (16)	85 (22)	
CD4 cell count/μL						
Median	223 (60, 398)	287 (117, 458)	0.03	152 (52, 303)	247 (117, 394)	<0.01
<200, no. (%)	55 (46)	172 (35)	0.02	42 (55)	150 (39)	0.01
Log HIV-1 RNA/mL	5.00 (4.29, 5.54)	4.90 (4.33, 5.51)	0.53	4.86 (4.47, 5.49)	4.73 (4.37, 5.32)	0.19
Hemoglobin, g/dL	13.2 (11.9, 14.2)	13.8 (12.6, 15.0)	<0.01	13.3 (11.9, 14.3)	13.8 (12.6, 14.8)	<0.01
Hypertension, no. (%)	11 (9)	27 (5)	0.12	9 (12)	28 (7)	0.19
Diabetes, no. (%)	2 (2)	7 (1)	0.83	1 (1)	15 (4)	0.26
Viral hepatitis co-infection, no. (%)	10 (8)	30 (6)	0.41	13 (17)	54 (14)	0.48
Proteinuria ≥ 1+, no. (%)	12 (12%)	27 (6%)	0.05	8 (11%)	26 (7%)	0.24

Note. All values are presented as median (interquartile range) unless otherwise specified.