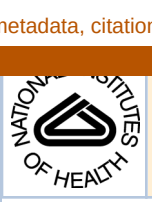

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Microalbuminuria predicts overt proteinuria among patients with HIV-infection

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Abstract

Background—This study examines the association between microalbuminuria and the development of proteinuria among HIV-infected persons.

Methods—948 subjects provided urine samples for albumin, protein, and creatinine measurements semiannually. Microalbuminuria was an albumin-to-creatinine ratio of >30 mg/gm. Proteinuria was a protein-to-creatinine ratio of ≥0.350 mg/mg. The progression from microalbuminuria to proteinuria was described.

Results—At baseline, 69.4% had no detectable proteinuria, 20.2% had microalbuminuria, and 10.4% had proteinuria. Subjects with microalbuminuria and proteinuria were more likely to be black (p=0.03), have lower CD4+ counts (p=0.02,0.0001 compared to subjects without abnormal proteinuria, respectively), and have a higher HIV RNA level (p=0.08,0.04). Among 658 subjects with normal urine protein, 82.7% continued to have no abnormality, 14.3% developed microalbuminuria, and 3.0% developed proteinuria. Subjects without baseline proteinuria (i.e. either normal protein excretion or microalbuminuria) who developed proteinuria were more likely to have microalbuminuria (p=0.001), a lower CD4+ count (p=0.06), and a higher plasma HIV RNA (p=0.03) than those who did not progress to proteinuria. In multivariate analysis, only microalbuminuria remained associated with the development of proteinuria (OR=2.9; 95% CI 1.5, 5.5; p=0.001).

Conclusion—Microalbuminuria predicts the development of proteinuria among HIV-infected persons. Because proteinuria has been linked to poorer outcomes, strategies to affect microalbuminuria should be tested.

Keywords

HIV-1; microalbuminuria; proteinuria; HIVAN; urine

Introduction

Survival among persons with HIV infection has improved significantly over the last decade (1). Concurrent with these improvements in morbidity and mortality, there has been an

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increase in the proportions of deaths among HIV-infected persons due to liver and kidney disease (2). As a result, there has been an increasing focus in research and clinical care into chronic liver and kidney conditions, including an enhanced understanding of their pathogenesis as long term complications of HIV infection, as toxicities related to the medications used to treat HIV infection, and as comorbidities in an aging population such as diabetes mellitus, hypertension, and hyperlipidemia.

Microalbuminuria and proteinuria both serve as markers of glomerular function. An intact glomerulus will maintain the barrier to filtration between the capillary and urinary spaces resulting in minimal levels of albumin or protein in the urine. Albumin excretion greater than 30 mg per day and protein excretion exceeding 350 mg per day are abnormal and generally signify a process or disease that is affecting this barrier to diffusion.

Among patients with diabetes mellitus, the presence of microalbuminuria is associated with the risk of developing overt proteinuria and death (3,4,5) and is considered a marker of progressive kidney disease. These associations suggest that microalbuminuria is likely a marker of early vascular damage related specifically to abnormal glycosylation in diabetes mellitus or to more general processes in other chronic illnesses. Among HIV-infected persons, the presence of proteinuria has been linked to increased risk of chronic kidney disease (CKD), end stage renal disease (ESRD), new AIDS-defining illness, and mortality (6,7,8). The association of proteinuria with these outcomes suggests that it might be a marker of a more diffuse vascular process and that this process might affect outcomes both within and outside of the kidney. Based on this, the identification of an earlier marker of patients at higher risk to develop proteinuria could be clinically advantageous. To properly design and test prevention or treatment strategies to lower the risk associated with proteinuria similar to those available in diabetic nephropathy (9-12), an understanding of the natural history of microalbuminuria in HIV is essential. This study was therefore undertaken to describe the abnormal patterns of urine protein excretion in a large HIV positive cohort and to test the ability of microalbuminuria to predict the development of overt proteinuria.

Methods

This is a prospective cohort study conducted in the Adult Infectious Diseases Clinics of Duke University Medical Center (Durham, NC) and the University of North Carolinas Hospitals (Chapel Hill, NC). This study was approved by the Institutional Review Boards of both sites. A convenience sample of subjects was enrolled by approaching all patients seen in the respective ID clinics on a particular day. The day of the week on which subjects were recruited varied to include patients of multiple providers. All subjects provided informed consent.

Data Collection

Baseline data collected included gender, age, race, height, weight, systolic and diastolic blood pressure, most recent CD4+ lymphocyte count and plasma HIV RNA level, and serum creatinine. Blood pressure measurements were obtained from review of the visit specific records. Subjects were approached at their routine clinical visit closest temporally to six month intervals from the date of their baseline exam for a period of two years to provide additional random (spot or untimed) urine specimens. All measurements for urine albumin, protein, and creatinine were performed by a single laboratory (LabCorp, Burlington, NC). Information on hepatitis B and C infection, intravenous drug use, diabetes mellitus and concomitant medications was not available.

Data Analysis

Urine albumin and protein excretion was estimated using the urine albumin to creatinine ratio and urine protein to creatinine ratio, respectively. Microalbuminuria was defined as an albumin to creatinine ratio of >= 30 mg/gm (3.5 mg/mmol in SI units). Abnormal protein excretion was defined as a protein to creatinine ratio of >=0.350 mg/mg. Estimated glomerular filtration rate (GFR) was calculated using the MDRD formula (13).

$$\mathrm{GFR}=186\times(\mathrm{Scr})^{-1.154}\times(\mathrm{Age})^{-0.203}\times(0.742\text{ if female})\times(1.210\text{ if African-American})$$

For each urine collection, each subject was described as being without abnormal urine protein excretion (i.e. no microalbuminuria or proteinuria) or as having microalbuminuria or proteinuria. The demographics and laboratory parameters were described for the cohort overall based on these groups at baseline evaluation. Values at subsequent time points were summarized within group. Clinical and demographic differences between groups were compared using the Chi-square and Student's T-tests for categorical and continuous variables, respectively.

Each subject with at least one follow up visit was included in the longitudinal analysis. The first available follow up visit for each subject after their baseline visit was used. Associations between clinical and demographic variables including age, gender, race, systolic and diastolic blood pressure, CD4+ lymphocyte count, plasma HIV RNA level, and GFR and outcomes such as progression to overt proteinuria were estimated using logistic regression. Multivariable risk ratios were calculated based on model parameter coefficients using standard methods. Entry and elimination criteria were set at a value of $p = 0.10$.

All p-values were reported as 2-sided, and all confidence intervals reported were 95% intervals. All analyses were performed using Stata (version 8.0, College Station, TX).

Results

Nine hundred and forty-eight HIV-infected subjects were enrolled and provided at least one urine sample (315 at Duke and 633 at UNC). At baseline, 69.4 percent had no detectable urine protein excretion, 20.2 percent had microalbuminuria, and 10.4 percent had proteinuria. In general, subjects with microalbuminuria and proteinuria were more likely to be black (p= 0.02), have a lower CD4+ lymphocyte count (p= 0.02 comparing subjects without abnormal urine protein excretion to subjects with microalbuminuria, p=0.0001 comparing subjects with microalbuminuria to subjects with proteinuria), and have a higher plasma HIV RNA level (p= 0.08 comparing subjects without abnormal urine protein excretion to subjects with microalbuminuria, p=0.04 comparing subjects with microalbuminuria to subjects with proteinuria) (Table 1). There was no difference in serum creatinine comparing subjects without abnormal urine protein excretion to subjects with microalbuminuria (p= 0.31); however, subjects with proteinuria had a lower GFR than subjects with microalbuminuria (p= 0.03). At baseline, a greater proportion of subjects with microalbuminuria or proteinuria had an eGFR< 90 ml/min (p<0.0001).

Approximately 75% of enrolled subjects had at least one follow-up urine exam after baseline. Those who did not have a follow-up exam were younger or more likely to be women or of black race (p= 0.003, 0.02, and 0.02, respectively) (Table 2). There were, however, no differences between those with and without follow-up with respect to CD4+ lymphocyte count, HIV-1 RNA level, blood pressure, kidney function, or urine protein excretion.

Clinical course for subjects without abnormal urine protein excretion at baseline

The proportions of subjects without abnormal urine protein excretion, microalbuminuria, and proteinuria on next follow-up exam varied based on the results of their initial examination (Figure 1). Almost 80% of subjects with no baseline abnormal urine protein excretion continued to be without abnormality on follow-up. However, 15.7 % and 5.3 % demonstrated microalbuminuria and proteinuria, respectively, on subsequent exams.

Clinical or demographic characteristics were not significantly different among subjects without abnormal urine protein excretion at baseline who continued to be without abnormality compared to those who developed microalbuminuria or proteinuria (Table 3a) with the exception of CD4+ lymphocyte count. Subjects who developed proteinuria tended to have a lower CD4+ lymphocyte count than those who continued to be without abnormality (p=0.06).

Clinical course for subjects with microalbuminuria at baseline

Among subjects with microalbuminuria, a substantial proportion did not demonstrate any abnormality on follow-up exam (46.5%) while 39.5% had continued microalbuminuria and 14.0 % demonstrated progression to proteinuria (Figure 1).

Subjects with baseline microalbuminuria who had subsequent urine examinations that continued to reveal abnormalities (microalbuminuria or proteinuria) were slightly older (p=0.003) and had slightly lower GFR (p=0.005) than those who had no urine abnormality on follow-up exam (Table 3b). In a multivariable model, older age and lower GFR were both associated with an increased risk of persistent abnormal urine examinations on follow-up (age OR=1.66 per 10 year increase, p=0.03, GFR OR=1.14 per 10 cc/min decrease, p=0.06).

Subjects without baseline proteinuria (i.e. those without abnormal urine protein excretion or those with microalbuminuria) who developed proteinuria were more likely to have microalbuminuria (p=0.001), a lower CD4+ lymphocyte count (p=0.06), and a higher plasma HIV RNA level (p=0.03) than those who did not develop proteinuria (Table 3c). In multivariate analysis among subjects without proteinuria at baseline, only microalbuminuria was significantly associated with the development of proteinuria on follow-up (OR=2.9; 95% CI 1.5, 5.5; p=0.001). While both decreasing CD4+ lymphocyte count and increasing plasma HIV RNA level were associated with an increasing risk for the development of proteinuria in univariate analyses (p=0.06 and 0.04, respectively), these variables did not maintain conventional levels of statistical significance when controlled for microalbuminuria.

Sensitivity analysis for subjects with three urine measurements

Because the clinical diagnosis of microalbuminuria was recently defined as requiring two consecutive measurements of elevated values, the above analyses were repeated using the subset of subjects in the cohort who had at least three urine exams and in whom the first two provided agreement as to the degree of protein excretion. The proportion of subjects who maintained their level of urine protein excretion or progressed or regressed to other levels of protein excretion was similar to the cohort overall (data not shown). The ability of two consecutive values of microalbuminuria to predict overt proteinuria increased substantially (OR= 21.7, 95% CI 10.8,43.8, p<0.001).

Discussion

This prospective cohort study demonstrates that a significant proportion of individuals infected with HIV have microalbuminuria or proteinuria and that the presence of subtle abnormalities like microalbuminuria portend an increased risk of potentially more clinically relevant abnormalities such as proteinuria. Over time the development of either microalbuminuria or proteinuria appeared to be associated with a lower CD4+ count or higher HIV RNA level. It further demonstrates that following an initial positive test for microalbuminuria subsequent urine may reveal no abnormality, particularly among younger subjects and those with a higher GFR. Finally, as a practical message, these data suggest that the use of a single urine exam might lead to misclassification and confirmation testing is an important consideration.

This is the initial description of the predictive role that microalbuminuria may play in the development of more clinically significant renal disease among HIV-infected individuals. Prior to this study, multiple cross-sectional studies had found a varied prevalence of microalbuminuria among patients with HIV infection of 10.9%, 19.4%, 29.8%, and 31.6% (14-17) among patients without hypertension or evidence of other renal disease. Given the associations between factors such as race, CD4+ lymphocyte count, and plasma HIV RNA level, these variations likely reflect the distribution of these predictive parameters in the population studied. Regardless of the exact prevalence, the proportion of patients with microalbuminuria in contemporary populations is likely substantial.

With respect to the immunologic associations, this study is similar to a prior cross-sectional analysis in which microalbuminuria was also associated with a lower CD4+ lymphocyte count (17). In this cross-sectional study of HIV infected subjects with lipodystrophy, urine albumin to creatinine ratios were measured and demonstrated to be associated with not only CD4+ lymphocyte count, but also cardiovascular risk factors such as increased insulin resistance and systolic blood pressure. This current cohort study confirms the association between CD4+ lymphocyte count and microalbuminuria. The lack of association with blood pressure here may simply reflect nonstandard measurements and lack of information concerning use of antihypertensive medications.

The ability of microalbuminuria to predict future proteinuria in this study is similar to the studies describing this relationship among patients with diabetes mellitus (3,4,18-21). Additionally, a similar phenomenon of regression from microalbuminuria to a urine exam that has no detectableprotein excretion as seen in this cohort has also been demonstrated among persons with diabetes (19). Among patients with diabetes, 50.6% with microalbuminuria demonstrated “regression” to normal protein excretion. Whether this regression reflects effective treatment or a higher rate of false positives in the use of microalbuminuria as a screening test cannot be determined from either this study or those in diabetics. However, with respect to the relationship between microalbuminuria and proteinuria, a key difference between this study and those assessing patients with diabetes mellitus is time course. The time point at which microalbuminuria develops into overt proteinuria cannot be truly assessed in either studies on diabetic nephropathy or using these data based on the fact that the event is the measurement of protein excretion in the specimen not the true date of progression. However the extent to which length of follow up can be used as a surrogate for the rate of progression, it should be noted that the studies of patients with diabetes mellitus had substantial lengths of follow-up (e.g. 7, 18 and 23 years) whereas this current study tested urine measurements within a much shorter time frame. While conservatively the time course of microalbuminuria transitioning into proteinuria may be similar among persons with HIV as compared with diabetes mellitus, the current findings of a significant association within 2 years of initial detection of microalbuminuria, suggests this

process may be accelerated among persons with HIV. Further, with longer follow up it is possible that the predictive ability of microalbuminuria is even stronger than that demonstrated here.

While this study presents data regarding the development of microalbuminuria and its progression to overt proteinuria among persons with HIV, it is not without limitation. Medication information including the use of antihypertensives such as angiotensin converting enzyme inhibitors and antiretroviral therapy shown to affect urine protein excretion was not available. While one study suggested that antiretroviral therapy benefited established proteinuria (22) and another demonstrated that women not treated with antiretroviral therapy have a greater progression of their microalbumin excretion over time as compared to women who were treated with highly active antiretroviral therapy (23), information on the use of antiretrovirals is similarly not available. If the use of these medications similarly slows the progression of microalbuminuria to overt proteinuria failure to account for the increasing use of therapy over time would bias these findings towards the null. So the relationships examined in this manuscript may be more significant than those demonstrated.

The first subject was enrolled in this study in the year 2000. At that time and around the time period during which this study was designed, the use of albumin to creatinine ratio in an untimed urine specimen was felt to be an adequate screening strategy for patients with diabetes mellitus (24-26). Recent trials have used more strict criteria for screening and confirmation of the presence of abnormal urinary excretion of albumin (27). Clearly, the use of a single urine specimen in this study may introduce misclassification bias primarily between the groups without abnormal urine protein excretion and those with microalbuminuria. While this method does mimic practically what may occur in the screening of individuals in the course of their clinical care, it also may serve to bias these results toward the null, potentially diluting an association that may be even more significant. These data therefore underscore that the common clinical practice of utilizing a single urine specimen should be carefully interpreted and consideration toward confirmation of a finding such as microalbuminuria before therapy is instituted given. However, it should be noted that when the data were analyzed in a manner consistent with the current criteria for the diagnosis of microalbuminuria, the relationships were persistent and perhaps stronger. Additionally, it should be noted in the application of these findings to clinical practice, that proteinuria can also originate from a pathology that affects tubular resorption of the normal filtered amount of protein. While microalbuminuria may similarly reflect a tubular process it is used clinically to reflect early glomerular disease.

Another limitation of this study is that it is based on population of convenience rather than the entire clinic population. While this should not affect the estimate of the predictive ability of microalbuminuria, it likely affects the estimate of prevalence of microalbuminuria and proteinuria. Therefore, it is recommended that prevalence estimates be interpreted cautiously. Finally, this cohort cannot examine the link between microalbuminuria and proteinuria and clinical outcomes such as mortality. While the link between proteinuria and mortality is demonstrated in prior studies (6,7), it has not been examined among persons with microalbuminuria. The inability of these data to examine this association is related to the number of individuals who changed their care provider during the course of their follow-up and subsequently did not present for additional clinical care after the visit in which they provided their baseline sample. The lack of follow-up information on approximately one quarter of the initial cohort does not allow the examination of the link between albuminuria and mortality. This will need to be examined in additional studies. Subjects who did not present for additional clinical care differed from those that did in terms of demographics such as age and gender. Given that association between microalbuminuria and progression

to proteinuria did not appear to be confounded by either of these variables, the impact of this loss to follow up must be considered but may not affect the conclusions substantively.

In summary, microalbuminuria is common in HIV infected persons and appears to be associated with immunologic parameters such as CD4+ lymphocyte count. While patients with microalbuminuria on initial evaluation may not continue to have similar findings on subsequent exams (i.e. revert to normal levels of albumin excretion), there appears to be a subgroup of persons partially identified by slightly older age and decreased GFR that have persistent urinary protein excretion abnormalities. Finally, microalbuminuria is predictive of the development of proteinuria. These findings may suggest a utility to the periodic screening of persons with HIV for the presence of microalbuminuria. However, the next integral step will be to determine if the efficacy of treatment strategies for albuminuria such as ACE inhibitors, angiotensin receptor blockers, and antiretroviral therapy improve clinical outcomes. Clinically, it should be considered that in the absence of a dedicated test for microalbuminuria, it is not possible to discern between patients with or without elevated levels of urinary albumin using only a urine dipstick. Given that microalbuminuria is a risk factor for proteinuria, knowledge of its presence through dedicated testing might be indicated to eventually guide clinicians to the optimal prevention of progression of renal disease in HIV-infected persons.

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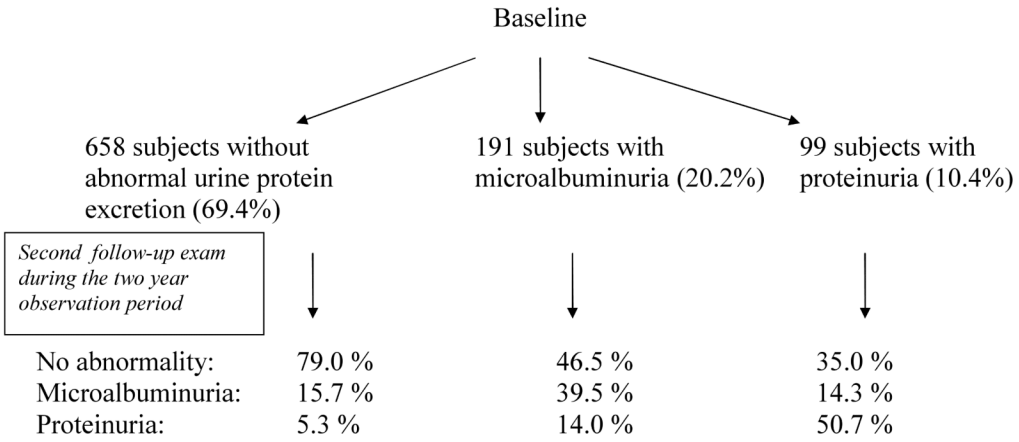

Figure 1. Flow diagram of urine examinations at baseline and follow up

Table 1
Clinical and demographic characteristics of subjects by baseline urine exam

Variable	No urinary abnormalities	Microalbuminuria	Proteinuria	P-value
Number of patients	658 (69.4%)	191 (20.2%)	99 (10.4%)	
Age (years)*	43.6 (9.1)	43.2 (9.2)	45.4 (9.7)	0.59 * 0.05 **
Gender				
Women	177 (26.9%)	63 (33.0%)	33 (33.3%)	0.15
Men	480 (73.1%)	128 (66.0%)	66 (66.7%)	
Race				
White	285 (43.3%)	76 (39.8%)	26 (26.3%)	0.02
Black	351 (53.3%)	105 (55.0%)	67 (67.7%)	
Other	21 (3.2%)	10 (5.2%)	6 (6.0%)	
$CD4^+$ lymphocyte count (cells/ml)	464 (322)	403 (302)	269 (230)	0.02 * 0.0001 **
HIV-1 RNA level (copies/ml)	35,744 (110,060)	53,688 (146,848)	97,161 (195,999)	0.08 * 0.04 **
Systolic blood pressure (mmHg)	123 (13)	126 (18)	121 (23)	0.08 * 0.34 **
Diastolic blood pressure (mmHg)	80 (10)	82 (11)	83 (16)	0.03 * 0.62 **
Creatinine (mg/dL)	0.95 (0.40)	0.99 (0.36)	1.18 (0.82)	0.31 *
SI units	83.98 (35.36)	87.56 (31.82)	104.31 (72.48)	0.005 **
Glomerular filtration rate (cc/min) by category				
>=90 cc/min	445 (67.6%)	112 (58.6%)	48 (48.5%)	<0.0001
60-90 cc/min	194 (29.5%)	64 (33.5%)	32 (32.3%)	
< 60 cc/min	19 (2.9%)	15 (7.8%)	19 (19.2%)	

Data is expressed as #(%) for categorical variables and mean (standard deviation) for continuous variables.

* Comparison of subjects with no detectableurine protein excretion to those with microalbuminuria

** Comparison of subjects with microalbuminuria to those with proteinuria

Table 2

Clinical and demographic characteristics of subjects by the availability of a follow-up urine exam

Variable	Follow up examinations	No follow up examination	P-value
Number of patients	698	250	
Age (years)*	44.2 (9.1)	42.2 (9.1)	0.003
Gender			
Women	187 (26.8%)	86 (34.4%)	0.02
Men	511(73.2%)	163 (65.2%)	
Race			
White	302 (43.3%)	85 (34.0%)	0.02
Black	366 (52.4%)	157 (62.8%)	
Other	30 (4.3%)	7 (2.8%)	
$CD4^+$ lymphocyte count (cells/ml)	441 (319)	400 (302)	0.08
HIV-1 RNA level (copies/ml)	44,673 (133,949)	48,391 (118,115)	0.71
Systolic blood pressure (mmHg)	124 (16)	124 (13)	0.83
Diastolic blood pressure (mmHg)	81 (11)	80 (11)	0.58
Creatinine (mg/dL)	1.0 (0.4)	1.0 (0.6)	0.54
SI units	88.4 (35.36)	88.4 (53.04)	
Glomerular filtration rate (cc/min) by category			
>=90 cc/min	430 (61.6%)	175 (70.0%)	0.06
60-90 cc/min	226 (32.4%)	64 (25.6%)	
<60 cc/min	42 (6.0%)	11 (4.4%)	
Urine protein excretion			
No abnormality	492 (70.5%)	166 (66.4%)	0.08
Microalbuminuria	129 (18.5%)	62 (24.8%)	
Proteinuria	77 (11.0%)	22 (8.8%)	

Data is expressed as #(%) for categorical variables and mean (standard deviation) for continuous variables.

Table 3

Clinical and demographic characteristics of subjects stratified on their initial and follow up urine exam

	Urine at baseline									
	(a) No detectable urine protein excretion				(b) Microalbuminuria			(c) Subjects without proteinuria (combination of those without abnormal urine protein excretion and those with microalbuminuria)		
Urine at next measurement	**No detectable urine protein excretion**	**Microalbuminuria**	**Proteinuria**	**P-value**	**No detectableurine protein excretion**	**Microalbuminuria or proteinuria**	**P-value**	**No proteinuria**	**Proteinuria**	**P-value**
N	388	77	26		60	69		576	44	
Age (years)	44.2 (9.2)	43.6 (8.0)	42.1 (9.8)	0.61 * 0.44 **	41.3 (8.0)	45.9 (9.1)	0.003	43.9 (9.0)	44.3 (9.5)	0.79
Gender (F/M)	99/289	18/59	8/18	0.75	17/43	24/45	0.43	150/426	16/28	0.14
Race										
White	173	36	11	0.69	27	32	0.83	260	19	0.80
Black	203	37	15		30	32		293	24	
Other	12	4	0		3	5		23	1	
$CD4^+$ lymphocyte (cells/ml)	480 (336)	442 (313)	352 (246)	0.36 * 0.19 ** 0.06 ***	438 (318)	441 (304)	0.95	469 (326)	374 (296)	0.06
HIV-1 RNA (copies/ml)	31,590 (111,198)	45,302 (123,577)	39,515 (65,155)	0.34 * 0.83 ** 0.73 ***	46,255 (134,911)	59,397 (159,752)	0.63	35,082 (115,842)	77,148 (161,665)	0.03
SBP (mmHg)	123 (13)	121 (14)	126 (11)	0.59 * 0.27 ** 0.35 ***	127 (14)	127 (22)	0.95	123 (15)	125 (12)	0.35
DBP (mmHg)	80 (9)	78 (11)	82 (9)	0.31 * 0.11 ** 0.14 ***	82 (11)	84 (11)	0.61	80 (10)	82 (8)	0.32
Serum creatinine (mg/dl)	0.94 (0.19)	0.98 (0.22)	0.95 (0.25)	0.11 * 0.56 **	0.95 (0.23)	1.02 (0.47)	0.10	0.95 (0.23)	1.02 (0.47)	0.10

	Urine at baseline									
	(a) No detectable urine protein excretion				(b) Microalbuminuria			(c) Subjects without proteinuria (combination of those without abnormal urine protein excretion and those with microalbuminuria)		
Urine at next measurement	**No detectable urine protein excretion**	**Microalbuminuria**	**Proteinuria**	**P-value**	**No detectableurine protein excretion**	**Microalbuminuria or proteinuria**	**P-value**	**No proteinuria**	**Proteinuria**	**P-value**
GFR (cc/min)	100 (21)	96 (23)	101 (24)	0.20 * 0.38 **	104 (30)	89 (28)	0.005	99 (23)	95 (30)	0.37
Microalbumin uria at baseline								111 (19%)	18 (41%)	0.001
Quantified levels of proteinuria			1193 mg (1648 mg)			1409 mg (1947 mg)				1292 mg (1785 mg)

Data is expressed as #(%) for categorical variables and mean (standard deviation) for continuous variables.

* Comparison of subjects with no detectableurine protein excretion to those with microalbuminuria

** Comparison of subjects with microalbuminuria to those with proteinuria

*** Comparison of subjects with no detectableurine protein excretion to those with proteinuria