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Risk Factors for Proteinuria in HIV-infected and -uninfected Hispanic Drug Users

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Abstract

Background—Proteinuria may be an early marker of chronic kidney disease in human immunodeficiency virus (HIV)-infected patients with coexisting chronic hepatitis and/or drug use. Minorities are at greater risk of chronic kidney disease. Data are limited on the risk factors for proteinuria in Hispanic drug users with and without HIV infection.

Study Design—A cross-sectional study.

Setting & Participants—A community-recruited Hispanic cohort to study the role of drug use in HIV-associated malnutrition, comprised of four groups (106 HIV-infected drug users; 96 HIV-uninfected drug users; 38 HIV-infected non-drug users; 47 healthy controls). Patients on renal replacement therapy were excluded.

Predictors—HIV infection, chronic hepatitis, history of hypertension or diabetes, and intravenous drug use (never, prior, or current).

Outcomes & Measurements—The presence of proteinuria was defined as urine dipstick >= 1+. Multivariable logistic regression was used to identify independent risk factors for proteinuria.

Results—Of 287 patients with available data, 24 (8.4%) had proteinuria. In univariate analyses, those with HIV infection, prior, but not current, intravenous drug use, and a history of hypertension or diabetes were more likely to have proteinuria. In multivariate analyses significant risk factors for

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proteinuria (OR, 95% CI) were HIV (9.2, 1.9 – 45.8, P=0.007), prior, but not current, intravenous drug use (4.7, 1.4 – 15.3, P=0.01), and a history of hypertension or diabetes (8.2, 3.1 – 21.7, P<0.001).

Limitations—The cross-sectional study design makes it difficult to establish the temporal relationship. The number of outcomes in relation to the number of predictors is small.

Conclusions—HIV and prior intravenous drug use, but not chronic hepatitis or current intravenous drug use, were independently associated with proteinuria in this Hispanic population. Longitudinal studies to assess the development of proteinuria and chronic kidney disease in this high-risk population are warranted.

Keywords

proteinuria; intravenous drug use; risk factor; HIV; renal; kidney

Introduction

Chronic kidney disease is an important co-morbid condition in human immunodeficiency virus (HIV)-infected patients, and current guidelines recommend that all patients undergo a kidney function assessment at time of HIV diagnosis.[1] Among HIV-infected patients, and particularly African Americans, HIV-associated nephropathy has been recognized as the most common form of nephropathy since the early years of the HIV epidemic. The incidence of HIV-associated nephropathy has declined dramatically with the widespread use of highly active antiretroviral therapy (HAART) over the past decade.[2] The pathogenesis of HIV-associated nephropathy is not clear, although direct viral involvement in the kidney is likely.[3–5] Both intravenous drug use and chronic hepatitis have been previously associated with kidney disease in persons not infected with HIV,[6;7] but their relative contribution in HIV-related kidney disease is not well described.

Persistent proteinuria is an early marker of kidney damage. Albuminuria is an especially sensitive marker for chronic kidney disease due to diabetes, hypertension, and glomerular diseases. In addition, proteinuria has been shown to be a risk factor for the progression of kidney disease.[8] Studies have shown an association between proteinuria or microalbuminuria and cardiovascular disease, cardiovascular mortality, and all-cause mortality in the general population.[9–11] In HIV patients, clinically significant proteinuria has been shown to be associated with the development of chronic kidney disease,[12] acquired immune deficiency syndrome (AIDS) defining illness, risk of death, and hospitalizations.[13]

Using data derived from a well-balanced cohort of Hispanics with problems of HIV /hepatitis co-infection and drug use (intravenous and non-intravenous), this study aimed to examine the risk factors for proteinuria. The specific interest was to disentangle the effects of HIV, chronic hepatitis and intravenous drug use.

Methods

The data used in the present study were derived for secondary analyses from the BIENESTAR study, which is a prospective cohort study of Hispanics to examine the roles of HIV, chronic hepatitis, and drug use in HIV/AIDS associated weight loss and malnutrition, conducted in Boston, USA. Kidney function and urinalysis were not the main outcome of the study, but were collected as explanatory variables since some micronutrients, such as vitamin A, are known to undergo partial renal excretion. A full description of the study participants and recruitment methods has been published elsewhere.[14] The open enrollment cohort of Hispanic adults was comprised of four groups: HIV-infected drug users (intravenous and non-intravenous drug use), HIV-uninfected drug users, HIV-infected persons who do not use drugs (non-drug users)

and healthy controls, defined as persons who reported a history of no chronic disease or drug use, and tested negative for HIV infection. Recruitment was done through outreach in streets, homeless shelters, urban health clinics and HIV support groups. Approximately half of the patients were recruited through announcements, flyers, or other participants in the community. The study participants were mostly of Puerto Rican origin, who are a mix of European (predominant), Amerindian, and African American race.[15] The inclusion criteria for the parent study were: self-identified Hispanic ethnicity; age over 18 years; Spanish fluency; HIV seropositive and/or current drug use. Exclusion criteria were: pregnancy at recruitment; non-HIV associated malignancies; refusal to sign a consent form to release medical records; and chronic renal replacement therapy. The Institutional Review Board at the Tufts-New England Medical Center (Boston, MA) approved the study, and informed consent was obtained from all participants.

Clinical data

Self-reported information on HIV history, HIV medications, and history of hypertension or diabetes was collected by standardized interview conducted in Spanish by Hispanic personnel. Drug use (intravenous and non-intravenous) was determined using a questionnaire that included items related to the type, mode and frequency of use. A participant was considered a drug user if he/she reported having used any one of heroin, cocaine, ‘speedball’ (heroin with cocaine) or methadone (prescription or non-prescription use) by any route at least once in the last six months. Other drugs, such as amphetamines, inhalants or barbiturates, were not considered in this study because the frequency of their use was low in this population. Alcohol and tobacco use were not considered drug use. Persons who reported marijuana use only were classified with the nonusers because marijuana and its legal derivatives are used as appetite stimulants among HIV-infected patients. Since the primary focus of our study was to investigate the effect of intravenous drug use on proteinuria, all patients, including healthy controls, were categorized into three mutually exclusive groups: 1) never intravenous drug use, 2) prior intravenous drug use, and 3) current intravenous drug use. Prior intravenous drug use included some current non-intravenous drug users as well as past intravenous drug users, and never intravenous drug use included some current and past non-intravenous drug users as well as healthy controls. For the analyses, the three categories of intravenous drug use were coded using two indicator variables, describing prior and current intravenous drug use, leaving never intravenous drug use as the reference category.

Laboratory data

Urine protein concentration was assessed semi-quantitatively in the clinical laboratories of the Tufts-New England Medical Center by commercial urine dipsticks using Clinitek Atlas® automated urine chemistry analyzer (Siemens, Tarrytown, N.Y. and Los Angeles, CA, USA). Urine protein concentrations with a single dipstick reading were interpreted as "none" or "trace" (<30mg/dL), "1+" (30–100mg/dL), "2+" (100–300mg/dL), "3+" (300–1000mg/dL), and "4+" (>1000mg/dL). Self-reported HIV status was confirmed by enzyme immunoassay (Genetic Systems TM HIV-1/HIV-2 Plus O EIA, Biorad Laboratories, Redmond, WA). HIV RNA was measured by reverse transcriptase polymerase chain reaction (PCR) with the Roche Amplicor Monitor (Roche Molecular Systems, Somerville, NJ, USA) which has a lower detection limit of 400 copies/ml. Undetectable viral loads were set to 200 copies/ml, the mid-point between 0 and 400. Absolute CD4 lymphocyte counts were assessed using a specific monoclonal antibody and fluorescence activated cell-sorting analysis. The presence in serum of hepatitis B surface antigen was determined with the Genetic Systems HBs Ag enzyme Immunoassay (EIA) 3.0 (Biorad Laboratories, Redmond, WA, USA). Antibody to the hepatitis B surface antigen (anti-HBs) was determined by EIA (DiaSorin Inc., Stillwater, MN, USA). The presence in serum of hepatitis C virus RNA was determined by PCR of cDNA (AMPLICOR Hepatitis C Virus test, Version 2.0; Roche Molecular Systems Inc., Branchburg,

NJ, USA). Chronic hepatitis was defined as either the presence of HbsAg without the presence of anti-HBs or the presence of hepatitis C viremia qualitatively. Glomerular filtration rate (GFR) was estimated by using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation.[16] The quantitative insulin check index (QUICKI) was used as a surrogate marker for insulin sensitivity, and was calculated using fasting glucose and insulin concentrations.[17]

Statistical Analyses

All analyses were done with SAS software, version 9.1 (SAS institute, Cary, NC, USA). The primary outcome of this study was the presence of proteinuria, defined as a reading greater than or equal to 1+ by urine dipstick. For patients with no available data for proteinuria at baseline but who were tested later, the data closest in calendar time to the baseline were used (n=8). We compared the characteristics of patients in each of the study groups and the characteristics of those with and without proteinuria. For the continuous variables with a normal distribution, differences between the groups were tested using the least squares means option in the SAS generalized linear models procedure. Continuous data with non-normal distribution were log transformed and the analyses conducted on the transformed data. When transformation did not adequately normalize the data, non-parametric tests were used. Categorical data were analyzed using either chi-square or Fisher's exact tests, where appropriate. Analyses were conducted on variables that were deemed potential risk factors for proteinuria including: age, sex, body mass index, serum creatinine, estimated GFR (eGFR), history of hypertension or diabetes, chronic hepatitis, intravenous drug use, and HIV infection. To summarize the effects of confounders more efficiently, we constructed a new variable defined as a history of either hypertension or diabetes. Multivariate logistic regression analyses were conducted using variables that were shown to be associated with proteinuria at a level of significance of $P<0.05$ in univariate analyses.

Results

There were 292 patients eligible for the present study: 107 HIV-infected drug users; 97 HIV-uninfected drug users; 38 HIV-infected non-drug users; and 50 healthy controls. Proteinuria data were available for this sub-study from 287/292 (98%) patients, and missing for 5 patients: one HIV-infected drug users, one HIV-uninfected drug users, and three healthy controls. The clinical data of the 287 patients according to the study group are shown in Table 1. HIV-infected drug users and non-drug users were slightly older than HIV-uninfected drug users and healthy controls. There were fewer men among HIV-infected non-drug users and healthy controls. The overall prevalence of proteinuria was 8.4% (24/287). All healthy controls had normal laboratory values by definition.

Clinical data

The clinical data of the 287 patients according to the presence and absence of proteinuria are shown in Table 2. There were no significant differences in age, sex, or body mass index between patients with or without proteinuria. Kidney function measured by serum creatinine and eGFR was similar between the two groups and was within normal ranges. Patients with proteinuria were more likely than those without to have history of hypertension, or diabetes. Patients with proteinuria had lower median QUICKI values. A greater proportion of patients with proteinuria were HIV infected and reported prior, but not current, intravenous drug use. There was no difference between the two groups in the proportion of patients with chronic hepatitis.

Characteristics of HIV-infected patients

Compared with HIV-uninfected patients, the 144 HIV-infected patients (50%) were more likely to have history of diabetes (11% vs. 3%, P=0.006) but not hypertension (14% vs. 11%,

P=0.5). Median log viral load was 2.7 $\log_{10}$ copies/ml (25^{th}–75^{th} percentiles: 2.3–4.3) with 48% having undetectable viral load. Median CD4 cell count was 350 cells/mm^3 (25_{th}–75_{th} percentiles: 219–589) with 22% having less than 200 cells/mm^3. Proteinuria was more common among HIV-infected patients compared to HIV-uninfected patients (15% vs. 1%, P < 0.001). The degree of proteinuria in 144 HIV-infected patients was as follows - none: 108 (75%), trace: 14 (10%), 1+: 10 (7%), 2+: 9 (6%), 3+: 3 (2%). In the 143 HIV-uninfected patients, the corresponding values were 131 (92%), 10 (7%), 1 (1%), 1 (1%), and 0 (0%). Between HIV-infected patients with and without proteinuria, there was no difference in median log viral load or in the proportion of patients with undetectable viral load. However, there was a trend among those with proteinuria toward a lower CD4 cell count and a greater proportion with CD4 cell count less than 200. There was a trend toward more tenofovir use among those with proteinuria (45% vs. 25%, P=0.06) but there was no difference in the use of non-nucleoside reverse transcriptase inhibitor (18% vs. 32%, P=0.2).

Risk factors for the presence of proteinuria

The prevalence of proteinuria in relation to the presence of history of hypertension or diabetes, HIV, chronic hepatitis or intravenous drug use is shown in Table 3. Table 4 shows unadjusted (univariate) and adjusted (multivariate) odds ratios and 95% confidence intervals for risk factors for proteinuria. In univariate analyses, HIV infection and prior, but not current, intravenous drug use were associated with the presence of proteinuria in addition to history of hypertension or diabetes. Chronic hepatitis was not associated with proteinuria. In multivariate analyses, HIV infection, prior intravenous drug use, and history of hypertension or diabetes were significant predictors of proteinuria. The conclusions were not altered when history of hypertension and diabetes were used as two separate variables in the multivariate analyses (data not presented).

Discussion

In a cohort of Hispanic drug users with and without HIV infection, the risk factors associated with the presence of proteinuria were found to be HIV infection, and prior, but not current, intravenous drug use. Chronic hepatitis, a factor of specific interest, was not associated with proteinuria.

The association of HIV infection with proteinuria we found is consistent with the study by Gardner et al in which HIV-infected women were more likely to develop proteinuria compared to HIV-uninfected women.[18] A recent study also found a strong and independent association of HIV infection with microalbuminuria in a large cohort of HIV-infected and -uninfected men and women.[19] We found HIV infection to be a risk factor for proteinuria independently of intravenous drug use, and chronic hepatitis.

Our study found a strong association of prior, but not current, intravenous drug use with the presence of proteinuria. Glomerular abnormalities were first described in heroin users in the early 1970s, even before the AIDS epidemic.[20–22] Heroin-associated nephropathy is a syndrome of massive proteinuria following prolonged heroin use, progressing to end stage renal disease.[23] Heroin-associated nephropathy was hypothesized to be caused by an immunological reaction to the injected substances, or to contaminating microbial antigens.[24] However, serologic testing was not available for HIV and hepatitis C virus until mid 1980s and early 1990s, respectively, making it impossible to separate the contributions of intravenous drug use, HIV and hepatitis C to kidney disease. In the early 1990's, as HIV-associated nephropathy became more common, heroin-associated nephropathy almost disappeared, possibly due to the increased purity of heroin.[25] In our study, prior intravenous drug users were older and had a longer history of drug use, and therefore may have had more exposure to impure substances compared with current users. However, there may be other unknown

differences between prior and current intravenous drug users, such as more exposure to other nephrotoxins.

Our study did not show any association between chronic hepatitis and proteinuria. Chronic hepatitis C, a common co-infection with HIV in intravenous drug users, is associated with glomerulopathy, including membranoproliferative glomerulonephritis with or without associated mixed cryoglobulinemia and membranous glomerulopathy. Hepatitis B antigenemia has also been associated with glomerulonephritis, mainly membranous nephropathy. A previous study of 2059 HIV-infected women found that hepatitis C antibody positivity was associated with proteinuria independently of its association with intravenous drug use or other demographic or clinical variables.[26] The authors suggested that concurrent infection with hepatitis C may result in a greater risk for the occurrence of kidney disease in HIV-infected patients. Other studies have also demonstrated an association between hepatitis C antibody positivity and the presence of either proteinuria or microalbuminuria.[27–30] Most of these studies did not adjust for HIV serostatus or intravenous drug use specifically, making it difficult to rule out the possibility of confounding effects by either factor. Our study was able to isolate the effect of chronic hepatitis on proteinuria by adjusting for HIV infection and intravenous drug use, and did not find any association of chronic hepatitis with proteinuria.

Although African American race has been found to be a strong risk factor for HIV-associated nephropathy,[31–33] little data are available on the risk of kidney diseases in HIV-infected Hispanics. To our knowledge, this is the first study to examine the risk factors of proteinuria in a cohort of Hispanics with and without HIV infection. HIV-infected patients with proteinuria, especially those with diabetes or hypertension, may be particularly at high risk of developing chronic kidney disease, as shown by Gupta et al[12]. Since Hispanics, now the largest minority groups in the United States, are twice as likely to develop kidney failure as non-Hispanic whites, largely due to the higher prevalence of diabetes mellitus in the Hispanic population,[34;35] they should be regarded as a group at high risk of developing HIV-related kidney dysfunction.

The greatest strength of our study is the community-based recruitment strategy, which was initially done through outreach in streets, homeless shelters, urban health clinics and HIV support groups, and later through participants themselves. Patients were recruited only based on self-reported HIV infection and drug use status regardless of their clinical status. This enabled us to avoid the selection bias that can result from clinic-based studies, and to create a cohort more representative of the Hispanic drug user community. Specifically, for kidney disease, the only exclusion criterion was chronic renal replacement therapy. Thus, the prevalence of proteinuria in each group is likely representative of that present in the community. Secondly, our cohort was well balanced between those with and without the potential risk factors (HIV, intravenous drug use, chronic hepatitis etc), which enabled us to adequately examine the independent association of each factor with proteinuria. Thirdly, although small in sample size, we were able to collect detailed information on drug use that larger studies did not, making it possible to assess the effect of current vs. prior intravenous drug use on proteinuria separately.

There are a few important limitations to our study. The cross-sectional study design makes it difficult to establish the temporal relationship between identified risk factors and the development of proteinuria. There were a small number of outcomes in relation to the number of predictors, which may cause our multivariate regression model to be overfit. By defining the proteinuria as greater than or equal to 1+ by a single urine dipstick measurement without confirmatory follow up tests, we might have misclassified some patients. Although the study cohort was community based, it was not a probability based sample but a convenience sample based on volunteers. Lastly, the history of hypertension and diabetes was self-reported, and

therefore no objective diagnostic assessments, such as blood pressure measurement, were available at the time of proteinuria measurement.

In summary, our study found that HIV infection, and prior intravenous drug use, but not chronic hepatitis were independently associated with the presence of proteinuria in this Hispanic population. Urine dipstick is considered the easiest and most practical way of screening for sub-clinical kidney disease in routine clinic settings. HIV-infected Hispanics with a prior history of intravenous drug use, particularly those with hypertension or diabetes, may be at high risk of proteinuria, and therefore should be screened routinely. Future investigations in this high-risk population should be directed toward studying the natural history of proteinuria and chronic kidney disease, and the use of microalbuminuria as a screening test for kidney disease. There is a need for effective interventions to slow the progression of kidney disease in these high-risk populations.

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REFERENCES

1. Gupta SK, Eustace JA, Winston JA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis 2005;40:1559–1585. [PubMed: 15889353]
2. Lucas GM, Eustace JA, Sozio S, Mentari EK, Appiah KA, Moore RD. Highly active antiretroviral therapy and the incidence of HIV-1-associated nephropathy: a 12-year cohort study. AIDS 2004;18:541–546. [PubMed: 15090808]
3. Bruggeman LA, Ross MD, Tanji N, et al. Renal epithelium is a previously unrecognized site of HIV-1 infection. J Am Soc Nephrol 2000;11:2079–2087. [PubMed: 11053484]
4. Marras D, Bruggeman LA, Gao F, et al. Replication and compartmentalization of HIV-1 in kidney epithelium of patients with HIV-associated nephropathy. Nat Med 2002;8:522–526. [PubMed: 11984599]
5. Green DF, Resnick L, Bourgoignie JJ. HIV infects glomerular endothelial and mesangial but not epithelial cells in vitro. Kidney Int 1992;41:956–960. [PubMed: 1513116]
6. Rao TK, Nicastri AD, Friedman EA. Natural history of heroin-associated nephropathy. N Engl J Med 1974;290:19–23. [PubMed: 4128109]
7. Johnson RJ, Gretch DR, Yamabe H, et al. Membranoproliferative glomerulonephritis associated with hepatitis C virus infection. N Engl J Med 1993;328:465–470. [PubMed: 7678440]
8. Peterson JC, Adler S, Burkart JM, et al. Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. Ann Intern Med 1995;123:754–762.
9. Grimm RH Jr. Svendsen KH, Kasiske B, Keane WF, Wahi MM. Proteinuria is a risk factor for mortality over 10 years of follow-up. MRFIT Research Group. Multiple Risk Factor Intervention Trial. Kidney Int 1997;52:S10–S14.
10. Wagner DK, Harris T, Madans JH. Proteinuria as a biomarker: risk of subsequent morbidity and mortality. Environ Res 1994;66:160–172. [PubMed: 8055838]
11. Hillege HL, Fidler V, Diercks GF, et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation 2002;106:1777–1782. [PubMed: 12356629]

12. Gupta SK, Mamlin BW, Johnson CS, Dollins MD, Topf JM, Dube MP. Prevalence of proteinuria and the development of chronic kidney disease in HIV-infected patients. Clin Nephrol 2004;61:1–6. [PubMed: 14964451]
13. Szczech LA, Hoover DR, Feldman JG, et al. Association between renal disease and outcomes among HIV-infected women receiving or not receiving antiretroviral therapy. Clin Infect Dis 2004;39:1199–1206. [PubMed: 15486845]
14. Forrester JE, Tucker KL, Gorbach SL. Dietary intake and body mass index in HIV-positive and HIV-negative drug abusers of Hispanic ethnicity. Public Health Nutr 2004;7:863–870. [PubMed: 15482611]
15. Choudhry S, Coyle NE, Tang H, et al. Population stratification confounds genetic association studies among Latinos. Hum Genet 2006;118:652–664. [PubMed: 16283388]
16. Levey AS, Greene T, Kusek JW, Beck GJ. MDRD Study Group. A simplified equation to predict glomerular filtration rate from serum creatinine[abstract]. J Am Soc Nephrol 2000;11:155A.
17. Katz A, Nambi SS, Mather K, et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000;85:2402–2410. [PubMed: 10902785]
18. Gardner LI, Holmberg SD, Williamson JM, et al. Development of proteinuria or elevated serum creatinine and mortality in HIV-infected women. J Acquir Immune Defic Syndr 2003;32:203–209. [PubMed: 12571531]
19. Szczech LA, Grunfeld C, Scherzer R, et al. Microalbuminuria in HIV infection. AIDS 2007;21:1003–1009. [PubMed: 17457094]
20. McGinn JT, McGinn TG, Cherubin CE, Hoffman RS. Nephrotic syndrome in drug addicts. N Y State J Med 1974;74:92–95. [PubMed: 4521711]
21. Kilcoyne MM, Gocke DJ, Meltzer JI, et al. Nephrotic syndrome in heroin addicts. Lancet 1972;1:17–20. [PubMed: 4108817]
22. Eknoyan G, Gyorkey F, Dichoso C, et al. Renal involvement in drug abuse. Arch Intern Med 1973;132:801–806. [PubMed: 4127933]
23. Dettmeyer RB, Preuss J, Wollersen H, Madea B. Heroin-associated nephropathy. Expert Opin Drug Saf 2005;4:19–28. [PubMed: 15709895]
24. Bakir AA, Dunea G. Drugs of abuse and renal disease. Curr Opin Nephrol Hypertens 1996;5:122–126. [PubMed: 8744532]
25. Friedman EA, Tao TK. Disappearance of uremia due to heroin-associated nephropathy. Am J Kidney Dis 1995;25:689–693. [PubMed: 7747721]
26. Szczech LA, Gange SJ, van der HC, et al. Predictors of proteinuria and renal failure among women with HIV infection. Kidney Int 2002;61:195–202. [PubMed: 11786101]
27. Huang JF, Chuang WL, Dai CY, et al. Viral hepatitis and proteinuria in an area endemic for hepatitis B and C infections: another chain of link? J Intern Med 2006;260:255–262. [PubMed: 16918823]
28. Liangpunsakul S, Chalasani N. Relationship between hepatitis C and microalbuminuria: results from the NHANES III. Kidney Int 2005;67:285–290. [PubMed: 15610253]
29. Muramatsu T, Hora K, Ako S, Tachibana N, Hora K, Tanaka E. The role of hepatitis C virus infection in glomerulopathy. Hepatol Res 2000;18:190–202. [PubMed: 11058824]
30. Tsui JI, Vittinghoff E, Shlipak MG, O'Hare AM. Relationship between hepatitis C and chronic kidney disease: results from the Third National Health and Nutrition Examination Survey. J Am Soc Nephrol 2006;17:1168–1174. [PubMed: 16524948]
31. Frassetto L, Schoenfeld PY, Humphreys MH. Increasing incidence of human immunodeficiency virus-associated nephropathy at San Francisco General Hospital. Am J Kidney Dis 1991;18:655–659. [PubMed: 1962649]
32. Shahinian V, Rajaraman S, Borucki M, Grady J, Hollander WM, Ahuja TS. Prevalence of HIV-associated nephropathy in autopsies of HIV-infected patients. Am J Kidney Dis 2000;35:884–888. [PubMed: 10793023]
33. Carbone L, D'Agati V, Cheng JT, Appel GB. Course and prognosis of human immunodeficiency virus-associated nephropathy. Am J Med 1989;87:389–395. [PubMed: 2801729]

34. National Institute of Health. Strategic development and planning meeting baseline report. Bethesda, MD: National Institute of Health: National Institute of Diabetes and Digestive and Kidney; 2001.

35. US renal data system. USRDS 2001 annual report: atlas of ESRD in the US. Bethesda, MD: National Institute of Health: National Institute of Diabetes and Digestive and Kidney; 2001.

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Demographic and Clinical Characteristics of Patients

	Group 1 HIV-infected DU (n=106)	**Group 2 HIV-uninfected DU (n=96)**	**Group 3 HIV-infected non-DU (n=38)**	**Group 4 Healthy Control (n=47)**	**P value[a]**
Age, years	40.7 (0.9)[b]	36.5 (0.9)[b]	40.7 (1.5)[b]	37.7 (1.3)[b]	<0.01
Sex (men)	82 (77)	72 (75)	17 (45)	17 (36)	<0.001
Proteinuria	21 (20)	1 (1)	1 (3)	1 (2)	<0.001
Body mass index (kg/m^2)	27.4 (0.6)	28.0 (0.6)	27.5 (1.0)	28.3 (0.9)	0.8
Creatinine (mg/dL)	0.85 (0.02)[c]	0.83 (0.02)[c]	0.78 (0.03)[c]	0.76 (0.03)[c]	0.02
eGFR (ml/min/1.73m^2)	106.0 (2.2)	107.2 (2.3)	106.8 (3.7)	107.9 (3.3)	0.9
QUICKI	0.325 (0.005)[d]	0.332 (0.004)[d]	0.347 (0.009)[d]	0.353 (0.006)[d]	<0.01
Chronic hepatitis[e]	76 (72)	51 (54)	7 (18)	0 (0)	
History of hypertension[e]	14 (13)	16 (17)	6 (16)	0 (0)	
History of diabetes[e]	11 (10)	4 (4)	5 (13)	0 (0)	
Intravenous drug use[e, f]					
Never IDU	27 (25)	28 (29)	37 (97)	47 (100)	
Prior IDU	57 (54)	23 (24)	1 (3)	0 (0)	
Current IDU	22 (21)	45 (47)	0 (0)	0 (0)	
HIV infection					
HIV RNA level, $\log_{10}$copies/ml	2.8 (2.3 – 4.4)	N/A	2.3 (2.3 – 3.7)	N/A	0.5
HIV RNA level <400 copies/ml	49 (46)	N/A	19 (51)	N/A	0.6
CD4 cell count, cells/mm^3	343 (201 – 578)	N/A	401 (268 – 617)	N/A	0.2
CD4 cell count < 200 cell/mm^3	26 (25)	N/A	5 (14)	N/A	0.2

[a] Test used: continuous variables, F-test or Wilcoxon test; categorical variables, Chi-square or Fisher's exact test.

[b] Group 1 vs. Group 2, P=0.001; Group 2 vs. Group 3, P=0.02

[c] Group 1 vs. Group 3, P=0.05; Group 1 vs. Group 4, P=0.008; Group 2 vs. Group 4, P=0.03

[d] Group 1 vs. Group 3, P=0.04; Group 1 vs. Group 4, P<0.001; Group 2 vs. Group 4, P=0.005

[e] The distributions of these variables were a result of the recruitment strategy.

[f] All patients were categorized into one of three IDU groups (never, prior, current). Never IDU include patients with non-intravenous drug use.

Note: Data are number (percent), mean (SE), or median (25^{th}–75^{th} percentiles). To convert serum creatinine in mg/dL to µmol/L, multiply by 88.4; eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667.

Abbreviations: HIV, human immunodeficiency virus; DU, drug user (intravenous and non-intravenous); eGFR, estimated glomerular filtration rate; QUICKI, quantitative insulin check index; IDU, intravenous drug use; N/A, not applicable.

Table 2

Demographic and Clinical Characteristics of Patients With and Without Proteinuria

	Without Proteinuria (n=263)	With Proteinuria (n=24)	P Value[a]
Age, years	38.8 (0.6)	39.0 (1.9)	0.9
Sex (men)	173 (66)	15 (63)	0.7
Body mass index (kg/m^2)	27.6 (0.4)	29.3 (1.2)	0.2
Serum creatinine (mg/dL)	0.82 (0.01)	0.82 (0.04)	0.9
eGFR (ml/min/1.73m^2)	106.5 (1.4)	110.3 (4.6)	0.4
History of hypertension	29 (11)	7 (29)	0.02
History of diabetes	10 (4)	10 (42)	<0.001
QUICKI	0.34 (0.31–0.36)	0.31(0.30–0.33)	0.03
HIV infection	122 (46)	22 (92)	<0.001
HIV RNA level, $\log_{10}$ copies/ml	2.3 (2.3–4.2)	3.5 (2.3–4.5)	0.1
HIV RNA level <400 copies/ml	61 (50)	7 (32)	0.1
CD4 cell count, cells/mm^3	392 (228–617)	251 (148–422)	0.07
CD4 cell count < 200 cells/mm^3	23 (19)	8 (36)	0.09
On HAART	89 (73)	17 (77)	0.7
Chronic hepatitis	121 (46)	13 (54)	0.5
Intravenous drug use			<0.001
Never IDU	134 (51)	5 (21)	
Prior IDU	66 (25)	15 (63)	
Current IDU	63 (24)	4 (17)	

[a] Test used: continuous variables, F-test or Wilcoxon test; categorical variables, Chi-square or Fisher's exact test.

[b] All patients were categorized into one of three IDU groups (never, prior, current). Never IDU include patients with non-intravenous drug use.

Note: Data are number (percent), mean (SE), or median (25^{th}–75^{th} percentiles). To convert serum creatinine in mg/dL to μmol/L, multiply by 88.4; eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667.

Abbreviations: QUICKI, quantitative insulin check index; HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; IDU, intravenous drug use; eGFR, estimated glomerular filtration rate.

Table 3

The Prevalence of Proteinuria in relation to the Presence of Hypertension or Diabetes, HIV, Chronic Hepatitis, and Intravenous Drug Use

	Hypertension or Diabetes (n=52)	No Hypertension or Diabetes (n=235)
HIV (+)	13/33 (39)	9/111 (8)
HIV (−)	1/19 (5)	1/124 (1)
Chronic hepatitis (+)	7/25 (26)	6/109 (6)
Chronic hepatitis (−)	7/27 (26)	4/125 (3)
Never IDU	3/22 (14)	2/117 (2)
Prior IDU	9/18 (50)	6/63 (10)
Current IDU	2/12 (17)	2/55 (4)

Note: Data are number (percent).

Abbreviations: HIV, human immunodeficiency virus; IDU, intravenous drug use.

Table 4

Risk Factors Associated With Proteinuria in Univariate and Multivariate Logistic Regression Models

Variables	Unadjusted (Univariate) Odds Ratio (95% CI)	P Value	Adjusted (Multivariate) Odds Ratio (95% CI)	P Value
HIV	12.7 (2.9–55.2)	<0.001	10.2 (2.2 – 48.3)	0.003
Chronic hepatitis	1.4 (0.6 – 3.2)	0.5		
Intravenous drug use:				
Prior IDU[a]	6.1 (2.1 – 17.5)	<0.001	5.2 (1.6 – 16.4)	0.005
Current IDU[a]	1.7 (0.4 – 6.6)	0.4	2.8 (0.6 – 12.3)	0.2
Hypertension or Diabetes	8.3 (3.4 – 20.0)	<0.001	8.2 (3.1 – 21.7)	<0.001

[a]Reference category is never IDU.

Note: Variables tested in the model but not found to be significant include age, sex, body mass index, and serum creatinine.

Abbreviations: HIV, human immunodeficiency virus; IDU, intravenous drug use.