The Morbidity and Mortality Associated with Kidney Disease in an HIV-infected Cohort in Puerto Rico

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Introduction: Nephropathy in HIV-infected patients has been associated with progression to AIDS and death. The virus, several co-morbid conditions and certain medications may contribute to the development and progression of kidney disease.

Methods: This study analyzed data collected from HIV-infected persons enrolled in a HIV registry in Puerto Rico during January 1998 through September 2006. Demographic factors, clinical manifestations, laboratory findings at enrollment, and antiretroviral therapy (ART) prescriptions were compared between patients with and without kidney disease. Death status and cause of death by December 2006 were also evaluated and compared.

Results: The study included 1,283 subjects, 69.0% male, 39.7% injecting drug users, 19.5% hepatitis C infected, 6.5% with diabetes mellitus (DM-2), 11.6% had hypertension (HTN) and 9.0% had kidney disease. Patients with kidney disease had significantly higher ($P<.05$) HIV viral load mean (273,499 vs 202,858 copies/mL), CD4 T-cell count < 200 (57.0% vs 44.4%), underweight (22.9% vs 10.9%), DM-2 (13.9% vs 5.8%), HTN (27.8% vs 10.0%) and mortality (15.9 vs 5.7 deaths per 100 years of follow-up) than those without it. Cox proportional hazard analysis showed that patients with kidney disease had a higher mortality risk (2.1) after controlling for age, sex, HIV risk factor, ART prescription in the last year and HIV disease duration.

Conclusions: This study demonstrated a substantial disparity in mortality for Puerto Rican HIV-infected patients with nephropathy. Kidney disease preventive strategies that include aggressive control of HIV-infection and chronic medical conditions, such as hypertension and diabetes, are recommend as an approach to reduce this health disparity. (*Ethn Dis*. 2010;20[Suppl 1]:S1-163–S1-167)

Key Words: Kidney Disease, Hispanic, HIV

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Introduction

The patterns of mortality among HIV-infected persons have been changing with the introduction of highly active antiretroviral therapy (HAART). More specifically, the presence of kidney disease has been increasing as a cause of death among HIV-infected patients. National trends derived from US death certificates among persons with HIV demonstrate that, from 1987 through 1999, the proportion of deaths associated with kidney disease accounted for 10.4%.[1] Similarly, mortality trends of a HIV-infected cohort followed in Puerto Rico since 1992 revealed an increase of renal disease as a clinical condition reported as a cause of death. With the introduction of HAART in Puerto Rico, kidney disease was associated as a cause of death in 7.3% of patients as compared to 6.3% before HAART.[2] While a decrease in AIDS-related opportunistic conditions has been documented, an increase in the presence of chronic conditions such as diabetes mellitus type 2 (DM-2), cardiovascular diseases (CVDs) and renal diseases have become more relevant in defining the prognosis among HIV-infected subjects.[3,4] The presence of kidney disease has been associated with the severity of HIV infection, rate of progression to AIDS, increased mortality, and has been identified as cause of hospital admissions.[4,5] Survival is adversely affected by the presence of end-stage renal disease particularly in the absence of antiretroviral therapy.[6,7]

The pathogenesis of kidney disease in HIV-infected patient is frequently multifactorial with a number of specific entities well-defined, including HIV-associated nephropathy (HIVAN) and diabetic nephropathy, among others.[8] While HIVAN has been described as occurring overwhelmingly in persons of African or Haitian descent, there is limited data describing the epidemiology of kidney disease in a Hispanic cohort and no published data from Puerto Rico.

Puerto Rico has a high prevalence of HIV and has the largest concentration of Hispanics within the United States and its territories.[9,10] National data on abnormal kidney function and chronic kidney disease are not available for Hispanic HIV-infected patients. The availability of this data is relevant for the planning of evidence-based prevention activities that may prolong the lives of the affected population. The present study examines the epidemiology of HIV-infected patients with and without kidney disease and the risk for death associated to kidney disease.

Methods

Study Population

The study evaluated the prevalence of kidney disease among a cohort of adult HIV-infected persons who entered the Retrovirus Research Center (RRC) at Bayamon, Puerto Rico between January 1998 through September 2006 and that had at least one serum creatinine measure. Demographic factors, clinical manifestations, laboratory findings, and antiretroviral therapy (ART) prescriptions at enrollment or

in the previous 12 months were compared between patients with and without kidney disease. Study participants were followed up to death or study end by December 2006 at the Ramón Ruiz Arnau University Hospital or in the HIV ambulatory clinic at our institution. The study was conducted with the approval of the institutional review board (IRB) of the Universidad Central del Caribe.

Once an informed consent was obtained, a baseline questionnaire was completed and laboratory testing was performed including CD4+ T-lymphocyte count, HIV viral load, HCV viral load (if co-infected), white and red blood cell count and a comprehensive panel of tests that included creatinine. Enrollment included a retrospective abstraction of clinical data and laboratory findings from the last 12 months. HIV risk behaviors and sociodemographic data were gathered via face-to-face 30-minute interviews. The information was supplemented with medical record abstractions, which included diseases, laboratory data, therapy-related information and medical complications. The AIDS-defining illnesses, including *Pneumocystis jirovecii* pneumonia (PJP), cerebral toxoplasmosis (CT), recurrent bacterial pneumonia (RP), pulmonary tuberculosis (PTb), and Kaposi's sarcoma (KS), were evaluated. HIV disease duration was estimated based on the initial positive HIV test reported. Kidney disease was defined as a glomerular filtration rate (GFR) below 60mL/min. The GFR was estimated by the Modification of Diet in Renal Disease (MDRD) equation that included standardized serum creatinine level, age and sex.[11] GFR was expressed in millimeters per minute per 1.73 m^2. The participants were considered to have a history of DM-2 or hypertension (HTN) if this was documented in the medical record. Body mass index (BMI) was calculated using weight divided by height squared (kg/m^2). Participants were classified as underweight if their BMI was <18.5 kg/m^2. Prescription of antiretroviral therapies (ART), including nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI) were also collected. The use of HAART was defined as the use of three or more antiretroviral drugs in the same regimen at or before enrollment.

Mortality analysis used death status available through December 2006. Mortality data were obtained from a review of the institutional medical records and the Puerto Rican AIDS surveillance system. The Puerto Rico demographic mortality registry was also used to establish date and certificate-based causes of death. The reported causes of death were tabulated and organized into systems or organ failure.

Statistical Analysis

The Statistical Package of Social Sciences (SPSS, Chicago, Ill.) program was used to perform univariate, and bivariate analyses. Differences between patients with and without kidney disease including enrollment findings, mortality rates and causes of death were analyzed with the Chi-square or Fisher exact test, and the student *t* test. Odds ratios and 95% confidence intervals (CI) were presented. In addition, Cox proportional hazard analysis with relevant covariates, including variables with *P* values $\leq .05$ in the bivariate analyses, were use to evaluate mortality risk in the cohort. The data were presented as mortality hazard ratios (HR) with their 95% CI. A *P* value $\leq .05$ was considered to be statistically significant.

RESULTS

General Findings

Of the 1,518 HIV-infected patients who visited the RRC during the study period, 1,440 entered the HIV cohort. Of them, 1,283 persons had at least one measure of serum creatinine level at enrollment. Among those with creatinine data, 69.0% were male, the mean educational level was below 9th grade, and the HIV transmission risk factor were 39.7%, injection drug users (IDU) and 27.3% men who have sex with men (MSM). The mean age was 40.8 $\pm$ 9.6 year. Approximately 2.3% had a history of PJP, 2.1% CT, 0.5% RP, 0.5% KS, 19.5% HCV, 11.6% HTN and 6.5% DM-2 at study entry (data not shown). A CD4+T cell count <200 cells/μl was observed in 45.3%, 9.0% had moderate-to-severe kidney disease with a GFR estimated by the MDRD study equation below 60mL x min, 11.9% were underweight and 57.3% had received HAART at enrollment or in the previous 12 months.

Characteristics of Patients with and without Kidney Disease

Patients with kidney disease were more likely to have a CD4+ T cell count <200 cells/μL, higher HIV mean viral load, and higher prevalence of underweight, CT, DM-2 and HTN at enrollment than patients without kidney disease (Table 1). Patients without kidney disease were more likely to be prescribed with HAART than those with kidney disease (Table 1).

Mortality Findings

Among the 1,283 HIV-infected patients, 323 (25.2%) had died at the end of the observation period, with a significantly higher mortality in patients with kidney disease (15.9 vs. 5.7 deaths per 100 years of follow up). Bivariate analysis demonstrated that patients with kidney disease were more likely to die during follow-up than those without kidney disease (OR = 5.2, 95% CI 2.18-12.48). Death was significantly more likely to be attributed to kidney disease and less likely to be attributed to liver disease among the patients with kidney disease (Table 2). Cox proportional hazard analysis confirmed that patients with kidney disease had a higher mortality than those without it (HR= 2.12, 95% CI1.50-3.00), after

Table 1. Demographic, clinical manifestations and outcome by study group

	With kidney disease *n*=115 (9.0%)	Without kidney disease *n*=1,168 (91.0%)	Odds ratio (95%CI)
Male (%)	62.6	69.6	0.73 (0.49–1.08)
HIV disease duration (mean)	4.8±4.7	4.9±4.6	-
Mean age at GRF (years)	44.1±10.1	40.4±9.4*	-
Mean time HIV-GRF (years)	3.5±4.7	3.6±4.6	-
Mean time GRF-Last (years)	2.7±2.7	3.9±2.6*	-
Injecting drug use (%)	47.0	39.0	1.38 (0.94–2.03)
Men sex with men (%)	21.2	27.8	0.70 (0.38–1.29)
Mean CD4+ cell count/µl	255±280	299±273	-
CD4+ T cell< 200/µl (%)	57.0	44.4†	1.66 (1.08–2.55)
Mean HIV viral load/mL	273,499±274,000	202,858±200,000†	-
Body Mass Index (%)			
Underweight	22.9	10.9*	1.92 (1.15–3.23)
Normal	52.4	48.1	Ref.
Overweight	14.3	28.3	0.46 (0.26–083)
Obese	10.5	12.7	0.76 (0.39–1.49)
Clinical manifestation (%)			
Diabetes mellitus type 2	13.9	5.8*	2.61 (1.46–4.68)
Hypertension	27.8	10.0*	3.46 (2.21–5.43)
PJP	4.3	2.1	2.08 (0.78–5.54)
Pulmonary tuberculosis	0.0	0.9	0.99 (0.99–1.00)
Cerebral toxoplasmosis	7.8	1.5*	5.43 (2.38–12.37)
Recurrent pneumonia	1.7	0.4	4.12 (0.79–21.46)
Kaposi's sarcoma	0.0	0.6	0.99 (0.99–1.00)
Esophageal candidiasis	7.8	4.7	1.72 (083–3.57)
Pulmonary candidiasis	0.9	0.2	5.11 (0.46–56.83)
HCV co-infection	20.9	19.3	1.09 (0.69–1.76)
HAART (%)	37.4	59.2*	0.41 (0.28–0.61)
Use of NRTI (%)	44.3	64.5*	0.44 (0.30–0.65)
Use of NNRTI (%)	4.3	12.4*	0.32 (0.13–0.80)
Use of PI (%)	33.0	47.7*	0.54 (0.36–0.81)
Mortality rate (%)	55.7	22.2*	4.40 (2.97–6.52)
Mortality (deaths × 100 years)	15.9	5.7*	

* $P<.01$ between kidney disease groups.

† $P<.05$ between kidney disease groups.

CI= confidence interval; GRF=glomerular filtration rate; PJP= pneumocystic jirovecii pneumonia; HCV= hepatitis C virus; HAART= highly active antiretroviral therapy; NRTI= nucleoside reverse transcriptase inhibitors; NNRTI= non nucleoside reverse transcriptase inhibitors; PI= protease inhibitors.

controlling for age, sex, estimated HIV disease duration, underweight, history of IDU, CD4+ T cell count, HTN, DM-2, HCV seropositive status, prevalent AIDS-defining conditions and history of HAART prescription. Additionally, mortality was associated with IDU, DM-2, underweight, PJP, lower CD4+T cell count, and the absence of HAART. (Table 3)

DISCUSSION

Most of the reported data about renal disease in HIV-infected patients are derived from studies in which there are few Hispanics. African Americans experience the highest rate of HIV infection and chronic kidney disease in the US.[12,13] The data from this study provide an estimate of the prevalence of kidney disease in Hispanic HIV-infected patients and more specifically in Puerto Ricans. The 9% prevalence rate of kidney disease in this cohort is slightly higher than that reported by previous studies. Gardner et al in their study of 885 US HIV-infected women, found a prevalence of 7.2% at baseline[14] and Choi et al in their study of 15,135 HIV-infected persons found that 7.3% of White and 6.9% of African American patients had a renal dysfunction.[15] Both Choi's study and our study used GFR levels to define kidney dysfunction. Other studies use the presence of proteinuria or an elevated serum creatinine as index of renal dysfunction.[14] GFR is accepted as the best overall measure of kidney function since it controls the variation in the serum creatinine levels causes by sex, age and BMI.[11] These variables are often quite critical in the evaluation of target organ damage. We believe that, along with Choi's study, we have utilized a more accurate measure of kidney function.

Chronic kidney disease is a serious condition associated with premature mortality, decreased quality of life and

Table 2. Mortality causes by kidney disease (%)

Causes of death	With kidney disease (*n*=64)	Without kidney disease (*n*=259)	Odds ratio (95% CI)
Cardiovascular conditions	25.0	17.8	1.54 (0.81–2.96)
Pulmonary conditions	56.3	43.6	1.66 (0.96–2.88)
Hematological conditions	10.9	9.3	1.20 (0.49–2.93)
Gastrointestinal conditions	14.1	17.8	0.76 (0.35–1.64)
Hepatic conditions	4.7	13.5	0.32 (0.94–1.06)
Renal conditions	18.8	4.2*	5.20 (2.18–12.43)
Metabolic conditions	3.1	5.0	0.61 (0.13–2.78)
Neurological conditions	9.4	8.1	1.17 (0.45–3.04)
Neoplasms	3.1	6.2	0.49 (0.11–2.19)
Sepsis	23.4	18.9	1.32 (0.68–2.53)

* $P<.01$ between kidney disease groups
CI= confidence interval

increased health-care expenditures.[13] Although our study did not examine end stage renal disease, it demonstrated a clinically and statistically significant increased risk for death among patients with kidney disease, even after controlling for other factors including prescription of HAART. Our findings highlight the importance of including this condition among the priority considerations when designing any intervention to prolong the lives of HIV-infected Puerto Rican patients. Our study suggests a higher degree of immune dysfunction in patients with kidney disease. Higher level of HIV-RNA viral load, lower CD4+ cell count and higher prevalence of AIDS-related conditions were significantly seen in patients with kidney disease. In addition low BMI, the presence of chronic conditions including DM-2 and HTN, were more common in these patients. Consistent with previous work, these findings supported an association between more advanced AIDS conditions and chronic medical conditions in HIV-infection patients with kidney dysfunction.[4,14]

With regard to disease outcome, our results demonstrate a substantial difference in mortality among HIV-infected patients with kidney disease. They have twice the risk of death than patients without renal disease (MR= 2.12), after controlling for cofactors.

Table 3. Mortality risk in HIV patients by Cox proportional hazard

	Mortality Hazard ratio	95% CI	*P*
Female	0.93	0.70–1.25	.635
Age at study entry	1.02	1.00–1.03	.053
IDU antecedent	1.63	1.21–2.18	.001
HIV duration	0.99	0.96–1.02	.495
Kidney disease	2.12	1.50–3.00	<.001
Diabetes mellitus type 2	1.64	1.05–2.57	.030
Hypertension	1.09	0.74–1.59	.691
HCV	1.17	0.86–1.60	.319
PJP	1.94	1.09–3.45	.023
Recurrent pneumonia	1.75	0.54–5.67	.355
Cerebral toxoplasmosis	1.41	0.71–2.80	.333
Underweight	1.89	1.37–2.60	<.001
CD4+T cell <200/µl	2.08	1.57–2.76	<.001
HAART	0.60	0.45–0.77	<.001

CI= confidence interval; IDU= injecting drug use; HCV= hepatitis C virus; PJP= pneumocystic jirovecii pneumonia; HAART= highly active antiretroviral therapy.

Our study demonstrates that the recommendation of the Infectious Diseases Society of America (which states that all patients should be assessed for existing kidney disease with a screening urine analysis and a calculated estimate of renal function at time of HIV diagnosis) is particularly important for Hispanic populations.[16] High-risk populations for developing kidney disease, including African American persons, those with CD4+ T cell count <200 cell/µL or HIV viral load >4000 copies/mL, or those with HTN, DM-2 or HCV should undergo annual screening for renal dysfunction. Patients with proteinuria or reduced renal function should be promptly referred to nephrologists and undergo additional evaluations. These recommendations highlight the importance of aggressively managing Puerto Rican HIV-infected persons, as having a high risk for developing kidney disease.

Our study had several limitations. First, the study group was selected from a passive surveillance cohort, where the patients had come to the center to have the data collected. This type of surveillance could increase the probability of being lost to followup for some participants, which would generate missing data that could affect the study findings. Second, many patients of the cohort had only one creatinine measure at the study time and it is highly recommended the use of at least two consecutive creatinine measures to evaluate the renal function.[4] Consecutive measures would minimize the transient creatinine variations related to nonintrinsic renal processes, increasing the accuracy of the kidney disease diagnosis.

Implications for Improving Health Disparities

Our study was performed in a Hispanic HIV-infected population and demonstrates an increased prevalence of

kidney disease. We recommend improvements in prevention strategies (particularly at time of diagnosis) targeted to this population to decrease health disparity in this population.

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REFERENCES

1. Selik RM, Byers RH, Dworkin MS. Trends in disease reported on US death certificates that mentioned HIV infection, 1987–1999. *J Acquir Immun Defic Syndr*. 2002;29:378–387.
2. Mayor AM, Gómez MA, Ríos-Oliveras, Hunter-Mellado RF. Mortality trends of HIV-infected patients after the introduction of Highly Active Antiretroviral Therapy: Analysis of 3,322 HIV-infected persons. *Ethn Dis*. 2005;15:S5-57–S5-62.
3. Samaras K, Emery S, Wand H, et al. Prevalence of metabolic syndrome in HIV-infected patients receiving highly active antiretroviral therapy using International Diabetes Foundation and Adult Treatment Panel III criteria. *Diabetes Care*. 2007;30(1):113–119.
4. Szczech L, Hoover D, Feldman J, et al. Association between renal disease and outcome among HIV infected women receiving or not receiving antiretroviral; therapy. *Clin Infect Dis*. 2004;39:1199–1206.
5. Szczech LA, Gange SJ, van der Horst C, et al. Predictor of proteinuria and renal failure among women with HIV infection. *Kidney Int*. 2002;61:195–202.
6. Tourret J, Tostivint I, Tezenas du Montcel s, et al. Outcome and prognosis factor in HIV-infected hemodialysis patients. *Clin L Am Soc Nephol*. 2006;1:1241–1247.
7. Ahuja TS, Grady J, Khan S. Changing trends in the survival of dialysis with human immunodeficiency virus in the United Stated. *J Am Soc Nephrol*. 2002;13:1889–1893.
8. Szczech LA, Gupta SK, Habash R, et al. The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection. *Kidney Int*. 2004;66: 1145–1152.
9. Lucas GM, Eustace JA, Sozio S, et al. Highly active antiretroviral therapy and the incidence of HIV-1 associated nephropathy; a 12 year cohort study. *AIDS*. 2004;18:541–546.
10. CDC, HIV AIDS Surveillance Report. Cases of HIV infection and AIDS in the United States and dependent areas. 2006. Available at: http://www.cdc.gov/hiv/topics/surveillance/resources/reports/past.htm#surveillance. Last accessed: November 23, 2009.
11. Steven LA, Coresh J, Greene T, Levey AS. Assessing kidney function measured and estimated glomerular filtration rate. *N Engl J Med*. 2006;354:2473–2483.
12. Dean HD, Brooke S, Satcher AJ, Nakashima AK. HIV/AIDS among minority races and ethnicities in the United States. 1999–2003. *J. Nat Med Assoc*. 2005;97:121–125.
13. Saydah S, Eberhardt M, Rios-Burrows N, Williams D, Geiss L, Dorsey R. Prevalence of chronic kidney disease and associated risk factors in United States, 1999–2004. *MMWR*. 2007;56:164–165.
14. Gardner LI, Holmberg SD, Williamson JM, et al. Development of proteinuria or elevated serum creatinine in HIV- infected women. *J Acquir Immune Defic Syndr*. 2003;32:203–209.
15. Choi AI, Rodriguez RA, Bacchetti P, Bertenthal D, Volberding PA, O'Hare AM. Racial differences in end stage renal disease rates in HIV-infected versus diabetes. *J Am Soc Nephrol*. 2007;18:2968–2974.
16. 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 Disease Society of America. *Clin Infect Dis*. 2005;40:1559–1585.