RISK FACTORS FOR THE DEVELOPMENT AND PROGRESSION OF CHRONIC KIDNEY DISEASE IN A MINORITY URBAN POPULATION WITH HIV INFECTION

Galant Au Chan
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A. STUDY PURPOSE AND RATIONALE

The widespread use of highly active antiretroviral therapy (HAART) in the management of HIV/AIDS in the developed world has transformed HIV infection into a chronic disease, introducing the relatively newer challenges of managing chronic morbidities developing in HIV-positive patients in the post-HAART era. Chronic kidney disease (CKD) is a significant contributor to morbidity and mortality in this population. In addition to the classic HIV-associated nephropathy (HIVAN), the spectrum of renal pathology seen in HIV patients includes membranoproliferative glomerulonephritis, amyloidosis, minimal change disease, cryoglobulinemia, IgA nephropathy, and membranous nephropathy.[1] The increased prevalence of CKD in the post-HAART era likely reflects changes in the natural history of HIV infection, but may partially be related to the increased prevalence of a number of associated co-morbidities that may play a causal role. For example, the prevalence of hypertension, diabetes mellitus and cardiovascular events such as myocardial infarction have all been found to be greater in HIV-infected individuals on HAART. [2,3,4] In addition, while the advent of HAART has been credited with halting the escalation of HIVAN incidence, the antiretroviral therapies themselves can also be associated with significant nephrotoxicity. [5,6]

Current recommendations regarding the management of CKD in HIV-positive patients include initial screening for proteinuria on urinalysis and estimated GFR at the time of HIV diagnosis, as well as annual screening thereafter for high risk individuals, including African Americans.[7] The immediate initiation of HAART for those with confirmed HIVAN is recommended, based on a number of studies that have pointed to the beneficial effects of HAART in the management of HIV-infected patients with CKD.[8,9,10] In fact, decreased rates of treatment with HAART and failure to adjust HAART dosage for renal function has been shown to be associated with increased mortality in HIV-infected patients with CKD.[11] Management of CKD in HIV-infected patients also includes the treatment of modifiable risk factors, such as hypertension. There is growing evidence for the role of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in the treatment of CKD in patients with HIV infection.[12] In addition, renal replacement therapy and transplantation are also current options for management.

Given the growing burden of CKD in this population, as well as increasing options for management, it will be important to elucidate factors associated with increased risk.

Compared to whites, African American patients with HIV have a substantially higher prevalence of CKD, with no slowing of the progression to renal replacement therapy even in the post-HAART era.[13,14] The disproportionate burden of chronic kidney disease on HIV-infected African Americans is also evident in studies in minority urban populations, as well as among women.[15,16] These racial differences may be partially related to differences in histopathology, as black race is more highly associated with HIVAN and less associated with CKD secondary to lesions other than HIVAN.[1] Compared to these other types of histopathology, HIVAN is known to progress more quickly to severe renal dysfunction requiring renal replacement therapy.[1] Such differences may point to the need for more specific therapies for particular subgroups. For example, in a study of a largely African American population, treatment with HAART was associated with decreased incidence of HIVAN, but the evidence for HAART in other minority groups or with other types of renal histopathology is less clear.[17,1] In fact, there has been little data on other minority populations, including Hispanic communities.

The New-York Presbyterian Hospital/Columbia University Medical Center HIV clinic provides care for a unique minority population consisting largely of African American and Hispanic individuals. Previous cross-sectional data from this population have shown the overall prevalence of CKD to be high-- approximately 25%.[18] In addition, although not as high as in African Americans, the prevalence of CKD in Hispanics was significant (29% vs 23%, respectively). However, there is little longitudinal data on the incidence of CKD and progression to advanced stages of CKD in this minority urban population.

The purpose of this study is to characterize the incidence of advanced stages of CKD in this population of HIV-infected patients between 2004 and 2009. Possible predictors for the progression of CKD, including age, gender, CD4 count, viral load, time on HAART, proteinuria, type of histologic lesion, intravenous drug use and co-morbid conditions such as hypertension, diabetes, cardiovascular disease, and hepatitis B and C will be examined. In addition, we will investigate any differences in the rate of development of advanced-stage CKD between African-American and Hispanic patients in this cohort and elucidate factors that may contribute to these differences. Our hypotheses include:

- Co-morbid conditions are associated with increased incidence of advanced CKD in HIV-infected patients.
- The rate of progression to advanced CKD differs between African-American and Hispanic patients with HIV infection.
- These racial differences in incidence of advanced CKD are associated with differences in rates of co-morbid conditions and type of histopathologic lesions.

B. STUDY DESIGN AND STATISTICAL ANALYSIS

This will be a longitudinal retrospective cohort study of African American and Hispanic HIV-infected patients receiving medical care at the HIV/AIDS clinic at New York-Presbyterian/Columbia University Medical Center who have CKD stage 0-1 in 2004, to assess for the time to development of advanced kidney disease. Patient data will be collected to assess for endpoints through 2009. The primary endpoint will be advanced chronic kidney disease, as defined by CKD stage 3-5 with estimated GFR < 60 mL/min. Secondary endpoints will include GFR<30 mL/min and the initiation of renal replacement therapy (RRT). With 200 subjects in each group, this study will have 80% power to detect a 5% or greater difference in the primary endpoint between the African American and Hispanic cohorts. Baseline characteristics of the two groups will be compared using chi-square and Student t test for categorical and continuous variables, respectively. Kaplan Meier curves will be constructed to compare the incidence of advanced CKD in the two cohorts. Possible risk factors for the time to progression to advanced CKD, including age, gender, hypertension, diabetes, hepatitis B and C, CD4 count, viral load, HAART, proteinuria, type of histologic lesion and intravenous drug use will be compared using Cox proportional hazards regression.

C. STUDY PROCEDURE

Study data will be collected and extracted from chart review of the electronic and paper medical records from 2004-2009 at New York-Presbyterian/Columbia University Medical Center. Study subjects will not be contacted at any point of this investigation.

D. STUDY DRUGS

No study drugs will be used in this study.

E. MEDICAL DEVICE

No study devices will be used in this study.

F. STUDY QUESTIONNAIRES

No study questionnaires will be used in this study.

G. STUDY SUBJECTS

Study subjects will be identified using the following inclusion criteria: 1) Age 18 or older 2) Confirmed diagnosis of HIV infection as documented by ICD-9 codes 3) African American or Hispanic as defined by self-report 4) At least 2 consecutive measurements of renal function from January 1, 2004 to December 31, 2004, separated by at least 3 months, demonstrating CKD stage 0-1 with GFR> 90 ml/min calculated using the MDRD formula. Patients with acute renal failure as documented by ICD.9 codes will be excluded from this study.

H. Recruitment of Subjects

Study subjects will be identified through a query of the Columbia University Medical Center Data Warehouse, using the inclusion criteria described above. Subjects in this study will not be contacted for recruitment.

I. Confidentiality of Study Data

In order to ensure confidentiality of study data, subject information extracted from the Columbia University Medical Center Data Warehouse will be recorded with coded forms, using a unique patient code without identifying patient information. Study data and files will be stored in a secure location and in a password-protected database that will be accessible only to study investigators.

J. Potential Conflict of Interest

The investigators of this study do not have any proprietary interest in aspects of this study or stand to benefit financially in any other way from the findings of this investigation.

K. Location of the Study

This study will be conducted at New York-Presbyterian Hospital, Columbia University Medical Center.

L. Potential Risks

There are no potential risks to subjects in this study.

M. Potential Benefits

By elucidating possible racial/ethnic differences in the incidence and progression of chronic kidney disease in HIV-infected patients, results from this study could contribute to improved management of HIV-infected patients with CKD in minority populations.

N. Alternative Therapies

This study does not involve an experimental therapy.

O. Compensation to Subjects

No compensation will be provided to study subjects.

P. Costs to Subjects

No additional costs will be incurred by subjects in this study.

Q. Minors as Research Subjects

This study will not involve the participation of subjects under the age of 18 years old.

R. RADIATION OR RADIOACTIVE SUBSTANCES

This study will not involve radiation or radioactive substances.

REFERENCES

[1] 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;66:1145-52.

[2]Seaberg EC, Munoz A, L Ming, et al. the Multicenter AIDS Cohort Study. Association between highly active antiretroviral therapy and hypertension in a large cohort of men followed from 1984 and 2004 *AIDS* 2005;953-60.

[3] Brown TT, Cole SR, Li X, et al. Antiretroviral Therapy and the Prevalence and Incidence of Diabetes Mellitus in the Multicenter AIDS Cohort Study. *Arch Intern Med* 2005;165:1179-1184

[4] Friis-Moller N, Sabin CA, Weber R, et al., Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Combination Antiretroviral Therapy and the Risk of Myocardial Infarction. *N Eng J Med* 2003;349:1993-2003.

[5] Wyatt CM, Klotman PE. Antiretroviral therapy and the kidney: balancing benefit and risk in patients with HIV infection. *Expert Opin Drug Saf*. 2006;5:275-87.

[6] Mocroft A, Kirk O, Gatell J, et al., EuroSIDA Study Group. Chronic renal failure among HIV-1-infected patients. AIDS 2007;21:1119-27.

[7] Gupta SK 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;40:1559-84.

[8] Cosgrove CJ, Abu-Alfa AK, Perazella MA. Observations on HIV-associated renal disease in the era of highly active antiretroviral therapy. Am J Med Sci 2002;323:102-6.

[9] Krawczyk CS, Holmberg SD, Moorman AC, et al., HIV Outpatient Study Group. Factors associated with chronic renal failure in HIV-infected ambulatory patients. AIDS 2004;18:2171-78.

[10] Schwartz EJ, Szczech LA, Ross MJ, et al. HAART and the epidemic of HIV+ end stage renal disease. J Am Soc Nephrol 2005;16:2412-20.

[11] Choi AI, Rodriquez RA, Bacchetti P, et al. Low Rates of Antiretroviral Therapy among HIV-Infected Patients with Chronic Kidney Disease. *Clin Infect Dis* 2007;45:1633-9.

[12] Burns GC. Effect of ACE-inhibitors in HIV-associated nephropathy. J Am Soc Nephrology 1997;8:1140-6.

[13] US Renal Data System. USRDS 2005 Annual Data Report: Atlas of End-stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive Diseases and Kidney Diseases; 2005. http://www.usrds.org. Accessed November 2009.

[14] Lucas GM, Mehta SH, Atta MG, et al. End-stage renal disease and chronic kidney disease in a cohort of African-American HIV-infected and at-risk HIV-seronegative participants followed between 1988 and 2004. *AIDS* 2007;21:2435-43.

[15] Wyatt CM, Winston JA, Malvestutto CD, et al. Chronic kidney disease in HIV infection: an urban epidemic. *AIDS* 2007;21:2101-3.

[16] Szczech LA, Gange SJ, van der Horst C, et al. Predictors of proteinuria and renal failure among women with HIV infection. *Kidney Int* 2002;61:195-202.

[17] Lucas GM, Eustace JA, Sozio S. Highly active antiretroviral therapy and the incidence of HIV-1-associated nephropathy: a 12-year cohort study. *AIDS* 2004;18:541-6.

[18] Pereira M, Miko B, Fatehi P. Prevalence and Risk Factors of Chronic Kidney Disease in an HIV-infected Minority Urban Population. Poster presentation, October 2008, 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy/Infectious Disease Society of America 46th Annual Meeting.