IMPACT OF EARLY VS. LATE HAART INITIATION ON INCIDENCE OF CHRONIC KIDNEY DISEASE AND PROGRESSION TO ESRD IN A MINORITY URBAN HIV-INFECTED POPULATION

A. STUDY PURPOSE AND RATIONALE

With the introduction of highly active antiretroviral therapy (HAART), mortality among HIV-infected patients has been significantly reduced, and the clinical focus has shifted to management of such chronic co-morbid conditions as cardiovascular disease, chronic kidney disease (CKD) and diabetes.[1,2] HIV-associated nephropathy or HIVAN is the renal lesion classically associated with the disease, however non-HIVAN renal lesions are becoming increasingly more common in HIV, likely due both to a change in the natural course of the disease and to the nephrotoxic effects of antiretroviral medications, such as Tenofovir and Indinavir.[3,4,5] Non-HIVAN lesions such as HIV-specific immune-complex mediated glomerulonephritis and thrombotic microangiopathy, as well as membranoproliferative glomerulonephritis and membranous nephropathy are becoming increasingly common. A large portion of CKD cases can also be attributed to non-HIV-related kidney disease, such as that associated with diabetes mellitus and hypertension, and a high prevalence of risk factors such as smoking, IV drug use, and hepatitis C co-infection in the HIV-infected population also play a role in the increased risk for kidney disease. [6,7]

Chronic kidney disease and end-stage renal disease (ESRD) are common co-morbid conditions in HIV-infected individuals, and recent studies have pointed to racial disparities in the incidence and prevalence of CKD and ESRD. There is extensive data on African American-white disparities in incidence of CKD and progression to ESRD, with the United States Renal Data System (USRDS) and the Johns Hopkins HIV Clinical Cohort showing in the African-American arm a higher risk for CKD, higher rates of HIVAN, greater incidence of ESRD, and faster rates of progression toward ESRD once CKD is diagnosed.[89] Less research has been done to characterize patterns of CKD development and progression to ESRD in the HIV-infected Hispanic population.

Previous studies have shown a significant reduction in progression to AIDS and mortality when HAART therapy is started at higher CD4+ T cell thresholds; the Strategies for Management of Antiretroviral Therapy (SMART) trial suggested that delaying HAART until the CD4 count decreased to < 250 was associated with significantly increased mortality compared with initiation of HAART at CD4 > 350, and a study by Kitahata et al showed significantly improved survival with initiation at CD4 >500. [10,11] When comparing groups in which HAART therapy was interrupted to groups in which it was continuous, the SMART trial also found that fatal and non-fatal renal-disease outcomes are significantly more common in the ARV-interruption group than in the continuous

therapy group. Also showing that mortality is increased with deferred HAART and that kidney disease outcomes might be modified by HAART therapy, the Hopkins study suggested that incidence of CKD decreased in successive calendar periods (following January, 1996, the dividing line between the pre-HAART and HAART eras) as a more diverse array of ARVs were developed, but that the risk of progression to ESRD was similar between pre-HAART and post-HAART eras and was not associated with the type of antiretroviral therapy used.[3] Other studies have shown that HAART therapy is associated with a slowed progression to ESRD in patients with HIVAN (however not in those with non-HIVAN pathology.)[12,13] There is little data, however, specifically addressing the question of whether early HAART initiation affects risk for CKD development, progression to ESRD, or rate of GFR decline after onset of CKD.

The New York Presbyterian Hospital/Columbia University Medical Center HIV clinic serves a minority population consisting predominantly of African American and Hispanic patients. Prevalence of CKD in this HIV-infected population has been estimated to be 25% in cross-sectional data collected between 2005 and 2007 through IRB protocol #AAAC4781.[14] The original study population consisted of 1029 patients (median age 47.1 +/- 11.0 years; 50% Latinos; 43% African Americans; 7% Other ethnicities), with 258 patients (25.1%) meeting the criteria for CKD. This data showed that most of the CKD present in this population is early-stage (26% stage 1, 31% stage 2.) Possible risk factors for CKD in this cross-sectional data were age, hypertension, IV drug use, cocaine and heroin abuse, and hepatitis C infection.

The study has been extended to evaluate this cohort of patients during the time period 1/1/2005 through 10/1/2010 to better assess the incidence of CKD in this population and to characterize the factors associated with progression to advanced stage CKD (stage 3-5.) Data will be collected on such factors as age, gender, ethnicity, CD4 count at CKD diagnosis and CD4 nadir, HAART, and IV drug use, among others. Data on co-morbid conditions such as hypertension, diabetes, cardiovascular disease, and Hepatitis B and C will also be analyzed. This data is being collected both through a Data Warehouse query and through manual chart review of WebCis records and paper charts.

This proposal seeks to extend the above-described data collection, additionally extracting data on CD4 count at onset of HAART therapy.

The hypotheses of this study include:

- Initiating HAART at a higher CD4 count in HIV-infected patients will decrease the incidence of CKD (stage 3-5.)

- Earlier initiation of HAART therapy will decrease the risk of progression to ESRD in HIV-infected patients diagnosed with CKD

- Early HAART initiation will lead to a slower rate of decline of GFR in HIV-infected patients diagnosed with CKD

B. Study Design and Statistical Analysis

This will be a longitudinal retrospective cohort study of HIV-infected patients receiving medical care at the HIV/AIDS clinic at New York-Presbyterian/Columbia University Medical Center who have no CKD stage 0 (normal GFR; no kidney damage) stage 1 (normal GFR; kidney damage) at the start of the study period in 1/1/2005 to assess for the development of advanced stage chronic kidney disease. GFR will be estimated by the Modification of Diet in Renal Disease equation.[15] Patient data through will be collected through 10/1/2010.

The primary endpoint will be advanced chronic kidney disease, defined as CKD stage 3-5, with estimated GFR on at least 2 measurements of < 60 mL/min separated by at least 3 months. Secondary endpoints will include ESRD (defined as GFR < 15 ml/min/1.73 m2 or initiation of renal replacement therapy [RRT]), time to development of advanced CKD, and GFR slope after onset of CKD (rate of change of GFR from diagnosis of CKD to the 1) last available GFR, 2) GFR < 15mL/min/1.73m2, or 3) initiation of RRT.)

The CD4 count at time of onset of HAART therapy will be the last CD4 count preceding initiation of therapy; the CD4 value should take place within a 6-month period preceding HAART initiation.

Variation I: The groups will be divided into 2 groups based on a diagnosis of CKD (GFR < 60mL/min, as defined above), and data will be collected on their Pre-HAART initiation CD4 cell count. Based on the unpaired t-test, assuming a standard deviation of 150 (CD4 T cells at HAART initiation), the study would need 65 subjects in each group (CKD and non-CKD groups) to have 80% power to detect a significant difference of 50 or greater CD4 T cells at HAART initiation.

Variation II: If the groups are divided based on CD4 count at HAART initiation (CD4 > 350 vs. CD4 < 250 at initiation), then based on a Chi-square test with 15% of the CD4 >350 group and 35% of the CD4 <250 group developing CKD, 82 subjects would be needed in each group to have 80% power to detect a significant difference in outcome.

C. Study Procedure

Study data will be collected and extracted from chart review of the electronic and paper medical records from 1/1/2005-10/1/2010 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, White, or Hispanic, as defined by self-report 4) At least 2 consecutive measurements of renal function from January 1, 2005 to December 31, 2005, 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. 5) Patients who are "engaged in care" i.e. with at least 3 clinic visits during the time period 1/1/2005 and 6/30/2007.

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

To ensure confidentiality of study data, subject information collected 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 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 better characterizing the effects of earlier HAART treatment on development of CKD and ESRD in HIV-infected patients, results from this study could further inform the debate on time of antiretroviral initiation and lead to improved renal disease outcomes in these patients.

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] Palella FJ Jr, Delaney KM, Moorman AC et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Eng J Med 1998:338:853-60.

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

[3] 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 Feb 20;18(3):541-6.

[4] Pardo V, Aldana M, Colton RM, et al. Glomerular lesions in the acquired immunodeficiency syndrome. Ann Intern Med 1984 Oct;101(4):429-34.

[5] Mocroft A, Kirk O, Reiss P et al. Estimated glomerular filtration rate, chronic kidney disease, and antiretroviral drug use in HIV-positive patients. AIDS 2010 Jul 17;24(11):1667-78.

[6] Selik RM, Byers Jr RH, Dworkin MS. Trends in diseases reported on U.S. death certificates that mentioned HIV infection, 1987-1999. J Acquir Immune Defic Syndr 2002 Apr 1;29(4):378-87.

[7] 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 Nov 30;21(18);2435-43.

[8] Lucas GM, Lau B, Atta MG et al. Chronic kidney disease incidence, and progression to end-stage renal disease, in HIV-infected individuals: a tale of two races. J Infect Dis 2008;197(11):1548-57.

[9] Eggers PW, Kimmel PL. Is there an epidemic of HIV Infection in the US ESRD program? J Am Soc Nephrol 2004;15:2477-85.

[10] El Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med 2006;355:2283-96.

[11] Kitahata MM, Gange SJ, Abraham AG et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. N Eng J Med 2009 April 30;360(18):1815-26.

[12] 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.

[13] Atta MG, Gallant JE, Rahman MH, et al. Antiretroviral therapy in the treatment of HIV-associated nephropathy. Nephrol Dial Transplant 2006;21:2809-13.

[14] 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.

[15] Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 2003;139:137-47.