Association between Renal Disease and Outcomes among HIV-Infected Women Receiving or Not Receiving Antiretroviral Therapy

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Background. The associations of proteinuria and an elevated creatinine level with progression to acquired immunodeficiency syndrome (AIDS) and death in the era of highly antiretroviral therapy (HAART) have not been fully described.

Methods. This analysis includes 2038 human immunodeficiency virus (HIV)–infected women from the Women's Interagency HIV Study. Time to the development of a new AIDS-defining illness (ADI) and death was modeled using proportional hazards regression before the widespread availability of HAART and after initiation of HAART.

Results. Of the 2038 subjects, the 14.1% of women with proteinuria had lower CD4 lymphocyte counts and higher viral loads ($P < .0001$ for all) at baseline and before initiation of HAART. Before the widespread availability of HAART, proteinuria was associated with an increased risk for development of ADI (hazard ratio [HR], 1.37; $P = .005$), and proteinuria and an elevated creatinine level were both associated with an increased risk of death (for proteinuria: HR, 1.35 [$P = .04$]; for creatinine: HR, 1.72 per decrease in the inverse unit [$P = .02$]). Among women initiating HAART, an elevated creatinine level remained associated with an increased risk of development of ADI (HR, 1.54 per decrease in the inverse unit; $P = .03$), and proteinuria and an elevated creatinine level were associated with an increased risk of death (for proteinuria: HR, 2.07 [$P = .005$]; for creatinine: HR, 1.96 per decrease in the inverse unit [$P = .04$]).

Conclusions. Proteinuria and an elevated creatinine level were associated with an increased risk of death and development of ADI. These associations may reflect the direct role of the kidney in modulating HIV disease, or they may act as markers of greater comorbidity.

The percentage of HIV-infected patients with proteinuria or an elevated creatinine level has been reported to be at least 7% [1]. Some observational data suggest that, among HIV-infected patients, proteinuria (defined by a dipstick reading of 2+ or greater on urinalysis) and an elevated creatinine level (≥1.4 mg/dL) are associated with an increased risk of death due to all causes (hazard ratio [HR], 2.5; $P < .0001$) after controlling for predictors of AIDS-related death, including the CD4 lymphocyte count, the HIV RNA level, and the use of HAART [1]. It is not clear whether these associations occur because proteinuria and an increased creatinine level are markers for such diseases as HIV-associated nephropathy (HIVAN) and other HIV-related glomerular diseases [2] or, instead, indicate the influence of poorer health status as a result of hypertension or cardiovascular pathologic findings, as is the case for

Received 19 February 2004; accepted 17 May 2004; electronically published 27 September 2004.

Presented in part: American Society of Nephrology annual meeting, San Diego, October 2003.

Data used in this article were collected by the Women's Interagency HIV Study (WIHS). Centers participating in the WIHS and their principal investigators are listed at the end of the text.

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Clinical Infectious Diseases 2004; 39:1199–206

1058-4838/2004/3908-0016$15.00

non–HIV-infected populations [3–5]. There are few data regarding the usefulness of proteinuria and an elevated creatinine level for the prediction of AIDS-specific morbidity.

A more complete understanding of the prognostic importance of proteinuria and the creatinine level among HIV-infected patients, regarding the development of an AIDS-defining illness (ADI) or death, may be useful in establishing the role of kidney disease in the progression of HIV infection. To this end, we investigated the associations of proteinuria and an elevated creatinine level with the development of a new ADI and death due to all causes in the Women's Interagency HIV Study (WIHS), a US longitudinal cohort study.

STUDY PARTICIPANTS AND METHODS

WIHS participants. The rationale and methods of the WIHS have been described elsewhere [6]. The WIHS, a prospective study of the natural history of HIV infection among women, is conducted in Chicago, Los Angeles, New York City, San Francisco, and Washington, DC. From October 1994 through November 1995, a total of 2628 participants were recruited from HIV primary care clinics, outpatient infectious diseases clinics, research programs, community outreach sites, women's support groups, drug rehabilitation programs, HIV testing sites, and referrals from previously enrolled participants. Participating institutions approved the present study and the consent forms provided to the study participants.

Women with HIV infection that was identified by ELISA and confirmed by Western blot analysis ($n = 2059$), as well as at-risk HIV-seronegative women ($n = 569$), were enrolled in the study. A standardized interview was used at enrollment to collect demographic data and prior medical, sexual, and drug-use histories. Women are evaluated biannually to obtain information on weight, urinalysis findings, CD4 lymphocyte count, and HIV RNA, albumin, and creatinine levels (with the creatinine level assessed annually). Urine samples were tested for proteinuria during the first 7 visits. After 5 years, the overall retention rate of the WIHS was ~81% [7]. Data obtained by the WIHS through 31 March 2002 were included in the present analysis.

Definition of variables. "Proteinuria" was defined by at least 2 consecutive urinalyses demonstrating a dipstick reading of 1+ or greater during the first 7 visits. This definition was chosen to minimize the inclusion of subjects with transient proteinuria related to nonintrinsic renal processes, and it indicates that at least 30–100 mg of protein/dL (or at least 450–1500 mg of protein/1.5 L of urine) were recorded for 2 consecutive measurements separated by at least 6 months. To reflect the nonlinear association between the serum level of creatinine and creatinine clearance, the inverse creatinine level (1/serum creatinine level) was used. A decreasing inverse creatinine level is a valid predictor of loss of kidney function [8], and it minimizes the influence of fluctuating weight associated with changes in body composition unrelated to lean body mass (i.e., edema).

At each study visit, self-reported history of ADI and use of HIV medication since the previous visit were recorded. "HAART" was defined as (1) $\geqslant$2 nucleoside analogue reverse-transcriptase inhibitors (NRTIs) given in combination with $\geqslant$1 protease inhibitor (PI) or nonnucleoside reverse-transcriptase inhibitor (NNRTI), (2) 1 NRTI given in combination with $\geqslant$1 PI and $\geqslant$1 NNRTI, (3) a regimen that contained ritonavir and saquinavir given in combination with 1 NRTI, and (4) a regimen that contained abacavir and $\geqslant$3 NRTIs in the absence of PIs and NNRTIs. In the present report, ADIs consistent with the 1993 clinical surveillance conditions of the Centers for Disease Control and Prevention (CDC [Atlanta]; excluding a CD4 lymphocyte count of <200 cells/mL) [9] were ascertained through self-report or events confirmed through the cancer and tuberculosis registries. Any new report of a condition included in the 1993 CDC definition was considered to be "incident," *except* for reports of chronic conditions that may relapse after initial therapy and remission; these chronic conditions are cervical cancer, Kaposi sarcoma, non-Hodgkin lymphoma, tuberculosis, or wasting syndrome in women who had reported that illness at any previous visit. The dates of initiation of HAART and development of ADI were considered to be a midpoint between the visit of first report and the previous visit. If an ADI was reported at the same visit that initiation of HAART was reported, then the ADI was considered to have occurred before (rather than after) initiation of HAART.

Deaths were ascertained by notification received from the friends, relatives, and medical providers of the participants and through the medical and death registries. Death certificates were requested for all women reported to have died. The date of death was ascertained, in descending order of priority, from the death certificate, medical records, medical provider, and family and/or friends of the study participants.

Data analysis. The clinical characteristics of women at the first WIHS visit were reported on the basis of the presence or absence of proteinuria. Continuous and categorical variables were compared using Student's t test and Fisher's exact test. Correlations were measured using Spearman's nonparametric coefficient. All P values are 2-sided, and the confidence intervals reported are 95% CIs. Analyses were performed using SAS software (version 8.0; SAS). Among women who used HAART, changes in the inverse creatinine level, CD4 lymphocyte count, and HIV RNA level, from the visit before initiation of HAART to the visit after the first report of initiation of HAART, were compared between women with proteinuria and women without proteinuria.

Kaplan-Meier and proportional hazards models evaluated unadjusted and adjusted associations of proteinuria, inverse

Table 1. Clinical and demographic characteristics, at study entry, of women with or without proteinuria.

Characteristic	Women with proteinuria (n = 287)	Women without proteinuria (n = 1751)	P
Age, mean years ± SD	38.13 ± 8.08	36.61 ± 7.76	<.0001
Race, no. (%) of women			<.0001
White			
Non-Hispanic	39 (13.59)	334 (19.07)	
Hispanic	5 (1.74)	37 (2.11)	
Black			
Non-Hispanic	197 (68.64)	933 (53.28)	
Hispanic	10 (3.48)	23 (1.31)	
Hispanic[a]	28 (9.76)	379 (21.64)	
Asian and/or Pacific Islander	0 (0.00)	13 (0.74)	
Native American and/or Alaskan	1 (0.35)	7 (0.40)	
Other	7 (2.44)	25 (1.43)	
CD4 lymphocyte count, mean cells/mL ± SD	282.90 ± 246.78	385.61 ± 289.51	<.0001
Log viral load, mean $\log_{10}$ HIV RNA copies/mL ± SD	4.67 ± 4.67	4.29 ± 0.96	<.0001
Albumin level, mean mg/dL ± SD	3.96 ± 0.50	4.20 ± 0.44	<.0001
Serum creatinine level, mean mg/dL ± SD	1.06 ± 0.88	0.95 ± 0.66	.02
Hematocrit, mean % ± SD	35.2 ± 5.07	37.0 ± 4.29	<.0001
Body mass index, mean ± SD	24.90 ± 4.81	26.00 ± 4.89	.0009
History of illness, % of patients			
Prior ADI	82 (28.57)	364 (20.79)	.003
Diabetes mellitus	20 (6.97)	69 (3.94)	.03
Hypertension	69 (24.04)	286 (16.33)	.002
Duration of follow-up, mean days ± SD	1400.55 ± 46.80	1372.07 ± 17.36	.65

NOTE. ADI, AIDS-defining illness.

[a] Other.

creatinine level, age, race, diabetes mellitus, hypertension, albumin level, body mass index, plasma HIV RNA level, CD4 lymphocyte count, and hepatitis B and C infection with time to death or ADI. Separate time-to-event analyses were performed using 2 starting times (i.e., index visits). The first of the starting times—study entry—was used for analysis of outcome before the widespread availability of HAART, with censoring at 31 October 1997. In a prior analysis of WIHS data, use of study entry as a starting time was demonstrated to include little effect of use of HAART [10]. (Laboratory values and other covariates used in this analysis were obtained from the baseline visit.) The second starting time—initiation of HAART—was used for analysis of post-HAART clinical outcomes of 2 clinical events (incident ADI and death), with censoring at 31 March 2002. (Laboratory values and other covariates used in this analysis were obtained from the last study visit before initiation of HAART, which, in the present report, is referred to as the "pre-HAART study visit.") To be included in this analysis, the pre-HAART study visit could occur no more than 12 months before the visit at which use of HAART was first reported. The logic behind the choice of time points was as follows: data from the analysis occurring before the widespread use of HAART would primarily reflect the prognosis for women who were not using HAART, whereas data from the analysis occurring after initiation of HAART would reflect the prognosis for women who were using HAART. In longitudinal models within our cohort, there is no direct way to evaluate the prognosis for women who do not use HAART by censoring women at initiation of HAART, because women with the poorest health would selectively be given HAART, which would lead to biased censoring and results [11]. There is a small amount of overlap (i.e., nonindependence) in the data for each model, because some women began using HAART before 31 October 1997.

For each of the time periods studied (i.e., baseline censored at 31 October 1997 and the period after initiation of HAART), 2 end points were considered (death and development of a new ADI), leading to 4 sets of time-to-event analyses (2 time periods with 2 outcomes). For each of the 4 analyses, (1) Kaplan-Meier curves were constructed for women stratified according to the presence or absence of proteinuria, (2) unadjusted proportional hazards models were fit using each of the laboratory values and

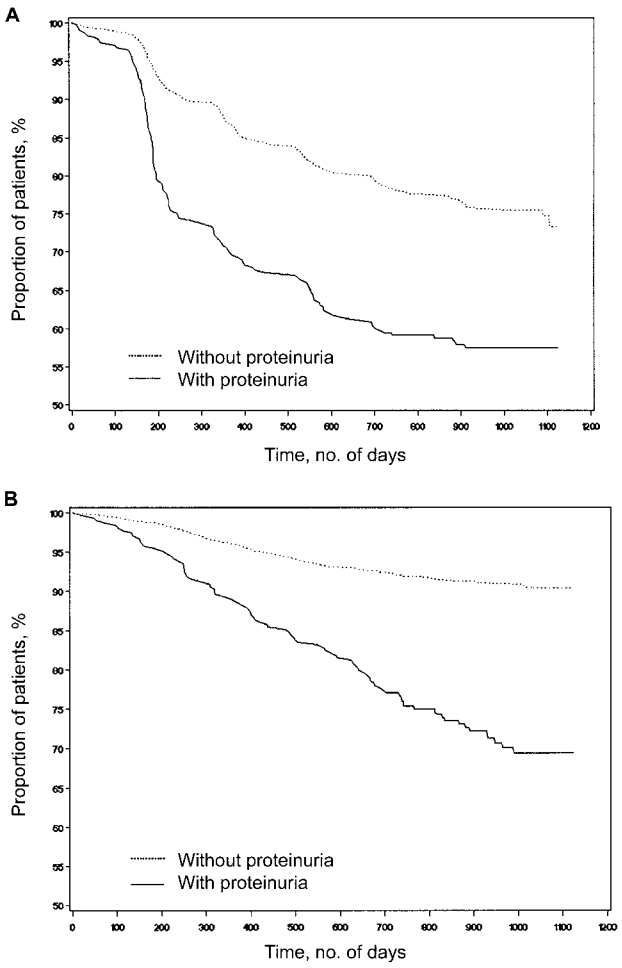

Figure 1. *A,* Time to development of AIDS-defining illness, before the widespread use of HAART, for women stratified according to presence or absence of proteinuria. *B,* Time to death, before the widespread use of HAART, for women stratified according to presence or absence of proteinuria.

other covariates described above as the only variable in the model, and (3) fully adjusted multivariate models were constructed using covariates significant in the unadjusted analyses and using backward stepwise selection with $P \leq .10$ required to remain in or enter the model. HRs are presented in the direction of change that increases risk (i.e., >1).

RESULTS

Of 2038 HIV-infected women who were enrolled in the WIHS, 287 had proteinuria. Compared with women without proteinuria, women with proteinuria were more likely to be older ($P < .0001$) and black ($P < .0001$) and to have diabetes mellitus ($P = .03$), hypertension ($P = .002$), a prior ADI ($P = .003$), a lower CD4 lymphocyte count, a higher HIV RNA level, a lower albumin level, and a lower hematocrit ($P < .0001$) (table 1). Women with proteinuria had a higher creatinine level (1.06 mg/dL vs. 0.95 mg/dL; $P = .02$) and a lower body mass index ($P = .0009$) than did women without proteinuria. At study entry, for all women, and at the pre-HAART study visit, for the women who initiated HAART, Spearman correlations between the creatinine level and the CD4 lymphocyte count, HIV RNA level, albumin level, and hematocrit were not significant (data not shown).

Among women with proteinuria, initiation of HAART was not associated with a significant change in the inverse creatinine level (decrease of 0.02 dL/mg; $P = .29$). Among women without proteinuria, initiation of HAART was associated with a statistically significant improvement in the inverse creatinine level (an increase of 0.04 dL/mg [$P < .0001$]; e.g., an increase in creatinine clearance from 77 mL/min to 80 mL/min).

Among women with or without proteinuria, initiation of HAART was associated with a similar increase in the CD4 lymphocyte count between the visit before initiation of HAART and the visit after initiation of HAART (63 cells/mL; $P < .0001$). However, women with proteinuria were less likely to achieve a nondetectable HIV RNA level at the visit occurring after initiation of HAART (relative risk, 1.10; 95% CI, 1.05–1.15; $P = .0004$).

Predictors of a new ADI or death before the widespread use of HAART. Proteinuria was associated with an increased risk of development of a new ADI among women who were followed up before the widespread use of HAART (HR, 1.72 [$P < .0001$] and 1.31 [$P = .02$] in univariate and multivariable models, respectively) (figure 1 and table 2). Other predictors of the development of an ADI among women before the widespread use of HAART included a lower CD4 lymphocyte count before HAART (HR, 1.11 per 100-cells/mL decrease; $P < .0001$), prior history of an ADI (HR, 1.50; $P < .0001$), a higher pre-HAART log plasma HIV RNA level (HR, 1.26 per increase of $\log_{10}$ HIV RNA copies/mL; $P < .0001$), hepatitis C infection (HR, 1.31; $P = .003$), and a lower pre-HAART albumin level (HR, 1.32; $P = .004$).

Proteinuria and an elevated creatinine level at study entry were both associated with an increased risk of death before the widespread use of HAART (for proteinuria: HR, 3.06 [$P < .0001$] and 1.35 [$P = .04$] in univariate and multivariable models, respectively; for creatinine: HR, 2.52 [$P < .0001$] and 1.72 [$P = .02$] per unit decrease in the inverse creatinine level in univariate and multivariable models, respectively) (figure 1 and table 2). Other predictors of death before the widespread availability of HAART included a decreasing absolute CD4 lymphocyte count before HAART (HR, 1.76 per 100-cells/mL decrease; $P < .0001$), an increasing plasma level of HIV RNA before HAART (HR, 2.09 per increase of $\log_{10}$ HIV RNA copies/mL; $P < .0001$), a decreasing hematocrit before HAART (HR, 1.20 per 1% decrease; $P < .0001$), and a decreasing albumin level before HAART (HR, 1.56 per 1-mg/dL decrease; $P =$

Table 2. Predictors of the development of AIDS-defining illness (ADI) and death among women before the widespread use of HAART, in a multivariate model.

Class of predictor, variable	Hazard ratio (95% CI)	*P*
Predictor of ADI		
Proteinuria, presence vs. absence	1.31 (1.05–1.64)	.02
CD4 lymphocyte count, per 100-cells/mL decrease	1.11 (1.06–1.16)	<.0001
Prior history of ADI	1.50 (1.23–1.81)	<.0001
Log viral load,[a] per 1-log increase	1.26 (1.13–1.41)	<.0001
Hepatitis C virus infection	1.31 (1.10–1.56)	.003
Albumin level, per 1-mg/dL decrease	1.32 (1.10–1.60)	.004
Predictor of death		
Proteinuria, presence vs. absence	1.35 (1.01–1.81)	.04
Inverse creatinine level, per 1-dL/mg decrease	1.72 (1.09–2.70)	.02
CD4 lymphocyte count, per 100-cells/mL decrease	1.76 (1.56–1.98)	<.0001
Log viral load,[a] per 1-log increase	2.09 (1.71–2.55)	<.0001
Hemoglobin, per 1-mg/dL decrease	1.20 (1.10–1.32)	<.0001
Albumin level, per 1-mg/dL decrease	1.56 (1.19–2.04)	.002
History of diabetes mellitus	1.59 (0.92–2.73)	.10

[a] Log_{10} HIV RNA copies/mL.

.002). A history of diabetes mellitus was associated with a trend toward an increased risk of death (HR, 1.59; $P = .10$).

Among women with or without proteinuria, a decreasing CD4 lymphocyte count was associated with an increased risk of death, and, at any given CD4 lymphocyte count, the hazard of death was greater among women with proteinuria (figure 2). In addition, the absolute hazard of death for women with proteinuria who had a CD4 lymphocyte count of ≤500 cells/mL was greater than the hazard of death for women without proteinuria who had a CD4 lymphocyte count of 350 cells/mL.

Predictors of a new ADI or death after initiation of HAART. Proteinuria was associated with an increased risk of a new ADI developing among women after the initiation of HAART in unadjusted analysis (HR, 1.81; $P < .0001$), but this association failed to remain significant in multivariable analysis (table 3). An elevated creatinine level (before initiation of HAART) was associated with an increased risk of development of ADI after initiation of HAART (HR, 1.53 [$P = .02$] and 1.42 [$P = .07$] per 1-dL/mg decrease in the inverse creatinine level in univariate and multivariable analyses, respectively) (figure 3 and table 3). Other predictors (from the visit before initiation of HAART) of a new ADI developing after initiation of HAART included prior history of an ADI (HR, 2.29; $P < .0001$), hepatitis C infection (HR, 1.58; $P = .0004$), a lower CD4 lymphocyte count (HR, 1.09 per 100-cells/μL decrease; $P = .02$), a higher $\log_{10}$ plasma level of HIV RNA (HR, 1.17 per increase of $\log_{10}$ HIV RNA copies/mL; $P = .02$), and a lower albumin level (HR, 1.32 per 1-mg/dL increase; $P = .07$). Although black race was associated with time to development of a new ADI in univariate analysis (HR, 1.31; $P = .01$), it failed to remain significant in the multivariable model after controlling for albumin level, creatinine level, prior ADI, HIV RNA level, and CD4 lymphocyte count.

In univariate models, proteinuria and an elevated creatinine level noted at the visit before initiation of HAART were both associated with an increased risk of death due to all causes after initiation of HAART (for proteinuria: HR, 3.70 [$P < .0001$]; for a decreasing inverse creatinine level: HR, 5.13 [$P < .0001$]) (figure 3*B*). In the multivariable analysis, proteinuria remained associated with an increased risk of death (HR, 2.21; $P = .002$) (table 3). Other predictors (from the visit before initiation of HAART) of death among women after initiation of HAART included a lower CD4 lymphocyte count (HR, 1.36 per 100-

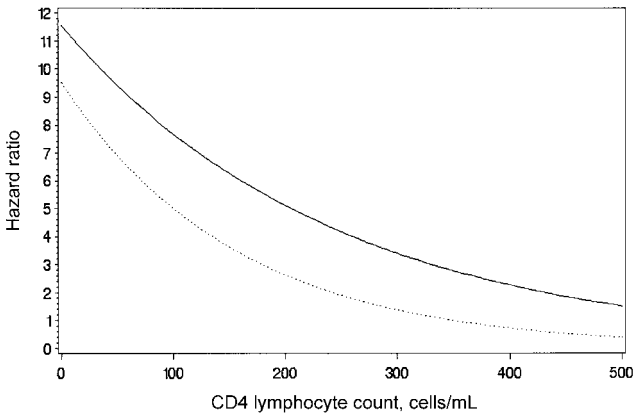

Figure 2. Relative hazard of death before the widespread use of HAART, according to absolute CD4 lymphocyte count for women with or without proteinuria. The baseline hazard ratio was 1 for women without proteinuria who had a CD4 lymphocyte count of 350 cells/mL. *Dotted line,* women without proteinuria; *solid line,* women with proteinuria.

Table 3. Multivariable predictors of the development of AIDS-defining illness (ADI) and death among women, after the initiation of HAART, in a multivariate model.

Class of predictor, variable	Hazard ratio (95% CI)	*P*
Predictor of ADI		
Inverse creatinine level, per 1-dL/mg decrease	1.42 (0.97–2.08)	.07
Prior history of ADI	2.29 (1.75–2.99)	<.0001
Hepatitis C virus infection	1.58 (1.23–2.04)	.0004
CD4 lymphocyte count, per 100-cells/mL decrease	1.09 (1.02–1.17)	.02
Log viral load,[a] per 1-log increase	1.17 (1.03–1.33)	.02
Albumin level, per 1-mg/dL decrease	1.32 (0.98–1.77)	.07
Predictor of death		
Proteinuria, presence vs. absence	2.21 (1.33–3.67)	.002
CD4 lymphocyte count, per 100-cells/mL decrease	1.36 (1.15–1.60)	.0003
History of hypertension	2.25 (1.37–3.68)	.001
Hepatitis C virus infection	2.13 (1.34–3.39)	.001
Albumin level, per 1-mg/dL decrease	2.04 (1.26–3.29)	.004
Prior history of ADI	1.81 (1.09–3.01)	.02

[a] Log_{10} HIV RNA copies/mL.

cells/mL decrease; $P = .0003$), hypertension (HR, 2.25; $P = .001$), hepatitis C infection (HR, 2.13; $P = .001$), a lower albumin level (HR, 2.04 per 1-mg/dL decrease; $P = .004$), and prior history of an ADI (HR, 1.81; $P = .02$). Although race was associated with death in univariate analysis (HR, 1.87; $P = .001$), the association failed to remain significant in the multivariable model when the model was controlled for proteinuria, CD4 lymphocyte count, hypertension, hepatitis C infection, albumin level, and prior ADI.

DISCUSSION

Proteinuria was independently associated with progression to an incident ADI among women before the widespread use of HAART and with an increased risk of death among women both before the widespread use of HAART and after the initiation of HAART. A higher creatinine level was independently associated with more-rapid progression to an incident ADI among women after the initiation of HAART and, also, with an increased risk of death among women before the widespread use of HAART.

To our knowledge, this is the first report of an association between proteinuria and the development of ADI among women before the widespread use of HAART. Although proteinuria has been demonstrated to be associated with more-advanced HIV infection manifested by a lower CD4 lymphocyte count and a higher HIV RNA level [12], the present study demonstrates an association with future development of ADI that is independent of those factors. The mechanisms for this association are unclear. Proteinuria may be a marker for diseases, such as HIVAN, that are associated with a reservoir of viral replication in the kidney and resultant systemic implications [2]. Among patients with kidney disease, immune dysfunction may manifest as a reduced rate of response to vaccination that potentially correlates with the degree of renal failure [13, 14]. Immune dysfunction associated with worsening renal disease could contribute to the risk of ADI among HIV-infected women with higher creatinine levels.

Our findings that proteinuria and an elevated creatinine level are associated with death are consistent with the findings of a previous analysis of the HIV Epidemiology Research Study (HERS), the cohort of which was recruited from April 1993 through January 1995 and was seen until October 1999 [1]. Although HERS did not examine proteinuria and the creatinine level separately, women with either proteinuria or an elevated creatinine level had an increased risk of death (HR, 2.5; $P < .0001$). The analysis presented in the current study extends the work of HERS by demonstrating that the risk of progression of HIV disease associated with renal dysfunction (1) exists for each of these 2 markers (proteinuria and an elevated creatinine level) independently, (2) begins at a potentially lower level of proteinuria, and (3) is present both before the era of HAART and among women receiving HAART.

Of importance, before the widespread use of HAART, for any given CD4 lymphocyte count, mortality among women with proteinuria was greater than that among women without proteinuria. This point is demonstrated by the fact that a CD4 lymphocyte count of 350 cells/mL is often considered to be a threshold for initiation of HAART [15]. However, the hazard of death for women without proteinuria who had a CD4 lymphocyte count of 350 cells/mL was less than the hazard of death for women with proteinuria who had a CD4 lymphocyte count of ⩽500 cells/mL.

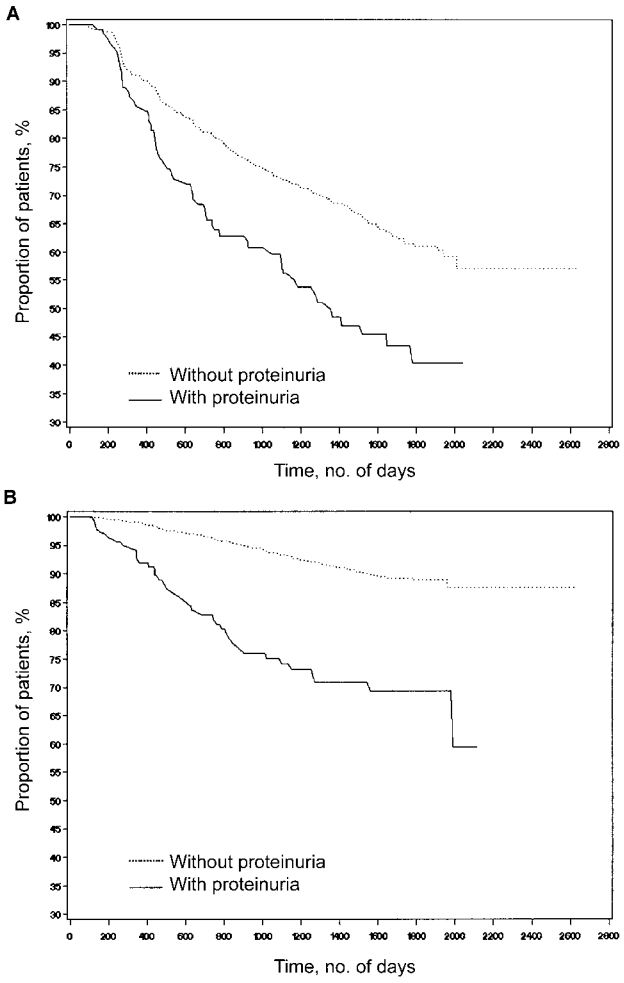

Figure 3. *A,* Time to AIDS-defining illness, after the initiation of HAART, for women stratified according to presence or absence of proteinuria. *B,* Time to death, after the initiation of HAART, for women stratified according to presence or absence of proteinuria.

Significant proteinuria is most often a marker of glomerular disease, and an elevated creatinine level indicates loss of kidney function. Although glomerular diseases related to HIV infection [16–18] have been shown to result both in significant degrees of proteinuria and in an elevated creatinine level, the present study demonstrates that an abnormality in either one of these markers alone may be associated with an increased risk for the development of an ADI or death. These findings may indicate that the patients have either early HIVAN, in which proteinuria is present but the creatinine level is normal, or a tubulointerstitial process, such as drug-related toxicity, that presents with an elevated creatinine level but without proteinuria. The findings may reflect a type II error, but they probably do not reflect collinearity, because proteinuria and the creatinine level (i.e., in table 1) were weakly, but not strongly, correlated with each other in the present study.

Proteinuria and/or an elevated creatinine level is associated with an increased risk of death among women before the widespread availability of HAART and after the initiation of HAART. Although proteinuria and an elevated creatinine level may indict the kidney as a reservoir of HIV replication, they are risk factors for death among patients with diabetes mellitus and hypertension [3–5], and they are markers for other comorbidities that confer additional risk. Given the association between renal disease and heart disease, as well as the dyslipidemia and risk of cardiac disease among HIV-infected patients, the present study may provide a link in the identification of a group of patients who should be followed up closely.

HIV-infected patients are subject to a variety of glomerular diseases that are identified by means of renal biopsy [12, 16–18]. Because the present study did not have the ability to identify specific types of renal disease, additional research describing the outcomes associated with specific histologic findings should be conducted. Although observational data suggest a beneficial effect resulting from the use of angiotensin-converting enzyme inhibitors [12, 19, 20] and prednisone [21], information on the use of these agents in the present study was not available. The WIHS cohort includes only women; therefore, generalizability of these conclusions to men must be considered. Although there are no data to suggest differences in the clinical course of HIV-related renal disease on the basis of sex, several studies have demonstrated a lower HIV RNA level among women—in particular, among those with early stages of disease [22, 23]. Other potential sex differences should be considered in the generalization of these results to men.

We find that proteinuria and an elevated creatinine level are independently associated with a greater risk of progression to AIDS and death. Given these poorer outcomes, the present study generates hypotheses regarding the need for better mentoring and more aggressive treatment of HIV-infected women with these findings. Antiretroviral medications dramatically prolong the survival of HIV-infected patients [24–27]. Given the higher prevalence of HIV-related renal disease among blacks [28, 29], and given the increasing numbers of HIV-infected black individuals of African descent worldwide and in the United States, further investigation of strategies to lessen the risk of AIDS and death among HIV-infected persons with renal disease is warranted.

WOMEN'S INTERAGENCY HIV STUDY PARTICIPATING CENTERS

Centers (principal investigator[s]) of the collaborative study group: New York City/Bronx Consortium (K.A.); Brooklyn, NY (Howard Minkoff); Washington DC Metropolitan Consortium (M.A.Y.); The Connie Wofsy Study Consortium (Ruth Greenblatt and Herminia Palacio); Los Angeles County/Southern Cal-

ifornia Consortium (Alexandra Levine); Chicago Consortium (M.H.C.); and Data Coordinating Center (Alvaro Muñoz).

Acknowledgments

Financial support. The Women's Interagency HIV Study is funded by the National Institute of Allergy and Infectious Diseases, with additional supplemental funding from the National Cancer Institute, the National Institute of Child Health and Human Development, the National Institute on Drug Abuse, and the National Institute of Craniofacial and Dental Research (grants U01-AI-35004, U01-AI-31834, U01-AI-34994, AI-34989, U01-HD-32632, U01-AI-34993, U01-AI-42590, and N01-AI-35161); and the National Institutes of Health (grant DK02724-01A1 to L.A.S.).

Conflict of interest. At the time of submission of the present article for review, S.J.G. was employed by Amgen, in addition to retaining an adjunct appointment with Johns Hopkins University. All other authors: no conflict.

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