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The Impact of Kidney Function at HAART Initiation on Mortality in HIV-infected Women

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Abstract

Background—In the early highly active antiretroviral therapy (HAART) era, kidney dysfunction was strongly associated with death among HIV-infected individuals. We re-examined this association in the later HAART period to determine whether chronic kidney disease (CKD) remains a predictor of death after HAART-initiation.

Methods—To evaluate the effect of kidney function at the time of HAART initiation on time to all-cause mortality, we evaluated 1415 HIV-infected women initiating HAART in the Women's Interagency HIV Study (WIHS). Multivariable proportional hazards models with survival times calculated from HAART initiation to death were constructed; participants were censored at the time of the last available visit or December 31, 2006.

Results—CKD (eGFR <60 ml/min/1.73 m^2) at HAART initiation was associated with higher mortality risk adjusting for age, race, hepatitis C serostatus, AIDS history and $CD4^+$ cell count (hazard ratio [HR]=2.23, 95% confidence interval [CI]: 1.45–3.43). Adjustment for hypertension and diabetes history attenuated this association (HR=1.89, CI: 0.94–3.80). Lower kidney function at HAART initiation was weakly associated with increased mortality risk in women with prior AIDS (HR=1.09, CI: 1.00–1.19, per 20% decrease in eGFR).

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No parts of the data have been previously presented at a meeting.

Conclusions—Kidney function at HAART initiation remains an independent predictor of death in HIV-infected individuals, especially in those with a history of AIDS. Our study emphasizes the necessity of monitoring kidney function in this population. Additional studies are needed to determine mechanisms underlying the increased mortality risk associated with CKD in HIV-infected persons.

Keywords

kidney disease; mortality; HIV; WIHS; antiretroviral therapy

Introduction

An earlier study in the Women's Interagency HIV Study (WIHS) showed that proteinuria and elevated serum creatinine were associated with earlier progression to AIDS and death in the pre- and early era of highly active antiretroviral therapy (HAART)[1]. Since that study, appreciation of co-morbid conditions which may contribute to chronic kidney disease (CKD) in HIV-infected persons such has hepatitis C co-infection, diabetes, and hypertension have increased. In the current era in which earlier antiretroviral initiation is being advocated[2], the relative contribution of such co-morbid factors to CKD in HIV infection will likely increase[3, 4]. Thus, it remains unclear whether CKD is simply an indicator of poor health or an independent contributor to mortality in HIV infection. The purpose of this study was to re-evaluate whether kidney function at HAART initiation is associated with subsequent mortality in the context of the modern HAART era.

METHODS

WIHS is an ongoing cohort study of HIV-infected women and a demographically similar group of HIV-negative women conducted at five U.S. metropolitan areas. Women were enrolled from October 1994 through November 1995 and from October 2001 through September 2002. The study is approved by all local institutional review boards. Clinical data, physical exams, and laboratory tests were obtained at enrollment and semi-annually[5]. Our study consisted of HIV-infected women receiving HAART with serum creatinine available within 1.25 years of HAART initiation. HAART was defined in accordance with US Department of Health and Human Services treatment guidelines (www.aidsinfo.gov). Baseline values reported are those obtained at the visit just prior to or at the time of HAART initiation. Kidney function was estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation[6]. CKD was defined as an eGFR <60 ml/min/1.73 m^2 on at least two consecutive visits as of the time of HAART initiation. Serum creatinine values within 1 year of a missing value were carried forward; these forwarded values were not used to meet the CKD criterion. AIDS history was based on self-reported AIDS-defining illnesses in the 1993 Centers for Disease Control and Prevention class C definition of AIDS and do not include the immunological criteria[7]. Laboratory measurements also assessed in this study include hepatitis C antibody at enrollment, serum albumin levels at baseline, and $CD4^+$ cell count and HIV-1 RNA levels at the visit prior HAART initiation and semi-annually. If pre-HAART $CD4^+$ cell count or HIV-1 RNA values were missing, values from up to the preceding 1.25 years were carried forward. Values no earlier than 1 year prior to a visit were carried forward for missing $CD4^+$ cell counts and HIV-1 RNA levels following HAART-initiation. Deaths were ascertained by notification from friends, relatives, or medical providers of WIHS participants. Death registry searches were performed regularly to obtain death information on all participants. The date of death and cause of death were confirmed through the National Death Index Plus and death certificates. Deaths were classified as AIDS-related, non-AIDS related, indeterminate and unknown as described previously[8].

Data were analyzed using Stata (version 11; College Station, TX, USA). Baseline characteristics were compared in women with and without CKD using the chi-square test, Student's t-test, and Wilcoxon rank-sum test, as appropriate. In parallel analyses, we evaluated the association of CKD and baseline eGFR (presented as increments of 20% difference in eGFR) with time to all-cause mortality using survival analysis methods. Survival times were determined from HAART initiation to death; participants were censored at the last available visit or December 31, 2006. Proportional hazards models adjusting for age, race, prior AIDS history, hepatitis C antibody serostatus, and time-varying values of $CD4^+$ cell count and HIV-1 RNA level were constructed. Additional models adjusted for diabetic and hypertensive history prior to HAART initiation. Covariates in the final models were chosen based on their clinical and statistical significance on univariate analyses. Serum albumin was not evaluated as a covariate since it may mediate the association of CKD with mortality and was not independently associated with mortality after HAART initiation in the prior WIHS analysis[1]. The proportionality assumption was tested by log-log plots and plots of Schoenfeld residuals versus time. To determine the effect of missing data on results, we performed three sensitivity analyses: 1) values carried forward for values missing at the visit just prior to HAART initiation and at the time of HAART initiation were limited to the preceding 6 months; 2) women with missing diabetes (n=246) data were included; and 3) last available visits were extended by the same length of time as values were carried forward at study entry (*i.e.* up to 1.25 years).

RESULTS

Of 1922 women who initiated HAART, 507 did not have baseline serum creatinine and were excluded. Excluded women were less likely to be injection drug users, diabetic, and hypertensive. They were also less likely to be hepatitis C antibody positive, have prior AIDS, or die. Of the 1415 HAART-users included in this study, 44 had CKD at HAART initiation. Women with CKD were older, had lower pre-HAART $CD4^+$ cell counts and serum albumin levels, and were more likely to have had AIDS, diabetes, and hypertension compared to those without CKD (Table 1). The median follow-up time for women with versus without CKD was shorter primarily due to earlier death in the former (3.5 years [IQR: 1.5–7.7 years]) versus 7.2 years, [IQR: 3.5–9.3 years], $P<0.01$).

During 8148 person-years of follow-up, 335 women died. Women with CKD had more than a 2-fold greater adjusted risk of death (CI: 1.45 – 3.43) compared to women without CKD (Table 2). Adjustment for hypertension and diabetes history attenuated the association (HR=1.89, CI: 0.94 – 3.80). The specific cause of death was missing in 21% and 16% of women with and without CKD, respectively. Among women with CKD, 17% died as a result of kidney failure. The proportions of deaths attributed to infectious causes and AIDS-related causes were similar between women with and without CKD. Heart disease was listed as the cause of death in 11% of women with CKD but in only 6% of those without CKD. No women with CKD died of cancer versus 14% of women without CKD. A history of clinical AIDS modified the association between baseline eGFR and all-cause mortality (Table, Supplemental digital content 1) (P-interaction <0.01 in Models 1 and 3). After adjustment for factors which are traditionally associated with death in HIV-infected individuals, lower eGFR at HAART initiation was modestly associated with higher risk of death in those with and without prior AIDS ([HR=1.28 per 20% decrease in eGFR, CI: 1.13 – 1.44] and [HR=1.11 per 20% decrease in eGFR, CI: 1.06 – 1.17], respectively). When we also adjusted for hypertension and diabetes history, this association did not remain significant in those without prior AIDS. None of our sensitivity analyses changed the risk estimates.

DISCUSSION

Our study demonstrates that established CKD at HAART initiation is associated with higher mortality risk independent of HIV-related risk factors for death (Model 1), consistent with the prior WIHS study in the early HAART era that was conducted through March 31, 2002[1]. Attenuation of the association between CKD and mortality after adjustment for diabetes (Model 2) suggests that CKD may mediate some of the effects of diabetes on mortality; however, we were unable to confirm this explanation due to lack of temporal data on diabetes in relation to kidney function in a large number of WIHS participants. Alternatively, exclusion of women who were missing diabetes data in the adjusted model may have diminished our ability to detect smaller increases in mortality risk associated with CKD. The statistical significance of the risk estimate for CKD upon inclusion of women missing diabetes data supports the latter explanation.

We also found that eGFR at HAART initiation was inversely, but weakly associated with mortality risk in women with prior AIDS and that proportion of women dying of heart disease and malignancy differed between those with and without CKD. In the general HIV-uninfected population, the risk of all-cause mortality increases progressively with lower eGFR; Go and colleagues showed that the risk of death was 1.2-, 1.8-, 3.2- and 5.8-fold higher in those with eGFRs of 45–59, 30–44, 15–29, and <15 ml/min/1.73 m^2, respectively[9]. This increased risk of death associated with CKD in the general population is driven primarily by cardiovascular death, with individuals who have CKD having more than 50% increased risk of death due to cardiovascular disease compared to persons with normal kidney function[10, 11]. Many of the same risk factors that lead to CKD also lead to cardiovascular disease. These CKD risk factors and CKD itself may lead to activation of the renin-angiotensin system, inflammation, extra-skeletal calcification, and dyslipidemia which, in turn, culminate in endothelial dysfunction[11]. This may explain why we observed a higher proportion of deaths from heart disease in HIV-infected women with CKD compared to women without CKD. In contrast, there is no apparent physiologic mechanism by which CKD is associated with the risk of malignancy to explain the disparity in cancer-related deaths between women with and without CKD in our study. Perhaps, women with CKD were more likely to die of other causes prior to having the opportunity to develop cancer.

Although HAART has greatly improved the survival of HIV-infected individuals[12], prior studies suggest that HIV-infected persons with CKD may not have the same degree of survival benefit as those without CKD[13]. Underutilization of HAART and improper dose adjustments of antiretroviral medications may partially explain the impact of kidney dysfunction on mortality among HAART-users that we observed[14]. Due to lack of data on drug dosages within WIHS, we were unable to explore this further. However, the mechanism by which HAART dose may mediate the effect of CKD on mortality may be more complex. A detailed pK study of atazanavir among 122 women in WIHS showed that the area under the curve of atazanavir concentration following its administration was increased by 1.58-fold (CI: 1.05 – 2.38) in women with CKD compared to those without CKD[15], suggesting that individuals with CKD may be exposed to higher concentrations of certain antiretroviral drugs than anticipated.

Our study has several limitations to consider. WIHS consists only of women; however, there is no evidence to date that the impact of CKD on mortality differs by gender in HIV infection. Selection bias may have occurred when women with missing serum creatinine values at HAART initiation were excluded. Although women who were excluded were less likely to die, we were unable to compare their CKD and immunological status to those of women included in our study due to missing data on these characteristics among the former. The MDRD equation has not been thoroughly validated in HIV-infected persons; therefore,

misclassifications for CKD may have occurred. However, most of the published data linking kidney disease to death are based on eGFR by the MDRD equation[9, 10, 16], and current evidence suggests that the MDRD equation is more accurate than other currently available estimates of GFR in HIV-infected individuals[17]. We also used two sequential eGFRs to define CKD status to minimize misclassifications.

In summary, our study suggests that pre-existing CKD at the time of HAART initiation leads to increased risk of death. Furthermore, kidney function level at HAART initiation is independently associated with mortality in those with a history of AIDS. Our study underscores the importance of early screening for kidney disease in HIV-infected women prior to HAART initiation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of WIHS participants at HAART initiation by CKD status

Characteristic	No CKD (n=1381)	Prevalent CKD (n=44)
Age, mean years (SD)[a]	38.9 (8.1)	44.0 (9.1)
Black, n (%)	774 (56)	28 (64)
Injection drug use, n (%)	489 (36)	20 (46)
Body mass index, median kg/m^2 (IQR)	26.1 (22.8 – 30.6)	23.8 (20.5 – 32.1)
CD4$^+$ cell count, median cells/mm^3 (IQR) [a,b]	271 (149 – 419)	171 (65 – 322)
HIV-1 RNA level, median copies/ml (IQR) [b]	17,000 (2300 – 80,000)	19,000 (935 – 115,000)
Serum albumin, median mg/dl (IQR) [a, b]	4.2 (3.9 – 4.4)	3.6 (3.2 – 4.0)
Serum creatinine, median mg/dl (IQR) [a]	0.8 (0.7 – 0.9)	1.5 (1.3 – 3.2)
Estimated GFR, median ml/min/1.73 m2 (IQR) [a]	92.6 (77.9 – 113.2)	40.8 (19.5 – 52.9)
Hepatitis C antibody positive, n (%)	505 (38)	21 (48)
History of illness, n (%)		
AIDS [a]	812 (59)	33 (75)
Diabetes mellitus [a]	99 (9)	9 (30)
Hypertension [a]	622 (46)	33 (75)

The following were missing: CD4$^+$ cell count (n=84), HIV-1 RNA level (n=86), serum albumin (n=122), hepatitis C antibody (n=41), diabetes (n=268) and hypertension (n=21).

[a] *P*-value <0.05;

[b] Values from visit just prior to HAART initiation

Table 2

Hazard ratios of mortality associated with CKD at HAART initiation

Variable	Unadjusted Model	Multivariable		
		Model 1[a]	Model 2[b]	Model 3[c]
		n=1374	n=1104	n=1353
Prevalent CKD	3.12 (2.04 – 4.76)	2.23 (1.45 – 3.43)	1.89 (0.94 – 3.80)	1.60 (1.03 – 2.48)
Age, per 1 year increase	1.04 (1.02 – 1.05)	1.03 (1.01 – 1.04)	1.04 (1.01 – 1.06)	1.02 (1.01 – 1.04)
Black	1.59 (1.26 – 1.99)	1.31 (1.04 – 1.65)	1.43 (1.02 – 2.01)	1.41 (1.11 – 1.79)
Hepatitis C seropositivity	2.30 (1.85 – 2.87)	1.81 (1.44 – 2.28)	2.04 (1.47 – 2.85)	1.93 (1.53 – 2.43)
History of clinical AIDS	3.82 (2.82 – 5.17)	1.90 (1.39 – 2.60)	2.11 (1.35 – 3.28)	1.56 (1.14 – 2.16)
CD4$^+$ cell count [d]	0.58 (0.54 – 0.62)	0.60 (0.55 – 0.64)	0.63 (0.57 – 0.69)	0.67 (0.62 – 0.71)
History of hypertension	1.00 (0.80 – 1.19)	---	0.75 (0.53 – 1.07)	0.92 (0.74 – 1.16)
History of diabetes	4.27 (2.96 – 6.17)	---	3.38 (2.26 – 5.03)	3.37 (2.30 – 4.94)

Data presented as hazard ratio (95% confidence interval);

[a] Model 1 adjusted for age, race, hepatitis C serostatus, AIDS history and CD4$^+$ cell count;

[b] Model 2 adjusted for covariates included in Model 1 and history of hypertension and diabetes; excludes women missing data on diabetes;

[c] Model 3 adjusted for all covariates included in Model 2; includes women missing data on diabetes;

[d] Per 100 cells/mm^3 increase; time-varying.