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Journal

Hepatology, 56(5)

ISSN

0270-9139

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Publication Date

2012-11-01

DOI

10.1002/hep.25859

Peer reviewed

Published in final edited form as:
Hepatology. 2012 November ; 56(5): 1699–1705. doi:10.1002/hep.25859.

Lower Liver-Related Death in African American Women With HIV/HCV Co-Infection Compared to Caucasian and Hispanic Women

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Abstract

Among individuals with and without concurrent human immunodeficiency virus (HIV), racial/ethnic differences in the natural history of hepatitis C virus (HCV) have been described. African-Americans have lower spontaneous HCV clearance than Caucasians, yet slower rates of liver fibrosis once chronically infected. It is not clear how these differences in the natural history of hepatitis C affect mortality, in either HIV positive or negative individuals. We conducted a cohort study of HIV/HCV co-infected women followed in the multicenter, NIH-funded Women's Interagency HIV Study (WIHS) to determine the association of self-reported race/ethnicity with all-cause and liver-related mortality. Survival analyses were performed using Cox proportional hazards models. The eligible cohort (n=794) included 140 Caucasians, 159 Hispanics, and 495 African Americans. There were 438 deaths and 49 liver-related deaths during a median follow-up of 8.9 years and maximum follow-up of 16 years. African American co-infected women had significantly lower liver-related mortality compared to Caucasian (HR 0.41 95% CI 0.19–0.88, p=0.022) and Hispanic co-infected women (HR 0.38 95% CI 0.19–0.76, p=0.006). All-cause mortality was similar between racial/ethnic groups (HRs for all comparisons 0.82–1.03, logrank p=0.8).

Conclusions—African American co-infected women were much less likely to die from liver disease as compared to Caucasians and Hispanics, independent of other causes of death. Future

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studies are needed to investigate the reasons for this marked racial/ethnic discrepancy in liver-related mortality.

Keywords

race; ethnicity; viral hepatitis; mortality; gender

In the United States, at least 5 million people are infected with hepatitis C, 80% of whom are estimated to be viremic.(1, 2) Due to shared modes of transmission, HCV infection in patients with HIV is common. Approximately one third of HIV positive patients are co-infected with HCV, and this number approaches 80% among those with injection drug user (IDU).(3) Among patients with HIV, hepatitis C related liver disease remains the second leading cause of death.(4) Data projecting liver-related mortality also indicate that deaths from hepatitis C are continuing to rise and remain an important cause of premature mortality.(5–7)

Racial/ethnic differences in the natural history of hepatitis C have been well described. Spontaneous HCV clearance is lower among African Americans compared to Caucasians and Hispanics, yet African Americans appear to develop less fibrosis and inflammation once chronically infected compared to other racial/ethnic groups.(8–10) It remains unclear how these racial differences in the natural history of hepatitis C may affect liver-related death, in either HCV mono-infection or HIV/HCV co-infected individuals.

Data on race and mortality in patients with chronic HCV infection are conflicting. Several recent studies have reported higher deaths rates among Caucasians with chronic hepatitis C compared to African Americans, although one large study observed opposite trends.(11–14) Most studies have also focused on male predominant cohorts, with limited available data on race and mortality among women with HCV or HIV/HCV co-infection.

Given conflicting prior data on race and mortality, and the absence of robust data in either female or HIV-infected populations, we aimed to determine the association between race/ethnicity and liver-related death in a large cohort of HIV/HCV co-infected women followed in the Women's Interagency HIV Study (WIHS). The rich ethnic diversity and long-term follow-up of WIHS participants has allowed us to address these important racial and ethnic distinctions.

METHODS

Study population

We conducted a cohort study of women participating in the Women's Interagency HIV Study (WIHS). The WIHS is an NIH-funded, prospective, multicenter cohort of women at risk for, or currently diagnosed with HIV. Enrollment in WIHS took place in two study cohorts, the first in 1994–1995 and the second in 2001–2002.(15) Women in WIHS are seen twice yearly and undergo detailed histories, physical exams, structured interviews, and laboratory testing. This study was approved by the WIHS Executive Committee and the Institutional Review Boards (IRB) at the six participating WIHS study sites. Study eligibility included HIV/HCV co-infection at WIHS study entry as defined by detectable HCV ribonucleic acid (RNA), HCV antibody, and positive HIV Western blot. Due to the small number of women who self-reported as other than Caucasian, Hispanic, or African American, these individuals were excluded from the analysis.

Predictor and Outcome Measures

The primary predictor was race/ethnicity determined by self-report at WIHS entry visit. We defined the "African American" group as non Hispanic African Americans. The "Caucasian" group was defined as non Hispanic Caucasians. The "Hispanic" group was defined as Hispanic Caucasians, Hispanic African Americans, and other Hispanics. Our outcome of interest was primary liver-related death as determined by death certificate verification. We also report data on all-cause mortality. Primary death certificate data were reviewed by two clinicians to determine cause of death. In some cases there was supplemental information from medical record review, communication with the primary clinician, or patient families. Primary liver-related deaths included those due to hepatic decompensation or hepatocellular carcinoma, although most death certificates simply recorded "hepatitis C" as the primary cause of liver death, without further specification.

The following covariates were included in our survival analysis: age; substance abuse history including intravenous (IV) drugs, non IV drugs, tobacco, and alcohol; HIV-related factors such as HIV RNA levels, CD4 count, and highly active anti-retroviral therapy (HAART); liver-related factors including HCV RNA levels, HCV genotype, HCV treatment history, and chronic hepatitis B virus (HBV); co-morbid factors such as diabetes (DM), hypertension (HTN), body mass index (BMI), glomerular filtration rate (GFR), and cancer history.

Laboratory Assays

Plasma HIV RNA levels were measured using the NASBA/NuciSens HIV RNA assay (bioMerieux, Durham, NC), in laboratories certified by the NIH National Institute of Allergy and Infectious Diseases Virology Quality Assurance Certification Program. HCV and HBV serologies were performed using standard commercial assays and included hepatitis C antibody by EIA 3.0 (Ortho-Clinical Diagnostics, Raritan, NJ); hepatitis B surface antigen (HBsAg) (Abbott Laboratories, Abbott Park, IL). HCV RNA levels were measured by the COBAS Amplicor Monitor 2.0 assay (Roche Diagnostics, Branchburg, NJ) with a linear range of 600–700,000 IU/ml, or COBAS Taqman (Roche Diagnostics), with a linear range of 10–2.0×10^8 IU/ml.

Statistical Analysis

Patient characteristics were compared using chi square, t tests, and Kruskal-Wallis tests, when appropriate. Cox regression models were used to calculate the hazards ratios (HR) and 95% confidence intervals (CI) for factors associated with all-cause and liver-related mortality. All survival analyses used age as the time scale, with age at study entry treated as a left-truncation time in order to reflect the fact that only living women could be enrolled. This automatically accounts for the important influence of age on mortality risk and is a more biologically meaningful time scale than time since study enrolment. All variables that were measured repeatedly were analyzed as time-varying covariates, with the most recent value carried forward until a new measurement was made. The only non-time varying covariates were race/ethnicity and HCV genotype, as these factors do not change over time. The final multivariate model was developed using forward selection of covariates, as well as inclusion of covariates with high biological plausibility of an association with death. A Fine-Gray competing risks analysis(16) as well as a survival analysis of non liver-related death was performed to assess the possibility that racial/ethnic differences in liver-related death could be attributed to a differential risk of non liver-related death among racial/ethnic groups. All analyses were performed using Stata software, version 11.0 (College Station, Texas).

RESULTS

We identified 794 women in WIHS with confirmed chronic hepatitis C and HIV infection. Of these, 62.3% (495/794) were African American, 20% were Hispanic (159/794), and 17.7% (140/794) were Caucasian. Women were followed for up to 16 years, with a median follow-up of 8.9 years. The median follow-up for Caucasians, African-Americans, and Hispanics was 9.0, 8.7, and 9.2 years, respectively. During this time there were 438 deaths from all causes, including 49 liver-related deaths. Among primary causes of death, HIV/AIDS (36.9%) was the most common cause of death, followed by liver-related disease (11.2%), and homicides, suicides, and accidents (9.0%). Approximately 55.8% (276/495) of African Americans, 52.2% (83/159) of Hispanics and 56.4% (79/140) of Caucasians died during follow-up. Liver disease was the primary cause of death in 7.6% (21/276) of African Americans, 20.5% (17/83) of Hispanics, and 13.9% (11/79) of Caucasians.

Compared to Hispanics and Caucasians, African American women were older at study entry and time of death, were more likely to have heavy alcohol and tobacco use, to be diagnosed with hypertension, and to be infected with HCV genotype 1. Compared to Hispanics and African Americans, Caucasian women were more likely to use IV drugs. There were no significant differences in median CD4 count, median HIV viral load, or HAART use between racial/ethnic groups. HCV treatment was uncommon, with similar percentages between racial/ethnic groups (Table 1).

We first analyzed racial/ethnic differences in all-cause mortality, which was similar between racial/ethnic groups on both univariate and multivariate models (HRs for all comparisons 0.82–1.03, logrank p=0.8). These results contrasted markedly from our analysis of liver-related mortality. On univariate analysis, there was a trend towards lower risk of liver-related death among African Americans compared to Caucasians (HR 0.48, 95% CI 0.23–1.03, p=0.058) and a statistically significantly lower risk of liver-related death among African Americans compared to Hispanics (HR 0.44, 95% CI 0.22–0.87, p=0.019). On multivariate analysis, adjusted for CD4 count and HIV RNA levels, we observed even stronger racial/ethnic differences in liver-related mortality, with a HR comparing African American to Caucasian women of 0.41 (95% CI 0.19–0.88, p=0.022) and a HR comparing African American to Hispanic women of 0.38 (95% CI 0.19–0.76, p=0.006). Liver-related mortality was similar between Caucasian and Hispanic co-infected women on univariate and multivariate analyses (Table 2). These associations are demonstrated graphically in an age-adjusted survival curve, with a logrank p=0.032 (Figure 1).

Additional factors that were associated with liver-related mortality on univariate analysis included CD4 count (HR 0.78 per 2-fold increase, 95% CI 0.67–0.91, p=0.002) and HIV RNA level (HR 1.47 per 10-fold increase, 95% CI 1.17–1.9, p=0.001), although there was no significant association with HCV RNA levels (HR 1.44, 95% CI 0.94–2.2, p=0.09). On multivariate analysis, HIV RNA levels were associated with liver-related death (HR 1.44, 95% CI 1.11–1.9, p=0.006) (Table 3).

We also assessed liver-related mortality after adjusting for categories of factors that could affect risk of death. We continued to observe marked racial/ethnic differences in liver-related mortality after adjusting for cardiovascular risk factors, HIV immune control and liver-related factors, suggesting that the observed racial/ethnic differences were not explained by these co-morbid conditions (Table 4).

Importantly, we performed a competing risks analysis to determine if the lower risk of liver-related mortality among African American women was due to African Americans dying at a higher rate from non liver-related diseases as compared to other racial/ethnic groups. In addition, we performed a survival analysis of non liver-related mortality. The competing

risks analysis estimated that African American HIV/HCV co-infected women had a similar risk of non liver-related mortality as other racial/ethnic groups, as did the survival analysis of non liver-related mortality (HR 1.01, 95% CI 0.75–1.36, p=0.95 vs Caucasian and HR 1.18, 95% CI 0.88–1.59, p=0.27 vs Hispanic). Therefore African American women had a lower risk of liver-related mortality as compared to Hispanic and Caucasian co-infected women, independent of other causes of death.

DISCUSSION

In this large cohort of HIV/HCV co-infected women, we investigated liver-related and all-cause mortality. We observed marked differences in liver-related death between racial/ethnic groups while all-cause mortality was similar between African American, Hispanic, and Caucasian co-infected women. African Americans were approximately 60% less likely to die from liver disease as compared to Caucasian and Hispanic women. This relationship persisted after adjusting for an extensive list of covariates that could possibly affect risk of death.

A previous investigation of HIV/HCV co-infected veterans identified important racial differences in all-cause mortality, with significantly higher mortality among Caucasian co-infected males compared to African Americans. Interestingly, these differences were not observed among HCV mono-infected patients.(14) Unlike our study, the Veteran study was predominantly male and limited by its cross sectional design, small number of Hispanic patients, and inability to investigate liver-related death. While the Veteran study did report important racial/ethnic differences in all-cause mortality among co-infected men, no prior data reflect liver-related mortality trends among co-infected populations, or in HIV/HCV co-infected women.

The reasons for the marked racial/ethnic differences in liver-related mortality in the current study certainly warrant further investigation. When we adjusted for many cofactors known to accelerate liver disease, such as HIV immune status, obesity, and alcohol use, we continued to observe significant differences between racial/ethnic groups. While African Americans are less likely to spontaneously clear HCV, previous data do suggest that once chronically infected, African Americans tend to have less liver inflammation as measured by ALT levels and necroinflammatory scores on liver biopsy.(10) Sugimoto et al. also investigated T cell response in patients with chronic HCV infection and found that African Americans had a significantly more robust T cell response than Caucasians, as well as higher platelet counts, lower bilirubin, and lower ALT levels.(17) These results were not due to alcohol use, gender differences, or HCV genotype, which were evenly distributed between African Americans and Caucasians. It is quite possible that differential immunologic response to HCV may account for differences in progression of HCV-related liver disease between racial/ethnic groups.

African Americans may also have slower rates of liver fibrosis than Caucasians or Hispanics chronically infected with hepatitis C. However, most studies on this topic have been limited by small sample size and these differences have generally not reached statistical significance.(9, 10, 18, 19) Two studies have noted a significantly increased rate of liver fibrosis in Hispanics compared to Caucasians and African Americans, after adjusting for co-morbid conditions that could accelerate liver fibrosis.(18, 20) Interestingly, these associations with fibrosis progression are similar to the racial/ethnic trends that we report for liver-related mortality, suggesting that differential rates of fibrosis progression may play an important role in explaining racial/ethnic differences in HCV-related mortality.

Recent data suggest that single nucleotide polymorphisms (SNPs) may play an important role in differential rates of liver fibrosis. A study by Barreiro et al found that the CC genotype associated with the *IL28B* SNP rs12979860 was predictive of cirrhosis in HIV/HCV co-infected patients.(21) As the frequency of the CC genotype is higher in Caucasians (39%) and Hispanics (35%) as compared to Africans Americans (16%)(22), these data could in part explain why African Americans may have slower rates of liver fibrosis. However, other studies investigating the association between *IL28B* and fibrosis progression have been conflicting.(23–25) A genome wide association study investigating the role of *IL28B* is currently underway within the WIHS to help further address differential rates of liver fibrosis between racial/ethnic groups.

There were several limitations in the current study. First we analyzed only primary cause of death, and therefore may have underestimated the true prevalence of liver-related death. Many patients with decompensated liver disease may die from infectious complications and these diagnoses may not have been coded as liver-related events. We also lacked data on the severity of liver disease, such as cirrhosis history or synthetic functions tests (albumin and INR). However, liver-related deaths are often due to hepatic decompensation or liver cancer, both of which were captured as liver-related events.(4) Additional data on severity of liver disease or secondary causes of death would likely have strengthened our findings.

There were important strengths of the current study, most notably our ability to separately analyze liver-related and non liver-related deaths. This showed that the lower risk of liver-related death among African American women was not simply due to African Americans dying at a higher rate from non-liver related deaths as compared to Hispanics and Caucasians. In addition, the primary cause of death was abstracted from death certificates, which are often subject to misclassification and miscoding. However, death data were ascertained in a similar fashion over time, and any misclassification would have unlikely varied by race. Finally, our survival analyses incorporated a time varying analysis of many time dependent factors that may have affected mortality risk. Alcohol use, for example, was analyzed over time rather than use at a fixed timepoint in the study period. This statistical method allowed us to capture the complex and changing effect of many risk factors for death over the course of each participant's lifetime.

In conclusion, we observed novel and important racial/ethnic trends in this large cohort of HIV/HCV co-infected women. Compared to Hispanic and Caucasian co-infected women, African American co-infected women were much less likely to die from liver-related disease, which did not appear to be due differential classification of cause of death. Previous data have revealed racial/ethnic differences in immunologic response to HCV which may affect rates of liver fibrosis. Future studies incorporating fibrosis progression may help us to better understand these marked racial/ethnic discrepancies in liver-related mortality.

Acknowledgments

Financial Support:

The WIHS is funded by the National Institute of Allergy and Infectious Diseases [UO1-AI-35004, UO1-AI-31834, UO1-AI-34994, UO1-AI-34989, UO1-AI-34993, and UO1-AI-42590] and by the National Institute of Child Health and Human Development [UO1-HD-32632]. The study is co-funded by the National Cancer Institute, the National Institute on Drug Abuse, and the National Institute on Deafness and Other Communication Disorders. Additional support was received through the National Institutes of Health, [T32 DK060414 to MS].

Abbreviations

HIV	Human immunodeficiency virus

HCV	hepatitis C virus
WIHS	Women's Interagency HIV Study
IDU	injection drug use
RNA	ribonucleic acid
HAART	highly active anti-retroviral therapy
DM	diabetes
HTN	hypertension
BMI	body mass index
GFR	glomerular filtration rate
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
SNP	single nucleotide polymorphisms

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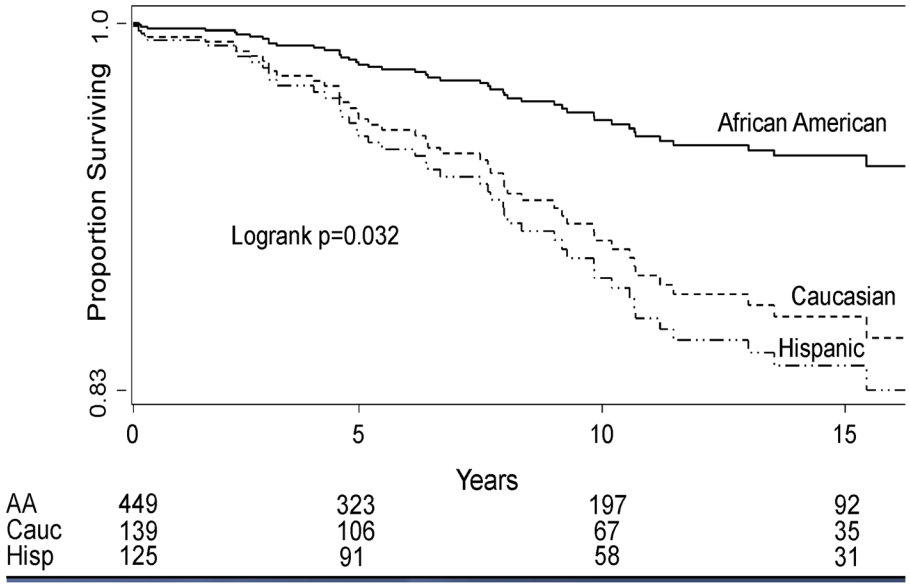

Figure 1.

shows an age-adjusted survival curve of liver-related mortality in HIV/HCV co-infected women during WIHS. African American (AA) women had greater survival than Caucasian (Cauc) and Hispanic (Hisp) women (logrank p=0.032).

Table 1

Cohort Characteristics

Variable	N	All (n=794)	Caucasian (n=140)	Hispanic (n=159)	African American (n=495)	p value
Mean Age at Entry ± (SD)	**794**	**39.7 (6.3)**	**37.4 (6.2)**	**37.5 (6.1)**	**41.0 (6.0)**	**<0.0001**
Mean Age at Death (± SD)	**438**	**46.1 (7.4)**	**43.6 (7.3)**	**44.5 (7.6)**	**47.3 (7.2)**	**<0.0001**
Tobacco Use at Entry (%)	**794**	**90.8**	**86.4**	**88.1**	**92.9**	**0.03**
Ongoing Tobacco Use (%)	794	85.3	85.0	81.1	86.7	0.23
IVDU at Entry (%)	794	84.1	88.6	82.4	83.4	0.27
Ongoing IVDU (%)	**794**	**34.4**	**45.7**	**32.1**	**31.9**	**0.01**
Non IVDU at Entry (%)	792	89.9	95.0	88.7	88.9	0.09
Ongoing Non IVDU (%)	794	68.6	71.4	66.0	68.7	0.61
Alcohol Use at Entry (%)	774	13.5	11.5	10.9	15.4	0.24
Ongoing Alcohol Use (%)	**791**	**31.1**	**23.7**	**27.9**	**34.2**	**0.04**
Median CD4 at Entry (IQR)	771	339 (179–545)	356 (208–584)	347 (191–551)	332 (172–516)	0.21
Median Nadir CD4 During Study (IQR)	787	145 (42–257)	160 (65–271)	130 (42–289)	137 (32–245)	0.39
Last Available CD4 (IQR)	787	280 (96–509)	295 (103–499)	294 (93–502)	274 (94–510)	0.76
Median Log HIV RNA at Entry (IQR)	773	4.3 (3.5–5.0)	4.4 (3.6–5.0)	4.0 (3.1–4.8)	4.3 (3.6–5.1)	0.35
Median Log Last Available HIV RNA (IQR)	793	3.4 (1.9–4.9)	3.0 (1.9–4.8)	3.2 (1.9–4.7)	3.5 (1.9–5.0)	0.61
HAART Use During Study (%)	794	69.9	71.4	71.7	68.9	0.73
Median Log HCV RNA at Entry (IQR)	782	6.3 (5.8–6.7)	6.3 (5.8–6.7)	6.4 (5.8–6.7)	6.3 (5.8–6.6)	0.87
Median Log Last Available HCV RNA (IQR)	794	6.4 (5.9–6.8)	6.3 (5.7–6.7)	6.5 (6.0–6.8)	6.4 (5.9–6.9)	0.19
HCV Treatment During Study (%)	399	7.0	5.8	7.5	7.2	0.91
HCV Genotype 1 (%)	**568**	**87.9**	**73.2**	**79.3**	**94.7**	**<0.0001**
Chronic Hepatitis B (%)	794	2.4	2.9	2.5	2.2	0.90
Diabetes History (%)	794	19.9	13.6	18.9	22.0	0.08
HTN History (%)	**794**	**49.8**	**42.9**	**39**	**55.2**	**<0.0001**
Median BMI at Entry (IQR)	745	25 (22–29)	24 (22–27)	25 (23–29)	25 (22–29)	0.21
Median GFR at Entry (IQR)	**788**	**91.8 (75–108)**	**90.6 (73.3–106)**	**84.7 (74.5– 104)**	**93.3 (77.4–109.3)**	**0.03**
Cancer History (%)	794	3.3	4.3	3.1	3.0	0.76

Hepatology. Author manuscript; available in PMC 2013 November 01.

Table 2

All-Cause and Liver-Related Mortality by Race/Ethnicity

	Deaths from All Causes (n=438)				Liver-Related Deaths (n=49)			
Racial/Ethnic Comparison	**Unadjusted* HR (95% CI)**	**p value**	**Adjusted HR** (95% CI)**	**p value**	**Unadjusted* HR (95% CI)**	**p value**	**Adjusted HR^{t} (95% CI)**	**p value**
Caucasian (Ref)	---	---	---	---	---	---	---	---
African American	0.92 (0.70–1.22)	0.58	0.82 (0.61–1.09)	0.17	0.48 (0.23–1.03)	0.058	**0.41 (0.19–0.88)**	**0.022**
Hispanic	0.89 (0.64–1.25)	0.51	0.90 (0.64–1.28)	0.56	1.11 (0.50–2.4)	0.79	1.09 (0.49–2.4)	0.83
Hispanic (Ref) versus African American	1.03 (0.79–1.35)	0.81	0.91 (0.69–1.19)	0.48	**0.44 (0.22–0.87)**	**0.02**	**0.38 (0.19–0.76)**	**0.006**

*Age is the time scale, therefore all analyses account for the effect of age; see Statistical Analysis

**Adjusted for BMI, CD4 count, GFR, HCV viral load, HIV viral load

^{t}Adjusted for CD4 count, HIV viral load

Table 3

Factors Associated with Liver-Related Mortality

	Univariate Analysis*		Multivariate Analysis**	
Variable	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Tobacco Use	1.15 (0.59–2.2)	0.68	1.0 (0.51–2.0)	0.99
IVDU	1.0 (0.39–2.6)	0.99	0.72 (0.27–1.9)	0.51
Non IVDU	0.81 (0.43–1.6)	0.54	0.64 (0.33–1.26)	0.20
Alcohol Use	0.64 (0.15–2.6)	0.53	0.53 (0.13–2.2)	0.38
CD4 count (per doubling)	**0.78 (0.67–0.91)**	**0.002**	0.88 (0.73–1.06)	0.19
Log HIV RNA	**1.47 (1.17–1.9)**	**0.001**	**1.44 (1.11–1.9)**	**0.006**
HAART	0.62 (0.34–1.13)	0.12	1.04 (0.53–2.0)	0.90
Log HCV RNA	1.44 (0.94–2.2)	0.09	1.35 (0.90–2.0)	0.15
HCV Genotype 1	1.20 (0.43–3.4)	0.73	1.5 (0.53–4.5)	0.43
Chronic HBV	1.5 (0.21–11.1)	0.68	---	---
Diabetes	0.58 (0.14–2.5)	0.46	0.65 (0.15–2.8)	0.56
HTN	0.85 (0.43–1.7)	0.64	1.04 (0.52–2.1)	0.92
BMI	0.95 (0.90–1.0)	0.10	0.98 (0.93–1.03)	0.48
GFR	0.99 (0.98–1.0)	0.27	0.99 (0.98–1.0)	0.35

*Age is the time scale, therefore all analyses account for the effect of age; see Statistical Analysis

**Adjusted for CD4 count, HIV viral load, Race/Ethnicity

Table 4

Liver-Related Death Adjusted For Categories of Risk Factors

Racial/Ethnic Comparison	Unadjusted* HR (95% CI)	p value	Cardiovascular Risk Factors HR** (95% CI)	p value	HIV-Related Factors HR*** (95% CI)	p value	Liver-Related Factors HR**** (95% CI)	p value
Caucasian (Ref)	---	---	---	---	---	---	---	---
African American	0.48 (0.23–1.03)	0.058	**0.44 (0.20–0.95)**	**0.038**	**0.41 (0.19–0.88)**	**0.022**	**0.46 (0.22–0.98)**	**0.043**
Hispanic	1.11 (0.50–2.4)	0.79	1.12 (0.51–2.5)	0.78	1.09 (0.46–2.4)	0.83	1.06 (0.48–2.3)	0.89
Hispanic (Ref) versus African American	**0.44 (0.22–0.87)**	**0.019**	**0.39 (0.19–0.80)**	**0.010**	**0.38 (0.19–0.76)**	**0.006**	**0.43 (0.22–0.87)**	**0.019**

* Age is the time scale, therefore all analyses account for the effect of age; see Statistical Analysis

** Adjusted for BMI, DM, HTN, Tobacco Use

*** Adjusted forCD4count, HIV treatment, HIV viral load

**** Adjusted for Alcohol Use, Chronic HBV, HCV viral load