HHS Public Access

Author manuscript

J Viral Hepat. Author manuscript; available in PMC 2015 December 01.

Published in final edited form as:

J Viral Hepat. 2015 December ; 22(12): 1055–1060. doi:10.1111/jvh.12431.

Association of IFNL3 and IFNL4 polymorphisms with liver-related mortality in a multiracial cohort of HIV/HCV-coinfected women

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SUMMARY

African Americans coinfected with HIV and hepatitis C virus (HCV) have lower liver-related mortality than Caucasians and Hispanics. While genetic polymorphisms near the IFNL3 and IFNL4 genes explain a significant fraction of racial differences in several HCV-related outcomes, the impact of these variants on liver-related mortality has not been investigated. We conducted a cohort study of HIV/HCV-coinfected women followed in the multicentre, NIH-funded Women's Interagency HIV Study (WIHS) to investigate whether 10 polymorphisms spanning the IFN-λ region were associated with liver-related mortality by dominant, recessive or additive genetic models. We also considered whether these polymorphisms contributed to previously reported differences in liver-related death by race/ethnicity (ascertained by self-report and ancestry

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

CONFLICTS OF INTEREST

None related to this work.

informative markers). Among 794 coinfected women, there were 471 deaths including 55 liver-related deaths during up to 18 years of follow-up. On adjusted analysis, rs12980275 GG genotype compared to AG+AA hazards ratios [(HR) 0.36, 95% CI 0.14–0.90, $P = 0.029$] and rs8109886 AA genotype compared to CC+AC (HR 0.67, 95% CI 0.45–0.99, $P = 0.047$) were most strongly associated with liver-related death although these associations were no longer significant after adjusting for race/ethnicity (HR 0.41, 95% CI 0.16–1.04, $P = 0.060$ and HR 0.78, 95% CI 0.51–1.19, $P = 0.25$, respectively). African American women had persistently lower liver-related death independent of IFN-λ variants (HRs ≤ 0.44, P values ≤ 0.04). The lower risk of death among African American HIV/HCV-coinfected women is not explained by genetic variation in the IFN-λ region suggesting, that other genetic, behavioural and/or environmental factors may contribute to racial/ethnic differences in liver-related mortality.

Keywords

death; ethnicity; genetic; interferon-λ; polymorphisms

INTRODUCTION

In the United States, 2.7 million people are chronically infected with hepatitis C virus (HCV) [1]. Due to shared modes of transmission, 10–30% of HIV-positive patients in the United States are coinfected with HCV [2–5], and this number approaches 80% among injection drug users (IDU) [6]. HIV/HCV coinfection disproportionately affects many individuals with high-risk behaviours and limited resources. While new, direct-acting antiviral agents should improve tolerability and response rates of HCV treatment, access to therapy and drug–drug interactions with antiretroviral agents continue to pose a barrier [7]. Therefore, liver-related morbidity and mortality from chronic HCV infection, particularly in those with concurrent HIV infection, remains an important area of healthcare disparity.

Racial/ethnic differences in HCV-related outcomes are well described. We have previously shown that African American women coinfected with HIV and HCV are 60% less likely to die from liver-related disease than coinfected Hispanic or Caucasian women, independent of competing causes of death [8]. The reasons for these marked racial/ethnic differences are unknown, but may be related to slower rates of liver fibrosis noted among African Americans with chronic HCV infection [9,10].

Single nucleotide polymorphisms (SNPs) within or near the IFNL3 and IFNL4 genes (e.g. rs12979860) explain a significant fraction of the observed racial/ethnic differences in spontaneous HCV clearance and response to interferon-based HCV treatment [11,12], and a dinucleotide insertion/deletion variant (rs368234815) in the recently discovered IFNL4 gene appears to be an even stronger predictor of these HCV-related outcomes [13,14]. The rs12979860 SNP is in strong linkage disequilibrium with rs368234815. Some data show a higher risk of fibrosis in HIV/HCV coinfection among individuals with the rs12979860 CC genotype [15] which is less prevalent in African American populations [11]. However, other data investigating the association between rs12979860 and liver fibrosis report opposite

[16,17] or equivocal [18] results. The contributions of variants in the IFNL3/IFNL4 region to liver-related death are not known.

In the current study, we investigate the association of ten polymorphisms in and around the IFNL3 and IFNL4 genes that have previously been studied in association with hepatitis C-related outcomes [11], as well as the more recently identified rs368234815 variant. We further explore whether these polymorphisms contribute to known racial/ethnic differences in liver-related death in a large cohort of HIV/HCV-coinfected women.

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, multicentre cohort of women at risk for, or currently diagnosed with HIV. Enrolment in WIHS took place in three waves, 1994–1995, 2001–2002 and 2011–2012. The current study utilizes the first two waves conducted at six clinical sites across the United States. Women are seen twice yearly and undergo detailed histories, physical examinations, structured interviews and laboratory testing. The current study was approved by the WIHS Executive Committee and the Institutional Review Boards at the six participating WIHS sites. Study eligibility included HIV/HCV coinfection at WIHS entry as defined by detectable HCV RNA, HCV antibody and positive HIV Western blot.

Predictor and outcome measures

Our predictors of interest included 10 polymorphisms in and around the IFNL3 and IFNL4 genes (rs12980275, rs12979860, rs8109886, rs4803223, rs11673485, rs16973285, rs809917, rs12972991, rs955155 and rs368234815). For each polymorphism, preliminary analyses identified the genetic model (i.e. additive, dominant or recessive) that was most predictive of liver-related death, and therefore best fit the data. The best fitting model was retained in subsequent analyses.

The primary outcome was liver-related death determined by death certificate verification. 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. Liver-related deaths included those due to hepatic decompensation or hepatocellular carcinoma and included documentation of 'hepatitis C' as the primary cause of liver death.

Covariates

Covariates initially considered in our survival analyses were selected based on biologically plausible associations with liver-related death. These included age; race/ethnicity, substance abuse including intravenous (IV) drugs, non-IV drugs and alcohol; HIV-related factors, such as HIV RNA levels, CD4 count, and highly active antiretroviral therapy (HAART); liver-related factors including HCV RNA levels, HCV genotype (available in 577 women), HCV treatment history and chronic hepatitis B virus (HBV); and factors associated with non-

alcoholic fatty liver disease (NAFLD) such as history of diabetes mellitus (DM), history of hypertension (HTN) and body mass index (BMI).

For race/ethnicity, both genetic ancestry principal components (PCs) and nongenetic (self-reported) parameters were examined. Genomic estimates of race/ethnicity were determined by principal component analysis of 185 independent ancestry informative marker SNPs from across the human genome that differed in allele frequency among the major racial/ethnic groups in WIHS. The first three PCs were selected to estimate race/ethnicity and used as covariates in multivariate models. The 'African American' group included non-Hispanic African Americans (n = 495). 'Caucasians' were defined as non-Hispanic Caucasians (n = 140), and 'Hispanics' were defined as Hispanic Caucasians (n = 23), Hispanic African Americans (n = 16) and other Hispanics (n = 120). Reclassification of the small number of Hispanic African Americans into the African American group and small number of Hispanic Caucasians into the Caucasian group was not found to affect risk estimates of liver-related death in prior work [8].

Laboratory assays

Plasma HIV RNA levels were measured using the NASBA/NuciSens HIV RNA assay (BioMerieux, Durham, NC, USA), in laboratories certified by the NIH National Institute of Allergy and Infectious Diseases Virology Quality Assurance Certification Program. HCV and HBV serological markers were performed using standard commercial assays and included hepatitis C antibody by EIA 3.0 (Ortho-Clinical Diagnostics, Raritan, NJ, USA) and hepatitis B surface antigen (HBsAg) (Abbott Laboratories, Abbott Park, IL, USA). HCV RNA levels were measured by the COBAS Amplicor Monitor 2.0 assay (Roche Diagnostics, Branchburg, NJ, USA) 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. Genotyping for rs368234815 (ss469415590) was performed at the Laboratory of Translational Genomics National Cancer Institute with custom TaqMan allelic discrimination genotyping assays, as previously described [14]. IFNL3/IFNL4 SNPs were genotyped as part of the WIHS genomewide association study using the IlluminaOmni2.5-quad beadchip (Illumina Inc, San Diego, CA, USA). Ancestry informative marker SNPs were selected using Helix Tree (Golden Helix, Bozeman, MT, USA).

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 liver-related mortality. Survival analyses used age as the time scale, with age at study entry treated as a left-truncation time 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. Variables that were measured repeatedly were analyzed as time-varying covariates, with the most recent value carried forward until a new measurement was made. We previously described the competing risk analysis to confirm that racial/ethnic differences in liver-related death were not attributed to differential risk of non-liver-related deaths among racial/ethnic groups [8]. Testing for interaction was

performed between race/ethnicity and the polymorphisms of interest. All analyses were performed using Stata software, version 12.0 (College Station, Texas, USA).

RESULTS

We identified 794 women in WIHS with confirmed chronic HCV and HIV infection. Of these, 62.3% (495/794) were African American, 20.0% were Hispanic (159/794) and 17.7% (140/794) were Caucasian. Women were followed for up to 18 years, with an average follow-up of 9.2 years. During this time, there were 471 deaths from all causes, including 55 liver-related deaths.

Among the 10 tested polymorphisms spanning the IFNL3 and IFNL4 genes, rs12980275, rs12979860 and rs8109886 were most strongly associated with liver-related death on age-adjusted analysis (Table 1). Among African Americans, Hispanics and Caucasians, the genotypic frequency of rs12980275 GG was 30%, 12.5% and 13.5%, ($P < 0.001$); the frequency of rs12979860 CC was 17.1%, 30.9% and 39.7%, ($P < 0.001$); and frequency of rs8109886 AA was 58.6%, 34.6% and 18.3%, respectively ($P < 0.001$).

On multivariate analyses adjusting for age and HIV control, rs12980275 GG genotype compared to AG+AA (HR 0.36, 95% CI 0.14–0.90, $P = 0.029$) and rs8109886 AA genotype compared to CC+AC (HR 0.67, 95% CI 0.45–0.99, $P = 0.047$) were associated with a lower risk of liver-related death (Table 2). However, addition of race/ethnicity to the model attenuated these effects (for rs12980275, HR 0.41, 95% CI 0.16–1.04, $P = 0.060$ and for rs8109886, HR 0.78, 95% CI 0.51–1.19, $P = 0.25$) (Table 2).

Consistent with our previous findings [8], African American HIV/HCV-coinfected women had persistently lower risk of liver-related death compared to Caucasians (HR 0.41, $P = 0.018$) and Hispanics (HR 0.36, $P = 0.003$) after adjusting for age and HIV control. This differential risk of liver-related death persisted despite adjustment for rs12980275, rs12979860 and rs8109886 SNPs (Table 3).

Given emerging data on the importance of IFNL4 rs368234815 in predicting HCV-related outcomes, we further explored the association between this polymorphism and liver-related death. The frequency of IFNL4 TT was 12.4% in African Americans, 25.7% in Hispanics and 38.1% in Caucasians ($P < 0.001$). There was no association between IFNL4 rs368234815 and liver-related mortality on univariate analysis (Table 1) or multivariate analysis adjusted for age and HIV control (HR 0.95, 95% CI 0.89–1.02, $P = 0.180$). Furthermore, adjustment for IFNL4 rs368234815 in the multivariate model did not explain the lower risk of liver-related death among African American women compared to either Caucasian (HR 0.44, 95% CI 0.19–0.99, $P = 0.049$) or Hispanic HIV/HCV-coinfected women (HR 0.34, 95% CI 0.16–0.70, $P = 0.004$).

Because genomic estimates of self-reported race/ethnicity resulted in virtually indistinguishable models predicting liver-related death in this study, self-reported race/ethnicity rather than PCs was selected in final models for ease of interpretation. Multivariate analyses demonstrating the effect of these PCs reveal that PC1, which primarily

differentiates African from non-African ancestry, (Fig. 1) accounted for most of the racial/ethnic differences in liver-related death (Table S1).

DISCUSSION

In this large cohort of HIV/HCV-coinfected women, we investigated the association of polymorphisms in and around the IFNL3 and IFNL4 genes and liver-related death, as well as the contribution of these polymorphisms to known racial/ethnic differences in liver-related mortality. On multivariate analyses adjusted for age and HIV control, we found that both rs12980275 GG *vs* AG+AA and rs8109886 AA *vs* AC+AA genotypes were predictive of lower liver-related death. The attenuated association between these individual SNPs and liver-related death after adjustment for race/ethnicity may reflect the higher frequency of these 'protective' genotypes in African American women. Additional as of yet unidentified genetic factors may account for the markedly lower risk of liver-related mortality in African Americans compared to other racial/ethnic groups. Nonetheless, the possible contribution of these genetic variants to liver-related mortality should not be dismissed.

The path by which IFNL3/IFNL4 polymorphisms could affect liver-related mortality may be through their effect on liver fibrosis. The IFNL4 rs12979860 CC genotype has been shown to predict cirrhosis in HCV-mono-infected [16] and HIV/HCV-coinfected individuals [15]. As the frequency of the CC genotype is higher in Caucasians (39%) and Hispanics (35%) as compared to Africans Americans (16%) [11], these data may help to explain why African Americans may have slower fibrosis progression. Another study of HCV-mono-infected individuals did not identify a higher risk of fibrosis in those with the CC genotype, although did find CC genotype to be significantly associated with a composite endpoint of adverse clinical outcomes including decompensated liver disease and liver-related death in 7 patients [19]. In the current study, we found little evidence that rs12979860 was associated with liver-related mortality, but we did observe a lower risk of liver-related death in women with the rs12980275 GG genotype, with the GG genotype being most common in African Americans (30%). Interestingly, the A allele of this SNP has been shown to increase the odds of rapid fibrosis progression in the setting of HIV/HCV coinfection [20]. The minor G allele of rs809917 has been shown to protect against HCV-related fibrosis progression in two studies [21,22], although a third found no association [18]. Given the wide confidence interval for the analysis of rs809917 in the current study, the association of this SNP with liver-related death remains uncertain.

The rs368234815 [ΔG] variant in the newly described gene-designated IFNL4 encodes the interferon-λ4 protein [14]. Within the WIHS and other cohorts, the TT/TT genotype of rs368234815 predicts spontaneous HCV clearance in HIV-infected African Americans even more strongly than the rs12979860 CC genotype. [13,14]. This polymorphism has recently been shown to explain much of the racial/ethnic differences in response to interferon-based HCV treatment [14]. These prior studies support the *IFNL4*-ΔG/TT polymorphism as the functional variant accounting for much of the observed associations of IFN-λ region variants with HCV clearance. However, we found no evidence of any substantial association between rs368234815 and liver-related mortality.

The current study is the first to investigate the effect of IFNL3 and IFNL4 polymorphisms on liver-related mortality. Of the 10 examined polymorphisms, the rs12980275 GG and rs8109886 AA genotypes were most strongly associated with lower risk of liver-related death in HIV/HCV-coinfected women, although these effects were attenuated by race/ethnicity. The functional rs368234815 variant was not associated with liver-related mortality in this analysis. African American-coinfected women remained at markedly lower risk for liver-related death compared to Hispanic women, independent of the three most predictive polymorphisms. Further investigation is warranted into additional genetic, behavioural and/or environmental factors that may contribute to racial/ethnic differences in liver-related mortality, including potential differences in rates of fibrosis progression. While new treatments for HCV should decrease the overall burden of disease, HCV-related morbidity and mortality remains an important global public health concern, particularly among those with concurrent HIV infection and limited access to new HCV therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

FINANCIAL SUPPORT

This study was supported by the American Association for the Study of Liver Diseases Sheila Sherlock Career Development Award [to MS].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. This research was supported by the Intramural Research Program of the US National Institutes of Health (National Cancer Institute, Division of Cancer Epidemiology and Genetics). The content of this publication does not necessarily reflect the views or policies of the US Department of Health and Human Services nor does mention of trade names, commercial products or organizations imply endorsement by the US government.

Abbreviations

BMI	body mass index
DM	diabetes mellitus
GFR	glomerular filtration rate
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HTN	hypertension
IDU	injection drug use
PCs	principal components
RNA	ribonucleic acid

SNPs	single nucleotide polymorphisms
WIHS	Women's Interagency HIV Study

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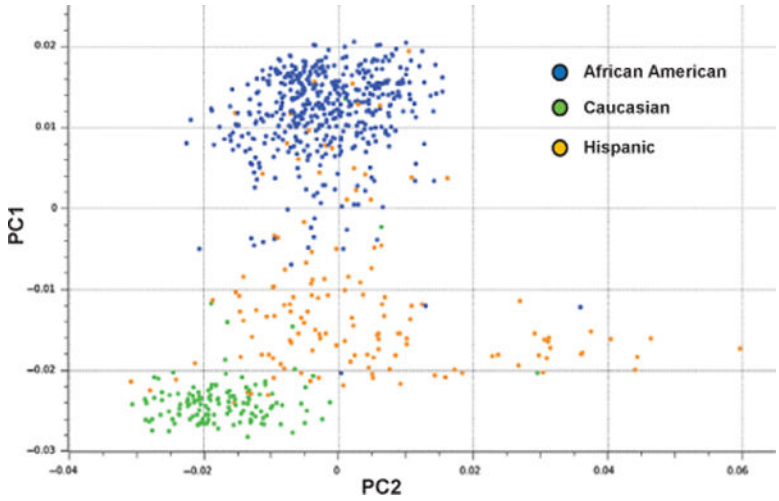

Fig. 1.

Principal component 1 (PC1) primarily differentiates between African American (blue) hispanic (orange) and caucasian (green) HIV/HCV co-infected women.

Table 1

Age-adjusted association between IFNL3/4 SNPs and liver-related mortality in HIV/HCV-coinfected women

Genetic Variant*	HR (95% CI)	*P* value
rs12980275 (A-to-G)**	0.33 (0.12–0.96)	0.020
rs8109886 (C-to-A)***	0.68 (0.46–1.00)	0.053
rs12979860 (C-to-T)	0.70 (0.48–1.03)	0.070
rs4803223 (A-to-G)	0.68 (0.34–1.36)	0.28
rs11673485 (G-to-T)	0.65 (0.09–4.75)	0.67
rs16973285 (C-to-T)	0.98 (0.45–2.13)	0.97
rs809917 (T-to-G)	0.80 (0.42–1.54)	0.51
rs12972991 (A-to-C)	0.89 (0.55–1.45)	0.64
rs955155 (C-to-T)	0.90 (0.53–1.52)	0.69
rs368234815 (TT/ΔG)	0.97 (0.91–1.03)	0.31

The reference allele for each SNP is listed first. For example, for rs12980275 (A-to-G), the reference is the ‘A’ allele.

* Best-fit model for all variants was additive unless otherwise noted.

** Recessive model selected.

*** Dominant model selected.

Table 2

Multivariate (MV) association between IFNL3/IFNL4 SNPs and liver-related mortality in HIV/HCV-coinfected women

Predictor	MV Model* HR (95% CI)	*P* value	MV model adjusted for race/ethnicity HR (95% CI)	*P* value
rs12980275 GG vs AA/AG	0.36 (0.14–0.90)	0.029	0.41 (0.16–1.04)	0.060
rs12979860 TT vs CC/CT	0.70 (0.47–1.04)	0.077	0.78 (0.52–1.17)	0.23
rs8109886 AA vs CC/AC	0.67 (0.45–0.99)	0.047	0.78 (0.51–1.19)	0.25

*Adjusted for age, HIV viral load, CD4 count and ART.

Table 3

Lower risk of liver-related mortality among African American HIV/HCV-coinfected women persists after adjustment for IFNL3/IFNL4 SNPs

	MV model*		MV model* adjusted for *rs12980275*		MV model* adjusted for *rs12979860*		MV model* adjusted for *rs8109886*	
Predictor	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
African American vs Caucasian	0.41 (0.20–0.86)	0.018	0.42 (0.20–0.92)	0.030	0.44 (0.20–0.96)	0.039	0.42 (0.19–0.92)	0.032
African American vs Hispanic	0.36 (0.19–0.70)	0.003	0.34 (0.17–0.69)	0.003	0.35 (0.17–0.70)	0.003	0.34 (0.17–0.68)	0.003

*Adjusted for age, HIV viral load, CD4 count and ART.