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Racial/Ethnic Differences in Spontaneous HCV Clearance in HIV Infected and Uninfected Women

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Abstract

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Background/Aims—Among individuals without human immunodeficiency virus (HIV), African Americans have lower spontaneous clearance of hepatitis C virus (HCV) than Caucasians, and women have higher clearance than men. Few studies report racial/ethnic differences in acute HCV in HIV infected, or Hispanic women. We examined racial/ethnic differences in spontaneous HCV clearance in a population of HCV mono- and co-infected women.

Methods—We conducted a cross sectional study of HCV seropositive women (897 HIV infected and 168 HIV uninfected) followed in the US multicenter, NIH-funded Women's Interagency HIV Study (WIHS), to determine the association of race/ethnicity with spontaneous HCV clearance, as defined by undetectable HCV RNA at study entry.

Results—Among HIV and HCV seropositive women, 18.7 % were HCV RNA negative, 60.9 % were African American, 19.3 % Hispanic and 17.7 % Caucasian. HIV infected African American women were less likely to spontaneously clear HCV than Hispanic (OR 0.59, 95 % CI 0.38–0.93, $p = 0.022$) or Caucasian women (OR 0.57, 95 % CI 0.36–0.93, $p = 0.023$). Among HIV uninfected women, African Americans had less HCV clearance than Hispanics (OR 0.18, 95 % CI 0.07–0.48, $p = 0.001$) or Caucasians (OR 0.26, 95 % CI 0.09–0.79, $p = 0.017$). There were no significant differences in HCV clearance between Hispanics and Caucasians, among either HIV infected (OR 0.97, 95 % CI 0.57–1.66, $p = 0.91$) or uninfected (OR 1.45, 95 % CI 0.56–3.8, $p = 0.45$) women.

Conclusions—African Americans were less likely to spontaneously clear HCV than Hispanics or Caucasians, regardless of HIV status. No significant differences in spontaneous HCV clearance were observed between Caucasian and Hispanic women. Future studies incorporating IL28B genotype may further explain these observed racial/ethnic differences in spontaneous HCV clearance.

Keywords

African American; Hispanic; Acute hepatitis C; Female

Introduction

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 infection is common. Approximately one-third of HIV infected patients are co-infected with HCV, and this number approaches 80 % in the intravenous (IV) drug using community [3]. Clearance of HCV avoids progression of liver disease and its related complications, which are typically more severe in co-infected patients than in HCV mono-infection. HIV/HCV co-infected patients have higher baseline HCV RNA levels and higher liver-related mortality, with faster rates of liver fibrosis. Most pertinent to this study, fewer patients with HIV and acute HCV spontaneously clear the virus as compared to those without HIV infection [4–7].

Gender differences in spontaneous HCV clearance in HCV mono-infection are well documented, with higher spontaneous clearance in women compared to men [8–10]. However, few studies have examined factors associated with spontaneous HCV clearance in HIV infected women. Studies among predominantly HCV mono-infected men have shown that race is an important predictor of spontaneous HCV clearance, with African Americans having lower spontaneous HCV clearance than Caucasians. No studies in either HIV infected or uninfected cohorts have characterized spontaneous HCV clearance in Hispanic individuals as compared to African Americans [11–13]. Data investigating racial/ethnic differences in spontaneous HCV clearance in women are also limited, and even fewer studies have investigated these trends in HIV infected women.

In the present study, we evaluate racial/ethnic differences in spontaneous HCV clearance and report factors associated with spontaneous HCV clearance in a large population of HIV infected, HCV seropositive women and a smaller sample of HIV uninfected women from the Women's Interagency HIV Study (WIHS). The diversity of the WIHS, which includes a large proportion of Hispanic and African American women, has allowed us to study the effect of race/ethnicity on the natural history of hepatitis C in this high risk female cohort.

Methods

Data Source

We conducted a cross sectional study of women participating in the WIHS. The WIHS is an NIH funded, prospective, multicenter US cohort of women at risk for, or currently diagnosed with HIV. The WIHS is comprised of women with high risk behaviors, with most women having a history of illicit drug use. Enrollment in WIHS occurred in two study cohorts, the first in 1994–1995 and the second in 2001–2002 [14]. Women in WIHS are seen twice yearly and undergo detailed histories, physical exams, structured interviews, and laboratory testing. Serum samples from these visits are stored for future analyses. This study was approved by the WIHS research committee and the Institutional Review Boards (IRB) at the six participating WIHS study sites.

Study Sample

The present study included all women with prior infection with hepatitis C as defined by positive HCV antibody at entry into WIHS. HIV was confirmed by positive Western blot. All eligible women were at least 18 years old at WIHS study entry. Women who had received prior treatment for hepatitis C of any duration were excluded.

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. The small number of women who self-reported as Asian, Pacific Islander, Native American, Alaskan or “other” were classified as “Other.” To evaluate the possibility of misclassification bias, all analyses were repeated after recategorizing Hispanic African Americans as African American, and also after recategorizing Hispanic Caucasians as Caucasian.

The outcome measure was presence or absence of HCV RNA by PCR at WIHS entry as the indicator of persistent or cleared HCV infection, respectively. HCV RNA was tested on 86.2 % of women at subsequent follow-up visits and >98 % were confirmed positive. The following characteristics were taken from WIHS entry: age, history of alcohol use, hepatitis B viral (HBV) status [hepatitis B surface antigen (HBsAg) and core antibody (HBcAb)], HIV RNA, CD4 count, and mode of possible HCV infection as measured by number of sexual partners, history of blood transfusion, and history of intravenous drug use (IVDU). Alcohol use was defined as 14 drinks per week. Blood transfusion history was defined as receipt of a transfusion before 1985, the year when donated blood became routinely screened for HIV.

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), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (anti-HBc) (Abbott Laboratories, Abbott Park, IL). HCV RNA was measured in HCV seropositive women, using either 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 × 10⁸ IU/ml.

Statistical Analysis

Patient characteristics were compared using chi square, *t* tests, and Kruskal–Wallis tests, when appropriate. Logistic regression was used to calculate odds ratios (OR) and the 95 % confidence intervals (CI) for factors associated with spontaneous HCV clearance. The multivariate model included variables with the strongest plausible biological association with spontaneous HCV clearance, or with a *p* value <0.2 on univariate analysis. In all analyses, age was treated as a continuous variable. HIV viral load and CD4 count were log transformed to account for non-linearity. All analyses were performed using Stata software, version 11.0 (Stata, College Station, Texas). A two tailed *p* value <0.05 was considered statistically significant on multivariate analyses.

Results

We identified 1,032 women in WIHS who tested positive for antibodies to HIV and HCV, of whom 897 had sufficient serum for testing of baseline HCV RNA. Of these 897 women, 18.7 % (168/897) were HCV RNA negative at study entry. The median HCV viral load among those with detectable baseline HCV viral load was 2.2 million IU/ml (IQR 720 K–4.8 million IU/ml). Among the HIV uninfected group (*n* = 171), 24 % (41/171) were HCV RNA negative at study entry. Compared to HIV infected women, a higher percentage of HIV uninfected women achieved spontaneous HCV clearance (24 vs. 18.7 %, *p* = 0.11), although this finding did not reach statistical significance. We observed a trend towards lower spontaneous HCV clearance among HIV infected women compared to HIV uninfected women on univariate (OR 0.73, 95 % CI 0.5–1.08, *p* = 0.11) and multivariate analysis (OR 0.76, 95 % CI 0.50–1.15, *p* = 0.19), after adjusting for age, race/ethnicity, alcohol use, and chronic hepatitis B.

Of the HIV infected women, 60.9 % were African American, 19.3 % Hispanic, 17.7 % Caucasian, and 2.1 % “other.” Compared to women with spontaneous HCV clearance, women with chronic infection had lower median CD4 counts, higher median HIV RNA levels, and a lower prevalence of chronic hepatitis B. The majority of women with chronic hepatitis C were infected with genotype 1 (Table 1). There were clear differences in spontaneous HCV clearance across racial/ethnic groups of HIV infected women (test for homogeneity, *p* = 0.023). On multivariate analysis among HIV infected women, African Americans were less likely to have spontaneously cleared HCV than Caucasians (OR 0.57, 95 % CI 0.36–0.93, *p* = 0.023) or Hispanics (OR 0.59, 95 % CI 0.38–0.93, *p* = 0.022). Spontaneous HCV clearance was similar between HIV infected Hispanic and Caucasian women (Table 2). These trends remained consistent after recategorizing African American Hispanics as African American, and also after recategorizing Hispanic Caucasians as Caucasian (see Supplementary Materials).

In the HIV infected cohort the presence of chronic hepatitis B was strongly associated with spontaneous HCV clearance on univariate analysis (OR 3.0, 95 % CI 1.40–6.2, *p* = 0.004). The magnitude of association was stronger after adjusting for age, race/ethnicity, alcohol use, CD4 count and HIV viral load (OR 3.5, 95 % CI 1.57–7.9, *p* = 0.002). Higher HIV RNA levels were inversely associated with HCV clearance on both univariate (OR 0.73, 95

% CI 0.62–0.85, $p < 0.0001$) and multivariate analyses (OR 0.75, 95 % CI 0.61–0.92, $p = 0.006$). There was a statistically significant association between spontaneous HCV clearance and higher CD4 count on univariate (OR 1.19, 95 % CI 1.05–1.34, $p = 0.006$) but not on multivariate analysis (OR 1.07, 95 % CI 0.93–1.24, $p = 0.324$). Age, alcohol use, and presumed mode of HCV transmission were not significantly associated with spontaneous HCV clearance, but age and alcohol were maintained in the final model due to strong biologically plausible effects on spontaneous HCV clearance (Table 3).

We also analyzed spontaneous HCV clearance in the subset of HIV uninfected women in WIHS ($n = 171$). Their racial/ethnic distribution was 52.1 % African American, 27.5 % Hispanic, 17.5 % Caucasian, and 2.9 % “other” (Table 4). Significant differences in spontaneous HCV clearance across racial/ethnic groups were observed (test for homogeneity, $p = 0.0022$), similar to those observed in HIV infected women. On multivariate analysis, African Americans were less likely to have spontaneously cleared HCV than Caucasians (OR 0.26, 95 % CI 0.09–0.79, $p = 0.017$) or Hispanic women (OR 0.18, 0.07–0.48, $p = 0.001$). These findings also remained consistent after recategorizing African American Hispanics as African American, and after recategorizing Hispanic Caucasians as Caucasian (see Supplementary Materials). No additional factors were associated with spontaneous HCV clearance in the HIV uninfected population (Table 5).

Discussion

In this large population of HIV infected women with prior exposure to hepatitis C, we investigated racial/ethnic differences in spontaneous HCV clearance and identified additional factors associated with spontaneous HCV clearance. We also investigated racial/ethnic trends in spontaneous HCV clearance in a smaller group of HIV uninfected women in WIHS. We found that compared to Caucasian and Hispanic women, African Americans were less likely to spontaneously clear HCV, regardless of HIV status. Hispanic women appeared similar in spontaneous HCV clearance to Caucasians. Among a comprehensive set of factors with possible biological effects on spontaneous HCV clearance, we found strong evidence that chronic hepatitis B and lower HIV RNA were associated with spontaneous HCV clearance among HIV infected women.

Racial/ethnic differences in spontaneous HCV clearance between African Americans and Caucasians are well documented, particularly among those without HIV infection. Among HIV uninfected individuals, African Americans are less likely to spontaneously clear the virus as compared to Caucasian or Asian patients, with a higher percentage of African Americans developing chronic HCV [10, 12, 13]. Similar trends were observed in a study of 478 HIV infected, HCV exposed hemophiliacs which found significantly reduced spontaneous HCV clearance among African Americans compared to non-African Americans [15]. Like most natural history studies, this cohort included only a handful of women (~1 %), although this was one of the first studies to document racial/ethnic differences in spontaneous HCV clearance between Caucasian and African American HIV infected patients.

A prior study of HIV infected women in WIHS also found that African-Americans have a higher likelihood of developing chronic HCV infection than Caucasians, with no significant differences between Caucasian and Hispanic women [16]. Our study adds to these findings by investigating spontaneous HCV clearance between African American and Hispanic women. In addition, we expanded HCV RNA testing to all HCV antibody positive women in WIHS; we repeated HCV viral load testing allowing for confirmation of HCV chronicity; and also report HCV genotype distribution among chronically infected women. Finally, in our study we repeated all analyses after re-categorizing racial/ethnic groups to further

evaluate for possible misclassification bias, and continued to observe lower HCV clearance in African Americans as compared to Caucasian and Hispanic women.

Although prior studies have documented racial/ethnic differences in HCV fibrosis progression between Hispanics, Caucasians and African Americans, no prior studies have investigated differences in spontaneous HCV clearance between African Americans and Hispanics [17]. As 20 % of our cohort was comprised of Hispanic women, we were able to report these novel results, showing lower spontaneous HCV clearance among African Americans as compared to Hispanics, in both our HIV infected and uninfected cohorts.

The mechanisms underlying these racial/ethnic differences in spontaneous HCV clearance are not fully defined. While it is possible that body mass index, baseline alcohol use, or baseline HCV RNA may account for differences seen among racial/ethnic groups, studies adjusting for these factors, including our study which accounted for a host of potential confounders, continue to observe marked racial/ethnic differences [18, 19]. Recent data show that immunogenetics explain a large part of spontaneous HCV clearance. A genome-wide association found that a single nucleotide polymorphism (SNP) upstream of the *IL28B* gene was strongly predictive of spontaneous HCV clearance in HIV uninfected patients [20]. The frequency of this beneficial genotype is higher in Caucasians (39 %) and Hispanics (35 %) as compared to African Americans (16 %) [21]. This explains in part why African Americans have lower spontaneous HCV clearance compared to other racial/ethnic groups. In HIV infected cohorts, two studies have identified additional SNPs in close proximity to the *IL28B* gene that are strongly associated with spontaneous HCV clearance. As these studies were conducted in homogenous European cohorts, the role of *IL28B* in explaining racial/ethnic differences in spontaneous HCV clearance among HIV infected individuals has yet to be determined [22, 23]. Genome wide association studies investigating the role of *IL28B* are currently underway within the WIHS and may help to explain why spontaneous HCV clearance differs so markedly between HIV infected racial/ethnic groups.

Independent of race/ethnicity, we identified lower HIV RNA as an important factor associated with spontaneous HCV clearance. While higher CD4 counts predicted increased clearance on univariate analysis, this finding was not statistically significant on multivariate analysis. Similar to our results, a study of mostly male HIV infected patients with hemophilia found little association between CD4 count and spontaneous HCV clearance. Although these authors found no association between detectable HIV RNA and spontaneous HCV clearance, they did not study the association between the degree of HIV viremia and HCV clearance, which we were able to investigate [15].

There were several limitations to our present study. Although we used self-report of race/ethnicity as our primary predictor, self-report may not accurately reflect genetic admixture [24]. To reduce possible misclassification of racial/ethnic groups in our study, we did analyze our results after recategorizing Hispanic African Americans as African American, and after recategorizing Hispanic Caucasians as Caucasian. We observed consistently lower spontaneous HCV clearance in African Americans as compared to Caucasians and Hispanics, for all analyses performed. Importantly, previous data suggest that in IV drug users, HCV is often acquired years before HIV, although the temporal association between HIV and HCV viral acquisition in our study cannot be confirmed [25]. HCV re-infection is also possible, although prior data within the WIHS indicate that this is a rare occurrence, at less than 1 % [26].

In summary, we observed significant racial/ethnic differences in spontaneous HCV clearance in a large HIV infected population and a smaller population of HIV uninfected women. In both groups, African American women had significantly lower spontaneous

HCV clearance than Hispanic or Caucasian women. Spontaneous HCV clearance in HIV infected women was associated with better HIV immune status, an effect that was independent of race/ethnicity. Immunogenetic studies are currently underway within the WIHS to help explain why spontaneous HCV clearance differs so markedly between racial/ethnic groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

HIV	Human immunodeficiency virus
HCV	Hepatitis C virus
WIHS	Women's Interagency HIV Study
RNA	Ribonucleic acid
IDU	Intravenous drug use
HAART	Highly active anti-retroviral therapy
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
SNP	Single nucleotide polymorphisms

Table 1
Characteristics of HIV infected women with prior HCV infection

Variable	<i>n</i>	All women (<i>n</i> = 897)	Spontaneously cleared HCV (<i>n</i> = 168)	Chronic HCV (<i>n</i> = 729)
Age (mean ± SD)	–	39.5 ± 6.5	39.3 ± 7.3	39.7 ± 6.1
Race/ethnicity (%)				
Caucasian	159	17.7	19.6	17.3
African American	546	60.9	48.2	63.8
Hispanic	173	19.3	28.0	17.3
“Other” ^a	19	2.1	4.2	1.7
CD4 count, median (IQR)	874	352 (189–546)	408 (257–660)	334 (183–531)
HIV RNA, median (IQR)	889	16,000(4,000–90,000)	7,700(1,900–50,000)	19,000(4,000–10,000)
HBsAg positive (%)	31	3.6	7.6	2.7
HBcAb positive (%)	198	23.4	19.4	24.3
History of >10 sexual partners (%)	322	36.0	40.7	34.9
History of IVDU (%)	769	85.7	83.9	86.2
History of alcohol use (%)	121	13.8	10.2	14.7
History of blood transfusion (%)	158	19.6	23.4	18.7
HCV genotype (%)				
1	393	–	–	89.1
2	11	–	–	2.5
3	25	–	–	5.7
4	12	–	–	2.7

^aSelf-report as Asian, Pacific Islander, Native American, Alaskan Native or “other”

Table 2
Spontaneous HCV clearance in HIV infected women by racial/ethnic group

Racial/ethnic group	Unadjusted OR (95 % CI)	<i>p</i> value	Adjusted OR (95 % CI) ^a	<i>p</i> value
<i>Caucasian reference</i>				
Race/ethnicity				
Caucasian	Ref		Ref	
African American	0.66 (0.42–1.03)	0.069	0.57 (0.36–0.93)	0.023
Hispanic	1.38 (0.84–2.3)	0.21	0.97 (0.57–1.66)	0.91
“Other” ^b	2.2 (0.81–6.1)	0.12	1.55 (0.49–4.9)	0.46
<i>Additional intergroup comparisons</i>				
African American versus Hispanic	0.47 (0.32–0.71)	<0.0001	0.59 (0.38–0.93)	0.022
African American versus “Other” ^b *	0.30 (0.11–0.77)	0.013	0.37 (0.12–1.13)	0.080
Hispanic versus “Other” ^b	1.61 (0.60–4.3)	0.34	1.59 (0.51–5.0)	0.80

The bold results reflect those that reach statistical significance with *p* values <0.05

^aAdjusted for age, HIV RNA, CD4 count, HBsAg positivity, and alcohol use

^bSelf-report as Asian, Pacific Islander, Native American, Alaskan Native or “other”

Table 3
Factors associated with spontaneous HCV clearance in HIV infected women

Variable	Univariate OR (95 % CI)	<i>p</i> value	Multivariate ^a OR(95 % CI)	<i>p</i> value
Log10 HIV RNA	0.73 (0.62–0.85)	<0.0001	0.75 (0.61–0.92)	0.006
HBsAg positivity	3.0 (1.40–6.1)	0.004	3.5 (1.57–7.9)	0.002
CD4 count (per doubling)	1.19 (1.05–1.34)	0.006	1.07 (0.93–1.24)	0.324
History of alcohol use	0.66 (0.39–1.14)	0.14	0.60 (0.33–1.08)	0.088
Age	0.99 (0.97–1.02)	0.53	1.01 (0.98–1.04)	0.49
History of IVDU	0.84 (0.53–1.33)	0.46	0.75 (0.44–1.28)	0.29
History of blood transfusion	1.33 (0.87–2.1)	0.19	1.49 (0.94–2.4)	0.087
History of >10 lifetime sexual partners	1.28 (0.91–1.81)	0.16	1.34 (0.92–1.98)	0.13

The bold results reflect those that reach statistical significance with *p* values < 0.05

^aAdjusted for race/ethnicity, age, HIV RNA, CD4 count, HBsAg positivity, and alcohol use

Table 4
Characteristics of HIV uninfected women with prior HCV infection

Variable	<i>n</i>	All women (<i>n</i> = 171)	Spontaneously cleared HCV (<i>n</i> = 41)	Chronic HCV (<i>n</i> = 130)
Age (mean ± SD)	171	38.1 ± 7.4	35.9 ± 6.7	39.1 ± 7.0
Race/ethnicity (%)				
Caucasian	30	17.5	24.4	15.4
African American	89	52.1	24.4	60.8
Hispanic	47	27.5	51.2	20.0
“Other” ^a	5	2.9	0	3.9
HBsAg positive (%)	0	–	–	–
HBcAb positive (%)	103	39.4	36.6	40.3
History of >10 sexual partners (%)	57	33.3	39.0	31.5
History of IVDU (%)	147	86.0	82.9	86.9
History of alcohol use (%)	28	17.2	13.2	18.4
History of blood transfusion (%)	24	16.9	15.2	17.4

Bold text indicates statistical significance

^aSelf-report as Asian, Pacific Islander, Native American, Alaskan Native or “other”

Table 5
Factors associated with spontaneous HCV clearance in HIV uninfected women

Variable	Univariate OR (95 % CI)	<i>p</i> value	Multivariate ^a OR (95 % CI)	<i>p</i> value
Race/ethnicity				
Caucasian	Ref		Ref	
African American	0.24 (0.09–0.67)	0.006	0.26 (0.09–0.79)	0.017
Hispanic	1.47 (0.57–3.8)	0.42	1.45 (0.56–3.8)	0.45
African American versus Hispanic	0.16 (0.07–0.40)	<0.0001	0.18 (0.07–0.48)	0.001
Age	0.94 (0.89–0.99)	0.015	0.97 (0.91–1.03)	0.29
History of alcohol use	0.67 (0.24–1.91)	0.46	0.85 (0.28–2.6)	0.78
History of IVDU	0.73 (0.28–1.91)	0.52	0.46 (0.14–1.49)	0.20
History of blood transfusion	0.85 (0.29–2.5)	0.76	1.05 (0.29–3.8)	0.95
History of >10 sexual partners	1.39 (0.67–2.9)	0.38	1.01 (0.45–2.3)	0.98

The bold results reflect those that reach statistical significance with *p* values < 0.05

^aAdjusted for age, alcohol use and race/ethnicity