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Correlates of High Hepatitis C Virus RNA Load in a Cohort of HIV-negative and HIV-positive Individuals with Hemophilia

Shahinaz M. Gadalla[1,2], **Liliana R. Preiss**[3], **M. Elaine Eyster**[4], and **James J. Goedert**[1]

[1] Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, 20892, USA

[2] Cancer Prevention Fellowship Program, National Institute of Heath, Bethesda, MD, 20892, USA

[3] RTI International, Rockville, MD 20852

[4] Department of Medicine, Division of Hematology and Oncology, Pennsylvania State University College of Medicine, Hershey, PA 17033

Abstract

Background—Hepatitis C virus (HCV) treatment failure and disease progression are more likely with high HCV-RNA load. Correlates of high HCV-RNA load in individuals with hemophilia are largely unknown.

Methods—Among 1,266 interferon naïve HCV-infected individuals with hemophilia, we compared those with high (> 2×10^6 HCV RNA copies/ml) to lower viral load, overall and stratifying on HIV co-infection status using logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI).

Results—Overall, high HCV load was independently associated with longer duration of HCV infection (P_{trend}=0.0001), body mass index ≥25 kg/m^2 (OR= 1.4, 95% CI=1.1-1.9), and HIV co-infection (OR=1.4, 95% CI=1.0-1.8). Among 795 HIV-negative participants, high HCV- RNA load was associated with older age at HCV acquisition (OR=1.9 for >15 years vs ≤2 years, P_{trend}=0.008), and lower AST/platelet ratio (P_{trend}=0.01), in addition to longer duration of HCV infection (P_{trend}=0.0008), and body mass index ≥25 kg/m^2 (OR=1.6, P=0.005). Among 471 HIV-positive individuals, anti-retroviral therapy (ART) was the only variable associated with high HCV-RNA load (OR=1.8, CI=1.1-2.9 for combination ART; OR=1.8, CI=0.9-3.4, for other ART vs. no treatment).

Conclusion—High HCV-RNA load with hemophilia is more likely with longer duration of infection, older age at infection, higher body mass index, and antiretroviral therapy. These findings may help identify individuals at increased risk of HCV treatment failure and progression to end-stage liver disease.

Keywords

HCV load; HCV/HIV co-infection; hemophilia

Corresponding author: Dr. James J. Goedert, Infections and Immunoepidemiology Branch, Room 7068. Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, 20892, USA. Telephone: 301-435-4724, Fax: 301-402-0817, goedertj@mail.nih.gov.

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Introduction

The majority of adults with hemophilia, who were treated with plasma and clotting factor concentrates before the mid-1980s, are chronically infected with hepatitis C virus (HCV) (1-4). Among them, 30% are co-infected with human immunodeficiency virus (HIV) (5). Chronic HCV infected individuals are at high risk of progression to liver fibrosis, cirrhosis, liver failure and hepatocellular carcinoma (6;7). HCV-RNA load predicts rates of heterosexual (8) and mother-to-infant HCV transmission (9), risk of developing advanced liver disease (10;11), and perhaps mortality (12), and response to interferon therapy (13-16). Several studies have evaluated correlates of high HCV-RNA load to better understand these associations. High HCV load has been consistently associated with older age and HIV co-infection (17;18). On the other hand, associations with HCV genotype (17-20) and degree of liver fibrosis (20;21) have been inconsistent.

HCV infection in individuals with hemophilia has unique features, such as young age at acquisition, long duration of infection, and repetitive exposure with evidence of genotype conversion or mixed infection (22). Data on correlates of HCV-RNA load in persons with hemophilia are scarce. Based on small studies (23;24), HIV co-infection, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and CD4 cell counts may be correlated with high HCV-RNA in plasma.

To clarify these issues, we used a large multicenter cohort of patients with hemophilia to 1) determine correlates of high HCV-RNA load in interferon naïve HCV infected persons with hemophilia overall and according to their HIV status, and 2) evaluate these factors according to HIV treatment regimen in HIV-positive persons.

Materials and Methods

Study subjects

Study subjects were participants in the second Multicenter Hemophilia Cohort Study (MHCS-II). Details were previously described (4;5). Briefly, the MHCS-II was established to quantify the impact of hepatitis C (HCV), hepatitis B (HBV) and human immunodeficiency virus (HIV-1) infections on persons with hemophilia. In this cohort all HCV-seropositive individuals with hemophilia, aged 13 years or older, at one of the 52 participating hemophilia treatment centers, were invited to participate between April 2001 and April 2005.

The study protocol was approved by the institutional review boards of the National Cancer Institute and the participating centers. Human experimentation guidelines of the US Department of Health and Human Services were followed; informed consent was obtained from all adult participants or from the parents of minors. For this analysis, we included MHCS-II participants who had detectable HCV viremia (HCV-RNA≥43 copies/ml) (5) at baseline and who had no history of interferon therapy (n=1,266); 471 (37.2%) of these were co-infected with HIV-1.

HCV -RNA data

HCV-RNA was quantified using real-time reverse transcription-polymerase chain reaction (RT-PCR) assay. HCV-RNA specimens with ≤100,000 copies/ml were independently validated using COBAS Amplicor HCV version 2.0 as described earlier (5;25). For this study, we used the value of 2 million copies/ml, which was associated with treatment response in several trials (26;27), as a cutoff to categorize high HCV-RNA ($> 2\times10^6$ copies/ml) versus low (HCV-RNA $\leq 2\times10^6$ copies/ml).

Baseline characteristics and variables evaluated as correlates with high HCV-RNA load

We evaluated age at enrolment, race, gender, body mass index (BMI, ≥ 25 vs. <25 kg/m^2), alcohol consumption and regular cigarette smoking. Alcohol consumption (number of drinks/week) in the three months prior to enrollment was self-reported. One drink of alcohol was defined as 45 ml of liquor, 120 ml of wine or 360 ml of beer. Regular smoking was defined as ever having smoked 10 cigarettes or more/week. Smokers who did not smoke in the past 6 months were considered to be former smokers.

In addition, we evaluated the following clinical factors: hemophilia type and severity, HBV and HIV co-infections, age and calendar year at primary HCV infection, duration of HCV infection, and presence or absence of anemia. Age and calendar year at HCV infection were statistically imputed as described previously (4;25). HBV co-infection was categorized into: a) uninfected, no detectable HBV serological markers or positive antibodies against HBV surface antigen (anti-HBs) in vaccinated individuals, b) chronic infection, positive serum HBs antigen (HBsAg) for more than 6 month, or c) resolved infection in individuals with other positive markers including anti-HBs in non-vaccinated individuals. HBV serological markers were available for 74.5% of the study participants.

Anemia was categorized into: a) mild (hemoglobin (Hgb) ranging between 10 and 12.99 or hematocrit (Hct) ranging between 30 and 38.9), else b) moderate/severe (Hgb<10 or Hct<30), and compared to c) no anemia.

For other laboratory markers, we included platelet, lymphocyte and neutrophil cell counts, and liver function tests [total bilirubin, serum albumin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST)]. We also included two combinations of these, AST/ALT ratio and AST/platelet ratio (APRI), which are reported to be surrogates for degree of liver fibrosis (28;29).

In HIV-positive participants, we also evaluated CD4 cell counts (<200, 200-500 vs. >500 cells/μL), current use of antiretroviral therapy (ART), (combination ART (cART), also known as HAART) or other ART vs. no ART), and the presence of detectable HIV viremia (HIV-RNA ≥33 copies/ml) (5)

Statistical analysis

We used logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to determine factors associated with high HCV-RNA load. Analysis was also stratified by participants' HIV status. HIV-positive participants were further stratified according to the ART regimen they were receiving at time of enrollment. All continuous variables such as age were categorized into quartiles.

Variables with $P \leq 0.15$ in the unadjusted analysis were entered in a multivariable logistic regression model and allowed to stay in the final model if the adjusted $P \leq 0.15$; variables with ≥15% missing data were excluded from the models. Based on the observed high correlations of age at enrollment with age at infection (r=0.89), calendar year of infection with duration of infection (r=0.99), and AST with AST/platelet ratio (r=0.74), we excluded age at enrollment, calendar year at infection and AST level from the models to avoid collinearity. Based on these rules, the final model for all participants included gender, BMI, duration of HCV infection, and HIV co-infection status. In this model, we tested the interaction between HIV co-infection status and BMI or duration of HCV infection. The final model for HIV-negative individuals included gender, age at infection, duration of HCV infection, BMI and AST/platelet ratio. In this model we tested the interaction between duration of HCV infection and age at infection. For HIV-positive individuals, only BMI and ART met the criteria of inclusion in the final model.

Results

Participants' demographic and clinical characteristics

The study included 1,266 persons with hemophilia (75% with hemophilia type A, 63.4% with severe coagulopathy), who had detectable HCV viremia and were interferon naïve at enrollment. The median age of the study participants was 36 years; most of them were white (79.1%); almost all were male (95.6%); and more than one third (37.2%) were co-infected with HIV. Compared to HCV mono-infected participants, HIV co-infected individuals were younger, more likely to have severe hemophilia (78.3% vs. 54.6%, $P<0.0001$), and evidence of past or current HBV infection (65.6% vs. 38.8%, $P<0.0001$). More than half of the participants (61.8%) had high HCV-RNA load (>2,000,000 copies/ml); this was more likely among HCV/HIV co-infected compared to HCV mono-infected participants (67.9% vs. 58.2%, $P=0.0006$). Among HIV-positive participants with available information on ART and CD4 count, 335 of 443 (75.6%) were receiving ART at enrollment, and 83 of 420 (19.8%) had CD4 cell count <200 cells/μL (Table 1).

Correlates of high HCV-RNA load in persons with hemophilia, overall and stratified by HIV co-infection status

Among all study participants, high HCV-RNA load was positively associated with male gender (OR=1.9, 95% CI=1.1-3.3), older age ($P_{trend}<0.0001$), longer duration of HCV infection ($P_{trend}<0.0001$), older age at primary infection ($P_{trend}=0.01$), overweight or obese (BMI≥25kg/m^2) (OR=1.6, 95% CI=1.2-2.1), resolved HBV infection (OR=1.6, 95% CI=1.2-2.1), and HIV co-infection (OR=1.5, 95% CI=1.2-1.9) (Table 2). None of the evaluated blood laboratory values was significantly associated with high HCV-RNA in the unadjusted analysis (Table 3). In the multivariable analysis, overweight or obesity (OR= 1.4, 95% CI=1.1-1.9), HIV co-infection (OR=1.4, 95% CI=1.0-1.8), and longer duration of HCV infection ($P_{trend}=0.0001$) remained significantly ($P<0.05$) associated with high HCV high load. There was no statistically significant interaction between HIV co-infection and BMI or duration of HCV infection.

Among HIV-negative individuals, unadjusted correlates of high HCV load were similar to those observed in the overall analysis (Table 2, 3). In the multivariable analysis, an upward trend was observed with longer duration of infection (OR=1.1, 1.4 and 2.1, $P_{trend}=0.001$) and with older age at acquisition (OR=1.2, 1.6. and 1.9, $P_{trend}=0.008$); no interaction was observed between the two variables. Additionally, overweight and obese individuals, and those with low AST/platelet ratio were more likely to have high HCV load (OR=1.6, 95% CI=1.14-2.3; and OR=2.0, 95% CI=1.1-3.6 with ratio <0.4 compared to a ratio ≥1.5, respectively).

Among HCV/HIV co-infected participants, none of the evaluated demographic or clinical variables explained high HCV-RNA load with the possible exception of antiretroviral therapy ($P=0.06$) (Table 2). Among evaluated laboratory tests, only neutrophil count reached significance ($P=0.05$) (Table 3). In the multivariable model, in which BMI was retained but not statistically significant ($P=0.11$), the use of ART was the only statistically significant variable associated with high HCV-RNA load (OR=1.8, 95% CI=1.1-2.9, $P=0.02$ for cART; 1.8, 0.95-3.4, $P=0.07$ for other ART regimens), when compared to no ART.

With stratification by ART regimen (cART, other ART, and none), no significant association was observed in any of the treatment groups, except for positive associations of high HCV-RNA load with BMI and AST/ALT ratio in participants who were not receiving ART (OR=3.6, 95% CI=1.6-8.5 for BMI ≥25; OR=3.8, 95% CI=1.0-15.2 for AST/ALT ratio≥1.2) (Data not shown)

Discussion

In this large multicenter cohort of individuals with hemophilia, who had detectable HCV viremia at baseline and no history of interferon therapy, we evaluated whether high HCV-RNA load was associated with several demographic, clinical, and laboratory parameters. As noted in many studies (17;18;24;30), we found that high HCV-RNA load was significantly more common with HIV co-infection. Among HIV-negative individuals, we found that high HCV-RNA load was associated with older age at infection, longer duration of infection, and being overweight or obese. With adjustment for these variables, high HCV-RNA load also was significantly associated with having a low AST/platelet ratio. This may seem paradoxical, because high AST/platelet ratio is a marker for significant liver fibrosis and cirrhosis (31). An inverse association between HCV load and hepatic cirrhosis has been reported previously and suggests that a critical mass of healthy hepatic parenchyma may be necessary to generate a high HCV-RNA load (20).

Longitudinal studies of both people with hemophilia (24) and injection drug users (17) have clearly shown that HCV-RNA level increases with duration of infection. An independent association between high HCV-RNA level and older age at primary infection has not been reported previously. Older age at primary HCV infection is strongly associated with lower likelihood of spontaneous clearance of HCV RNA (25;32;33), and thus it is quite plausible that it also would be associated with high HCV-RNA level in those who fail to clear the virus spontaneously. Zhang and colleagues postulated that this may have been due to a smaller inoculum of HCV in clotting factor therapy administered to younger patients, thereby affording a better chance for an effective immune response against the virus (25).

In HIV-positive individuals, none of the variables evaluated were associated with high HCV load except for current use of cART or other ART, both of which were associated with an 80% increase in the odds of having high viral load compared to no ART. The observed null association with duration of HCV infection or age at acquisition might be affected by survival bias, where individuals who were HCV/HIV co-infected for longer duration were more likely to die and therefore not be included in this study. This possibility does not seem to fully explain this null association, as HIV co-infected individuals in this study were more likely to have longer duration of HCV infection (>25 years) than HCV mono-infected individuals (70.2% vs. 50.6%, respectively). Our results on cART agree with the results from a longitudinal study of 21 patients with hemophilia, in which HCV load increased at 48 and 96 weeks after cART initiation and dropped after cART discontinuation (34). Two other studies have pointed to a specific relationship of protease inhibitors (PI) on HCV load (35;36), suggesting that differences in the use of PI-based and non-PI-based ART may yield inconsistent associations with HCV load.

High HCV-RNA level was significantly associated with being overweight or obese in the HIV-negative participants. A similar association was reported previously for non-hemophilic HIV-negative patients (37). We also noted that high BMI was associated with high HCV-RNA in the subgroup of HIV-positive participants who were not on ART, which has not been previously reported and will require corroboration. An association between BMI and HCV-RNA level might be mediated through interferon-gamma inducible protein 10 (IP-10), a chemokine that is over-expressed in the liver of obese infected individuals (38). IP-10 was directly correlated with HCV-RNA load in an earlier study (39).

Our study is the largest to evaluate HCV-RNA levels in individuals with hemophilia. However, we could not assess temporal relationships, because our study was cross-sectional. In addition, our results may not easily generalize to non-hemophilic patients, as almost all of our participants were male, infected at a young age and repeatedly exposed to HCV. Further,

we lacked liver biopsies to directly assess the degree of liver fibrosis. Instead, as a surrogate marker for advanced liver fibrosis and cirrhosis, we used AST/platelet ratio, which is reported to have sensitivity and specificity >80% in non-hemophilic patients (40).

Despite some limitations, our study of chronic HCV infection suggests that the infection may be more poorly controlled, and thereby more pathogenic and resistant to treatment, in people who are overweight or obese. Corroboration and deeper understanding of this are needed, aiming to identify individuals for whom current HCV therapy is likely to be inadequate.

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Table 1

Characteristics of study participants, overall and stratified by HIV co-infection status

	Total (N=1,266)	HIV-negative (N=795)	HIV-positive (N= 471)	P-value*
		N (%)		
Age at enrollment (yr)				
Median (range)	36 (13-88)	37 (13-82)	35 (17-88)	
13-26	325 (25.7)	241 (30.3)	84 (17.8)	<0.0001
27-35	292 (23.0)	135 (17.0)	157 (33.3)	
36-46	343 (27.1)	181 (22.8)	162 (34.4)	
47-88	306 (24.2)	238 (29.9)	68 (14.5)	
Race				0.26
White	1,002 (79.1)	637 (80.1)	365 (77.5)	
Black	153 (12.1)	85 (10.7)	68 (14.4)	
Hispanic	61 (4.8)	41 (5.2)	20 (4.2)	
Others	50 (4.0)	32 (4.0)	18 (3.8)	
Gender				<0.0001**
Male	1,210 (95.6)	741 (93.2)	469 (99.6)	
Female	56 (4.4)	54 (6.8)	2 (0.4)	
Hemophilia Type				<0.0001
A	950 (75.0)	539 (67.8)	411 (87.3)	
B	223 (17.6)	166 (20.9)	57 (12.1)	
Others	93 (7.3)	90 (11.3)	3 (0.7)	
Hemophilia severity				<0.0001
Severe	803 (63.4)	434 (54.6)	369 (78.3)	
Moderate	218 (17.2)	151 (19.0)	67 (14.3)	
Mild	242 (19.1)	207 (26.0)	35 (7.4)	
Missing	3 (0.3)	3 (0.4)	0	
HCV genotype				<0.0001
1	697 (55.0)	418 (52.6)	279 (59.3)	
2 or 3	219 (17.3)	131(16.5)	88 (18.7)	
Others	57 (4.5)	29 (3.6)	28 (5.9)	
Missing	293 (23.2)	217 (27.3)	76 (16.1)	
HBV co-infection				<0.0001
Uninfected	487 (38.5)	371(46.7)	116 (24.6)	
Resolved infection	422 (33.3)	218 (27.4)	204 (43.4)	
Chronic infection	34 (2.7)	17 (2.1)	17 (3.6)	
Missing	323 (25.5)	189 (23.8)	134 (28.4)	
Current Antiretroviral therapy				
No		N/A	108 (24.4)	
Combined			246 (55.5)	
Other			89 (20.1)	

	Total (N=1,266)	HIV-negative (N=795)	HIV-positive (N= 471)	P-value*
		N (%)		
CD4 counts (cells/μL)				
>500		N/A	129 (30.7)	
200-500			208 (49.5)	
<200			83 (19.8)	
HCV load (copies/ml)				
Median	3.2 ×10^6	2.7×10^6	4.7×10^6	0.0006
(range)	(210-162.9×10^6)	(215-162.9×10^6)	(215-132.9×10^6)	
≤ 2×106	483 (38.1)	332 (41.7)	151 (32.1)	
> 2×106	783 (61.8)	463 (58.2)	320 (67.9)	

* chi-square test for the difference between HIV-negative and positive participants

** Fisher-exact test

Table (2)

Associations between HCV high viral load* and participants' demographic, lifestyle and clinical characteristics overall and stratified by their HIV status

	Overall (N=1,266)	HIV negative (N=795)	HIV-positive (N=471)
	OR (95% CI) ‡		
Race			
Non Hispanic White	Ref	Ref	Ref
Others	1.1 (0.8-1.5)	1.2 (0.8-1.7)	1.0 (0.6-1.6)
Gender			
Male	Ref	Ref	Ref
Female	0.5 (0.3-0.9)	0.6 (0.3-1.0)	0.5 (0.03-7.6)
Age at enrollment (yr)			
13-26	Ref	Ref	Ref
27-35	1.8 (1.3-2.6)	1.7 (1.1-2.7)	1.5 (0.8-2.7)
36-46	1.9 (1.4-2.6)	1.9 (1.3-2.9)	1.5 (0.9-2.7)
47-88	2.3 (1.6-3.2)	2.5 (1.7-3.7)	1.9 (0.9-4.0)
Body Mass Index			
<25	Ref	Ref	Ref
>=25	1.6 (1.2-2.0)	1.8 (1.3-2.4)	1.4 (0.9-2.1)
Alcohol consumption§			
None	Ref	Ref	Ref
1- < 2 drinks/week	10 (0.7-1.4)	1.2 (0.8-1.8)	0.7 (0.4-1.2)
2+ drinks/week	1.2 (0.9-1.6)	1.3 (0.9-1.8)	1.1 (0.6-1.8)
Smoking regularly			
Never	Ref	Ref	Ref
Former	1.3 (0.9-1.9)	1.4 (0.9-2.3)	1.2 (0.6-2.4)
Current	1.2 (0.9-1.6)	1.2 (0.9-1.7)	1.2 (0.7-1.8)
Hemophilia type			
A	Ref	Ref	Ref
B	10 (0.7-1.4)	1.1 (0.8-1.6)	1.0 (0.5-1.9)
Others	0.6 (0.4-1.0)	0.8 (0.5-1.2)	0.2 (0.01-3.3)
Hemophilia severity			
Severe	Ref	Ref	Ref
Moderate	1.1 (0.8-1.6)	1.2 (0.8-1.9)	1.2 (0.7-2.1)
Mild	0.8 (0.6-1.1)	1.0 (0.7-1.4)	0.8 (0.4-1.6)
Duration of HCV infection (yr)			
11-21	Ref	Ref	Ref
22-27	1.4 (1.0-1.9)	1.1 (0.8-1.7)	1.4 (0.7-2.8)
28-32	1.7 (1.2-2.5)	1.9 (1.2-3.1)	1.1 (0.6-2.5)
33-55	2.4 (1.7-3.4)	2.5 (1.6-3.9)	1.7 (0.8-3.5)
Calendar year at HCV infection			

	Overall (N=1,266)	HIV negative (N=795)	HIV-positive (N=471)
	OR (95% CI) ‡		
1947-1969	Ref	Ref	Ref
1970-1975	0.9 (0.6-1.3)	0.8 (0.5-1.2)	1.1 (0.6-1.8)
1976-1980	0.6 (0.4-0.9)	0.5 (0.3-0.7)	0.9 (0.5-1.6)
1981-1990	0.5 (0.3-0.7)	0.4 (0.3-0.6)	1.0 (0.5-2.1)
Age at HCV infection			
0-2	Ref	Ref	Ref
3-7	1.4 (1.0-2.0)	1.3 (0.8-2.1)	1.4 (0.8-2.4)
8-15	1.6 (1.2-2.3)	2.0 (1.3-3.1)	1.3 (0.7-2.2)
16-60	1.5 (1.1-2.2)	1.9 (1.3-2.9)	1.4 (0.6-3.0)
Age at infection/duration			
Before age 10, for ≤25 years	Ref	Ref	Ref
Before age 10, for >25 years	2.0 (1.4-2.8)	2.3 (1.5-3.7)	1.2 (0.7-2.1)
At/after age 10, for ≤25 years	1.3 (0.9-1.9)	1.4 (0.9-2.2)	1.3 (0.5-3.2)
At/after age 10, for >25 years	2.1 (1.5-2.9)	2.5 (1.7-3.6)	1.3 (0.7-2.5)
HCV genotype			
1	Ref	Ref	Ref
2 or 3	1.2 (0.9-1.7)	1.4 (0.9-2.1)	0.9 (0.5-1.6)
others	1.2 (0.7-2.1)	1.2 (0.5-2.6)	1.1 (0.4-2.6)
HBV co-infection			
Uninfected	Ref	Ref	Ref
Chronic	1.3 (0.5-2.3)	1.0 (0.4-2.6)	1.0 (0.3-2.9)
Resolved	1.6 (1.2-2.1)	1.7 (1.2-2.4)	1.2 (0.7-2.0)
Undetermined	1.4 (1.0-1.9)	1.3 (0.9-1.9)	1.2 (0.7-2.1)
HIV co-infection			
No	Ref	N/A	
Yes	1.5 (1.2-1.9)		
Current antiretroviral therapy			
None			Ref
Combination		N/A	1.7 (1.1-2.8)
Other			1.7 (0.9-3.2)

* High viral load is >2 million copies/ml

‡ Odds ratios (OR) and 95% confidence intervals (CI) comparing subjects with high HCV viral load to those with low viral load

Underlined OR are significant at $p<0.05$

§ In the past 3 months

Table (3)

Associations between HCV high viral load* and participants' laboratory results stratified by their HIV status and treatment

	Overall (N=1,266)	HIV negative (N=795)	HIV-positive (N=471)
	OR (95% CI) ‡		
Anemia			
None	Ref	Ref	Ref
Mild	0.9 (0.6-1.3)	0.7 (0.5-1.1)	1.1 (0.7-1.9)
Moderate/Severe	0.5 (0.2-1.2)	0.7 (0.2-2.2)	0.8 (0.3-2.4)
Platelet counts (cells/μL)			
≥150,000	Ref	Ref	Ref
<150,000	1.0 (0.7-1.3)	0.9 (0.6-1.3)	0.9 (0.6-1.4)
Lymphocyte count (cells/μL)			
≥1,500	Ref	Ref	Ref
<1,500	1.2 (1.0-1.6)	1.1 (0.7-1.5)	1.4 (0.9-2.1)
Neutrophil count (cells/μL)			
<3000	Ref	Ref	Ref
≥3000	1.1 (0.8-1.4)	1.1 (0.8-1.5)	1.5 (1.0-2.4)
Serum albumin (g/dl)			
<3.8	Ref	Ref	Ref
≥3.8	0.9 (0.6-1.3)	1.2 (0.7-1.9)	0.7 (0.4-1.3)
Alanine aminotrasferase (ALT)			
Normal	Ref	Ref	Ref
<3 fold elevation	1.0 (0.7-1.3)	1.2 (0.8-1.8)	0.6 (0.3-1.0)
≥3 fold elevation	0.9 (0.6-1.3)	1.0 (0.6-1.6)	0.6 (0.3-1.1)
Aspartate aminotransferase (AST)			
Normal	Ref	Ref	Ref
<3 fold elevation	1.2 (0.9-1.5)	1.3 (0.9-1.8)	0.6 (0.3-1.1)
≥3 fold elevation	1.0 (0.7-1.5)	0.8 (0.5-1.4)	0.7 (0.3-1.4)
AST/ALT ratio			
<1	Ref	Ref	Ref
1-<1.2	1.3 (0.9-2.0)	1.0 (0.6-1.8)	1.6 (0.9-2.9)
≥1.2	0.9 (0.6-1.2)	0.6 (0.4-0.9)	1.2 (0.7-1.9)
APRI (AST/platelet)			
<0.4	Ref	Ref	Ref
0.4-1.49	1.2 (0.9-1.7)	1.3 (0.9-1.9)	0.6 (0.3-1.3)
≥1.5	1.0 (0.7-1.5)	0.9 (0.5-1.5)	0.6 (0.2-1.2)
Total bilirubin (mg/dl)			
≤1	Ref	Ref	Ref
>1	1.2 (0.9-1.7)	1.0 (0.6-1.6)	1.3 (0.8-2.2)
Detectable HIV-1 viremia			

	Overall (N=1,266)	HIV negative (N=795)	HIV-positive (N=471)
	OR (95% CI) ‡		
No		N/A	Ref
Yes			1.1 (0.8-1.7)
CD4 count (cells/μL)			
>500		N/A	Ref
200-500			1.3 (0.8-2.5)
<200			1.4 (0.7-2.5)

‡Odds ratios (OR) and 95% confidence intervals (CI) comparing subjects with high HCV viral load to those with low viral load

Underlined OR are significant at $p<0.05$