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Association Of Hepatitis C With Markers Of Hemostasis In HIV-Infected and Uninfected Women in the Women's Interagency HIV Study (WIHS)

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Abstract

Coinfection with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) is common. HIV infection and treatment are associated with hypercoaguability; thrombosis in HCV is under-investigated. Proposed markers of hemostasis in HIV include higher D-dimer, Factor VIII% and Plasminogen Activator Inhibitor-1 (PAI-1Ag), and lower total Protein S% (TPS), but have not been examined in HCV. We assessed the independent association of HCV with these four measures of hemostasis in a multicenter, prospective study of HIV: the Women's Interagency HIV Study (WIHS).

We randomly selected 450 HCV-infected (anti-HCV+ with detectable plasma HCV RNA) and 450 HCV-uninfected (anti-HCV−) women. HCV was the main exposure of interest in regression models.

443 HCV+ and 425 HCV− women were included. HCV+ women had higher Factor VIII% (124.4% ±3.9 vs. 101.8% ±3.7, p <0.001) and lower TPS (75.7% ±1.1 vs. 84.3% ±1.1, <0.001) than HCV−, independent of HIV infection and viral load; there was little difference in PAI-1Ag or log10 D-dimer. After adjustment for confounders, these inferences remained. HIV infection was independently associated with higher Factor VIII% and log10 D-dimer, and lower TPS.

HCV was independently associated with higher Factor VIII% and lower TPS consistent with hypercoaguability. Higher Factor VIII % and D-dimer and lower total Protein S % were also strongly associated with HIV infection and levels of HIV viremia, independent of HCV infection.

Further investigation is needed to determine if there is increased thrombotic risk from HCV. Studies examining hemostasis markers in HIV infection must also assess the contribution of HCV infection.

INTRODUCTION

Coinfection with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) is common in the United States [1,2]. HIV infection itself and HIV treatment with highly active antiretroviral therapy (HAART) have been associated with a hypercoaguable state [3,4] and increased risk for thrombotic events such as deep vein thrombosis (DVT) or pulmonary embolism (PE) [5–10]. However, thrombosis in HCV has been evaluated mainly in end-stage liver disease and cirrhosis[11–16].

Proposed markers of hemostasis in HIV include higher levels of D-dimer, Factor VIII% and Plasminogen Activator Inhibitor-1 antigen (PAI-1), and lower levels of total Protein S%, both in patients on ART and in the pre-HAART era [17–23]. HCV coinfection occurs commonly in HIV-infected patients and may accelerate immunologic progression of HIV infection [24]. However, little is known about the independent association between HCV and markers of hemostasis.

Our main objective in this study was to investigate the independent association of HCV with each of four measures of hemostasis: D-dimer, Factor VIII %, total protein S %, and PAI-1, in a sample of HIV and HCV infected and uninfected women in the United States. In order to isolate the independent effect of HCV on levels of these four measures of hemostasis, we strategized to adjust for known confounders of this relationship, including HIV and other covariates, which are associated with HCV itself, and are possible predictors of the outcome measures of hemostasis.

METHODS

Study Participants

The Women's Interagency HIV Study (WIHS) is a multicenter, prospective study of the natural history of HIV-infection and associated diseases in women. Women with HIV and women at risk for HIV were recruited at six national sites (Los Angeles, CA; San Francisco, CA; Chicago, IL; Bronx, NY; Brooklyn, NY; and Washington, DC) from October 1994 through November 1995 and from October 2001 through September 2002. Detailed methods and characteristics of the study population have been previously published [25]. At the enrollment visit (Visit 1) and then prospectively every six months interviews were conducted, a physical exam performed, and blood specimens collected. The protocol was approved by the Institutional Review Boards at each study site, and all participants provided written informed consent.

This study presents cross-sectional analyses of data and specimens collected from participants during their first year of enrollment in WIHS. We randomly selected 450 HCV positive (HCV seropositive with detectable plasma RNA) from 1,023 potentially eligible non-pregnant HCV-infected women, and 450 HCV negative (HCV seronegative) from 2,709 potentially eligible non-pregnant HCV-uninfected women. All HIV seroprevalent and HIV seronegative women in the WIHS were eligible to be part of the population. Samples were selected from the WIHS central repository. We limited the population to women with known HCV status (as described above) and with available plasma in our national specimen repository. These women were randomly assigned a sorting (selection) value using the RANUNI function in SAS, and the 450 lowest randomly assigned values within each

population of interest were selected for testing. The repository contains all WIHS sites, and selection was thus random across all of the WIHS sites.

Outcome variables: Measures of hemostasis

Factor VIII %, D-dimer, total Protein S %, and PAI-1 were the main outcomes (dependent variables) of interest. These measures of hemostasis were measured at the University of Vermont, Laboratory for Clinical Biochemistry Research in previously unthawed serum collected at the first visit after study enrollment and frozen at −80°C. All tests assays used Stago products (Parsippany, NJ). D-dimer was measured on citrated plasma using the immunoturbidimetric method for quantitative determination. PAI-1 was measured on citrated plasma using PAI-1 the quantitative determination of PAI-1 Antigen by ELISA. Factor VIII % was measured on citrated plasma via a clot-based FVIII activity assay using a Diagnostica Stago STA-R Evolution coagulation analyzer. Total protein S% was measured by quantitative determination by ELISA. The laboratory was blinded to HCV and HIV status.

Primary Exposure of Interest: HCV infection

Presence of active HCV infection (HCV seropositivity with a detectable plasma HCV RNA) was the main exposure of interest. At enrollment, all women were screened for HCV using HCV antibody enzyme immunoassay Abbott EIA 2.0 and 3.0 assays (Abbott Laboratories, Abbott Park, IL). As previously described [26], HCV RNA was measured on frozen specimens from HCV seropositive women using either the COBAS Amplicor Monitor 2.0 assay (Roche Diagnostics, Branchburg, NJ), or the COBAS Taqman assay (Roche Diagnostics).

Covariates

We included covariates with known associations (from the literature) with HCV, and with any of our four measures of hemostasis.

HIV has known associations with HCV and is associated with higher levels of D-dimer, Factor VIII% and PAI-1, and with lower levels of Total Protein S% [17,19–23]. HIV infection was defined as HIV positive antibody status using commercial enzyme immunoassay (EIA) kits and Western Blot confirmation, with HIV negative serostatus confirmed at all visits. We further characterized a positive HIV infection by CD4 count and viral load (VL). HIV antibody, CD4 counts, and VL were obtained from the first visit after enrollment, which was the same visit that specimens were collected for the main outcomes of interest. If CD4 or VL was missing at that visit, they were obtained from the enrollment visit. CD4 was categorized as CD4 >500, 350 – 500, 200 – 350, or <200 cells/μL. VL was divided into approximate distribution tertiles: 0 4000 copies, 4001 – 55000 copies, and > 55000 copies/mL. HIV treatment was self-reported among those with HIV, and defined as none, monotherapy (single agent use), combination therapy (more than one antiretroviral agent not meeting definition of HAART), or highly active antiretroviral therapy (HAART). The definition of HAART was guided by the DHHS/Kaiser Panel guidelines and was defined as: use of three or more antiretroviral medications, one of which had to be a PI, an NNRTI, one of the NRTIs abacavir or tenofovir, an integrase inhibitor (e.g., raltegravir), or an entry inhibitor (e.g., Maraviroc or enfuvirtide) [27].

Demographic covariates included age (in years) and race/ethnicity (self reported and defined as black including Hispanics, white including Hispanic and other), as both HCV and measures of hemostasis are noted to vary by age and race [28–34].

Behavioral covariates from the visit of blood draw included smoking status, use of drugs including cocaine and heroin, alcohol use, and female sex hormone use. Smoking has been

associated with higher prevalence of HCV, and is theorized to interact with HCV to accelerate hepatocellular damage [35–38]; smoking is also a predictor of several measures of hemostasis[39–41]. Smoking status was defined as never, former, or current (in the last 6 months). Alcohol use in the last 6 months was categorized as abstinent, light, moderate, and heavy use. Drug use and alcohol use have been associated with both HCV [42–44] and measures of hemostasis [45–47]. Estrogen has been associated with decreased viremia in HCV and predicts measures of hemostasis[48–55]. Drug use was a composite variable which included crack, cocaine, heroin, or injection drug use (IDU), and defined as never, previous or current (in the last 6 months). Hormone use in the last 6 months was a composite variable comprised of oral contraceptive use, estrogen replacement therapy (alone or in combination), Norplant, or Depo-Provera.

We included a non-invasive calculated measure of fibrosis, FIB-4, which has been developed and validated in HIV/HCV coinfected individuals [56] and predicts fibrosis in HCV, Hepatitis B, HIV, and non-alcoholic fatty liver disease [57–61]. Liver fibrosis is associated with the predictor variable HCV [1,62,63] and fibrosis/cirrhosis is also associated several of markers of hemostasis [12,16,64,65]. We calculated FIB-4 from the Sterling's formula using aspartate aminotransferase (AST) and alanine aminotransferase (ALT) [56]: [Age (in years)*AST] / [platelet(10^9/L) * ALT^1/2].

Other clinical covariates from the visit of blood draw included any history of diabetes mellitus, a history of a prior AIDS defining illness (ADI), and body mass index (BMI). Diabetes has been associated with both HCV and markers of hemostasis [66–73]. There is some evidence that development of ADIs are associated with HCV infection [74,75], and worsening HIV/AIDS increases the risk of thrombosis [8,22,76]. Obesity has known associations with HCV progression and treatment [77–79] and the development of thrombosis [80–83]. Diabetes and a history of AIDS defining illness (ADI) were self-reported. Body mass index was calculated as weight in kilograms divided by height (in meters squared).

Statistical Analysis

Our strategy in this paper was to examine the independent effect of HCV infection on levels of each of four measures of hemostasis, adjusting for known confounders of this relationship.

We examined the distribution of each of the four markers of hemostasis for normality. Three markers, Factor VIII %, total Protein S %, and PAI-1, were reasonably close to normally distributed. The distribution of D-dimer was skewed to the right and was log transformed to $\log_{10}$ D-dimer for statistical analysis. We present the geometric mean of the D-dimer in the figures for easier interpretation.

As other studies of clotting factors and related measures have observed and referred to as a "batch effect" [84–88], we noted that all four hemostasis measures varied systematically by WIHS site / laboratory testing date of the sample units. As these previous studies concluded, this likely reflected differences in sample preparations and testing and were not of direct interest to the analysis; we thus adjusted for these WIHS site / laboratory test date "batch effects" when performing our analyses of markers of hemostasis in an approach analogous to age adjustment [89]. For example, using the LS means statement in SAS (Version 9.2, SAS Institute, Cary, NC), the descriptive means and other statistics reported here are adjusted to the overall marginal distributions of WIHS site / test date among all women in the study. We examined the association between HCV and markers of hemostasis in WIHS site/test date effect adjusted linear models which have been noted to give the same results for linear models such as these as does a recently published conditional likelihood approach to

incorporate batch effects [90]. It should be noted that the qualitative direction and statistical significance of the results observed here were the same in models that did not adjust for these WIHS site / test date effects. We examined HCV positive compared to HCV negative women across tertiles of HIV status/VL in generalized linear models for each of the four markers of hemostasis and present LS mean and standard errors for these groups.

The distribution of FIB4 in this population was right skewed. We therefore log transformed the data for use in our analyses.

Backwards stepwise linear regression analysis was used to identify independent predictors of each of the four markers of hemostasis. A p value of ≤ 0.1 kept variables in the model, and a p value of ≤ 0.05 was otherwise used as criteria for significant variables. In regression models including all women, and in models limited to HIV positive women only, we preliminarily assessed the comparative relationship of both CD4 and viral load with each of the four markers of hemostasis. After adjusting for HIV viral load, there was no significant association between CD4 and each of the four markers of hemostasis (data not shown): however there were strong associations between viral load and the marker outcomes even after adjusting for CD4. Therefore, as CD4 and viral load are inversely collinear, in multivariate analysis among all women we used viral load and not CD4 as our predictor variable for HIV stage of disease. We forced HCV into multivariate models as it was the primary predictor; WIHS site, lab test date, and HIV status/VL were forced into the models as well.

RESULTS

Demographics

The 443 HCV positive and 425 HCV negative women were included in this study; 121 were both HCV negative and HIV negative; 304 were HIV positive only (one person was missing CD4 count) ; 73 were HCV positive only; and 370 were coinfected with both HCV and HIV (one person was missing CD4 count). Table 1 compares HCV positive and negative women by demographic and clinical characteristics. Compared with HCV-uninfected women, women with HCV were older, more likely to be black, and more likely to use tobacco. HCV positive women were more likely to abstain from alcohol and to be heavy drinkers, but less likely to be non-heavy drinkers compared to HCV negatives. HCV positives were more likely to use drugs, to be HIV-infected, have a higher viral load and lower CD4 count, to have reported a prior ADI and less likely to be on HAART compared to HCV negatives. The HCV negative women were more likely to use hormones and have a higher BMI. As expected, HCV negative women had lower FIB-4 scores.

Markers of hemostasis by HCV status

Table 2 reports markers of hemostasis by HCV status. There were 5 specimens for FVIII% and 1 specimen for PAI-1 Ag with insufficient volume remaining in the sample to run the test and were reported as missing. HCV positive women had higher levels of Factor VIII % (mean±std-err) (124.4% ± 3.9 vs. 101.8% ± 3.7, p <0.001) and lower levels of Total Protein S % (75.7% ± 1.1 vs. 84.3% ± 1.1, <0.001), independent of HIV status. There was no significant association of HCV with levels of PAI-1 or $\log_{10}$ D-dimer (p=0.42 and p=0.41, respectively).

Markers of hemostasis levels by HCV and HIV status

Figures 1 and 2, and Supplemental Figures 3 and 4 display the predicted LS mean levels of each marker of hemostasis by HCV status (dark grey bars vs. light grey bars) and HIV status/VL (HIV negative, HIV positive with low, medium, and high tertiles of VL). Factor

VIII% was higher in HCV positive women compared to HCV negative women of the same HIV status/VL. These differences were statistically significant in the HCV/HIV coinfected women with a low VL compared to HIV positives with low VL alone, and those with HCV/HIV coinfection and medium HIV VL compared to HIV positives with medium VL alone (Figure 1). Total Protein S% was statistically lower in HCV positive compared to HCV negative women across all categories of HIV/VL (Figure2). Higher HIV VL was associated with higher Factor VIII and lower total Protein S% (p-value for the trend $p<0.0001$ and $p<0.0001$, respectively, Figures 1 and 2). There was no significant difference in PAI-1 between HCV positive and negative women, and PAI-1 was not significantly higher with increasing HIV VL (Supplemental Figure 3). Supplemental Figure 4 shows the geometric mean of D-Dimer. D-Dimer was not associated with HCV infection, but was significantly higher with higher HIV VL ($p=0.0001$, Supplemental Figure 4).

Multivariate Analysis

We examined the independent association of HCV with the markers of hemostasis in multivariate analyses as described in the statistical methods, adjusting for both HIV status and treatment and other covariates: age, race, smoking status, drug use, alcohol use, hormone use, history of diabetes, history of AIDS defining illness and BMI. In addition, we adjusted for WIHS study site and date of laboratory test. Significant associations from multivariate analysis are shown in Table 3. HCV was independently significantly associated with higher levels of Factor VIII % (adjusted difference +11.70%, $p=0.008$) and lower levels of total Protein S % (adjusted difference −7.55%, $p<0.0001$) after adjustment. Thus, an HCV positive woman would have 11.70% higher Factor VIII % compared to an HCV negative woman with all other variables in the model equal. An HCV positive woman would have 7.55% lower total Protein S % compared to an HCV negative woman with all other variables equal. HCV was not significantly associated with PAI-1 or $\log_{10}$ D-dimer ($p=0.34$ and $p=0.91$, respectively). HCV remained an independent predictor of Factor VIII and total Protein S even after adjusting for FIB-4.

In these multivariate models, HIV status/VL was significantly and independently associated with higher Factor VIII % and $\log_{10}$ D-dimer and lower total Protein S % but was not statistically associated with PAI-1. In models restricted to HIV infected women, higher tertiles of VL were statistically associated with higher Factor VIII % and $\log_{10}$ D-Dimer levels (data not shown). Self reported HIV treatment category was also significantly associated with Total Protein S %: for example, compared to no treatment, HAART therapy was associated with higher total Protein S % levels (4.92%, $p=0.05$) after adjustment for all other variables in the model.

Higher log FIB-4 scores were independently associated with higher Factor VIII% and lower total Protein S (in the direction of worse thrombosis) ($p=.0014$ and $p<0.0001$, respectively). Age, race, smoking, drug use, hormone use, and BMI were significant independent predictors for some of the markers of hemostasis in multivariable models. In particular, higher BMI was significantly associated with higher Factor VIII %, PAI-1, and also total Protein S % (all $p<0.05$). Hormone use was independently associated with *a lower level* of Factor VIII % (adjusted difference 6.71% lower, $p=0.04$) and current smoking was independently associated with greater PAI-1 (adjusted difference 6.87 ng/mL, $p=0.02$). Black compared to white race was independently associated with higher Factor VIII % and $\log_{10}$ D-dimer (adjusted differences 22.23% and 0.09 μg/mL higher, $p<0.0001$ and $p=0.01$ respectively). Older age was associated with higher Factor VIII and total Protein S (adjusted differences 5.25% and 4.65% higher per 10 years, $p=0.068$ and $p<0.0001$, respectively).

DISCUSSION

This study of 868 women in the WIHS cohort found a highly statistically significant association of hepatitis C infection, defined by HCV viremia, with both higher Factor VIII % and lower Total Protein S %, independent of HIV infection. Higher Factor VIII % and D-dimer and lower total Protein S % were strongly associated with HIV infection and levels of HIV viremia, independent of HCV infection. Greater levels of Factor VIII % and lower total Protein S % are consistent with hypercoaguability. Thus, both HCV and HIV infection were each independently associated with markers of hypercoaguability. Coinfection with both HCV and HIV was associated with greater Factor VIII% among women with low and medium VL, and lower total Protein S% across all tertiles of VL, compared to HIV infection alone. To our knowledge, this is the first study to examine the associations of these markers of hemostasis in a large cohort of HIV-infected and uninfected women with and without HCV infection.

These markers have not been well characterized in general HCV infection. Previous studies examined the association between advanced HCV disease state and hemostasis marker levels. Abdo et al. found significant differences in total Protein S levels in a small number of patients with HCV and elevated liver enzymes, and patients with liver cirrhosis [91]. In a study of markers of hemostasis among 34 patients with HCV and extensive fibrosis and/or cirrhosis compared to 34 patients with HCV but without extensive fibrosis and/or cirrhosis, Factor VIII % was significantly elevated in the group with more advanced disease (160% vs. 120%, respectively) [92]. Among patients with cirrhosis, including those with HCV, Fimognari et al. found higher levels of D-dimer associated with advanced liver disease [12]. Hepatocellular damage from HCV may explain some of these marker levels, as HCV targets primarily hepatocytes in vivo [93,94]. Hepatocytes are the primary site for synthesis of Protein S, PAI-1 and fibrinogen, the source of the fibrin degradation product, D-dimer [1,95,96], whereas Factor VIII is made primarily by sinusoidal epithelial cells [2].

HIV has known associations with the markers of hemostasis measured here [17–19,21,23,97,98]. Our results were similar to another analysis from the WIHS study which showed decreases in Protein S and increases in factor VIII among women with advancing HIV disease compared to controls [22], and a study by Abdollahi et al. showing greater Factor VIII and decreased Protein S in HIV-infected patients compared to controls in Tehran, Iran [97]. Trotti et al. showed significantly higher levels of PAI-1 in a small number of HIV infected patients compared to healthy controls [17]. Bissuel et al. examined HIV-infected patients compared to healthy controls and found significantly decreased plasma free protein S levels in HIV-infected patients [98]. Some of these studies reported the exclusion of liver disease [17], however most investigations of the associations of HIV infection with measures of clotting diathesis did not adjust for infectious hepatitis or report liver disease [18–21,23,99].

HCV and HIV occur commonly together [1,2], and we found in this study that HIV/HCV coinfection was significantly associated with higher levels of Factor VIII%, among those with low and medium viral load, compared to HIV infection alone, and lower levels of total Protein S %, among those with low, medium and high viral load, compared to HIV infection alone. This pro-thrombotic profile may have clinical implications in the form of plaque formation or cardiovascular outcomes such as stroke or myocardial infarction. While HIV infection and treatment has known associations with cardiovascular disease [100–106] and endothelial dysfunction [107], the association between HCV infection and cardiovascular risk is less clear. A small number of studies have reported increased risk of CAD in HCV [108,109], or increased risk of intermediate outcomes such as subclinical atherosclerosis [110–112]. Ishizaka et al. found an independent association between HCV seropositivity, and carotid artery plaques and intimal media thickening among patients in Japan; these associations

were also confirmed using an HCV core protein assay as a better marker of active virus [111,112]. However, this result was not replicated in the WIHS cohort: Tien et al. found the prevalence of carotid plaques was higher in HIV/HCV coinfected women in the WIHS study group, compared to HCV monoinfected women, with a higher carotid intimal media thickness (CIMT) in the coinfected group compared to HCV monoinfected women, but after adjustment, HCV was not associated with greater CIMT, in contrast to other studies [113]. Thus, further investigation is needed to determine if HCV might be an independent risk factor for cardiovascular disease through pro-thrombotic mechanisms.

We confirmed several other previously observed associations with these four markers of hemostasis. Greater age, a known risk factor for thrombosis [114], was associated with higher Factor VIII and lower total protein S in our study. Higher body mass index, also a known risk factor for thrombosis [114] was significantly associated with all of the clotting factors except D-dimer. Interestingly, hormone use was associated with lower Factor VIII %. One previous study has shown no association of oral or transdermal contraception with Factor VIII % levels [54].

We found that self-reported antiretroviral therapy was associated with an increase in Total Protein S levels compared to no treatment. Monotherapy and HAART were significantly associated with this increase but combination therapy was not, perhaps reflecting Type 2 error. There is some prior evidence that HAART is associated with increases in Protein S [115]. However, Protease inhibitors have also been linked to an increase in thrombotic events and a decrease in Protein S [116,117]. Viral replication may play a role in modulating these markers; others have found that interruptions in HAART based on CD4 counts, compared to continuous treatment, resulted in increases in D-dimer[118].

This study has several limitations. We cannot make any causal inferences from the study, as it is a cross sectional design. The generalizability of this study to the modern HIV era may be limited as nearly 40% of HIV infected women were not treated, and only 23% were taking HAART. However, new studies have suggested that markers of hemostasis such as D-Dimer are elevated in those not on continuous HAART [118], and we would hypothesize that the overall effect of HAART would lead to markers of hemostasis in the direction of decreased thrombosis. In addition, the WIHS cohort may not be representative of women living with HIV or HCV in the United States and caution must be used in applying these results from this cohort study to the general population. Finally, very few patients were receiving treatment for HCV, so this paper cannot address whether HCV treatment improves markers of hemostasis. We also acknowledge that FIB-4 is an imperfect measure of fibrosis, and may not be completely capturing the influence of fibrosis on these markers of hemostasis.

In summary, in a large group of women with and without HCV defined by viremia, we found an independent association of HCV infection with 2 markers of hemostasis, Factor VIII and Total Protein S%, independent of HIV infection. We have also have found a significant association of level of HIV-viremia with 3 of these markers, Factor VIII %, D-dimer and Total Protein S %. These findings suggest that prior studies demonstrating an association of markers of hemostasis with HIV infection may have been partially confounded by coinfection with HCV. Future studies of hemostatic markers in HIV/HCV co-infected populations should control both for level of HIV viremia and for HCV-infection. Further investigation of HCV and markers of hemostasis in clinical outcomes is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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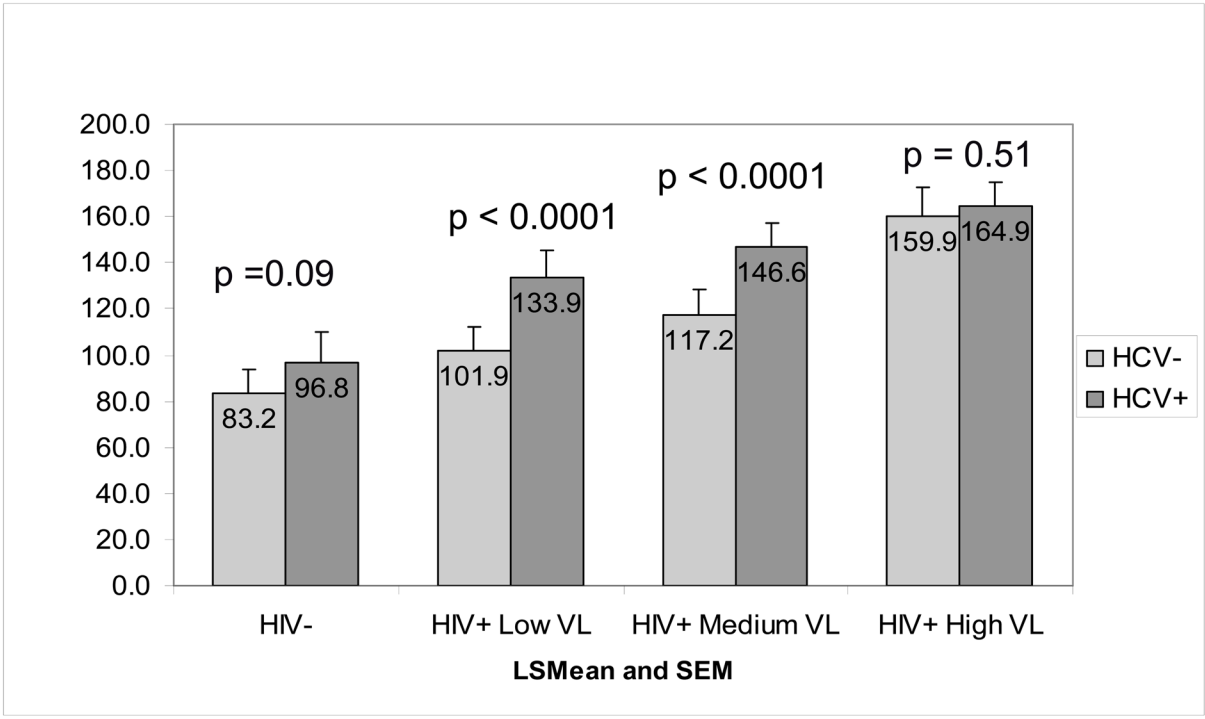

Figure 1. Factor VIII % by HCV and HIV Viral Load

* Population margins adjusted for WIHS site and test date; SEM: standard error of the mean; VL: Viral Load; Error bars indicate SEM. Low VL: 0 – 4000 copies/mL, Medium VL: 4001 – 55000 copies/mL, high VL: > 55000 copies/mL. P-value above each HIV group compares HCV-negative vs. HCV-positive in each HIV group; P-value for the trend of HIV – to High VL, $p<0.0001$.

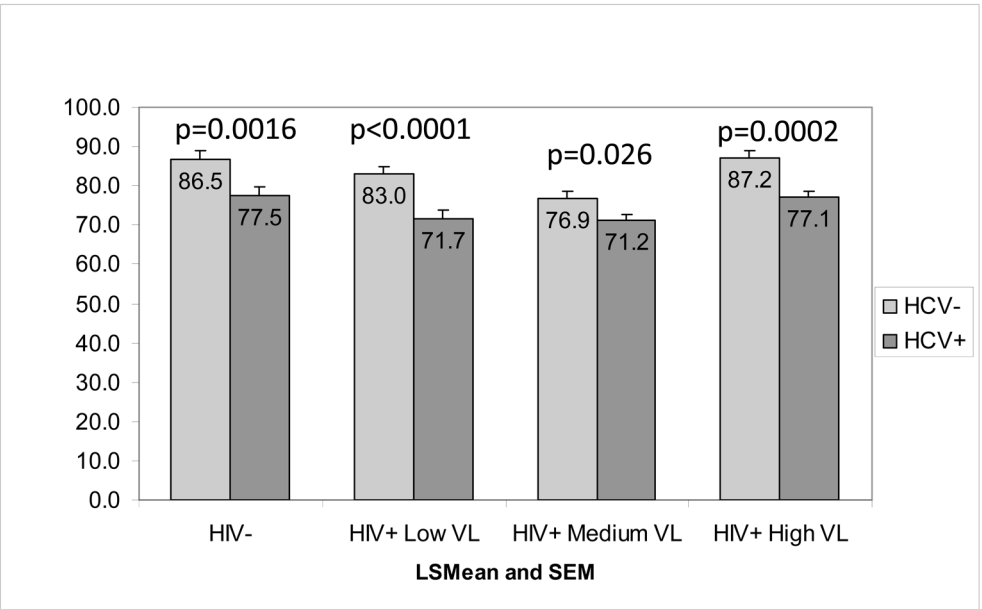

Figure 2. Total Protein S% by HCV and HIV Viral Load

* Population margins adjusted for WIHS site and test date; SEM: standard error of the mean; VL: Viral Load; Error bars indicate SEM. Low VL: 0 – 4000 copies/mL, Medium VL: 4001 – 55000 copies/mL, high VL: > 55000 copies/mL. P-value above each HIV group compares HCV-negative vs. HCV-positive in each HIV group; P-value for the trend of HIV – to High VL (adjusted for HCV),, $p<0.0001$.

Table 1

Demographic, Behavioral, and Clinical Characteristics of Study Group

	HCV− n = 425		HCV+ n = 443		p
	n		n		
Age, year (mean±SD)	424	34.2 ± 8.2	443	40.3 ± 6.0	<0.0001
Race (%)					0.003
White (including Hispanic)	102	24.1	90	20.3	
Black (including Hispanic)	226	53.3	285	64.3	
Other	96	22.6	68	15.4	
Smoking (%)					<0.0001
Never	164	38.8	38	8.6	
Former	75	17.7	71	16.0	
Current	184	43.5	334	75.4	
Drug use (crack, cocaine, heroin, IDU) (%)					<0.0001
Never	238	56.1	29	6.6	
Previous user	147	34.7	280	63.2	
Current user	39	9.2	134	30.3	
Alcohol use (%)					<0.0001
Abstainer	216	51.8	256	58.5	
Light (<3 drinks/wk)	125	30.0	81	18.5	
Moderate (3–13 drinks/wk)	67	16.1	49	11.2	
Heavier (>= 14 drinks/wk)	9	2.2	52	11.9	
Hormone use, past 6 months (%)	40	9.4	11	2.5	<0.0001
History of diabetes (%)	40	9.4	45	10.2	0.71
FIB-4 (mean±SD)	423	0.83± 0.57	441	2.14±2.89	p<0.0001
logFIB-4 (mean±SD)	423	−0.15± 0.23	441	0.19±0.30	p<0.0001
HIV status/CD4 count (%)					
HIV−	121	28.5	73	16.5	<0.0001
HIV+, CD4 > 500 cells/μL	93	21.9	85	19.2	
HIV+, CD4 350–500 cells/μL	63	14.9	71	16.1	
HIV+, CD4 200–350 cells/μL	72	17.0	93	21.0	

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	HCV− n = 425		HCV+ n = 443		p
HIV+, CD4 < 200 cells/μL	75	17.7	120	27.2	
HIV status/viral load (%)					<0.0001
HIV−	121	28.5	73	16.5	
HIV+, VL 4000 copies	127	30.0	104	23.5	
HIV+, VL 4000–55000 copies	97	22.9	131	29.6	
HIV+, VL > 55000 copies	79	18.6	134	30.3	
HIV treatment since last visit *(%)					<0.0001
None	124	40.8	184	49.7	
Mono therapy	65	21.4	101	27.3	
Combination therapy	43	14.1	63	17.0	
HAART	72	23.7	22	6.0	
History of ADI (%)	39	9.2	76	17.2	0.0005
Body Mass Index (mean ± SD)	416	28.2±7.5	420	26.8±6.2	0.03

IVDU: Intravenous drug use; FIB-4: [Age (in years)*AST] / [platelet(10^9/L) * ALT^1/2], where AST: aminotransferase and ALT: alanine aminotransferase

VL: viral load; HAART: highly active antiretroviral therapy; ADI: AIDS defining illness

*Among HIV positive women only

Table 2

Association of Hepatitis C and Markers of Hemostasis*

Marker of Hemostasis	HCV− n = 425		HCV+ n = 443		
	n	mean±SE	n	mean±SE	p
Factor VIII (%)	423	101.8±3.7	440	124.4±3.9	<0.001
Total Protein S (%)	425	84.3± 1.1	443	75.7±1.1	<0.001
PAI-1 Ag (ng/mL)	425	50.6 ±1.8	442	52.5 ±1.9	0.42
Log10 D-Dimer (ug/mL) (Geometric Mean)	425	−0.53±0.03 0.30	443	−0.50± 0.03 0.32	0.41

*adjusted for WIHS study site /date of laboratory test (batch effect), and HIV status

Table 3

Significant associations of Factor VIII, total Protein S%, PAI-1 Ag, and Log_{10}D-Dimer, in multivariate analysis *

Predictor	Factor VIII%		Total Protein S%		PAI-1 Ag, ng/mL		Log_{10} D-Dimer, ug/mL	
	Beta Coefficient	p	Beta Coefficient	p	Beta Coefficient	p	Beta Coefficient	p
HCV+ (Vs. HCV−)	11.70	0.008	−7.55	<0.0001	2.43	0.34	0.004	0.91
Age, per 10 year	5.25	0.068	4.65	<0.0001				
Race								
White (including Hispanic)	reference				reference		reference	
Black (including Hispanic)	22.23	<0.0001			2.76	0.09	0.09	0.01
Other	4.40	0.46			−1.50	0.46	0.01	0.82
Smoking								
Never					reference			
Former					0.29	0.93		
Current					6.87	0.02		
Drug use (crack, cocaine, heroin, IDU) (%)								
Never							reference	
Previous user							−0.02	0.65
Current user							0.08	0.08
Hormone use, past 6 months (Vs. None)	−6.71	0.04						
Log $_{10}$ FIB-4	25.44	0.0014	−10.86	<0.0001				
HIV status/viral load								
HIV−	reference		reference		reference:		reference	
HIV+, VL ≤ 4000 copies	22.64	<0.0001	−6.21	0.003	0.64	0.84	0.04	0.29
HIV+, VL 4000–55000 copies	36.11	<0.0001	−8.35	<0.0001	2.86	0.39	0.12	0.004
HIV+, VL > 55000 copies	58.95	<0.0001	−0.12	0.96	0.13	0.97	0.17	<0.0001
HIV treatment since last visit								
None			reference					
Mono therapy			4.59	0.01				
Combination therapy			2.61	0.22				
HAART			4.92	0.05				
Body Mass Index,per 5 kg/m^2	4.07	0.002	1.58	0.0007	2.54	0.002		

* Multivariate models are adjusted for WIHS study site, /date of laboratory test(batch effect), HCV, age, race, smoking status, drug use, alcohol use, hormone use, history of diabetes, logFIB-4, HIV status, HIV treatment, history of AIDS defining illness and BMI; HIV status/VL and HCV forced into the model

VL: viral load; HAART: highly active anti-retroviral therapy