

Hepatitis C Virus Load Is Associated with Human Immunodeficiency Virus Type 1 Disease Progression in Hemophiliacs

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Hepatitis C virus (HCV) and human immunodeficiency virus type 1 (HIV-1) coinfection is common in hemophiliacs and injection drug users. To assess the interaction between HCV load and HIV-1 disease progression, we examined 207 HIV-1/HCV-coinfected patients. Patients were followed prospectively for ~7 years, and annual measurements of CD4⁺ cell counts and HCV and HIV-1 loads were obtained. Survival analysis was used to define the independent effects of HCV load on HIV-1 progression. After controlling for CD4⁺ cell count and HIV-1 RNA level, every 10-fold increase in baseline HCV RNA was associated with a relative risk (RR) for clinical progression to acquired immunodeficiency syndrome (AIDS) of 1.66 (95% confidence interval [CI], 1.10–2.51; *P* = .016) and an RR for AIDS-related mortality of 1.54 (95% CI, 1.03–2.30; *P* = .036). These findings emphasize the need for further research regarding the use of HIV-1- and HCV-specific therapy in coinfecting individuals.

Virtually all human immunodeficiency virus type 1 (HIV-1)-infected hemophiliacs have been coinfecting with hepatitis C virus (HCV) [1]. HCV, primarily a parenteral pathogen, has infected most hemophiliacs who have received clotting factor concentrates before the initiation of heat treatment in 1985 and continues to infect injection drug users who are also at risk for HIV-1 infection [2, 3]. Infection by HCV is rarely transient, with viremia persisting in 85% of infected persons [4].

The relationship between HCV RNA and HIV-1 infection has been partially characterized by means of both longitudinal and cross-sectional studies, which have shown an increase in

HCV RNA shortly after HIV-1 seroconversion, with persistently higher levels in HIV-1-coinfecting patients versus HIV-1-uninfected patients [1, 5–8]. In addition, several studies of coinfecting patients have shown an inverse relationship between CD4⁺ cell count and HCV RNA level, which possibly is due to immune deregulation of HCV replication [6–8]. Preliminary studies also suggest that, among HCV-infected hemophiliacs, liver disease is more frequent among HIV-1-infected patients than among HIV-1-uninfected patients [9, 10].

In contrast, the effect of HCV infection on HIV-1 disease progression is not well understood. There are conflicting results from several longitudinal and cross-sectional studies that

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The human subjects committees of the collaborating institutions approved the Hemophilia Growth and Development Study, and informed consent was obtained from all participants or from their parents or legal guardians in compliance with human experimentation guidelines of the US Department of Health and Human Services.

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Table 1. Unadjusted and adjusted effects of HCV RNA level on survival, for HIV-1-infected hemophiliacs.

HCV RNA level	AIDS				AIDS-related death			
	Unadjusted		Adjusted ^a		Unadjusted		Adjusted ^a	
	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
Baseline	2.09 (1.42–3.09)	<.001	1.66 (1.10–2.51)	.016	2.09 (1.48–2.95)	<.001	1.54 (1.03–2.30)	.036
Change from baseline	0.67 (0.41–1.07)	.096	1.07 (0.72–1.60)	.726	0.71 (0.49–1.02)	.062	0.95 (0.68–1.32)	.752

NOTE. Cox proportional hazards models with time-varying covariates were fitted to determine the RR that measures the increase in risk due to a 10-fold increase in HCV RNA level (in copies/milliliter). CI, confidence interval; HCV, hepatitis C virus; HIV-1, human immunodeficiency virus type 1; RR, relative risk.

^a RRs are adjusted for HIV-1 RNA level and CD4⁺ cell count.

showed [11, 12], or failed to verify [2, 13–15], an effect of HCV infection on HIV-1 disease progression. This study examines data from a well-characterized, prospectively followed cohort of HIV-1/HCV-coinfected hemophiliacs, to assess the independent effect of HCV RNA levels on progression to AIDS and AIDS-related mortality.

Patients and Methods

Study population and samples stored. The Hemophilia Growth and Development Study was a multicenter, US study that enrolled from 1989 through 1990 207 HIV-1-infected hemophiliacs who were HCV infected. Enrolled patients were 6–19 years old. Details of recruitment and the characteristics of this cohort have been reported elsewhere [16, 17]. Eligibility for enrollment was based on age (date of birth between September 1970 and September 1982), clotting factor usage, and English fluency (since many of the neuropsychological test instruments were only normed in English). A census was taken at participating centers, with a total of 2105 children and adolescents identified. Of the 481 eligible patients, 333 (69.2%) enrolled. Of those who refused to enroll, most cited the burden of participation as the reason, whereas only 17 (3.5%) refused to enroll because of being too ill. All patients acquired HIV-1 infection from exposure to blood products, in most cases from 1982 to 1983. The racial and ethnic composition of the group was as follows: 72% white, 15% Hispanic, 11% black, and 2% other, which is similar to that of the hemophiliac population in the United States [18]. Loss to vital status follow-up was only 0.48% during the 7 years of follow-up. Although enrolled patients necessarily excluded those who died before enrollment (estimated mean infection period, 7 years), there is little other evidence of bias introduced into the study due to selection or loss to follow-up of cohort participants.

Every six months, an interval patient history was obtained, and a physical examination was performed. Blood samples were taken for lymphocyte subsets and were processed within 24 h for cryopreservation of plasma, serum, and peripheral blood mononuclear cells.

Measurements of HIV-1 and HCV RNA concentrations. Plasma and serum samples that were collected during annual visits were shipped fresh from the clinical sites to the central repository and were stored, within 24 h of collection, at -70°C . Plasma samples were freeze thawed once before HIV-1 RNA measurements were obtained by use of the branched-DNA (bDNA) assay (Quantiplex HIV-1 RNA, version 2.0; Chiron). The studies were performed at Chiron Reference Testing Laboratory (Emeryville,

CA), with assays having a lower limit of quantitation for HIV-1 RNA of 500 copies/mL and a linear distribution of HIV-1 RNA level to concentrations as high as 1.6×10^6 copies/mL (1 copy of HIV-1 RNA is equal to 1 molecule of HIV-1 RNA) [19]. Baseline plasma HIV-1 RNA measurements and validation of the reliability of the specimens for this cohort have been described elsewhere [17]. HCV RNA concentrations were measured in annually stored serum samples that were not previously freeze thawed, by use of bDNA assay 2.0 (Quantiplex HCV RNA; Chiron). The assay has a lower limit of quantitation for HCV RNA of 2.0×10^5 equivalents (copies)/mL and was performed at Mayo Medical Laboratories (Rochester, MN) [8]. Since a subset of individuals clear HCV infection, for the purposes of this study we defined patients with chronic infection as having at least 1 detectable HCV RNA level by the bDNA assay. Only those patients who had consistently undetectable levels of HCV RNA, as determined by the bDNA assay, and who subsequently proved to be negative for HCV RNA, as determined by the highly sensitive COBAS AMPLICOR polymerase chain reaction-based assay (Roche Diagnostic Systems), were considered to have cleared HCV infection [20]. Patients who were defined as having cleared HCV infection were excluded from the analysis, whereas all others were considered to be chronically infected and were included.

Study variables. CD4⁺ cell counts and HIV-1 and HCV RNA levels were measured annually from baseline to 7 years of follow-up. For the current investigation, baseline HIV-1 and HCV RNA levels represent either the study enrollment visit or the first visit for which stored plasma or serum samples were available for virus quantitation. Patients were categorized as having progressed to AIDS if they met the Centers for Disease Control and Prevention (CDC) 1987 surveillance definition [21] or as having an AIDS-related death if they died during the first 7 years of follow-up. Twelve individuals had not met the CDC 1987 AIDS definition at their time of death and thus were considered censored in the AIDS-related mortality analyses at time of death: 4 died of liver failure secondary to hepatitis B and/or C, 4 died of hemorrhage, 1 died of trauma, 1 died of pulmonary hypertension, 1 died of pneumonia, and 1 died of an unknown cause. HIV-1 and HCV RNA levels below the quantitation limit were estimated by use of multiple imputation [22].

Statistical methods. Cox proportional hazards models with time-varying covariates were fitted to examine the effects of HCV RNA on progression to AIDS and on AIDS-related mortality. The unadjusted and adjusted effects of HCV RNA were assessed to examine the effectiveness of predicting survival on the basis of HCV RNA level alone and after accounting for HIV-1 RNA level and

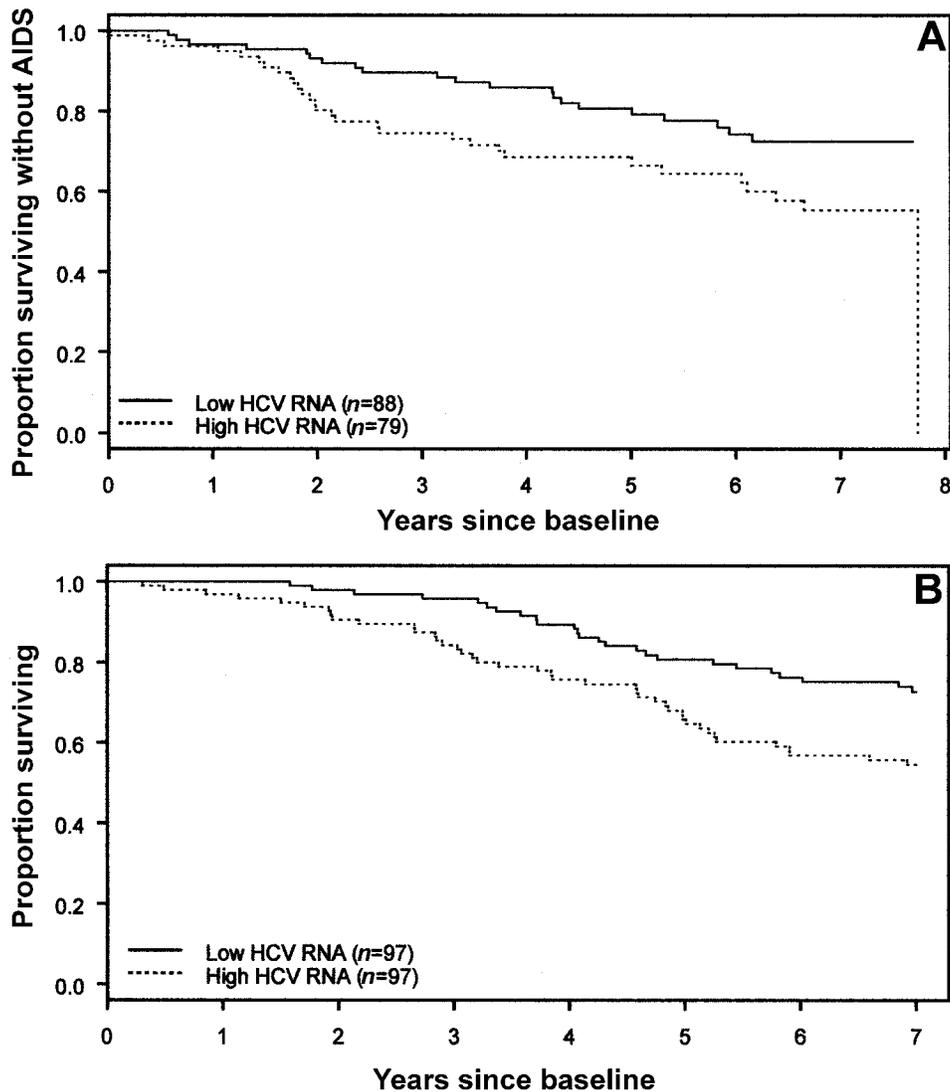


Figure 1. Kaplan-Meier estimates of proportion of patients without progression to clinical AIDS (Centers for Disease Control and Prevention 1987 surveillance definition [21]) (*A*) or of those who had an AIDS-related death (*B*), divided into groups based on whether hepatitis C virus (HCV) RNA levels were above or below the median of 6.7 log₁₀ copies/mL. The no. of patients followed beyond year 7 was very small; the rapid decrease of the high HCV RNA group after year 7 represents progression to AIDS by only 1 patient.

CD4⁺ cell count. In these models, the time-varying measurements of HCV RNA and HIV-1 RNA levels and CD4⁺ cell count were partitioned into baseline and change-from-baseline components, which are useful for examining both the cross-sectional and longitudinal effects, respectively, in a longitudinal study [23].

To further examine the clinical impact of HCV RNA on survival, each patient's sequential measurements were averaged and dichotomized into high or low, using the median value of 6.7 log₁₀ copies/mL. This parameterization addresses whether "average HCV RNA" is of prognostic value for HIV-1 disease progression, and dichotomizing at the median can be useful in contrasting the impact of low versus high virus load [24]. In addition, sequential HIV-1 RNA measurements were averaged and dichotomized into high or low categories on the basis of the median (3.49 log₁₀ copies/mL) and then

were crossed with the high and/or low HCV RNA categories, to examine how the average HCV and HIV-1 RNA combination affects HIV-1 disease progression.

For all of the above-described analyses, HIV-1 and HCV RNA levels were log transformed, whereas CD4⁺ cell counts were square-root transformed to better comply with the assumptions of the models.

Results

At the time of enrollment, mean age was 13.2 ± 3.1 years, median CD4⁺ cell count was 418 cells/μL, median HIV-1 RNA level was 3167 copies/mL, and median HCV RNA level was 4 × 10⁶ copies/mL. Of the 975 samples tested for HCV RNA

Table 2. Effects of average HCV and HIV-1 RNA levels on survival, for HIV-1-infected hemophiliacs.

HIV-1 RNA/ HCV RNA levels	AIDS				AIDS-related death			
	Unadjusted		Adjusted ^a		Unadjusted		Adjusted ^a	
	RR (95% CI)	<i>P</i>	RR (95% CI)	<i>P</i>	RR (95% CI)	<i>P</i>	RR (95% CI)	<i>P</i>
Low/high	8.82 (1.90–40.90)	.005	5.22 (1.10–24.88)	.038	5.57 (1.81–17.07)	.003	1.58 (0.47–5.35)	.462
High/low	19.89 (4.62–85.68)	<.001	5.50 (1.20–25.31)	.029	10.04 (3.44–29.32)	<.001	1.96 (0.59–6.52)	.274
High/high	20.75 (4.85–88.32)	<.001	8.67 (1.96–38.24)	.004	10.63 (3.73–30.26)	<.001	3.07 (0.97–9.69)	.056

NOTE. Each patient's sequential HCV and HIV-1 RNA values were averaged and classified as higher or lower than their respective median values. Cox proportional hazards models then were fitted to address whether those who were in the high HIV-1 RNA and/or high HCV RNA groups have a greater risk for HIV-1 progression vs. those in the low HIV-1 RNA and/or low HCV RNA groups. CI, confidence interval; HCV, hepatitis C virus; HIV-1, human immunodeficiency virus type 1; RR, relative risk.

^a RRs are adjusted for CD4⁺ cell count.

and the 957 tested for HIV-1 RNA, 129 (13%) and 198 (21%), respectively, were below the limit of detection. Of the 207 HIV-1/HCV-coinfected patients, 8 did not meet the criteria for chronic HCV infection and were repeatedly HCV RNA negative by the bDNA assay and by the COBAS assay, and 5 lacked complete data to determine HCV and HIV-1 RNA levels and CD4⁺ cell counts. Therefore, 194 HIV-1-infected individuals with chronic HCV infection and complete covariate data were included in the survival analyses that examined the progression to AIDS-related death. Twenty-four individuals were diagnosed with clinical AIDS before baseline; of these, 3 were not followed clinically after the baseline examination and thus were excluded in the analyses examining the progression to AIDS, but they were included in the analyses examining AIDS-related death. Of the evaluable patients for each clinical outcome, there were 51 (31%) who progressed to AIDS and 67 (35%) who had an AIDS-related death.

Baseline HCV RNA levels were associated significantly with progression to clinical AIDS ($P = .016$) and AIDS-related death ($P = .036$), even after controlling for HIV-1 RNA level and CD4⁺ cell count. In fact, for every 10-fold increase in HCV RNA level, there was a 1.66 increase in the relative risk (RR) for progression to AIDS, as well as a 1.54 increase in the RR for AIDS-related death (table 1). In contrast, the HCV RNA change from baseline was not a significant predictor of HIV-1 clinical progression, even after controlling for HIV-1 RNA level and CD4⁺ cell count.

When each person's sequential HCV RNA values were averaged and classified as high or low, we found that the 50% of the cohort that had average HCV RNA levels higher than the median value had a greater risk for progression to AIDS and AIDS-related death, compared with those who had an average HCV load lower than the median value (figure 1). Moreover, significant differences persisted between the high versus low HCV RNA categories for progression to AIDS (RR, 1.99; 95% confidence interval [CI], 1.12–3.53; $P = .019$) and for AIDS-related death (RR, 1.68; 95% CI, 1.01–2.81; $P = .048$), even after controlling for HIV-1 RNA level and CD4⁺ cell count.

When examining the combined effects of high or low HCV RNA levels and high or low HIV-1 RNA levels, we continued to see that those patients with high HCV RNA levels had a

greater risk of progressing to AIDS and of AIDS-related death, even for those with low HIV-1 RNA levels (table 2 and figure 2). Significant relationships remained even after controlling for CD4⁺ cell count, with the RR for progression to AIDS being higher among those with high HCV RNA levels (RR, 5.22; $P = .038$) or high HIV-1 RNA levels (RR, 5.50; $P = .029$), compared with those who had low levels of both. The RR of progression to AIDS was greatest for those who had high levels of both HIV-1 and HCV RNA (RR, 8.67; $P = .004$; table 2). However, for predicting progression to AIDS-related death, only those who had high levels of both HCV and HIV-1 RNA showed indications of a greater risk. Although all of these analyses used imputed values for HIV-1 and HCV RNA levels below the limits of detection, the same conclusions were obtained when RNA values were substituted with 50% of the lower limit of detection (250 and 100,000 copies/mL for HIV-1 RNA and HCV RNA, respectively; data not shown).

Discussion

In this analysis, we demonstrate for the first time the significant relationship between HCV load and progression to clinical AIDS and AIDS-related mortality, which is independent of HIV-1 RNA load and CD4⁺ cell count. This also was confirmed when we examined the effect of high versus low HCV RNA levels on progression to clinical AIDS and AIDS-related mortality.

Prior studies have had conflicting results regarding the influence of HCV infection on HIV-1 disease progression. Piroth et al. [11] demonstrated in a multivariate analysis of 119 coinfected individuals that clinical progression, broadly defined to include the development of AIDS-defining illnesses, declining Karnofsky index, or a 20% loss of body weight, occurred more frequently in HCV-infected patients, with an RR of 10.9 (95% CI, 1.09–109.3). Similarly, immunologic progression, defined as a 50% decrease in CD4⁺ cell count, had an RR of 2.31 (95% CI, 1.16–4.62) for patients with initial CD4⁺ cell counts >600 cells/ μ L [11]. The same authors recently have reported similar results for progression to AIDS-defining illness after controlling for CD4⁺ cell count [12]. In contrast, other studies have not seen an effect of HCV infection on HIV-1 disease progression [2, 13–15]. Previous studies were smaller [15], retrospective, or

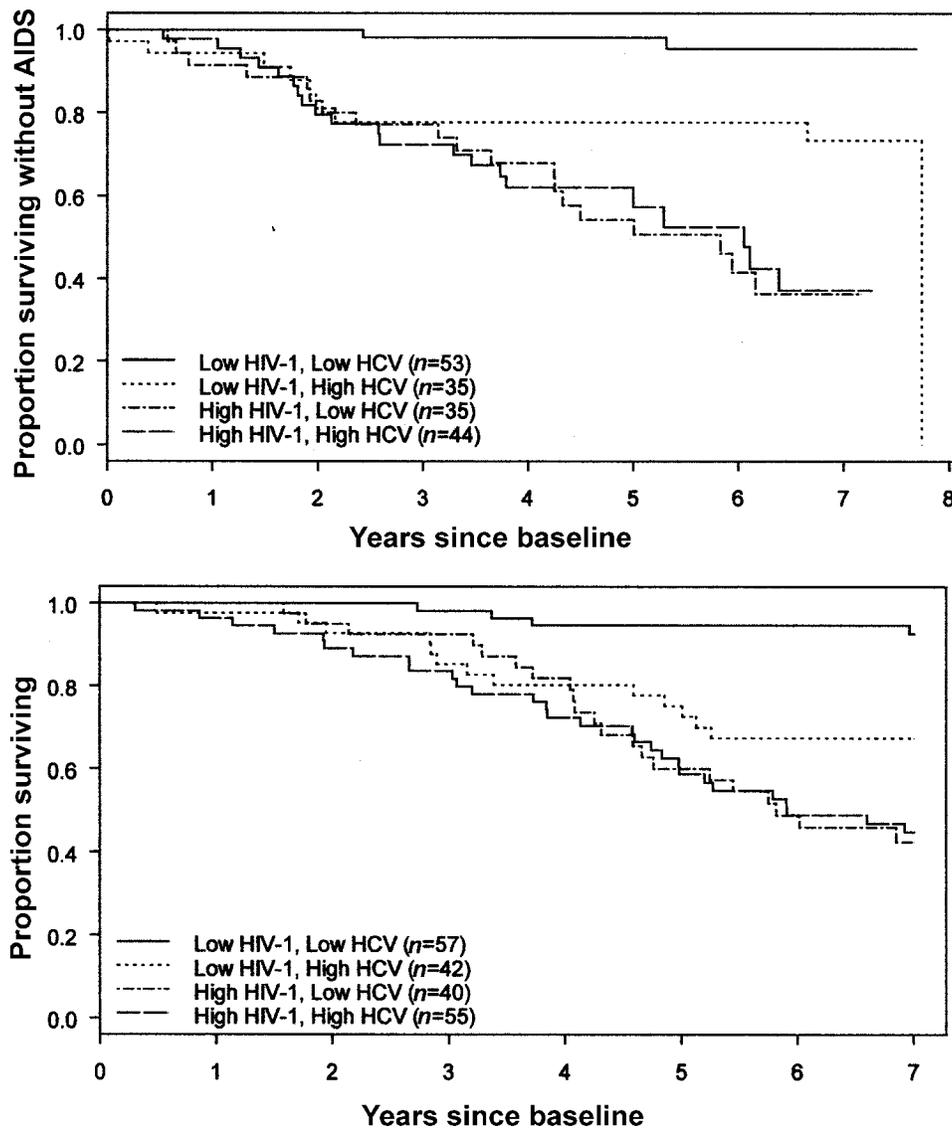


Figure 2. Kaplan-Meier estimates of proportion of patients without progression to clinical AIDS (Centers for Disease Control and Prevention 1987 surveillance definition [21]) (A) or of those who had an AIDS-related death (B), divided into groups based on whether hepatitis C virus (HCV) RNA and human immunodeficiency virus type 1 (HIV-1) RNA levels were above or below the medians of 6.7 and 3.49 log₁₀ copies/mL, respectively. The no. of patients followed beyond year 7 was very small; the rapid decrease of the low HIV-1 RNA/high HCV RNA group after year 7 represents progression to AIDS by only 1 patient.

cross-sectional [13, 14] or had relatively short follow-up [2], compared with that in the present study. Moreover, these studies usually compared HCV-infected and HCV-uninfected individuals, without controlling for other important markers for HIV-1 disease progression, such as HIV-1 load. The present study includes substantially larger numbers of patients, is prospective with 7 years of follow-up, and controls for both CD4⁺ cell count and HIV-1 RNA level. Our analysis also categorizes patients on the basis of HCV and HIV-1 RNA levels, showing that HCV RNA level is associated in an independent manner with HIV-1 clinical progression to AIDS. In fact, the adjusted

RR for progression to AIDS was similar for the high HCV RNA/low HIV-1 RNA and the low HCV RNA/high HIV-1 RNA groups (table 2). Moreover, those in the low HCV RNA/low HIV-1 RNA group appeared to be at very low risk for clinical progression to AIDS, with only 2 (4%) of 53 in this group progressing to AIDS, compared with 26%–54% of those with high levels of HCV RNA, HIV-1 RNA, or both.

The mechanism by which increased HCV RNA levels might enhance HIV-1 clinical progression is not well understood. One possibility is that HCV load is associated with intolerance to antiretrovirals. Although 85% of patients in this cohort were

on antiretroviral therapy during the course of follow-up, only 9 were treated with protease inhibitors during the study period, 5 of whom began treatment <6 months before the final follow-up point. The minimal use of what is considered to be potent antiretroviral therapy makes it less likely that therapy had an impact on the outcomes of our study. In addition, the results of our analysis showed minimal changes after controlling for antiretroviral use as a time-varying covariate, and during the follow-up period there was no difference between groups in the percentage of patients on antiretroviral therapy at each visit (data not shown). Alternative explanations may be related to patient age, duration of HIV-1 infection, or HCV genotype. Age seems to be an unlikely cofactor, since the enrollment age was fairly similar among groups, ranging from 6 to 19 years, and the effect of baseline HCV RNA levels on clinical progression was unchanged when the analysis adjusted for age. Although duration of HCV infection and HCV genotype were not known for this population, these potential cofactors might strengthen the predictive value of HCV RNA levels. However, the relationship between HCV genotype and HCV RNA levels, as well as the effect of HCV genotype on HIV-1 and HCV disease progression, has been conflicting [25–29]. An additional explanation is that higher rates of HCV replication may result in generalized immune activation, which has been shown to be a potent marker for HIV-1 disease progression [30].

There is considerable evidence that cellular immunity is important for controlling HCV infection [31, 32]. The independent effect of HCV RNA levels on disease progression suggests that the control of HCV replication may be a marker for a robust cellular immune response. Such cellular immunity may contribute to long-term control of HIV-1, as well as prevention of select AIDS-defining clinical conditions. This hypothesis is supported by the extraordinarily low risk of progression in the low HCV RNA/low HIV-1 RNA group. An additional explanation for our findings relate to recent studies showing HCV replication in lymphoid tissue [33, 34]. Although not proven, it is conceivable that this could be a mechanism by which HCV infection could influence HIV-1 replication and/or pathogenesis.

This study demonstrates that HCV RNA concentration is independently associated with HIV-1 disease progression. Although these studies do not prove causality, they suggest a possible interaction between these two RNA viruses that often results in chronic infection in coinfecting individuals. Although the implications of these observations are not fully understood and the effect that potent antiretroviral therapy might have on these outcomes is not known, this study does provide a rationale for further research related to the coadministration of HIV-1- and HCV-specific therapy in coinfecting patients. Nevertheless, clinicians must proceed with caution because current therapies have substantial toxicities, as well as potential drug-drug interactions that need to be defined in clinical trials before definitive guidelines regarding concomitant treatment for HIV-1 and HCV can be routinely recommended.

Hemophilia Growth and Development Study

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