Effect of Hepatitis C Virus (HCV) Genotype on HCV and HIV-1 Disease

Thomas W. Yoo,1 Sharyne Donfield,2 Alice Lail,2 Henry S. Lynn,3 and Eric S. Daar,1 for the Hemophilia Growth and Development Study

1Los Angeles Biomedical Research Institute at Harbor–University of California at Los Angeles Medical Center, Divisions of HIV Medicine and Infectious Diseases, Department of Medicine, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles; 2Rho, Chapel Hill, North Carolina; 3The Chinese University of Hong Kong, Department of Community and Family Medicine, Hong Kong, China

(See the editorial commentary by Núñez and Soriano, on pages 1–3.)

The relationship between hepatitis C virus (HCV) genotype and HCV and human immunodeficiency virus (HIV) type 1 disease is not well defined. The present study analyzed data from a cohort of 207 HIV-1–infected and 126 HIV-1–uninfected children and adolescents with hemophilia who enrolled in the Hemophilia Growth and Development Study and were followed for 7 years. The mean HCV RNA level was higher in the participants in the HCV genotype 1 group than in the participants in the HCV non–genotype 1 group, among both the HIV-1–infected (difference, +0.33 log10 copies/mL; P = .038) and HIV-1–uninfected (difference, +0.59 log10 copies/mL; P = .008) participants. Although HCV genotype was not associated with differences in HIV-1 RNA level, a significantly lower mean CD4+ T cell count (difference, –127 cells/μL; P = .026) and percentage of CD4+ T cells (difference, –4.3%; P = .027) were observed in the participants in the HCV genotype 1 group, compared with those in the participants in the HCV non–genotype 1 group. In addition, the participants in the HCV genotype 1 group were at increased risk for progression to AIDS-related mortality (hazard ratio, 2.44; P < .001). The present study suggests that HCV infection and genotype may influence the natural history of HCV and HIV-1 disease.

HIV-1 and hepatitis C virus (HCV) coinfection is common in various at-risk groups [1, 2]. Moreover, coinfected individuals have lower rates of HCV clearance [3, 4], and several studies have shown that HCV RNA levels are higher and that CD4+ T cell counts may be lower in coinfected individuals [4–7]. There is also growing evidence that HCV-related hepatic disease progression is accelerated in the setting of HIV-1 coinfection [8–11]. Although several studies have suggested that HCV infection may adversely influence the clinical progression of HIV-1 disease [4, 6, 12–16], other studies have not [17–24]. These conflicting studies differ in the populations studied, the extent of potent antiretroviral therapy use, the ability to adjust for immunologic and virologic parameters, and the duration of follow-up. In addition, we and others have shown that, in cohorts of coinfected individuals who were followed up long term, HCV RNA levels independently predict the clinical progression of HIV-1 disease [6, 25].

The relationship between HCV genotype and HIV-1 and HCV infection has also been explored. Although HCV genotype is unequivocally an important predictor of response to anti-HCV treatment [26], there have been suggestions that it might also influence HCV RNA levels and even the natural history of HCV and HIV-1 disease [6, 12]. In the present study, we assess the relationship between HCV genotype and (1) HCV RNA levels in HIV-1–uninfected participants with hemophilia and (2) CD4+ T cell counts, HIV-1 RNA levels, HCV RNA levels, and clinical progression of HIV-1 disease in HIV-1/HCV–coinfected participants with hemophilia.
Table 1. Characteristics of HIV-1–infected and –uninfected study participants.

<table>
<thead>
<tr>
<th>Characteristic, parameter</th>
<th>HIV-1 infected (n = 207)</th>
<th>HIV-1 uninfected (n = 126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV RNA positive, no. (%) of total</td>
<td>199 (96.1)</td>
<td>103 (81.8)</td>
</tr>
<tr>
<td>HCV genotype available, no. (%)</td>
<td>181 (91.0)</td>
<td>94 (91.3)</td>
</tr>
<tr>
<td>Genotype, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype 1</td>
<td>152 (84.0)</td>
<td>72 (76.6)</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>7 (3.9)</td>
<td>13 (13.8)</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>14 (7.7)</td>
<td>6 (6.4)</td>
</tr>
<tr>
<td>Genotype 4</td>
<td>8 (4.4)</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>Progression to AIDS, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All genotypes</td>
<td>57 (31.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Genotype 1</td>
<td>45 (79.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Genotypes 2–4</td>
<td>12 (21.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Progression to AIDS-related mortality, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All genotypes</td>
<td>69 (38.1)</td>
<td>NA</td>
</tr>
<tr>
<td>Genotype 1</td>
<td>63 (91.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Genotypes 2–4</td>
<td>6 (8.7)</td>
<td>NA</td>
</tr>
<tr>
<td>AIDS at baseline, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All genotypes</td>
<td>19 (10.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Genotype 1</td>
<td>18 (94.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Genotypes 2–4</td>
<td>1 (5.3)</td>
<td>NA</td>
</tr>
</tbody>
</table>

NOTE. NA, not applicable.

a Percentage values reflect the percentage of the participants positive for HCV RNA. Data are missing because participants tested negative for HCV antibodies (n = 4), samples were not available (n = 4), participants were not HCV viremic (n = 22), or the genotype assay failed (n = 30).
b Percentage values reflect the percentage of the participants for whom genotype data were available (n = 181 for HIV-1 infected; n = 94 for HIV-1 uninfected).
c Percentage values reflect either the percentage of the participants for whom genotype data were available (n = 181) or the percentage of the participants who progressed to AIDS (n = 57).
d Percentage values reflect either the percentage of the participants for whom genotype data were available (n = 181) or the percentage of the participants who progressed to AIDS-related mortality (n = 69).
e Percentage values reflect either the percentage of the participants for whom genotype data were available (n = 181) or the percentage of the participants who received a diagnosis of AIDS before study entry and were censored from the analysis of progression to AIDS (n = 19).

PARTICIPANTS, MATERIALS, AND METHODS

Study population. The Hemophilia Growth and Development Study (HGDS) is a multicenter US study that enrolled a population-based cohort of 6–19-year-old participants with hemophilia during 1989–1990. The cohort included 207 HIV-1–infected participants who were infected with HIV-1 through exposure to blood products (in most cases during 1982–1983) and 126 HIV-1–uninfected participants (the control subjects). Chronic HCV infection was noted in 199 (96.1%) of the HIV-1–infected participants and in 103 (81.8%) of the HIV-1–uninfected participants. Participants were followed for 7 years (up to ~15 years after the time of infection). The details of recruitment and the characteristics of this cohort have been reported elsewhere [27, 28]. The ethnic composition—72% white, 15% Hispanic, 11% black, and 2% of other ethnicity—resembles that of the general hemophilia population in the United States [29]. During the 7 years of follow-up, 2.1% of the cohort was lost to follow-up with respect to vital status. This proportion was lower, 0.48%, in the HIV-1–infected participants. Although the study selected against enrollment of those who died before recruitment, there is little other evidence of introduced selection bias. At baseline and at 6-month intervals thereafter, assessments were made of medical histories, physical examinations were performed, and CD4+ T cell counts were measured in both the HIV-1–infected and –uninfected participants. Blood samples were processed within 24 h, for cryopreservation of cells, plasma, and serum. During the course of follow-up, antiretroviral therapy was prescribed at the discretion of the primary providers. Four of the participants included in the analysis received triple-drug therapy that included protease inhibitors; only 2 received this treatment for >6 months.

The human-subjects committees of the collaborating institutions approved the HGDS. Informed consent was obtained from all parents and legal guardians, and informed consent or assent was obtained from all participants, in compliance with the human-experimentation guidelines of the US Department of Health and Human Services.
Measurement of HIV-1 and HCV RNA levels and assessment of HCV genotype. From stored samples, plasma HIV-1 RNA levels were measured at baseline and annually thereafter at a central laboratory by use of an HIV-1 branched-DNA (bDNA) assay (Versant HIV-1 RNA, version 2.0; threshold of detection, <500 copies/mL; Bayer Diagnostics) [7]. Samples with undetectable levels of virus were retested by use of version 3.0 of the assay (threshold of detection, 50 copies/mL) [30]. From stored samples, plasma HCV RNA levels were measured at baseline and annually thereafter at the Mayo Medical Laboratories (Rochester, MN) in the HIV-1–infected and –uninfected participants by use of an HCV bDNA assay (Versant HCV RNA, version 2.0; threshold of detection, 2.0 \times 10^3 \text{ copies/mL}; Bayer Diagnostics) [7]. Samples with undetectable levels of virus were retested at a central laboratory by use of version 3.0 of the assay (threshold of detection, 3200 copies/mL) [31]. Baseline samples with detectable levels of HCV RNA were submitted for assessment of HCV genotype by use of a line probe assay (LiPA; Bayer Diagnostics) [32]. If a baseline sample was not available, a sample from the closest available time point was selected.

Study variables. The 1987 Centers for Disease Control surveillance definition [33] for AIDS was used to categorize participants. Four HIV-1–uninfected participants were found to be negative for HCV antibodies. Among the remainder of the cohort, HCV genotype data were not available for inclusion in the analysis, either because samples were not available (n = 2), the participants were not HCV viremic (n = 22), or the genotype assay failed (n = 30). Of the 181 HIV-1–infected participants for whom HCV genotype data were available, 19 had progressed to AIDS before baseline and were excluded from the analysis of progression to clinical AIDS (table 1) [33].

Statistical analysis. The difference in the distribution of HCV genotypes between HIV-1–infected and –uninfected participants was compared by use of Pearson’s χ² test. Because genotype 1 (both 1a and 1b) occurs most frequently and has been most clearly associated with differences in response to therapy [26]—and, in some studies, with differences in HCV RNA levels [6, 34–37]—the present study focused on comparing participants infected with genotype 1 with those infected with all other genotypes (2–4). The repeated measurements of HCV RNA levels, HIV-1 RNA levels, and CD4+ T cell counts were based on random coefficient regression models [38]. Each participant’s viral loads and CD4+ T cell counts were modeled through time as a linear function of age, with each participant having a different intercept and slope. In the regression models, the effect of HCV genotype on mean HCV RNA level, HIV-1 RNA level, and CD4+ T cell count at baseline and on the rate of change of HIV-1 RNA level and CD4+ T cell count was examined by use of approximate F tests. In all of the models, HCV and HIV-1 RNA levels were log₁₀ transformed, and absolute CD4+ T cell counts were square-root transformed, to better comply with the assumptions of the models.

Cox proportional-hazards models were used to examine the effect of HCV genotype on progression to clinical AIDS and AIDS-related mortality in the HIV-1/HCV–coinfected participants [33]. Both unadjusted effects and adjusted effects were assessed, to examine the effectiveness of predicting survival on the basis of HCV genotype alone and after adjustment for baseline HIV-1 and HCV RNA levels. Kaplan-Meier curves were also plotted, to provide a graphical comparison of time to progression to clinical AIDS and AIDS-related mortality by HCV genotype.

### Table 2. Relationship between hepatitis C virus (HCV) genotype and HIV-1 RNA level, HCV RNA level, and CD4+ T cell counts and percentages.

<table>
<thead>
<tr>
<th>Group, parameter</th>
<th>HCV genotype 1, mean (95% CI)</th>
<th>HCV non–genotype 1, mean (95% CI)</th>
<th>P²</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV uninfected, b HCV RNA level, log₁₀ copies/mL</td>
<td>5.90 (5.71–6.09)</td>
<td>5.31 (4.92–5.70)</td>
<td>.008</td>
</tr>
<tr>
<td>HIV infected c HCV RNA level, log₁₀ copies/mL</td>
<td>6.60 (6.45–6.74)</td>
<td>6.26 (5.98–6.54)</td>
<td>.038</td>
</tr>
<tr>
<td>HCV</td>
<td>3.42 (3.32–3.52)</td>
<td>3.38 (3.16–3.60)</td>
<td>.710</td>
</tr>
<tr>
<td>CD4+ T cells</td>
<td>CD4+ T cell count, cells/µL d</td>
<td>324 (275–377)</td>
<td>451 (351–563)</td>
</tr>
<tr>
<td>Percentage of CD4+ T cells</td>
<td>19.8 (18.0–21.7)</td>
<td>24.1 (20.8–27.4)</td>
<td>.027</td>
</tr>
</tbody>
</table>

**NOTE.** Shown are mean values at baseline as predicted by the random coefficient model, which modeled HCV RNA level, HIV-1 RNA level, CD4+ T cell count, and percentage of CD4+ T cells through time as a linear function of age. CI, confidence interval.

a By the approximate F test, comparing the mean values at baseline between HCV genotype 1 and HCV non–genotype 1.

b For HIV-1–uninfected participants for whom genotype data were available, n = 94.

c For HIV-1–infected participants for whom genotype data were available, n = 181.

d Estimates of the mean and CIs for CD4+ T cells were obtained by back transforming (i.e., squaring) the original estimates, which were in the square-root scale.
Table 3. Cox proportional-hazards model for progression to clinical AIDS and AIDS-related mortality, for participants infected with hepatitis C virus (HCV) genotype 1 vs. HCV non–genotype 1.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Progression to clinical AIDS (n = 162)†</th>
<th>Progression to AIDS-related mortality (n = 181)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Univariable</td>
<td>0.81 (0.43–1.54)</td>
<td>.524</td>
</tr>
<tr>
<td>Adjusted for HCV RNA level</td>
<td>0.79 (0.41–1.53)</td>
<td>.485</td>
</tr>
<tr>
<td>Adjusted for HIV-1 RNA level</td>
<td>0.76 (0.38–1.50)</td>
<td>.425</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval; HR, hazards ratio.
† Excludes 19 participants who received a diagnosis of AIDS before baseline.

RESULTS

Persistent HCV infection was present in 96.1% of the 207 HIV-1–infected hemophiliacs and in 81.8% and of the 126 HIV-1–uninfected hemophiliacs. Of the 275 participants for whom HCV genotype data were available, a higher percentage of the HIV-1–infected participants were infected with HCV genotype 1, compared with that of the HIV-1–uninfected participants (P = .03) (table 1). The mean baseline HCV RNA level was higher in the participants in the HCV genotype 1 group than in the participants in the HCV non–genotype 1 group, among both the HIV-1–infected and –uninfected participants, with a difference of 0.33 (95% confidence interval [CI], 0.02–0.65; P = .038) and 0.59 (95% CI, 0.16–1.02; P = .008) log_{10} copies/mL, respectively (table 2).

HIV-1 RNA levels and CD4+ T cell counts in the HIV-1/HCV–coinfected participants are summarized in table 2. There was no difference in HIV-1 RNA level at baseline (P = .71) or the rate of change of HIV-1 RNA level (P = .64) between the participants in the HCV genotype 1 and HCV non–genotype 1 groups. In contrast, both absolute CD4+ T cell counts (324 vs. 451 cells/μL; P = .026) and percentages of CD4+ T cells (19.8% vs. 24.1%; P = .027) at baseline were significantly lower in the participants in the HCV genotype 1 group than in the participants in the HCV non–genotype 1 group; however, there was no difference in the rate of change of absolute CD4+ T cell counts (P = .38) or percentages of CD4+ T cells (P = .57) between the participants in these 2 groups. Among the HIV-1–uninfected participants, there was no difference in (1) absolute CD4+ T cell counts (P = .26) and percentages of CD4+ T cells (P = .84) at baseline or (2) the rate of change of absolute CD4+ T cell counts (P = .24) and percentages of CD4+ T cells (P = .70) by genotype group.

The relationship between HCV genotype and progression to clinical AIDS and AIDS-related mortality was examined. Nineteen participants had been diagnosed with AIDS before study entry and were not included in the analysis of progression to AIDS; 18 of them (94.7%) were infected with HCV genotype 1. During the course of the study, AIDS diagnoses were made in an additional 57 individuals. There was no difference in the risk for progression to clinical AIDS by HCV genotype (table 3). In contrast, the risk for progression to AIDS-related mortality during follow-up, which included all study participants, was greater in the participants in the HCV genotype 1 group (41%) than in the participants in the HCV non–genotype 1 group (21%) (P = .03; figure 1). In a univariable analysis, the hazard ratio for progression to AIDS-related mortality in the participants in the HCV genotype 1 group, compared with that in the participants in the HCV non–genotype 1 group, was 2.44 (95% CI, 1.06–5.64; P = .037). After adjustment for age at baseline and either HCV or HIV-1 RNA level, the hazard ratios were 2.26 (P = .060) and 2.24 (P = .063), respectively (table 3).

DISCUSSION

Studies conflict on the issue of how HCV genotype might influence HCV and HIV-1 disease. Congruent with other studies [6, 34–37], the present study showed that HCV RNA levels
were significantly higher in the participants infected with HCV genotype 1, regardless of HIV-1–infection status (table 2). Although some studies have not found this association [39, 40], they tend to have had fewer participants.

The present study also showed that the participants in the HCV genotype 1 group had significantly lower absolute CD4+ T cell counts (difference, −127 cells/µL; \( P = .026 \)) and percentages of CD4+ T cells (difference, −4.3%; \( P = .027 \)) than did the participants in the HCV non–genotype 1 group (table 2). Furthermore, the analyses demonstrated that the participants in the HCV genotype 1 group were at increased risk for progression to AIDS-related mortality, a risk that was only marginally changed when adjustments were made for HIV-1 or HCV RNA levels (figure 1 and table 3). Other studies have suggested that HCV infection may influence the natural history of HIV-1 disease; some studies have reported an adverse effect [6, 12, 14–16], whereas other studies have not [21–24]. The variability of the results of these studies is almost certainly related to differences in the study populations, the type of cohort (e.g., seroprevalent vs. seroincident), duration of follow-up, ability to control for confounding variables (such as HIV-1 RNA level), and whether participants received potent antiretroviral therapy during the course of follow-up [15, 17, 18, 41, 42].

Sabin et al. have observed that individuals infected with HCV genotype 1 are at increased risk for progression to clinical AIDS (\( P = .009 \)) and AIDS-related mortality (\( P = .007 \)) [12]. Although the present study also showed a relationship between HCV genotype and progression to AIDS-related mortality, we did not observe increased progression to clinical AIDS. A possible explanation for the difference between these 2 studies relates to the shorter follow-up in the HGDS—follow-up began, on average, 7 years after the estimated date of HIV-1 seroconversion and included 7 years of follow-up. Our inability to show a difference in progression to clinical AIDS was further influenced by the fact that one-third of the participants in the cohort who developed AIDS had been diagnosed before baseline and, thus, were not included in the survival analysis. Another study, by Piroth et al., did not observe a relationship between HCV genotype and HIV-1 disease progression in a subset of HIV-1/HCV–coinfected subjects [43]; however, the analysis was limited, because it used a historical cohort with relatively small numbers. Furthermore, the duration of follow-up in the study was a median of only 3 years [15, 43].

Although the present study has a well-characterized cohort, the sample size may not be large enough to observe differences in some highly variable measures. Moreover, results from this population of children and adolescents with hemophilia cannot necessarily be extrapolated to other HIV-1/HCV–coinfected groups. The number of participants infected with HCV genotypes other than genotype 1 was too small to permit examination of individual genotypes, requiring that the data be collapsed into 2 groups: genotype 1 versus non–genotype 1. This makes it impossible to exclude a relationship between other genotypes and progression of HIV-1 disease. Because genotypes 1 and 4 are often considered to be poor prognosticators of response to anti-HCV therapy, we did analyze the data grouping genotypes 1 and 4 versus non–genotypes 1 and 4 and saw no difference in the overall results (data not shown). Finally, although participants did receive antiretroviral therapy at the discretion of their primary providers, the effect of therapy on the natural history of HIV-1 disease is likely to have been modest. At baseline, most participants were receiving either no therapy or single nucleoside analogue reverse-transcriptase inhibitors, with not more than 4 participants receiving therapy with protease inhibitors during the course of the study. Moreover, the results of the analyses were unchanged when follow-up for these individuals was censored at the time they initiated protease-inhibitor therapy (data not shown).

The observation in the present study that both the absolute CD4+ T cell count and the percentage of CD4+ T cells were significantly decreased in the participants in the HCV genotype 1 group is a novel finding that will need to be confirmed in other cohorts. To explain these findings, several hypotheses can be considered. We and Herrero-Martinez et al. previously showed that increased HCV RNA levels were associated with increased progression of HIV-1 disease [6, 25]. It is unlikely that the effect of HCV genotype on progression relates to differences in HCV RNA levels, because the relative hazard ratio in the univariable analysis and that after adjustment for HCV RNA level—2.44 and 2.26, respectively—were very similar (table 3). Differential use of antiretrovirals is also unlikely to explain these findings, because more participants in the HCV genotype 1 group than in the HCV non–genotype 1 group were receiving therapy at baseline (37.6% vs. 24.1%). The results of the present study could also reflect a direct effect of HCV on lymphoid tissue, as has been described elsewhere [44]. It is notable that, in the present study, CD4+ T cell counts were not different in the participants infected with HCV only on the basis of HCV RNA levels or HCV genotype. Finally, it is conceivable that HCV infection and HCV genotype may affect the progression of HIV-1 disease by as-yet undefined viral or immunologic mechanisms.

In conclusion, the present study has demonstrated that HCV genotype has an effect on HCV replication in both individuals infected with HCV only and individuals coinfected with HIV-1 and HCV. In addition, the present study has shown that HCV infection may adversely influence the natural history of HIV-1 disease in HIV-1/HCV–coinfected individuals. Additional studies are needed to further define the virologic and/or immunologic mechanisms behind these observations, because such mechanisms may provide valuable insight into how to prioritize the...
timing of HCV treatment in HIV-1/HCV–coinfected individuals [45] and into HIV-1 and HCV immunopathogenesis.

HEMOPHILIA GROWTH AND DEVELOPMENT STUDY

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