Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) Dynamics during HCV Treatment in HCV/HIV Coinfection

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We studied hepatitis C virus (HCV) and human immunodeficiency virus (HIV) dynamics in 10 coinfected subjects in a trial of pegylated interferon-α2a (PEG-IFN) alone or combined with ribavirin (RBV), compared with IFN plus RBV for the treatment of HCV. Five subjects, 4 of whom were treated with PEG-IFN, achieved a sustained virological response, although it was delayed by \( \geq 1 \) week in 3 subjects. The median treatment efficacy in blocking virion production was 99.7% in the PEG-IFN group and 60% with standard IFN. In 2 patients with detectable HIV loads before starting HCV study drugs, we observed a 1-log decrease in HIV RNA load. The estimated HCV virion half-life was longer in the HIV-coinfected subjects, which suggests that coinfection may contribute to a slower clearance of HCV. Although the early viral kinetics of coinfected subjects treated with PEG-IFN or IFN differ from those of singly infected subjects, the treatment response seems unaffected.

Potent antiretroviral therapy (ART) has dramatically reduced AIDS-related complications and deaths [1] and increased the recognition of concomitant comorbidities, such as hepatitis C virus (HCV) infection [2, 3]. Approximately 25% of persons infected with human immunodeficiency virus (HIV) are also infected with HCV, and the prevalence of coinfection can be \( \geq 75\% \) in selected at-risk populations, such as injection drug users and those who have received contaminated blood products [4, 5].

In patients with persistent HCV infection, HIV coinfection, heavy alcohol use, and hepatic steatosis are associated with accelerated and more-severe progression to cirrhosis and related complications [2, 6–10]. In addition to the HIV-mediated effects on liver disease progression, plasma and hepatic HCV RNA levels are higher in coinfected persons than in those infected singly with HCV [11–14]. Preliminary data from trials with interferon (IFN)–α and ribavirin (RBV) combinations have suggested that sustained virological responses are lower in coinfected subjects [15–31].

With pegylated IFN-α (PEG-IFN) and RBV treatment, HCV eradication in singly infected individuals is achieved in up to 63% of patients, but HCV genotype 1, high pretreatment HCV RNA levels, and cirrhosis are associated with significantly lower sustained virological response rates [32–34]. Little is known about the efficacy of PEG-IFN for the treatment of coinfected patients. A large multicentered
study, the AIDS PEGASYS and Ribavirin International Co-Infection Trial (APRICOT), is under way to address this question.

Several studies have characterized HCV viral kinetics during treatment with IFN and have advanced the understanding of possible treatment mechanisms [35–38]. During IFN treatment of HCV infection, HCV RNA decay follows a biphasic curve when IFN-naive patients are treated subcutaneously with high doses of IFN (5, 10, and 15 MIU/day). The first phase of decline is exponential over the first 2 days of therapy, is dose dependent, and is thought to reflect virus clearance, with the free virion half-life of HCV genotype 1 estimated at 2.7 h [35]. The second phase of decline is variable, slower, and inversely correlated with pretreatment HCV load. The slope of the second phase is thought mainly to represent the loss of productively infected hepatocytes [35]. The effects of HIV coinfection on HCV dynamics during IFN treatment are unknown. We hypothesized that, in coinfected patients, HCV RNA decay would be slower than in patients singly infected with HCV. Here we present the results of a substudy of APRICOT that focused on HCV and HIV kinetics during treatment in 10 coinfected subjects.

MATERIALS AND METHODS

**Study population.** Between August 2000 and March 2002, adult participants coinfected with HIV/HCV who entered APRICOT at the University of California, San Diego (UCSD) Antiviral Research Center were eligible for the viral dynamics substudy. APRICOT is an ongoing, partially blinded, international trial of the treatment of HCV in 868 coinfected subjects. Its objective is to compare the efficacy and safety of PEG-IFN (Hoffmann-La Roche) 180 µg subcutaneously once weekly coadministered with oral RBV, 400 mg twice daily (Hoffman-La Roche) or RBV placebo (PLA) with that of standard subcutaneous IFN (Hoffmann-La Roche), 3 MU 3 times weekly, coadministered with oral RBV, 400 mg twice daily for 48 weeks. The Human Research Protection Program of UCSD approved the study protocol, and informed consent was obtained from each subject before inclusion in the study. The human experimentation guidelines of the US Department of Health and Human Services and those of UCSD were followed in the conduct of the clinical research.

Criteria for inclusion in the studies were a positive anti-HCV antibody test, plasma HCV RNA detectable by the Roche Amplicor HCV Monitor Test (version 2.0; >1000 copies/mL or >600 IU/mL), serum alanine aminotransferase (ALT) concentrations above the upper limit of normal, liver biopsy results consistent with chronic HCV infection, no prior history of treatment with IFN, and the detection of HIV-1 antibody or HIV-1 RNA. Subjects were required to be either on stable ART for at least 6 weeks prior to study entry, without changes for the first 8 weeks of the study, or not on ART for at least 8 weeks prior to randomization and a willingness to delay the initiation of ART for at least 6 weeks. Participants who met the inclusion criteria were assigned through central randomization to 1 of 3 study arms. For participants in the viral dynamics substudy, PEG-IFN and IFN injections were administered in the clinic, and RBV or PLA ingestion was directly observed.

**Sampling and clinical evaluations.** Blood for HCV and HIV RNA quantitation was collected before starting HCV treatment on day 0 (D0) and at 6, 8, and 12 h after the first injection, on day 1 (at 24 and 32 h), on day 2 (at 48 h), and on days 3, 4, 7, 9, 11, 14, 21, and 28 and at weeks 12, 24, 36, and 48. The sampling schedule was based on pharmacokinetics with thrice-weekly IFN and weekly PEG-IFN, as described elsewhere [39, 40]. To capture the dynamics of HCV rebound after the completion of the 48 weeks of treatment, blood was collected on days 2, 4, 7, 9, 11, 14, 21, and 28 after stopping HCV study medications. Subsequently, subjects returned for scheduled main study visits and had blood drawn at weeks 60 and 72. ALT levels were measured prior to treatment (D0) and at 7, 14, and 28 days and 6, 8, 12, 18, 24, 36, 48, 52, 60, and 72 weeks of study. Absolute and percentage CD4+ cell counts were measured at screening, baseline, and at 4, 8, 12, 24, 36, 48, 60, and 72 weeks after study entry.

**HCV and HIV RNA quantification.** Blood samples for HCV and HIV quantitation were centrifuged within 1 h of phlebotomy, aliquoted, and stored at −80°C. The concentration of plasma HCV RNA was determined using a quantitative reverse-transcription polymerase chain reaction (RT-PCR) assay (Cobas Amplicor HCV Monitor Test, version 2.0; Roche Molecular Systems), done using methods described elsewhere [11, 41, 42]. The reporting range was 600–850,000 IU/mL, with test kit–specific approximate conversion to 1500–2,125,000 HCV RNA copies/mL. The Cobas Amplicor Analyzer was used to perform the RT-PCR amplification of HCV target RNA and the internal quantitation standard and colorimetric detection (Roche Molecular Systems). The concentration of HIV RNA was determined using a quantitative RT-PCR assay (AMPLICOR HIV-1 Monitor Test; Roche Molecular Systems).

**Histological evaluations** Liver biopsy samples were obtained at baseline (within 15 months of starting HCV study drugs) and after reaching week 72 of the study. Biopsy results were interpreted by a study pathologist experienced in liver diseases who used the Ishak-modified histology activity index score to grade necrosis and inflammation (0–18) and to stage fibrosis/cirrhosis (0–6) [43].

**Mathematical model for the estimation of HCV and HIV kinetics.** We estimated the dynamic parameters of HCV and HIV RNA decay during IFN therapy using a model described by Neumann et al. [35] in which the virus load, $V(t)$, is initially
given by \(0.5(c + d)\), where \(t\) is treatment time, \(\lambda_1\) and \(\lambda_2\) (the eigenvalues) are given by \(0.5(c + \delta + \Theta)\) and \(0.5(c + \delta - \Theta)\), respectively, and \(\Theta = \sqrt{(c - \delta)^2 + 4(1 - e)c\delta}\). The parameter \(c\) is the rate of clearance of free virus, \(\delta\) is the rate of the loss of infected cells, and \(\tau\) corresponds to a possible delay between the administration of therapy and its effect in reducing virus load. This form of \(V(t)\) is valid for \(t > \tau\). For \(t < \tau\), \(V(t) = V_o\). The model assumes that IFN treatment blocks the production of new virus, with an efficacy \(e\), but that it has no effect in blocking de novo infections. The model also assumes that uninfected cells susceptible to infection are present at approximately a constant level during the time of therapy.

Data fitting. We fitted the logarithm of the HCV RNA data obtained during the first 28 days of treatment to the logarithm of the equation above using a standard nonlinear least-squares algorithm, as implemented in the subroutine DNLS1 from the Common Los Alamos Subroutine Library. In some patients, we could only fit the data obtained over the first 3–10 days of treatment, which corresponds to the first phase of decline [35], either because HCV RNA became undetectable very early (S1 and S4) or because the patients only showed a transient early response to treatment that was followed by viral rebound (S3, S7, and S8). (Note that virus levels in S5 also became undetectable but only after week 12.) In these fits of the first phase of the HCV RNA decline, we assumed \(\delta = 0\), as has been done elsewhere [35]. Two patients (S2 and S6) had a late response that could not be fitted with a double exponential model; for these data, we used a single exponential decay (with delay) to calculate the slope and considered it to be representative of \(\delta\), the loss rate of infected cells. For patient S9, we were unable to reliably fit both \(c\) and the initial delay \(\tau\). Thus, for this patient’s data, we fixed the initial delay at the estimated median delay of 0.5 days. Using a bootstrap procedure [44] in which each experiment was simulated 500 times, we also estimated 68% confidence intervals of the parameter estimates (see table 1; these intervals correspond to approximately \(\pm 1\ SE\) in a normal distribution).

Statistical analyses. Median values of continuous variables were compared with the use of nonparametric tests. \(P \leq .05\) in a 2-sided test was considered to indicate statistical significance.

RESULTS

Study participants. Of the 26 subjects who enrolled in APRICOT at our site, 11 declined participation in the viral dynamics substudy because of the extensive time commitment required during the initial week, 5 did not wish to commit to an additional study, and 10 opted to participate. All substudy participants were middle-aged men infected with HCV genotype 1; 5 were white, 3 were black, and 2 were Hispanic. None of 10 identified previous injection drug use as their risk factor for acquiring HCV (table 2). In 9 subjects, HIV-1 infection was well controlled with a stable antiretroviral regimen for a median duration of 2.9 years (range, 1–5 years). The remaining subject (S10) had stopped ART 14 months before enrolling after experiencing virological failure to all 3 available ART classes. Median CD4+ cell counts were 593 cells/mm3 (range, 336–1181 cells/mm3), and, in 8 subjects, plasma HIV RNA was <50 copies/mL prior to HCV treatment (median, 1.7 log10 copies/mL; range, <1.7–4.9 log10 copies/mL). The median plasma HCV RNA level before treatment was 5.6 log10 IU/mL (range, 2.8–6.6 log10 IU/mL). All participants tested negative for hepatitis B surface antigen. Levels of ALT were elevated in all subjects (range, 64–199 IU/L). In pretreatment hepatic biopsy samples, modified Ishak scores for necrosis and inflammation ranged 3–10 on a scale of 18 and, for fibrosis, grade 0–5 on a scale of 6. At baseline, only 1 subject (S4) had a biopsy-proven transition to cirrhosis (table 2).

Clinical course. All subjects completed 72 weeks of observation. Nine subjects received the study medications for the entire 48 weeks, and 1 subject (S2) stopped after 38 weeks because of severe depression that was unresponsive to medication. An increase in plasma HCV RNA levels from 770 log10 IU/mL at week 4 to 70,400 IU/mL at week 36.

Changes in HCV and HIV medications. One hundred five days after starting HCV medications, S1 discontinued ART and held HCV treatment for 1 week because of symptomatic hyperlactatemia. S4 missed HCV study medications between weeks 28 and 34, when he entered a drug rehabilitation program. S9 had his weekly PEG-IFN dosage decreased from 180 to 135 mg at week 2, then to 90 mg during weeks 12–18 because of neutropenia. Thereafter, his PEG-IFN dose was resumed at 135 mg until week 48 of the study. In the remaining 7 subjects, doses of HCV and HIV medications were unchanged throughout the study.

HCV response to treatment. At the end of HCV treatment (week 48), HCV RNA was below the limit of detection of the assay (600 IU/mL) in all 5 subjects who received PEG-IFN (S1, S4, S5, S6, and S9) and in only 1 subject (S10) who received IFN and RBV. The remaining 4 subjects who had been randomized to receive IFN and RBV had detectable plasma HCV RNA levels between 345,000 and 7,970,000 IU/mL. The subject who responded at the end of treatment (S10) was unusual in...
<table>
<thead>
<tr>
<th>Infection, patient</th>
<th>Therapy</th>
<th>Genotype</th>
<th>$V_0^{a}$</th>
<th>$c$/day</th>
<th>$d$/day</th>
<th>$\epsilon$, % efficacy</th>
<th>$\tau$, day</th>
<th>Daily virus production$^b$</th>
<th>$t_{1/2}$</th>
<th>First phase, h</th>
<th>Second phase, day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HCV</strong></td>
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<tr>
<td>S1</td>
<td>PEG ± RBV</td>
<td>1A</td>
<td>2.1 (1.7–2.7)</td>
<td>2.5 (2.2–3.2)</td>
<td>ND</td>
<td>99.6 (99.5–99.8)</td>
<td>1.0 (0.8–1.2)</td>
<td>0.69</td>
<td>6.7</td>
<td>Undetectable</td>
<td></td>
</tr>
<tr>
<td>S2</td>
<td>IFN + RBV</td>
<td>1A</td>
<td>4.6 (4.2–5.0)</td>
<td>NA</td>
<td>0.30 (0.28–0.31)</td>
<td>NA</td>
<td>6.0 (5.3–6.6)</td>
<td>NA</td>
<td>2.3</td>
<td>6.8</td>
<td>NA</td>
</tr>
<tr>
<td>S3</td>
<td>IFN + RBV</td>
<td>1B</td>
<td>38 (30–53)</td>
<td>2.4 (0.8–9.3)</td>
<td>NA</td>
<td>59.5 (49.1–83.3)</td>
<td>0.0 (0.0–0.2)</td>
<td>12</td>
<td>6.8</td>
<td>NA</td>
<td></td>
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<tr>
<td>S4</td>
<td>PEG ± RBV</td>
<td>1A</td>
<td>2.1 (1.8–2.4)</td>
<td>2.4 (2.2–2.7)</td>
<td>ND</td>
<td>99.7 (99.6–99.8)</td>
<td>0.5 (0.4–0.6)</td>
<td>0.68</td>
<td>7.0</td>
<td>Undetectable</td>
<td></td>
</tr>
<tr>
<td>S5</td>
<td>PEG ± RBV</td>
<td>1</td>
<td>3.5 (3.1–3.8)</td>
<td>4.2 (2.1–5.7)</td>
<td>ND</td>
<td>70.2 (63.6–80.5)</td>
<td>0.8 (0.5–1.0)</td>
<td>1.9</td>
<td>3.9</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>S6</td>
<td>PEG ± RBV</td>
<td>1A/1B</td>
<td>5.5 (5.2–5.9)</td>
<td>NA</td>
<td>0.17 (0.15–0.20)</td>
<td>NA</td>
<td>13.6 (12.4–14.5)</td>
<td>NA</td>
<td>4.0</td>
<td>8.3</td>
<td>NA</td>
</tr>
<tr>
<td>S7</td>
<td>IFN + RBV</td>
<td>1B</td>
<td>12 (11–14)</td>
<td>2.0 (0.9–6.8)</td>
<td>NA</td>
<td>56.2 (47.7–73.9)</td>
<td>0.2 (0.0–0.4)</td>
<td>3.3</td>
<td>3.6</td>
<td>1.1</td>
<td></td>
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<tr>
<td>S8</td>
<td>IFN + RBV</td>
<td>1A</td>
<td>23 (20–28)</td>
<td>3.2 (2.7–6.7)</td>
<td>NA</td>
<td>74.1 (65.7–88.1)</td>
<td>0.5 (0.4–0.8)</td>
<td>9.5</td>
<td>5.3</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>S9</td>
<td>PEG ± RBV</td>
<td>1</td>
<td>2.9 (2.3–4.2)</td>
<td>4.7 (2.1–32)</td>
<td>0.63 (0.37–0.78)</td>
<td>76.9 (67.8–91.3)</td>
<td>0.5</td>
<td>1.8</td>
<td>3.6</td>
<td>ND</td>
<td></td>
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<tr>
<td>S10</td>
<td>IFN + RBV</td>
<td>1B</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>5.9</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td></td>
<td></td>
<td>4.6</td>
<td>2.5</td>
<td>0.30</td>
<td>74.1</td>
<td>0.5</td>
<td>1.9</td>
<td>6.7</td>
<td>2.3</td>
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<tr>
<td><strong>Mean</strong></td>
<td></td>
<td></td>
<td>10</td>
<td>3.0</td>
<td>0.36</td>
<td>76.6</td>
<td>2.6</td>
<td>4.3</td>
<td>5.9</td>
<td>2.5</td>
<td></td>
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<tr>
<td><strong>HIV</strong></td>
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<td></td>
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<tr>
<td>S6</td>
<td></td>
<td></td>
<td>0.11 (0.09–0.13)</td>
<td>6.8 (3.5–102)</td>
<td>0.45 (0.30–0.57)</td>
<td>51.8 (42.9–66.7)</td>
<td>0.3 (0.2–0.3)</td>
<td>0.97</td>
<td>2.4</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>S10</td>
<td></td>
<td></td>
<td>6.8 (6.1–8.3)</td>
<td>4.3 (1.6–39)</td>
<td>0.58 (0.28–0.81)</td>
<td>36.1 (28.3–57.1)</td>
<td>0.5 (0.3–1.0)</td>
<td>39</td>
<td>3.9</td>
<td>1.2</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** The 68% confidence interval is shown in parentheses below each fitted estimate. ±, addition unknown; $c$, rate of free virus clearance; IFN, interferon; NA, not applicable; ND, not determined; PEG, pegylated IFN-α2a; RBV, ribavirin; $V_0$, virus load at baseline; $d$, rate of infected cell loss; $\epsilon$, efficacy of therapy in blocking new virus production; $\tau$, delay between the administration of therapy and its effect.

$^a$ Units are $10^5$ IU for HCV and $10^4$ copies for HIV.

$^b$ Units are $10^10$ IU for HCV and $10^10$ copies for HIV.
that his HCV RNA level was 14,200,000 IU/mL at screening and 3 times during the previous year but was below detection at baseline. In this subject, HCV RNA was only detected at 6 and 12 h after the start of study medications (1170 and 775 IU/mL, respectively). At week 72, 4 of 5 participants (S1, S4, S6, and S9) who received PEG-IFN had a sustained virological response (plasma HCV RNA <50 IU/mL), whereas only 1 subject in the IFN and RBV group (S10) had a level below detection. The 5 nonresponders had plasma HCV RNA levels >1,000,000 IU/mL.

**HCV RNA dynamics during HCV treatment.** We used the model of Neumann et al. [35] to fit the decrease in HCV load during treatment. Figure 1A shows the data and model fits for the 3 subjects who had an early virological response (i.e., whose HCV RNA levels went below the limit of detection before week 2 of treatment: S1, S4, and S9). Figure 1B shows the data and the fits for 3 participants who showed a delayed response to treatment (S2, S5, and S6). In subject S2, HCV RNA levels remained at baseline levels until day 7, decreased rapidly to 770 IU/mL between days 7 and 28, and then rebounded to pretreatment levels. Participant S5 showed a response after week 12, showed HCV RNA levels below the limit of detection by week 36, and relapsed 17 days after the completion of PEG-IFN treatment. In S6, who also received PEG-IFN therapy, the HCV load started to decrease only after 21 days of HCV therapy, was below the limit of detection by week 12, and remained undetectable until the end of follow-up (sustained virological response). Figure 1C shows the responses of the remaining subjects. HCV RNA levels decreased slightly and transiently in 2 subjects (S7 and S8) and were unchanged overall in 1 (S3). S10 was excluded from this analysis because his HCV RNA level was below the limit of detection at baseline (figure 1C).

Pretreatment HCV RNA levels, the estimated kinetic param-
eters, and virological outcome are shown in table 1. Subjects with no virological decline had higher HCV RNA levels before treatment than those who had a decrease in HCV plasma virus levels (figure 1) \( (p = 0.05, \text{Mann-Whitney } U \text{ test}) \). In the 7 subjects who had a first phase of decline (S1, S3, S4, S5, S7, S8, and S9), the median estimated clearance rate of HCV was 2.5/day (range, 2.0–4.7/day). The median estimated HCV virology half-life was 6.7 h (range, 3.6–8.3 h). In the few subjects who had a slower phase of decline (see Materials and Methods), the productively infected cell death rate was 0.17–0.63/day, which corresponds to an infected cell half-life range of 1.1–4.0 days. The median total virus production, calculated by multiplying the HCV clearance rate by the pretreatment HCV RNA level and correcting for the extracellular fluid volume (assumed to be 13,360 mL [35]), was 1.9 \( \times 10^{10} \text{ virions/day} \) (range, 6.6–123 \( \times 10^9 \) virions/day). In the 7 subjects who had discernible HCV RNA decay, the median estimated efficacy of treatment in blocking HCV production was 60% (range, 56%–74%; \( n = 3 \)) for the group that received IFN with RBV and 88% (range, 70%–99%; \( n = 4 \)) for the group that received PEG-IFN with RBV or PLA. The efficacy calculation was based on estimating the first phase of HCV RNA decay and did not account for whether treatment resulted in a sustained virological response. The delay in the HCV RNA decline after the administration of the first IFN or PEG-IFN injection was variable, with a median of 0.5 days and a range of 0.0–13.6 days. After an initial transient decline, HCV RNA levels in S6 decreased to below the limit of detection only after 12 weeks of treatment, yet this subject had a sustained virological response. Unlike patients singly infected with HCV who receive daily IFN, only one phase of decline could be discerned in most subjects exhibiting a treatment response.

**ALT response during HCV treatment.** As shown in figure 2, the ALT decline closely paralleled the plasma decrease in HCV RNA in all 6 subjects whose HCV RNA went below or close to the detection limit. Furthermore, ALT levels increased concomitantly with plasma HCV rebound at –12 weeks in S2 (figure 2), S3, and S5 (data not shown).

**HIV RNA dynamics during HCV treatment.** Of the 8 subjects with HIV RNA levels <50 copies/mL when they entered the trial, only 1 (S3) had occasional detectable viremia (<290 copies/mL) during the study, despite no changes in ART. S4 voluntarily interrupted ART and had an early exponential rise in plasma HIV RNA between weeks 46 and 52 of the study. During the first 14 days, his HIV load increased from 84 to 31,000 copies/mL, which corresponds to a doubling time of 3.5 days. In 2 participants, S6 and S10, HIV RNA was detectable at baseline. Plasma HIV RNA was 1007 copies/mL in S6, and it decreased to below the limit of detection of the assay by day 9, with occasional blips until the end of follow-up. In S10, who was not receiving ART, HIV RNA decreased from 72,700 to

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**Table 2. Baseline characteristics of the study subjects.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SE</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>44 ± 2</td>
<td>44</td>
<td>34–55</td>
</tr>
<tr>
<td>History of IVDU, %</td>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receiving ART, %</td>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time on ART, years</td>
<td>3.1 ± 0.5</td>
<td>2.9</td>
<td>1–5</td>
</tr>
<tr>
<td>CD4+ cell count, cells/mL</td>
<td>597 ± 78</td>
<td>593</td>
<td>336–1181</td>
</tr>
<tr>
<td>CD4+ cells, %</td>
<td>28.6 ± 3.2</td>
<td>27.5</td>
<td>15–50</td>
</tr>
<tr>
<td>HIV RNA, log_{10} copies/mL</td>
<td>2.1 ± 0.3</td>
<td>&lt;1.7</td>
<td>&lt;1.7–4.9</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/mL, %</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA, log_{10} IU/mL</td>
<td>5.5 ± 0.3</td>
<td>5.6</td>
<td>2.8–6.6</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>122 ± 17</td>
<td>111</td>
<td>64–199</td>
</tr>
<tr>
<td>Necroinflammatory score (0–18)</td>
<td>5.8 ± 0.7</td>
<td>5.0</td>
<td>3–10</td>
</tr>
<tr>
<td>Fibrosis score (0–6)</td>
<td>1.9 ± 0.5</td>
<td>2.0</td>
<td>0–5</td>
</tr>
</tbody>
</table>

**NOTE.** ALT, alanine aminotransferase; ART, antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IVDU, intravenous drug use.
Figure 1. Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) RNA decrease in subjects who responded to treatment early (A), subjects who had a delayed response to treatment (B), and subjects who did not have a HCV response to treatment (C) (note the different Y-axes). Black circles, HCV RNA measurements; black squares, HIV RNA measurements; solid thick line, best fit of the model (see Materials and Methods); thin horizontal line, limit of HCV RNA detection (600 IU/mL).
9100 copies/mL on day 9, then gradually increased during the ensuing weeks to 52,000 copies/mL at week 48 and remained elevated through week 72. Because the early decrease in HIV RNA in S6 and S10 may have been due to an antiretroviral effect of IFN, we applied the model used to analyze HCV kinetics to the decay of HIV RNA (table 1). The average half-life of HIV in plasma was estimated at 3.2 h, and the mean efficacy of IFN at stopping HIV production was 44%. These results are only indicative, because they represent 2 subjects.

**Changes in CD4+ cell counts during IFN therapy.** Absolute CD4+ cell counts decreased from a median of 187 cells/mm³ at baseline to week 48 ($P = .008$) and then increased a median of 107 cells/mm³ by week 72 (not significant) (figure 3). However, the percentage of lymphocytes that were CD3+/CD4+ remained approximately constant.

**DISCUSSION**

In the present study, we characterized the kinetics of plasma HCV RNA load decay in 10 HIV/HCV genotype 1 coinfected subjects who were receiving either weekly PEG-IFN, with or without RBV, or IFN plus RBV 3 times weekly. All 5 subjects who received PEG-IFN had HCV RNA levels below the limit of detection at the end of treatment, whereas 4 of 5 subjects who received IFN had virological failure. Although the sample size is small, these data suggest that, even in coinfection, the improved pharma-
of PEG-IFN, with or without RBV, results in a higher proportion of virological responses. This is probably attributable to the enhanced antiviral pressure of IFN \( \alpha \)-2a that is afforded by pegylation. This observation is supported by the higher efficacy of PEG-IFN in blocking the production of virions from infected cells (median \( \epsilon \), 99.7% and 60.3%, respectively, for PEG-IFN and IFN). In addition, because the estimated mean HCV virion half-life of 7 h in our cohort was longer than the 2.7 h reported elsewhere in patients infected with HCV genotype 1 alone [35], it is possible that HCV RNA decay is slower in coinfectected subjects.

Unexpectedly, 3 of the patients who responded to HCV therapy, S2, who received IFN plus RBV, and S5 and S6, who received PEG-IFN, had large delays, ranging from 6 days to \( \geq \)12 weeks, before we observed any decline in HCV load. Because the clinic personnel administered the IFN injections, problems of adherence can be excluded. Lower levels of systemic IFN due to decreased or variable absorption of the compounds and a longer time to reach steady-state IFN levels may account for this delayed response. However, this cannot be ascertained, because pharmacokinetic measurements of IFN and RBV were not obtained. Alternatively, for unknown reasons, this delay may be a specific outcome of HCV treatment in patients who are coinfectected with HIV. Of interest, despite the delays, both S5 and S6 had a sustained virological response.

Except for S9, we also did not observe the usual biphasic decline in HCV RNA after starting therapy. There may be 3 reasons for this observation. First, as previously discussed, 3 subjects (S2, S5, and S6) had a delayed response to treatment. When the virological response occurred, blood sampling was less frequent, and the first-phase decline may have been missed. Second, the second phase of HCV decay may not have been observable in 2 subjects (S1 and S4) whose HCV RNA levels dropped very rapidly, within 5 days, below the limit of detection (600 IU/mL). Third, although other studies have documented biphasic declines in HIV/HCV-coinfected patients [45] (A. H. Talal, M. T. Shata, G. Dorante et al., unpublished data), HIV coinfection may intrinsically affect the HCV kinetic responses to an IFN-based regimen. It is possible that the burden of simultaneously having to clear both HIV and HCV could slow the first phase and that the HIV-induced blunting of HCV-specific immune responses could result in a reduced clearance of HCV-infected cells, with a longer second phase of HCV RNA decline. This deficiency in cellular immunity may also be responsible for the higher pretreatment HCV RNA levels typically seen in HIV coinfection [46]. Indeed, a sustained virological response in our cohort was associated with lower pretreatment plasma HCV RNA levels. We also observed that the ALT decrease paralleled the plasma HCV RNA decay in all subjects who responded to HCV therapy and rebounded if HCV RNA levels increased. If this observation is confirmed in larger studies, then a more frequent determination of ALT levels may be an inexpensive alternative to monitoring plasma HCV RNA levels.

Our results also have important implications for HIV treatment in coinfectected patients. In the 2 individuals (S6 and S10) who had detectable HIV loads at baseline, we observed a decay of \( \sim \)1 log in plasma HIV RNA levels at the start of therapy, which suggests that IFN can also block HIV production [47]. We could fit this early decrease to the data (figure 1), and we calculated that IFN efficacy in blocking HIV production was 52% and 35%, respectively, in these 2 patients. The estimated half-life for HIV was \( \sim \)3 h, \( \sim \)3 times that measured by plasma apheresis in coinfected patients. In addition to the partial inhibition of HIV replication, IFN-based therapies resulted in a decrease in absolute CD4+ cell counts that slowly returned to pretreatment levels after the completion of HCV therapy. Because the percentage of CD4+ cells was not affected, this decrease probably reflects the antiproliferative effects of IFN therapy on leukocyte production in the bone marrow.

To our knowledge, this is the first report on HIV/HCV dynamics with PEG-IFN treatment. Although small, our data set may be helpful in designing new studies and individualized patient regimens. For instance, the finding of a delayed response in our small cohort may suggest exploring whether treating patients with HIV and HCV genotype 1 coinfection for longer periods of time results in higher sustained virological responses. Moreover, the high HCV burden seen in HIV/HCV coinfected patients supports the rationale of evaluating whether higher induction doses of IFN during the first few weeks of treatment would result in higher sustained virological responses [36, 48].

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