Response-Guided Therapy for Chronic Hepatitis C Virus Infection in Patients Coinfected with HIV: A Pilot Trial

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Background. To study the feasibility of a response-guided therapy for chronic hepatitis C virus (HCV) infection in patients coinfected with human immunodeficiency virus (HIV) in a tertiary care hospital.

Methods. Treatment duration was individualized on the basis of week 4 and week 12 virologic response. Sixty patients were enrolled and received pegylated interferon alfa-2b (1.5 μg/kg per week) plus weight-based ribavirin (800–1400 mg/day). Patients who achieved a rapid virologic response, defined as viral load <50 IU/mL at treatment week 4, completed 24 weeks of therapy. Patients who did not achieve a rapid virologic response were reassessed at treatment week 12. Patients with a complete early virologic response, defined as an HCV RNA level <600 IU/mL, were treated for 48 weeks. Patients with a partial response, defined as a decrease in the viral load ≥2 log10 and an HCV RNA level ≥600 IU/mL, who attained an undetectable viral load at week 24 were treated for 60 weeks. The primary efficacy end point was sustained virologic response, defined as HCV RNA <50 IU/mL, 24 weeks after the end of treatment.

Results. Overall, 33 (55%) of 60 patients achieved a sustained virologic response: 11 (44%) of 25 patients with HCV genotype 1, 3 (27%) of 11 patients with genotype 4, and 19 (79%) of 24 patients with genotype 3. One-third of patients showed a rapid virologic response. Of patients with genotype 1, there was a rapid virologic response in 4 (16%) of 25; with genotype 4, in 1 (9%) of 11; and with genotype 3, in 14 (58%) of 24. Of the 19 patients with a rapid virologic response, 17 (89.5%) eradicated the virus after 24 weeks of therapy. The rate of sustained virologic response was significantly higher among patients with genotype 3 and low pretreatment HCV RNA levels. A high relapse rate (46%) after 48 weeks of therapy occurred among patients infected with genotypes 1 or 4 who first achieved undetectable viral load at treatment week 12.

Conclusion. A response-guided therapy is feasible and may be useful to optimize the individual outcome of HCV treatment in patients coinfected with HIV.

Pegylated IFN and ribavirin is the standard of treatment for chronic hepatitis C virus (HCV) infection both in patients monoinfected with HCV [1, 2] and in patients coinfected with HIV [3, 4]. Treatment duration for HCV mono-infection is based on HCV genotype: 24 weeks is recommended for genotypes 2 or 3 and 48 weeks for genotypes 1 or 4 [1, 2].

Virologic response kinetics has emerged as the best prognostic factor of treatment outcome. A lack of early viral response (EVR) at treatment week 12, defined as HCV RNA reduction <2 log compared with baseline, identifies a subset of both patients monoinfected with HCV [5] and patients coinfected with HIV [6] who have a very low probability of viral eradication. Early detection of virologic failure helps to reduce additional cost and the adverse effects of an ineffective therapy. Moreover, among patients monoinfected with HCV, time to achievement of an undetectable viral load is the best predictor of sustained virologic response (SVR) [5, 7] and can be used as a guide to individualize treatment duration. Patients who show a rapid virologic response (RVR) may be able to shorten therapy to a duration...
of 12–16 weeks, for patients with genotypes 2 or 3 [8–11], or to a duration of 24 weeks, for patients with genotypes 1 or 4 [7, 12, 13]. Conversely, other difficult-to-treat patients who clear the virus later than treatment week 12 may benefit from extending treatment duration from 48 to 72 weeks [14–16].

A fixed course of 48 weeks, irrespective of genotype, has been recommended to optimize HCV treatment in HIV-coinfected patients who achieve an EVR [3, 4]. However, the optimal treatment duration across different genotypes in this population remains to be elucidated, and the individual outcome could be improved by tailoring treatment duration according to the time to undetectable viral load. Previous reports consistently showed that SVR rates are very high among coinfected patients who achieve an RVR [17–21].

In a randomized trial conducted in our hospital, SVR rates were very high among patients coinfected with HIV who achieved an RVR, even in those assigned to standard IFN plus ribavirin [22]. Furthermore, the risk of viral relapse was very low among patients infected with genotype 3 who showed an RVR, after completion of 24 weeks of therapy [22, 23]. Taken together, these data encouraged us to conduct an exploratory trial to study the feasibility of a response-guided therapy for chronic HCV infection in patients coinfected with HIV, individualizing the duration of treatment according to the virologic response attained at weeks 4, 12, and 24 of treatment.

**METHODS**

**Patient selection.** Eligible patients were adults with untreated HCV infection who had detectable HCV RNA and alanine aminotransferase levels (>44 IU/L in men and >34 IU/L in women); patients were required to have a CD4+ T cell count ≥200 cells/mm^3^ and an HIV RNA level <50 copies/mL for patients who were receiving HAART or <10,000 copies/mL for HAART-naïve patients. Exclusion criteria were the following: decompensated cirrhosis; active injection drug use or alcohol dependence (self-reported intake, ≥60 g/day); pregnancy or breast-feeding; an opportunistic infection within the previous 6 months; serum creatinine level ≥1.5 times the upper normal limit; hemoglobin concentration, <11 g/dL in women or <12 g/dL in men; neutrophil count, <1500 cells/mm^3^; platelet count, <70,000 platelets/mm^3^; a major psychiatric illness; seizure disorders; or active autoimmune disease.

**Study design.** This open-label, investigator-promoted study was conducted in a single tertiary hospital in Barcelona, Spain. All patients received pegylated IFN-alfa-2b, 1.5 μg/kg per week (PegIntron; Schering-Plough), and weight-based ribavirin, according to the following patient weights: <65 kg, 800 mg/day; 65–84 kg, 1000 mg/day; 85–104, 1200 mg/day; and ≥105 kg, 1400 mg/day (Rebetol; Schering-Plough).

Treatment duration was individualized on the basis of a qualitative HCV RNA analysis (detection limit, 50 IU/mL) at week 4 of treatment and a quantitative analysis (detection limit, 600 IU/mL) at treatment week 12 (figure 1). Patients who achieved an RVR completed 24 weeks of therapy. Those who did not achieve an RVR were reassessed at treatment week 12. Patients with a complete EVR, defined as an HCV RNA level <600 IU/mL, were treated for 48 weeks. Those with a partial EVR, defined as a decrease in the viral load ≥2 log_{10}, but with an HCV RNA level ≥600 IU/mL at treatment week 12, completed 60 weeks of therapy, provided that the HCV RNA level was <50 IU/mL at treatment week 24. Patients showing a null virologic response, defined as a decrease in the HCV RNA level <2 log_{10} after 12 weeks of treatment or detectable viral load at week 24, were considered nonresponders and discontinued therapy. All patients were followed up for 24 weeks after the end of therapy (figure 1).

The Institutional Review Board approved the protocol, and all participants provided written informed consent. The study followed the Helsinki Declaration and Good Clinical Practices guidelines.

**Assessment of safety.** Safety was assessed by laboratory tests and evaluation of adverse events at weeks 1, 2, 4, and 8 then monthly thereafter during treatment and at weeks 8 and 24 after therapy discontinuation. Serum HCV and HIV RNA levels and CD4 cell counts were determined at baseline; at weeks 4, 8, 12, 24, 48, and 60 during treatment; and at 8 weeks and 24 weeks after treatment end. Any life-threatening adverse event or progression to AIDS prompted treatment withdrawal. Stepwise reduction of the ribavirin dosage to 200 mg/day and reductions of the pegylated IFN dose to 1.0, 0.75, and 0.5 μg/kg were permitted to manage adverse events or laboratory abnormalities. The use of hemopoietic growth factors was authorized for the management of significant hematological toxicity.

**HCV RNA analysis and efficacy assessment.** The primary efficacy end point was to achieve SVR, defined as an HCV RNA level <50 IU/mL 24 weeks after the end of treatment. Secondary end points were to study the variables associated with RVR and SVR and to investigate the utility of week 4 and week 12 virologic response to predict treatment outcome.

HCV RNA levels were assessed at baseline and at treatment week 12 by a quantitative PCR assay (COBAS AmpliCord HCV Monitor Test, version 2.0; limit of detection, 600 IU/mL). A qualitative PCR assay (COBAS AmpliCord HCV Test, version 2.0; limit of detection, 50 IU/mL) was used to analyze the HCV RNA level at weeks 4, 24, 48, and 60 during treatment and at weeks 8 and 24 of follow up.

To study whether the sensitivity of the assay used to assess the virologic response at treatment week 12 (EVR) had any impact on long-term outcome, a real time PCR assay (COBAS Ampliprep–COBAS-TaqMan 48; limit of detection, 15 IU/mL) was used to retest treatment week 12 cryopreserved serum sam-
Figure 1. Flow diagram of patients’ disposition through the study. HCV, hepatitis C virus; RVR, rapid viral response (undetectable HCV load [<50 IU/mL] at week 4). *Undetectable HCV RNA level (<600 IU/mL) at treatment week 12. #HCV RNA reduction ≥2 log10 from baseline, but HCV RNA still detectable (>600 IU/mL) at treatment week 12. †HCV RNA reduction <2 log10 from baseline at treatment week 12.

Variables with a P value <.1 were included in a backward step multivariate model to identify independent predictors of treatment outcome.

RESULTS

Sixty patients coinfected with HCV and HIV were recruited from January 2005 through December 2006 and received at least 1 treatment dose.

Patient characteristics. Table 1 summarizes baseline char-
Table 1. Demographic and clinical baseline characteristics of patients coinfected with hepatitis C virus and HIV, overall and according to virological response at weeks 4 and 12 of treatment.

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 60)</th>
<th>RVR (n = 19)</th>
<th>EVR (n = 27)</th>
<th>Null EVR (n = 14)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>47 (78.3)</td>
<td>15 (78.9)</td>
<td>22 (81.5)</td>
<td>10 (71.4)</td>
<td>.478</td>
</tr>
<tr>
<td>Age, years</td>
<td>42.0 (39.3–44.5)</td>
<td>42.1 (38.1–45.2)</td>
<td>41.0 (39.1–44.2)</td>
<td>42.7 (40.1–45.6)</td>
<td>.319</td>
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<tr>
<td>Weight, kg</td>
<td>68 (59–74.7)</td>
<td>69.5 (58–76)</td>
<td>67.6 (61.5–72.6)</td>
<td>59.1 (55.1–79.0)</td>
<td>.159</td>
</tr>
<tr>
<td>Prior injection drug use</td>
<td>52 (88.7)</td>
<td>16 (84.2)</td>
<td>23 (85.2)</td>
<td>13 (92.9)</td>
<td>.667</td>
</tr>
<tr>
<td>HAART</td>
<td>47 (78.3)</td>
<td>17 (89.5)</td>
<td>20 (74.1)</td>
<td>10 (71.4)</td>
<td>.355</td>
</tr>
<tr>
<td>2 NRTIs plus 1 NNRTI</td>
<td>27 (45)</td>
<td>10 (52.6)</td>
<td>11 (40.7)</td>
<td>6 (42.9)</td>
<td></td>
</tr>
<tr>
<td>2 NRTIs plus 1 PI</td>
<td>13 (21.7)</td>
<td>4 (21.1)</td>
<td>5 (18.5)</td>
<td>4 (26.8)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7 (11.7)</td>
<td>3 (15.8)</td>
<td>4 (15.8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Abacavir-based HAART</td>
<td>17 (28.3)</td>
<td>4 (21.1)</td>
<td>9 (33.3)</td>
<td>4 (26.8)</td>
<td>.661</td>
</tr>
<tr>
<td>HIV RNA level &lt;50 copies/mL</td>
<td>46 (76.7)</td>
<td>17 (89.5)</td>
<td>18 (66.7)</td>
<td>11 (78.8)</td>
<td>.847</td>
</tr>
<tr>
<td>CD4+ cell count, cells/mm³</td>
<td>521 (415–673)</td>
<td>518 (397–825)</td>
<td>519 (378–665)</td>
<td>578 (496–671)</td>
<td>.282</td>
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<tr>
<td>HCV genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype 1</td>
<td>25 (42)</td>
<td>4 (21)</td>
<td>14 (51.9)</td>
<td>7 (50)</td>
<td>.004</td>
</tr>
<tr>
<td>Genotype 4</td>
<td>11 (18)</td>
<td>1 (5.3)</td>
<td>4 (14.8)</td>
<td>6 (42.9)</td>
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<tr>
<td>Genotype 3</td>
<td>24 (40)</td>
<td>14 (73.7)</td>
<td>9 (33.3)</td>
<td>1 (7.1)</td>
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<tr>
<td>HCV RNA, log₁₀ IU/mL</td>
<td>6.4 (5.9–7)</td>
<td>6.0 (5.3–6.6)</td>
<td>6.5 (6.0–7.2)</td>
<td>6.6 (6.4–7.1)</td>
<td>.112</td>
</tr>
<tr>
<td>HCV RNA level &lt;800,000 IU/mL</td>
<td>13 (21.7)</td>
<td>8 (42.1)</td>
<td>5 (18.5)</td>
<td>0</td>
<td>.227</td>
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<tr>
<td>ALT level, IU per L</td>
<td>75 (52.2–122)</td>
<td>82 (47–168)</td>
<td>84 (66–114)</td>
<td>64 (51.5–110)</td>
<td>.064</td>
</tr>
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<td>Pegylated IFN dosage, mg/kg per week</td>
<td>1.45 (1.36–1.53)</td>
<td>1.48 (1.42–1.54)</td>
<td>1.40 (1.32–1.51)</td>
<td>1.46 (1.41–1.54)</td>
<td>.350</td>
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<tr>
<td>Dose reduction</td>
<td>25 (41.7)</td>
<td>6 (31.6)</td>
<td>16 (59.3)</td>
<td>3 (21.4)</td>
<td>.181</td>
</tr>
<tr>
<td>Ribavirin dose, mg per kg per day</td>
<td>14.2 (13.2–15.2)</td>
<td>13.6 (12.5–14.6)</td>
<td>14.4 (13.5–15.6)</td>
<td>14.5 (13.8–15.4)</td>
<td>.290</td>
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<td>Liver fibrosis Ishak score, b proportion (% of patients with liver fibrosis)</td>
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<td></td>
<td></td>
<td></td>
<td>.406</td>
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<tr>
<td>Any score</td>
<td>50/50 (100)</td>
<td>12/12 (100)</td>
<td>25/25 (100)</td>
<td>13/13 (100)</td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>9/90 (18)</td>
<td>3/12 (25)</td>
<td>4/25 (16)</td>
<td>2/13 (15.4)</td>
<td></td>
</tr>
<tr>
<td>2–4</td>
<td>19/50 (38)</td>
<td>5/12 (41.7)</td>
<td>10/25 (40)</td>
<td>4/13 (30.8)</td>
<td></td>
</tr>
<tr>
<td>5–6</td>
<td>22/50 (44)</td>
<td>4/12 (33.3)</td>
<td>11/25 (44)</td>
<td>7/13 (53.8)</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients or median value (range), unless otherwise indicated. ALT, alanine aminotransferase; EVR, early virologic response (HCV RNA reduction ≥2 log₁₀ at week 12); null EVR, null early virologic response (HCV RNA reduction ≥2 log₁₀ at week 12); NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; RVR, rapid virologic response (undetectable HCV load [<50 IU/mL] at week 4).

* Between patients achieving an RVR or an EVR and those with a null response.

b Liver fibrosis was evaluated according to the Ishak modified histological activity index scoring system. Fifty patients underwent percutaneous biopsy, a median of 3.1 months (interquartile range, 1.2–4.6 months) before starting therapy.

Characteristics of patients. Most patients were men (47 [78.3%]), former injection drug users (52 [86.7%]), and recipients of HAART according to current guidelines. Patients who attained a viral response during the first 12 weeks of therapy (an RVR or an EVR) differed significantly from null responders with regard to HCV genotype (P = .004; table 1).

**Virologic response.** Overall, 40 (66.7%) of 60 participants achieved an end-of-therapy response. Of these 40 patients, 7 (17.5%) experienced relapse during follow up; and of the 60 participants overall, 33 (55%) achieved an SVR (figure 2A). The SVR rate by genotype of patients was as follows: genotype 1, 44% (11 of 25 patients); genotype 4, 27.3% (3 of 11 patients); and genotype 3, 79.2% (19 of 24 patients) (figure 2A).

**Treatment outcome according to week 4 virologic response.** Nineteen patients (31.7%) showed an RVR and completed 24 weeks of therapy. By genotype, 14 (58.3%) of 24 patients with genotype 3, 4 (16%) of 25 patients with genotype 1, and 1 (9.1%) of 11 patients with genotype 4 were rapid responders. Among the rapid responders, all 5 patients with genotypes 1 or 4 (including 1 patient who discontinued treatment at week 16 because of anemia) eradicated the virus, and 12 (85.7%) of the 14 patients with genotype 3 eradicated the virus. Of the 13 patients with genotype 3 and an RVR who remained with no detectable viral load at the end of 24-week therapy, only 1 (7.7%) relapsed (figure 2B). The probability that a patient attaining an RVR eventually eradicated HCV infection was 89.5% (figure 2B).

**Treatment outcome according to week 12 virologic response.** Forty-one patients (68.3%) did not achieve an RVR and were evaluated at treatment week 12. Of the 41 patients evaluated at week 12, 24 (40%) of all 60 participants obtained a complete EVR and continued treatment until week 48. The SVR rate among them was 58.3%, representing 5 (45.5%) of the 11 patients with genotype 1; 2 (50%) of the 4 patients with genotype 4; and 7 (77.8%) of the 9 patients with genotype 3 (figure 2C). A high relapse rate (46.2% [6 of 13 patients]) was observed.
among the subset of patients with genotypes 1 or 4 who cleared the virus between week 4 and 12 of treatment and who completed 48 weeks of therapy. Cryopreserved serum samples recovered at treatment week 12 were available for 11 of these 13 patients and were retested by COBAS-TaqMan (detection limit, 15 IU/mL). Residual viremia was detected in 3 serum samples, and all 3 of the corresponding patients experienced relapse. Conversely, only 1 of 8 patients with no detectable viral load, as determined by this ultrasensitive test, experienced relapse (relative risk, 8.0; 95% CI, 1.3–50.0).

Finally, 3 (12%) of the 25 patients with genotype 1 showed a partial EVR, cleared the virus between treatment week 12 and 24, and completed 60 weeks of therapy. Of these 3 patients, 1 experienced virologic failure at treatment end and 2 eradicated the virus.

**Predictors of RVR and SVR.** Overall, the probability of achieving an RVR was significantly higher among patients with genotype 3 (OR, 16.0; 95% CI, 3.15–81.4) and low pretreatment viral load (OR, 12.1; 95% CI, 2.0–72.8). Genotype 3 (OR, 4.9; 95% CI, 1.14–21.3) and a low HCV RNA level (OR, 14.8; 95% CI, 1.51–145) were also independently associated with the likelihood of obtaining an SVR. Sex, age, weight, alanine aminotransferase level, aspartate aminotransferase level, gammaglutamyl transpeptidase level, CD4+ cell count, abacavir-based antiretroviral treatment, HIV load, and liver fibrosis stage did not influence treatment outcome.

Among patients with genotypes 1 or 4, a low pretreatment viral load was the only variable associated with RVR (OR, 27.0; 95% CI, 2.38–306). A low viral load and the absence of cirrhosis were associated with the likelihood of achieving an SVR, but
only a low viral load (OR, 6.0; 95% CI, 1.03–34.8) remained in the logistic regression model as an independent predictor of viral eradication. Of note is the fact that, when dynamic variables were included in the regression model, the strongest predictor of SVR was achievement of an RVR, because all 5 patients with genotypes 1 or 4 who achieved an RVR eradicated the virus after completing 24 weeks of treatment.

**Tolerance and safety assessment.** Seven patients (11.7%) discontinued treatment because of intolerance or severe adverse events (table 2). A dose reduction of pegylated IFN was required in 25 patients (41.7%), of ribavirin in 7 patients (11.7%), and of both medications in 3 patients (5%) (table 2). Erythropoietin was administered in 5 (8.3%) cases with symptomatic anemia, whereas colony-stimulating factor was not used at all.

With regard to HIV infection, neither virologic failure nor clinical progression occurred during the study.

### DISCUSSION

The results of this exploratory trial suggest that monitoring the viral response may be useful to individualize treatment duration and to optimize the individual outcome of HCV treatment in patients coinfected with HIV. In spite of several baseline characteristics that indicate a difficult-to-treat population, 55% of patients treated with pegylated IFN-alfa-2b plus weight-adjusted ribavirin for 24 to 60 weeks achieved an SVR. Similar results were observed in a previous randomized trial conducted in our hospital, and this rate of achievement of an SVR is among the highest reported in patients coinfected with HIV who are treated according to the current standard of care [6, 24–26].

The treatment outcome in patients with genotype 3 is particularly relevant, because this genotype is highly prevalent among former injection drug users in Europe [27] and is present in one-third of patients coinfected with HIV enrolled in randomized trials [6, 24–26]. In our study, almost 60% of patients with genotype 3 attained an RVR and received an abbreviated 24-week regimen. Among these patients, the risk of viral relapse was 8%, and 89% of them eradicated the virus. Moreover, 70% of patients with genotype 3 who cleared the virus between treatment week 4 and 12 achieved an SVR, and no patient experienced relapse after 48 weeks of therapy. These data are consistent with our previous reports [22, 23] and with data reported by other authors [28] and suggest that week 4 virologic response is useful to stratify the risk of viral relapse and to guide treatment duration for HCV genotype 3 infection in patients coinfected with HIV: therapy may be shortened to 24 weeks in patients achieving an RVR, whereas extension to 48 weeks can reduce the risk of viral relapse in those who clear the virus later than treatment week 4.

Abbreviated regimens have proven to be sufficient to treat patients monoinfected with HCV genotypes 1 or 4 who achieve an RVR [7, 29], mainly in those patients with low pretreatment viral load [12, 13]. On the basis of data reported by Zeuzem et al. [12], the European Medicines Agency changed the indication label to allow rapid responders with genotype 1 and low pretreatment viral load to be treated for 24 weeks.

In our study, among patients with genotypes 1 or 4, the likelihood of achieving an SVR was higher in those with low pretreatment viral load and no cirrhosis. However, the strongest predictor of viral eradication was obtaining an RVR. All rapid responders with genotypes 1 or 4 eventually eradicated HCV infection after completing 24 weeks of therapy. Because of the small number of patients we analyzed, however, the ability to draw conclusions is very limited, and further evidence is necessary before an abbreviated regimen can be generally recommended. Meanwhile, our results could assist the management of individual patients coinfected with HIV and HCV genotypes 1 or 4, with low pretreatment viral load and no cirrhosis, who achieve an RVR, for whom this strategy is most attractive, or those who cannot tolerate treatment or who experience on-treatment serious adverse events.

Notably, in our study 87% of patients with genotypes 1 or 4 who showed a complete EVR at treatment week 12 remained with no detectable viral load at the end of 48-week therapy. However, 46% of them experienced relapse during follow-up. Residual viremia at treatment week 12 was detected using a very sensitive assay (COBAS TaqMan; limit of detection, 15 IU/mL) in 3 of 11 patients with complete EVR who had available cryopreserved serum samples, and all 3 patients experienced relapse. In comparison, only 1 viral relapse occurred among 8 patients with no residual viremia at treatment week 4.
12. Taken together, this data suggests that the sensitivity of the analysis used to evaluate week 12 virologic response is a valuable prognostic tool in predicting long-term outcome and that the definition of a complete EVR should be based on a very sensitive assay.

According to the predictive model of Drusano and Preston [30], keeping viral load undetectable for at least 36 weeks is required to reduce relapse risk to 10%. On the basis of these data, we decide to prolong therapy to 60 weeks in those patients showing a partial EVR. During the study, 3 (12%) of 25 patients with genotype 1 showed a partial EVR and cleared the virus between week 12 and 24 of treatment. Of these patients, 1 had detectable viral load at the end of 60-week therapy, and 2 achieved an SVR.

Results from different trials conducted with patients mono-infected with HCV consistently demonstrated that slow viral responders who cleared the virus later than week 12 of treatment benefit from extension of treatment to 72 weeks, because the extension reduces the risk of viral relapse [14–16]. To date, 2 reported nonrandomized trials failed to show benefit from treatment extension in patients coinfect ed with HCV and HIV [31, 32]. Nevertheless, the rate of premature discontinuation among patients with prolonged treatment in these studies was extraordinarily high. Moreover, this strategy has not been properly evaluated in the subset of patients who showed a slow response and who would probably most benefit from prolonging treatment.

In our trial, all patients received a weight-adjusted dose of ribavirin (800–1400 mg/day). Ribavirin is known to play a critical role in the prevention of relapse [33, 34] and may play a crucial role, enhancing the viral kinetics response of IFN in difficult-to-treat patients [35]. Moreover, although the impact of a weight-adjusted dose of ribavirin seems to not be as significant in genotypes 2 or 3 as in genotype 1 [33, 36], higher doses of ribavirin might be useful to maximize the chance of response in patients with genotype 3 who do not achieve an RVR and in those with an RVR treated with abbreviated courses of therapy [8–11].

With regard to safety, no unexpected adverse events were observed in our study, and the rate of premature discontinuation was low (12%). Because zidovudine and didanosine increase ribavirin toxicity [22, 37–39], coadministration of these drugs was avoided, and ribavirin dose reduction was necessary in very few patients. Of interest, up to 42% of patients required pegylated IFN dose modification. Active management of adverse effects and judicious dose modification might be crucial in reducing the number of early drop-outs and in maximizing the likelihood of eradicating HCV infection [22, 24].

The main study limitation is the absence of a control group treated according to the current standard of care. In addition, the small sample size limits the conclusions to be drawn. However, our results are useful for gaining insight into the feasibility of tailoring the duration of HCV treatment according to the kinetics of response for individual patients coinfected with HIV.

In conclusion, the results of this exploratory study suggest that a response-guided therapy may be very useful to optimize HCV treatment in patients coinfected with HIV. The SVR rates for each genotype are among the highest reported to date for patients coinfected with HIV. Shortening treatment duration to 24 weeks may be sufficient in patients with genotype 3 who achieve an RVR and could be considered in patients with genotypes 1 or 4 and 4 or 5 and low pretreatment viral load who achieve a rapid response. More than 48 weeks of therapy may be necessary to reduce the high risk of relapse observed among slow responders with residual viremia at week 12 of treatment. Prospective randomized trials should be undertaken to evaluate this response-guided strategy in a large number of patients coinfected with HCV and HIV.

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