Impact of Hepatitis C Virus on Immune Restoration in HIV-Infected Patients Who Start Highly Active Antiretroviral Therapy: A Meta-analysis

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Background. There are conflicting data in the medical literature regarding the degree of immune restoration (as measured by CD4 cell count) in patients who commence highly active antiretroviral therapy (HAART) when coinfected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV), compared with those with HIV infection alone.

Methods. We performed a meta-analysis that compared CD4 cell count increases after HAART initiation in HCV-negative and HCV-positive patients who were infected with HIV. Published studies in the English-language medical literature that involved cohorts of HCV-negative and HCV-positive patients who were coinfected with HIV were obtained by searching the Medline, Embase Drugs and Pharmacology, and EBM Review-Cochrane Central Register of Controlled Trials databases. Data were extracted independently from relevant studies by 3 investigators and were used in a fixed-effects meta-analysis to determine the mean difference in the expected CD4 cell count change in the 2 groups.

Results. Eight trials involving 6216 patients were analyzed. Patients with HIV-HCV coinfection had a mean increase in the CD4 cell count that was 33.4 cells/mm³ (95% CI, 23.5–43.3 cells/mm³) less than that for HIV-infected patients without HCV infection. The results of the meta-analysis were independent of any one study and were not influenced by the year in which HAART was started.

Conclusions. This meta-analysis shows that patients with HIV-HCV coinfection do, in fact, have less immune reconstitution, as determined by CD4 cell count after 48 weeks of HAART, than do patients with HCV infection alone. Future research should examine whether an impaired immunologic response corresponds with meaningful virologic and clinical outcomes.

Hepatitis C virus (HCV) infection is estimated to occur in 30% of HIV-infected patients in the United States [1]. HIV-HCV coinfected patients have higher levels of HCV RNA, an accelerated progression to liver disease with more rapid development of liver fibrosis and cirrhosis, and greater morbidity and mortality compared to those infected with HCV alone [2, 3]. Some studies have suggested that HIV-HCV coinfected patients have a blunted immune response to HAART, compared with those with HIV infection alone [4, 5], although others have found comparable degrees of immune restoration in persons with HIV-HCV coinfection [6–11].

There is a need to determine the expected response in the CD4 cell count in the large subset of HIV-infected patients with HCV coinfection, to help with clinical decision-making. If patients with hepatitis C have a less robust immune response when they commence HAART, clinicians may start to administer HAART earlier to optimize immune restoration. Additionally, this might lend support for the earlier treatment of hepatitis C in HIV-HCV–coinfected patients, because eradication of hepatitis C may improve the patient’s response to HAART and also to decrease the likelihood of liver-associated toxicity when these patients ultimately start receiving HIV therapy.

We conducted a meta-analysis to examine the difference in the increases in the CD4 cell count at least 12 months after HAART initiation in HCV-negative
and HCV-positive patients who are infected with HIV. The objective of the meta-analysis was to determine whether there is a blunted increase in the CD4 cell count after initiation of HAART in HIV-HCV–coinfected patients relative to patients with HIV infection alone.

METHODS

**Identification of studies.** Relevant studies were identified by searching the Medline database (a computerized bibliographic database of the National Library of Medicine [Bethesda, MD] that spans the years from 1966 to the present), the Embase Drugs and Pharmacology database (a bibliographic database of Elsevier Science, Excerpta Medica, that spans the years from 1991 to the present), and the EBM Review-Cochrane Central Register of Controlled Trials database (a database of the Cochrane Collaboration [Oxford, UK] that spans the years from 2001 to the present) for all English-language, published studies through April 2004. The Medline search terms included medical subject heading (MeSH) terms of “Hepatitis C,” “Anti-HIV Agents/therapeutic use,” “Antiretroviral Therapy, Highly Active,” and the general term “CD4.” “HAART,” “hepatitis C,” and “CD4” were used in the Embase and Cochrane database searches. The searches were completed on 10 May 2004.

**Inclusion criteria.** Cohort studies were included in the analysis if they analyzed HIV-infected patients who were being treated with HAART and if patients with and without HCV coinfection were included in the study. We then selected studies with the outcome measure of interest (the CD4 cell count after commencement of therapy if the baseline CD4 cell count was provided or the change in CD4 cell count while the patient was receiving HAART) with at least 48 weeks of follow-up (i.e., the time since initiation of HAART). Articles that were selected for inclusion in the study were also reviewed to look for further references to studies that met the aforementioned criteria and could be included as part of the meta-analysis.

Studies were not rejected if they included infection with hepatitis B virus because of the fact that some studies did not record this variable as a baseline characteristic. The modes of transmission of hepatitis B virus include both transmission related to injection drug use and sexual transmission, and there could be a high proportion of both HIV-monoinfected patients and HIV-HCV–coinfected patients with this infection. Furthermore, there is no evidence that hepatitis B status significantly impacts the response to HAART with respect to CD4 cell count; therefore, such patients were not restricted from the analysis [12].

Studies used multiple means to report HCV infection status. Therefore, studies that reported HCV antibody status, studies that reported HCV load, and those that used both HCV antibody status and HCV load to define HCV positivity were all included in the analysis.

**Data extraction.** Three investigators independently assessed the suitability of each study for inclusion in the meta-analysis. When the outcome measure was reported at multiple follow-up times, the time point greater than and closest to 1 year was used. If the study reported a subgroup analysis by hepatitis B status in addition to the overall results, the overall results were used.

The outcome of interest in this meta-analysis, change in the CD4 cell count, was a secondary outcome in all the individual studies. Because of the limited number of studies available that fit the inclusion criteria, and because the outcome of interest was a secondary outcome, we made no further attempt to score the methodological quality of the individual studies.

The primary response variable, $Y_i$, was the difference in the mean or median CD4 cell count increase after at least 1 year of HAART in HCV-positive and HCV-negative subjects infected with HIV. We accepted mean or median CD4 cell count increases under the assumption that, for large samples, the median is equivalent to the mean, and the distribution of CD4 cell count increases is approximately normal. For simplicity, we used the mean value to describe the difference in CD4 cell count increases in the results. If the difference was not reported in the published report, we calculated the difference. In the case of the articles by Greub et al. [4] and Macias et al. [6], the corresponding authors of the papers were contacted for the mean (±SE) increase in the CD4 cell counts shown, because only a bar graph was provided in the published document. We calculated the variability in $Y_i$ using the data available in the published report or provided by the corresponding author. If multiple linear regression was performed with the CD4 cell count increase as the dependent variable and HCV infection status as an independent covariate, we used the $P$ value of the effect estimate to calculate the standard normal variate and thus estimate the variability of the effect estimate. In the case that the median and interquartile range were reported for the increase in the CD4 cell count, we estimated the variability in the increase as 3/4 (interquartile range).

**Statistical analysis.** The overall mean difference was estimated from a fixed-effects model [13]. Because the total variance for the study mean difference is different from one study to the next, the best estimate for the overall mean is a weighted mean difference, in which the weights are equal to the inverse of the SE.

Even though the between-study heterogeneity was minimal, we hypothesized a priori that the response to HAART might be influenced by the following variables: (1) calendar year when HAART was initiated in the study cohort, (2) whether the study was prospective or retrospective, and (3) length of the follow-up period. We explored these possible sources of heterogeneity by both visual inspection of the mean differences for subgroups of studies and also by formal random-effects meta-regression

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analyses, in which study characteristics were used to explain mean differences. The number of studies available limited the number of possible explanatory variables in the regression analysis, and we examined each explanatory variable separately in bivariate models. We also examined the year of HAART initiation and the publication year in a cumulative analysis.

Formal analyses were completed to detect possible publication bias. We used the Begg and Mazumdar adjusted rank correlation test for publication bias [14] and the regression asymmetry test of Egger et al. [15] for publication bias. We examined the influence of individual studies by omitting 1 study at a time. Analyses were conducted with Stata software, version 8.0 (Stata).

RESULTS

Description of studies and study subjects. After searching the Medline, Embase Drugs and Pharmacology, and EBM Review-Cochrane Central Register of Controlled Trials databases with the strategy described above, a total of 152 studies were identified and screened for retrieval. One hundred nine studies were excluded because they were either case reports, case-control studies, or review articles or they were focused on the effect of HIV on hepatitis C progression. Forty-three studies were collected for further review. Of these 43 studies, 34 were excluded for lack of information on changes in the CD4 cell count after initiation of HAART and lack of an HCV-negative control group. One was excluded from the meta-analysis because it did not provide follow-up data for subgroups, although the baseline CD4 cell counts were provided [16]. The remaining 8 studies [4–11] were included in the analysis (figure 1).

The general characteristics of these studies and their participating subjects are shown in table 1. All 8 studies were cohort studies; 3 were retrospective in design, and 5 were prospective in design. One-half of the studies were conducted in western Europe ($n = 4$), and the remaining studies were conducted in North America ($n = 3$) and Australia ($n = 1$). The years that subjects entered the cohorts ranged between 1992 and 2002. Sample sizes ranged from 68 to 2333 subjects (mean, 777 subjects). The median age of HCV-negative subjects was 36 years, and it was 35 years for HCV-positive subjects. Although actual percentage differences were not available for all studies, there were disproportionate numbers of injection drug users in the HCV-positive subgroups. Of the 4 studies that included mean or median pre-HAART CD4 cell counts, averages of these measurements revealed that the average pre-HAART CD4 cell count was 291 cells/mm$^3$ for HCV-negative subjects and 307 cells/mm$^3$ for HCV-positive subjects. Four of the studies included patients with prior use of antiretroviral therapies. Durations of follow-up ranged from 48 weeks to 4 years, with a mean duration of follow-up of 1 year, 9 months.

Homogeneity of study-level outcomes. Although there was heterogeneity in study design between selected studies, this did not result in heterogeneity of the study-level differences in the
Table 1. Descriptions of 8 cohort studies used in the analysis of the difference in CD4 cell count increases between hepatitis C virus (HCV)-negative and HCV-positive patients coinfected with HIV after initiation of HAART.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Date of cohort entry</th>
<th>Study population or group</th>
<th>Means of diagnosis of HCV infection</th>
<th>Duration of follow-up</th>
<th>Treatment regimen</th>
<th>Prior ART use, % of patients</th>
<th>HIV acquisition group, % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>IDU</td>
</tr>
<tr>
<td>[4]</td>
<td>Prospective</td>
<td>1996–1999</td>
<td>Swiss HIV Cohort Study</td>
<td>HCV antibody ELISA and positive results confirmed by immunoblot</td>
<td>12 months</td>
<td>Combination therapy, including ≥3 drugs with ≥1 PI</td>
<td>HCV-negative patients, 48%; HCV-positive patients, 41%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>[7]</td>
<td>Prospective</td>
<td>1992–1999</td>
<td>Aquitaine cohort; subjects from southwest France</td>
<td>At least 1 detection of HCV antibodies or positive plasma HCV RNA test result</td>
<td>24 months</td>
<td>76% received dual NRTIs, and 24% received a combination including PI</td>
<td>None</td>
<td>3</td>
</tr>
<tr>
<td>[8]</td>
<td>Retrospective</td>
<td>1997–1998</td>
<td>AIDS Clinical Trials Group Study 343 population</td>
<td>HCV antibody EIA and plasma HCV RNA</td>
<td>48 weeks</td>
<td>Months 0–6, indinavir, lamivudine, and zidovudine; months 6–24, random assignment to maintenance regimen</td>
<td>None</td>
<td>NA</td>
</tr>
<tr>
<td>[5]</td>
<td>Prospective</td>
<td>1997–2001</td>
<td>Italian cohort of antiretroviral-naive patients</td>
<td>Detection of HCV antibodies</td>
<td>Median, 36.8 months</td>
<td>Combination of at least 3 antiretroviral agents</td>
<td>None</td>
<td>NA</td>
</tr>
<tr>
<td>[9]</td>
<td>Retrospective</td>
<td>1996–1999</td>
<td>Immunodeficiency Clinic at the Montreal Chest Institute</td>
<td>For positive results, positive ELISA results and confirmed RIBA finding; for negative results, negative ELISA results and no RIBA performed</td>
<td>24 months</td>
<td>84% received protease inhibitor-based therapy</td>
<td>HCV-negative patients, 3%; HCV-positive patients, 8%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5</td>
</tr>
<tr>
<td>[10]</td>
<td>Retrospective</td>
<td>1999–2002</td>
<td>Australia HIV Observa- tional Database</td>
<td>Detection of HCV antibodies</td>
<td>24 months</td>
<td>NA</td>
<td>41%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NA</td>
</tr>
<tr>
<td>[11]&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Prospective</td>
<td>1995–2001</td>
<td>The Johns Hopkins Hos- pital HIV Clinic</td>
<td>HCV antibody EIA</td>
<td>1–2 years</td>
<td>PI or NNRTI; effective HAART</td>
<td>HCV-negative patients, 28%; HCV-positive patients, 25%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>[6]</td>
<td>Prospective</td>
<td>1997–2001</td>
<td>Infectious diseases unit at Hospital Universitario de Valme, Seville, Spain</td>
<td>EIA and viral RNA detected by PCR</td>
<td>12 months</td>
<td>Combination of ≥2 nucleoside analogues plus 1 PI or 1 NNRTI</td>
<td>None</td>
<td>NA</td>
</tr>
</tbody>
</table>

NOTE.  
- IDU, injection drug user; MSM, men who have sex with men; NA, information not available; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; RIBA, recombinant immunoblot assay.
- <sup>a</sup> Patients in the larger cohort.
- <sup>b</sup> The authors noted that 93.3% of IDUs and 11.7% of MSM were HCV positive.
- <sup>c</sup> The data represent an analysis of subjects from an initial cohort of 2237 subjects. The 187 patients with ≥1 year of follow-up of a subset of 208 HAART recipients with well-controlled HIV replication (defined as a viral load of <400 HIV-1 copies/mL recorded at ≥75% measurements) were used in the analysis.
- <sup>d</sup> The authors noted that the HCV-positive group was composed mostly of IDUs.
mean CD4 cell count increase ($Q = 2.55$ on 7 degrees of freedom; $P = .92$).

**Fixed-effects results.** Table 2 shows the study-specific differences, SEs, sample sizes, and statistics corresponding to a total of 6216 patients. The studies with the largest weights associated with the largest number of patients correspond to those by Greub et al. [4], De Luca et al. [5], and Rancinan et al. [7]. With use of a fixed-effects model, the combined estimate of the difference in CD4 cell count increase between HCV-infected and HCV-uninfected patients is $-33.4$ cells/mm³ (figure 2). The 95% CI for the mean difference is $-43.3$ to $-23.5$ cells/mm³, indicating a less robust increase in the CD4 cell count among HCV-HIV–coinfected subjects when analyzed $\geq 48$ weeks after the initiation of HAART.

**Diagnostics.** The pooled estimate appears insensitive to any one study (data not shown) when studies are dropped individually from the analysis under a fixed-effects model. The calendar year when the first subject of a cohort initiated HAART had little effect on the difference in CD4 cell count between HCV-positive and HCV-negative patients (figure 3). In meta-regression analysis, there was no impact on the pooled estimate of a retrospective study design ($P = .80$), duration of HAART therapy ($P = .67$), or whether cohorts initiated HAART therapy after the year 2000 ($P = .36$), as expected on the basis of the homogeneity of study-level outcomes. There was no evidence of publication bias by either Begg and Mazumdar’s test ($P = .46$) or the test of Egger and colleagues ($P = .88$).

**DISCUSSION**

This review of 8 cohort studies showed that the CD4 cell count response for patients with HIV-HCV coinfection when they started receiving HAART was less than that for patients with HIV infection alone by an average $33.4$ cells/mm³ (range, $23.5–43.3$ cells/mm³). This result was statistically significant and suggests that HIV-infected patients are likely to have a better immunological response to antiretroviral therapy if they are not coinfected with HCV.

The discrepancy in the CD4 cell count increase with HAART between these 2 groups may have implications for HIV care, particularly for subjects who initiate HAART at lower CD4 cell counts. Current HIV guidelines published by the US Department of Health and Human Services suggest that HAART should commence when the CD4 cell count decreases to $<350$

<table>
<thead>
<tr>
<th>Study</th>
<th>HCV-negative patients</th>
<th>HCV-positive patients</th>
<th>Difference in CD4 cell count increase, cells/mm³</th>
<th>$p$</th>
<th>SE$_{\text{diff}}$</th>
<th>Weight$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>[4]</td>
<td>152 ± 4$^a$</td>
<td>1473</td>
<td>119 ± 5</td>
<td>860</td>
<td>$-33$</td>
<td>NA$^l$</td>
</tr>
<tr>
<td>[8]</td>
<td>151 ± 160$^b$</td>
<td>53</td>
<td>137 ± 134$^b$</td>
<td>15</td>
<td>$-14$</td>
<td>.85$^h$</td>
</tr>
<tr>
<td>[5]</td>
<td>NA</td>
<td>720</td>
<td>NA</td>
<td>600</td>
<td>$-47.1^i$</td>
<td>&lt;.001$^l$</td>
</tr>
<tr>
<td>[9]</td>
<td>135 ± 14</td>
<td>263</td>
<td>124 ± 61</td>
<td>52</td>
<td>$-11$</td>
<td>.87</td>
</tr>
<tr>
<td>[10]</td>
<td>185 ± 176$^k$</td>
<td>772</td>
<td>150 ± 178$^k$</td>
<td>108</td>
<td>$-32.1^t$</td>
<td>.061</td>
</tr>
<tr>
<td>[6]</td>
<td>204 ± 25$^a$</td>
<td>58</td>
<td>147 ± 16</td>
<td>60</td>
<td>$-57$</td>
<td>.14$^n$</td>
</tr>
</tbody>
</table>

Total: ... 4037 ... 2179 ... ...

NOTE. NA, not available; SE$_{\text{diff}}$, standard error of the difference in CD4 cell count increase.

- $^a$ Data are either mean ± SE or median (interquartile range).
- $^b$ $P$ values were reported in the published report.
- $^c$ Weight = 100.
- $^d$ Weight$^d$ was estimated on the basis of the data available in the published report.
- $^e$ Corresponding author provided data.
- $^f$ The magnitude of the $P$ values was not reported, but the difference was statistically significant.
- $^g$ Mean ± SD.
- $^h$ Determined by Kruskal-Wallis test.
- $^i$ Adjusted for sex, active injection drug use, age, baseline CD4 cell count, baseline and ongoing plasma HIV RNA concentration, AIDS stage at HAART initiation, and type of HAART drug included in the treatment regimen.
- $^j$ In hepatitis B virus–infected patients; unadjusted time-weighted change; mean ± SD.
- $^k$ In hepatitis B virus–uninfected patients; adjusted for age, sex, exposure category, viral load at baseline, CD4 cell count at baseline, and previous HAART received.
- $^l$ Determined by Mann-Whitney test.
- $^m$ Post hoc $P$-value.
cells/mm³ or when the patient has an HIV load of >55,000 copies/mL [17]. Additionally, clinical decisions regarding chemoprophylaxis for the prevention of opportunistic infections in patients with HIV infection, such as *Pneumocystis jiroveci* pneumonia and disseminated *Mycobacterium avium* complex infections, are based largely on CD4 cell count.

Treatment of hepatitis C with pegylated IFN and ribavirin results in viral eradication in a substantial fraction of patients with HCV-HIV coinfection [18, 19]. The result of this study should prompt further investigations designed to determine whether there is benefit for earlier treatment of hepatitis C in HIV-coinfected patients in the hope of eradicating this infection before the initiation of HAART, to allow optimal immune reconstitution. In addition to preventing a weakened CD4 cell response to HAART, earlier therapy for HCV infection may help reduce potential liver toxicity associated with antiretroviral therapy.

There are limitations, however, to this type of analysis. Initially, we sought to examine potential effect modification by baseline CD4 cell count, but several studies did not report a baseline measurement for the analytic subgroup. We cannot determine, for example, whether the effect is the same or different for individuals with a baseline CD4 cell count of <100 cells/mm³, compared with patients with higher values. There appeared to be a wide range in baseline CD4 cell counts in those studies that did report their values, and it would have been productive to have been able to stratify the changes in the groups on the basis of the baseline CD4 cell counts. In some studies, only the change was noted, and not the actual starting CD4 cell count, and in 2 instances, crude data were not provided and only adjusted data were given. The clinical significance of an impaired increase in the CD4 cell count may be different for someone who initiates HAART with a CD4 cell count of 100 cells/mm³, compared with someone who initiates it with a CD4 cell count of 300 cells/mm³. Whether immune reconstitution differs in these subgroups of patients with HCV-HIV coinfection and the clinical significance of this, in terms of the frequencies of opportunistic infections, should be explored in prospective studies.

Another limitation of this study is that many of the studies we used in our analysis reported only HCV antibody positivity. However, at least 15% of patients with HCV seropositivity will, in fact, have cleared HCV [18]. If a significant percentage of patients in these studies are, in fact, not viremic, if anything, we would expect the difference in immune reconstitution to be greater when only viremic patients were included. Furthermore, there is no information about the degree of liver dysfunction in the patients in these studies. It is possible that underlying liver dysfunction may be related to the changes in CD4 cell count.

This meta-analysis is dependent on the published literature, and the studies reviewed are very different in their design. In all of the studies, the increase in the CD4 cell count was a secondary outcome, and many of the studies are statistically

**Figure 2.** Fixed-effects model of the difference in increases in the CD4 cell count after at least 1 year of HAART between hepatitis C virus (HCV)–negative and HCV-positive patients infected with HIV.
underpowered to examine the specific question of interest to us. Although the formal tests for heterogeneity among studies did not demonstrate any significant differences, there are clearly differences between populations coinfected with HCV-HIV and those infected with HIV alone. HCV-HIV–coinfected individuals are far more likely to have contracted HIV infection via injection drug use. This population often has less access to health care and typically has worse adherence to HIV regimens, compared with the population of patients who contracted HIV infection by other means. Adherence to HAART in this population may be directly related to improvements in the CD4 cell count [20]. Interestingly, in the large study by Greub et al. [4], there was an equivalent response in the nearly 1600 HCV-positive and HCV-negative patients with respect to their ability to suppress HIV while receiving HAART. Six of the 7 remaining studies commented similarly on this finding, suggesting that adherence to treatment is unlikely to play a role in the findings of this meta-analysis [5, 7–11].

We found no evidence of publication bias, but we recognize that the Begg and Mazumdar’s and Egger and colleagues’ tests are limited in their ability to indicate publication bias when there are a limited number of studies. We cannot exclude the possibility of reporting bias, in that studies with a negative finding (i.e., no association between CD4 cell count response and HCV infection status) may not have been deemed by study authors or editors to be of sufficient interest to warrant publication.

The clinical consequences of a blunted CD4 cell count response are not yet known in this context. Care of patients with HIV infection is not limited to simply measurements of CD4 cell counts but also depends on knowledge of both clinical and virologic status. This analysis does not attempt to account for the clinical outcome in patients stratified by HCV infection status because of the wide degree of variation in methods of reporting clinical outcomes in the 8 studies. Viral load data, before and after the initiation of HAART, were not provided in all 8 studies and were not further analyzed. As noted above, however, in 7 of the 8 studies, there was no difference in the ability to suppress HIV virologically in the 2 different groups. The clinical consequences of the observed difference in CD4 cell count response described in this analysis should be further explored.

Our meta-analysis showed that the increase in the CD4 cell count in patients who started receiving HAART for HIV infection is significantly lower if they have HCV coinfection. To gain a better understanding of the true nature of the effect of HCV infection on the response to HAART in HIV-infected patients, prospective cohort studies should be conducted that account for multiple variables, such as degree of liver disease, duration of HIV and HCV infection, baseline HIV load, and different treatment regimens. The best time to initiate hepatitis C treatment in HIV-infected individuals remains unknown. Additional prospective studies need to be conducted to provide
the definitive answer to patients and clinicians, so that both infections can be treated in the most effective manner.

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