Role of Hepatitis C Virus (HCV) Viremia and HCV Genotype in the Immune Recovery from Highly Active Antiretroviral Therapy in a Cohort of Antiretroviral-Naive HIV-Infected Individuals

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Background. The roles of hepatitis C virus (HCV) viremia and HCV genotype in the immune response to highly active antiretroviral therapy (HAART) are poorly understood. Our aim was to assess the CD4+ cell count recovery after HAART in human immunodeficiency virus (HIV)–infected patients with HCV viremia and HIV-infected patients who tested negative for HCV antibody (HCV-Ab). We also aimed to assess whether the response to HAART in these patients varied according to HCV genotype.

Methods. The analysis focused on 1219 HCV-Ab–negative patients and 284 HCV-viremic patients from a cohort of HIV-infected subjects that includes persons who were antiretroviral naive before initiating HAART after cohort enrollment. HCV RNA load and HCV genotype were determined in plasma specimens obtained and stored during the 6-month period preceding the initiation of HAART.

Results. The chance of achieving a CD4+ cell count increase of $\geq 100$ cells/$\mu$L from the pre-HAART level tended to be poorer in HCV-viremic patients than in patients who tested negative for HCV-Ab (adjusted relative hazard [RH], 0.82; 95% confidence interval [CI], 0.66–1.01; $P = .06$). In contrast, a comparison of patients who had a HCV RNA load $1 \times 10^5$ IU/mL with patients who had a HCV RNA load of $5 \times 10^4$ IU/mL revealed no significant association between HCV RNA load and achievement of an increased CD4+ cell count (adjusted RH, 0.97; 95% CI, 0.75–1.27; $P = .83$). There was no clear association between HCV genotype and the probability of achieving a CD4+ cell count increase.

Conclusions. An association between the presence of HCV-Ab and immune reconstitution after HAART has been shown elsewhere. Results of our large, prospective study support a direct role of HCV viremia in the CD4+ cell count response to HAART. Moreover, our results underline the fact that, in individuals coinfected with HIV and HCV, the goal of treating HCV infection is to eradicate HCV, to both slow the rate of HCV progression and limit potential interference with the response to HAART.
Improving our knowledge about the effects of HCV viremia and HCV genotype in HIV-infected patients receiving HAART may be useful to better understand the interaction between these 2 viruses and to optimize the timing of antiviral therapies in coinfected patients. In the present analysis, we evaluated whether the CD4+ cell count response to HAART in patients with HCV viremia was different from the response in HCV-Ab–negative patients using data from the Italian Cohort Naïve for Antiretrovirals (I.Co.N.A.), which includes persons who were antiretroviral naive at the time of enrollment. We also aimed to assess whether the response to HAART varied according to HCV RNA load or HCV genotype. In a previous analysis of patients included in the I.Co.N.A. cohort, the CD4+ cell count response to HAART in subjects with serological evidence of HCV infection was impaired, compared with the response in HCV-Ab–negative subjects [3].

PATIENTS AND METHODS

Study population. I.Co.N.A. is an Italian, multicenter, prospective, observational study cohort started in 1997 that includes HIV-infected adults who were antiretroviral naive at the time of enrollment. Demographic characteristics, clinical and laboratory values, and treatment history are recorded at enrollment and at intervals of at least 6 months thereafter. Plasma samples are prospectively collected and stored on a voluntary basis by participating centers [10]. The present study involves subjects from I.Co.N.A. who were antiretroviral naive before I.Co.N.A. enrollment and received a HAART regimen of ≥3 drugs after enrollment, who were tested for HCV-Ab and were negative for hepatitis B virus surface antigen during the 6-month period before starting HAART, who had at least 1 CD4+ cell count measurement and 1 HIV RNA measurement during the 6-month period before starting HAART, who had at least 1 CD4+ cell count measurement and 1 HIV RNA measurement during the 6-month period before starting HAART, who had at least 1 HIV RNA load measurement after at least 1 week of HAART, and who, if HCV-Ab positive, had at least 1 plasma sample stored during the 6-month period before starting HAART to distinguish between those who were and those who were not HCV viremic (HCV RNA loads >5 and ≤5 IU/mL, respectively) and to assess HCV genotype. Subjects treated at any time with IFN or other immunomodulating agents were excluded from the study.

Laboratory testing. Plasma samples were stored at −80°C, and the HCV RNA load was measured with Versant HCV RNA Ultrasensitive, version 3.0 (Bayer Diagnostics). If HCV RNA levels were less than the lower limit of quantification (521 IU/mL), HCV viremia was determined by a qualitative test that was based on a transcription-mediated assay (TMA; Bayer Diagnostics) with a sensitivity of 5 IU/mL. HCV genotype was assessed in HCV RNA–positive samples by the reverse hybridization method (InnoLipa HCV II; Bayer Diagnostics); in subjects with HCV RNA levels of 5–521 IU/mL, TMA amplicons were used as starting materials for PCR before reverse hybridization was performed. HCV-Ab seropositivity was confirmed in stored plasma specimens by a third-generation immunoassay (AxSYM HCV, version 3.0; Abbott Laboratories).

Statistical analysis. To test whether HCV-Ab–positive patients for whom a stored plasma specimen was available were systematically different from those for whom no sample was available, we compared the baseline demographic and clinical characteristics of these 2 groups using the χ2 test (for categorical variables) and Wilcoxon’s test (for continuous variables) for independent samples. Patients were characterized as HCV-Ab negative or HCV viremic. In turn, we grouped HCV-viremic patients according to HCV genotype (genotypes 1–4) and HCV RNA load (with a cutoff of 1 × 10⁶ IU/mL, the approximate median HIV RNA load among viremic subjects). Subjects in these groups were compared with respect to demographic, clinical, and therapeutic characteristics using the χ2 test. Median age at enrollment, HIV RNA and HCV RNA loads, serum alanine aminotransferase (ALT) level, and CD4+ cell count at the time of HAART initiation were compared between groups using the Kruskall-Wallis test. HIV RNA and HCV RNA levels were measured on a log₁₀ scale. For HCV RNA or HIV RNA loads less (or greater) than the lower (or upper) limit of detection, we simply imputed the logarithm of the lower (or upper) detection limit.

The end point of the analysis was the CD4+ cell count response to HAART. This was defined as the time required to initially achieve a specified CD4+ cell count increase (≥100, ≥200, and ≥300 cells/μL) from pre-HAART levels after starting HAART. Follow-up immunological data for individual patients were truncated at the first date on which virological failure was observed (i.e., the date on which the first of 2 consecutive HIV load measurements >500 copies/mL was recorded), and analyses were performed according to an intention-to-treat principle (i.e., treatment modifications were ignored). We also performed a “during treatment” analysis by censoring follow-up data at the time of discontinuation of ≥1 of the drugs contained in the original HAART regimen. A standard multivariable Cox regression analysis was used, and the relative hazard (RH) of achieving a CD4+ cell count response was determined for subjects with a HCV RNA load >1 × 10⁶ IU/mL (high HCV RNA load), subjects with a HCV RNA load of 5–1 × 10⁶ IU/mL (low HCV RNA load), and subjects who were HCV-Ab negative. In HCV-viremic subjects for whom the HCV genotype could also be assessed, the time required to achieve the end points defined above was compared on the basis of HCV genotype.

RESULTS

Of the 5843 subjects enrolled as of 10 May 2004 in I.Co.N.A., 2910 (49.8%) initiated HAART as their first antiretroviral regimen; 2071 (71.2%) of these 2910 met the inclusion criteria.
A total of 1219 (58.9%) of the 2071 patients were HCV-Ab negative, 527 (25.4%) were HCV-Ab positive and had no stored plasma specimen, and 325 (61.7%) were HCV-Ab positive and had a plasma sample obtained and stored a median of 2 weeks before HAART initiation. There were no significant differences between the baseline characteristics of these 325 patients and those of the 527 HCV-Ab–positive subjects who did not have a stored plasma specimen (data not shown). We found that 41 (12.6%) of 325 subjects had a HCV RNA load <5 IU/mL. These patients were excluded from the analysis, because our aim was to restrict the comparison to HCV-Ab–negative patients and HCV-viremic patients.

The characteristics of the 1503 subjects included in the analysis (1219 HCV-Ab–negative patients and 284 HCV-viremic patients grouped according to HCV RNA load) are summarized in table 1. HCV-Ab–negative participants were significantly more likely to be female (P < .05). Conversely, they were less likely to be injection drug users (P < .001) and to have started treatment with the hard-gel formulation of saquinavir as a single PI (P < .001). ALT levels were significantly higher in HCV-viremic patients, compared with HCV-Ab–negative patients (P < .001). At HAART initiation, HCV-Ab–negative patients seemed to have higher HIV RNA levels than did HCV-viremic patients (0.2 log₁₀ difference; P = .0001), but the result may not be clinically significant, because the measurement error of the viral load assays we used can be as high as 0.17 log₁₀ IU/mL [11, 12].

In the 284 HCV-viremic subjects, the median pre-HAART HCV RNA load was 6.09 log₁₀ IU/mL (range, 2.72–6.92 log₁₀ IU/mL); HCV isolates from 138 patients (48.6%) were classified as genotype 1, isolates from 93 (32.7%) were classified as genotype 3, isolates from 46 (16.2%) were classified as genotype 4, and isolates from 7 (2.5%) were classified as genotype 2. Patients carrying HCV genotype 1 had a median CD4⁺ cell count (260 cells/µL) that was lower than that for patients with genotype 3 (315 cells/µL) and patients with genotype 4 (305 cells/µL) (P = .04). Patients with HCV genotype 3 had a median ALT level (63 U/L) that was significantly higher than that...
for patients with HCV genotype 1 (44 U/L) and patients with HCV genotype 4 (47 U/L) (P = .01).

HCV Viremia Analysis

Time required to achieve a CD4 cell count increase of ≥100 cells/μL from pre-HAART levels. A total of 1258 patients (83.7%) achieved an increase of ≥100 CD4+ cells/μL after starting HAART. The median time required to achieve this CD4+ cell count response was 23.1 weeks (95% CI, 22.0–24.1 weeks) for HCV-Ab negative patients, 29.3 weeks (95% CI, 24.1–43.1 weeks) for patients with a HCV RNA load of 5–1 × 10^6 copies/mL, and 28.1 weeks (95% CI, 24.6–38.9 weeks) for patients with a HCV RNA load ≥1 × 10^6 copies/mL (figure 1). The log-rank test revealed a statistically significant difference between the 3 groups (P = .0001), possibly signaling a difference between the 2 curves for the HCV-viremic individuals and the curve for the HCV-Ab–negative individuals. In fact, when patients with low HCV RNA loads were used as the reference group in a comparison of patients with high and patients with low HCV RNA loads, the results of a multivariable Cox proportional hazards model revealed no evidence of a difference in the RH of achieving our definition of a CD4+ cell count response (adjusted RH, 0.97; 95% CI, 0.75–1.27; P = .83). In addition of this finding, we introduced a binary covariate comparing HCV-viremic patients with HCV-Ab–negative patients in the final multivariable proportional hazards model. The results of this model are shown in table 2; age, previous diagnosis of AIDS, pre-HAART CD4+ cell count, and HIV RNA load were independently associated with the chance of achieving a CD4+ cell count increase of ≥100 cells/μL. Most importantly, the chance of achieving this end point appeared to be less for HCV-viremic patients than it was for patients with negative results of HCV-Ab tests (adjusted RH, 0.82; 95% CI, 0.66–1.01; P = .06). Results were similar after adjusting for each specific drug included in the original HAART regimen and for a time-dependent covariate indicating the change in virus load from pre-HAART levels (data not shown). Furthermore, when the analysis was repeated after censoring follow-up data at the time of discontinuation of ≥1 of the drugs included in the original regimen, results were again similar (data not shown). In addition, for a given HCV RNA load, injection drug users were less likely than other patients to achieve a CD4+ cell count increase, but the difference was not statistically significant (adjusted RH, 0.86; 95% CI, 0.69–1.06; P = .15).

Sensitivity analyses. A multivariable Cox regression model revealed that HCV viremia, rather than HCV-Ab negativity,
Table 2. Cox proportional hazards model of the relative hazard (RH) of achieving a CD4+ cell count increase of ≥100 cells/μL from pre-HAART levels.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Crude RH (95% CI)</th>
<th>P</th>
<th>Adjusted RHa (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV antibody negative</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>HCV RNA load &gt;5 IU/mL</td>
<td>0.72 (0.63–0.84)</td>
<td>&lt;.0001</td>
<td>0.82 (0.66–1.01)</td>
<td>.06</td>
</tr>
<tr>
<td>Pre-HAART HIV RNA load, per unit increase of 1 log10 copies/mL</td>
<td>1.81 (1.01–1.15)</td>
<td>.02</td>
<td>1.07 (1.00–1.15)</td>
<td>.04</td>
</tr>
<tr>
<td>Pre-HAART CD4+ cell count, per unit increase of 100 cells/μL</td>
<td>0.97 (0.95–1.00)</td>
<td>.02</td>
<td>0.96 (0.94–0.99)</td>
<td>.04</td>
</tr>
<tr>
<td>Mode of HIV transmission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection drug use</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td>.15</td>
</tr>
<tr>
<td>Other</td>
<td>0.74 (0.64–0.85)</td>
<td>&lt;.0001</td>
<td>0.86 (0.69–1.06)</td>
<td></td>
</tr>
<tr>
<td>Age, per unit increase of 10 years</td>
<td>0.96 (0.90–1.02)</td>
<td>.56</td>
<td>0.93 (0.87–0.99)</td>
<td>.03</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.99 (0.88–1.12)</td>
<td>.85</td>
<td>1.05 (0.92–1.19)</td>
<td>.49</td>
</tr>
<tr>
<td>Previous diagnosis of AIDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.96 (0.83–1.10)</td>
<td>.56</td>
<td>0.82 (0.70–0.97)</td>
<td>.02</td>
</tr>
<tr>
<td>Pre-HAART ALT level, per unit increase of 50 U/L</td>
<td>0.96 (0.85–1.08)</td>
<td>.47</td>
<td>0.96 (0.86–1.08)</td>
<td>.53</td>
</tr>
<tr>
<td>HAART regimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 NRTIs + PI</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>2 NRTIs + NNRTI</td>
<td>1.02 (0.89–1.16)</td>
<td>.80</td>
<td>1.06 (0.91–1.20)</td>
<td>.52</td>
</tr>
<tr>
<td>Other</td>
<td>1.21 (0.94–1.56)</td>
<td>.14</td>
<td>1.18 (0.91–1.53)</td>
<td>.22</td>
</tr>
</tbody>
</table>

**NOTE.** ALT, alanine aminotransferase; HCV, hepatitis C virus; NNRTI, nonnucleoside-analogue reverse-transcriptase inhibitor; NRTI, nucleoside-analogue reverse-transcriptase inhibitor.

a Adjusted for saquinavir (hard-gel formulation) as the only protease inhibitor (PI) received.

tended to be associated with the time required to achieve an increase of ≥200 cells/μL in the CD4+ cell count (adjusted RH, 0.82; 95% CI, 0.64–1.06; P = .12). Moreover, HCV viremia, rather than HCV-Ab negativity, was significantly associated with the time required to achieve an increase of ≥300 cells/μL (adjusted RH, 0.69; 95% CI, 0.52–0.92; P = .01).

**HCV Genotype Analysis**

**Time required to achieve a CD4+ cell count increase of ≥100 cells/μL from pre-HAART levels.** After excluding subjects with HCV genotype 2 because of their low number, we repeated the analyses for the remaining 277 subjects for whom the HCV genotype was known. Results of the log-rank test revealed no evidence of a genotype-based difference associated with achieving an increase of ≥100 cells/μL from the pre-therapy CD4+ cell count (P = .81) (figure 2). Overall, results of multivariable analyses were inconclusive regarding differences in the chance of achieving a CD4+ cell count reconstitution to a level of ≥100 cells/μL above pre-HAART levels between patients with HCV genotype 1 and patients with either HCV genotype 3 (adjusted RH, 1.08; 95% CI, 0.81–1.47; P = .60) or HCV genotype 4 (adjusted RH, 0.90; 95% CI, 0.61–1.32; P = .59) (table 3).

**Sensitivity analyses.** Patients with HCV genotype 3 had a significantly reduced chance of achieving a CD4+ cell count increase of ≥300 cells/μL, compared with patients with HCV genotype 1 (adjusted RH, 0.61; 95% CI, 0.40–0.93; P = .02). However, this association was not confirmed in the analysis of the time required to achieve an increase of ≥200 CD4+ cells/μL (adjusted RH, 0.84; 95% CI, 0.60–1.18; P = .30). In contrast, no significant differences in the chance of achieving an increase of ≥200 cells/μL (adjusted RH, 0.89; 95% CI, 0.55–1.45; P = .64) or ≥300 CD4+ cells/μL (adjusted RH, 0.85; 95% CI, 0.55–1.31; P = .45) were observed in patients with HCV genotype 4.

**DISCUSSION**

In this cohort of antiretroviral-naive, HIV-infected subjects, we prospectively investigated the effect of plasma HCV viremia and HCV genotype on the CD4+ cell count response after initiation of HAART. After eliminating the possibility that HCV-Ab-positive patients were misclassified as HCV infected and adjusting for potential confounders, we found that the chance of achieving a CD4+ cell count reconstitution to a level of ≥100 cells/μL above pre-HAART levels was 18% less than the chance for HCV-Ab-negative patients, although results of Kaplan-Meier analysis suggest that the effect of HCV infection on CD4+ cell count response may be negligible. This difference was not statistically
Figure 2. Kaplan-Meier estimates of the probability of achieving a CD4+ cell count increase of $\geq 100$ cells/$\mu$L from pre-HAART level for patients with hepatitis C virus (HCV) genotype 1 (solid line), HCV genotype 3 (short-dashed line), and HCV genotype 4 (long-dashed line). Numbers of patients still at risk at various time points after the initiation of HAART are shown at the bottom. Log-rank analysis of the difference between groups revealed that $P = .81$.

Table 3. Cox proportional hazards model of the relative hazard (RH) of achieving a CD4+ cell count increase of $\geq 100$ cells/$\mu$L from pre-HAART levels, according to hepatitis C virus (HCV) genotype.

<table>
<thead>
<tr>
<th>HCV genotype</th>
<th>Crude RH (95% CI)</th>
<th>$P$</th>
<th>Adjusted RH* (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Genotype 3</td>
<td>1.03 (0.77–1.38)</td>
<td>.86</td>
<td>1.08 (0.81–1.47)</td>
<td>.60</td>
</tr>
<tr>
<td>Genotype 4</td>
<td>0.90 (0.62–1.32)</td>
<td>.60</td>
<td>0.90 (0.61–1.32)</td>
<td>.59</td>
</tr>
</tbody>
</table>

* Adjusted for pre-HAART HIV RNA load, pre-HAART CD4+ cell count, mode of HIV transmission, sex, age, previous AIDS diagnosis, pre-HAART alanine aminotransferase level, type of HAART, and the hard-gel formulation of saquinavir as the only protease inhibitor received.

significant at the conventional $\alpha$ of .05 ($P = .06$), but similar effects were observed in sensitivity analyses using alternative end points. In particular, for HCV-viremic patients, the adjusted RH of achieving a CD4+ cell count increase of $\geq 300$ cells/$\mu$L was significantly reduced by 31% after initiation of HAART ($P = .01$). Nevertheless, this effect does not seem to be related to different HCV RNA loads. Interestingly, our analysis suggests that HCV viremia was a stronger predictor of a poorer CD4+ cell count response than was injection drug use.

Our results are consistent with those of previous prospective studies in which an impairment of the immune response to HAART associated with HCV infection was reported. However, all of these studies defined HCV infection on the basis of the presence of HCV-Ab and therefore potentially included HCV-nonviremic patients in the group of HCV-infected patients [1, 2]. Specifically, because 5%–10% of HCV-Ab–positive, HIV-coinfected individuals naturally clear the infection [13], a definition of HCV infection that is based on the presence of HCV-Ab could lead to a misclassification of such patients.

One retrospective study comparing the immunological response to HAART after 1 year of therapy in HCV RNA–positive patients with the response in HCV RNA–negative patients did not find any relationship between HCV RNA positivity and the overall mean increase in the CD4+ cell count [14]. Differences in the study designs and in the clinical and demographic characteristics of the study populations might explain these inconsistencies.

The mechanisms by which HCV may alter immune recovery after HAART, irrespective of the amount of circulating virus, can only be speculated. HCV is essentially an hepatotropic tropic.
virus, but it may be also lymphotropic [15–19]. Moreover, the presence of the HCV RNA–negative strand in CD4+ cells as well as in lymph nodes of coinfected patients suggests that HCV may actively replicate in the same T cells as HIV [19, 20]. The recent in vitro observation that HCV infection of native human monocytes-macrophages may be facilitated by HIV also supports the hypothesis of a negative effect of HCV on the kinetics of T cells—especially CD4+ cells—in HIV-infected patients [21, 22].

In our study, the CD4+ cell count response to HAART was similar for all patients with a HCV RNA load ≥5 IU/mL. Although data from simultaneous measurements of plasma HCV RNA load and HCV replication in T cells are lacking in our study, some studies involving in vivo and in vitro analyses suggest that HCV replicates slowly into lymphocytes and that the rate of HCV replication may be independent of the plasma HCV levels [16, 23]; the rate of HCV replication in T cells is generally very low [19, 24], and different ratios of positive strands to negative strands of HCV RNA between hepatocytes and monocytes-macrophages have been detected [25].

We also analyzed the association between HCV genotype and the CD4+ cell count response to HAART. Recently, in a population of young, hemophiliac, antiretroviral-naïve, HIV-infected patients, coinfection with HCV genotype 1 was associated with faster progression to HIV disease than was coinfection with other HCV genotypes [8]. In our analysis, patients infected with HCV genotype 3 seemed to have a slower immune recovery than patients infected with HCV genotype 1, but we found inconsistent results overall. However, a real difference between HCV genotype and the CD4+ cell count response to HAART may exist, but it could not be detected by our test, because of the small sample size and/or the short follow-up period. Our data are consistent with those of a previous report showing that coinfected subjects with well-controlled HIV replication and a CD4+ cell count increase of <50 cells/μL during HAART frequently harbored HCV genotype 3a [2]. Moreover, HCV genotype 3 has been related to hepatic steatosis [26, 27], increased ALT level, and the risk for developing a severely increased ALT level after HAART [28]. Therefore, an association between HCV genotype 3 and an impaired CD4+ cell count response to HAART would be an important finding, because current HCV treatment seems to be more effective against HCV genotype 3 [29].

Our study has some possible limitations. Measurement of the HCV RNA load was performed only for HCV-Ab–positive patients for whom stored plasma specimens were available. However, we have shown that baseline demographic and clinical characteristics for this group of patients were similar to those for HCV-Ab–positive subjects for whom no stored plasma specimens were available. Similarly, it is unlikely that frozen storage and thawing could have substantially affected the results of this analysis [30]. Samples obtained from persons enrolled in the I.Co.N.A. are frozen within hours after collection, and virological tests were performed on aliquots that had not previously been thawed. We measured the pre-HAART HCV RNA load only once, and we could have misclassified subjects who had fluctuating HCV RNA loads. However, no significant changes in HCV RNA levels were observed over time in patients coinfected with HIV and HCV [31]. Also, a false-negative result of a HCV-Ab test could have led to a misclassification of some subjects. However, in populations at high risk for HCV infection, such as HIV-infected patients, the probability of false-negative results of anti-HCV immunoassays is negligible [32].

Because it was not possible to reasonably distinguish between active and nonactive injection drug users in the I.Co.N.A., we cannot rule out the presence of residual confounding. Moreover, our analysis lacks adjustment for adherence to therapy. Because adherence is strongly associated with a better virological response to HAART and because coinfected patients have a higher rate of therapy discontinuation [33, 34], confounding cannot be ruled out. Finally, because enrollment in the cohort started in 1997, a proportion of subjects have been treated with HAART regimens that are considered to be suboptimal according to current standards. However, we included this factor in the multivariable analysis.

Overall, data from this large, prospective study confirm that HCV infection seems to be associated with an impaired CD4+ cell count response to HAART. To our knowledge, this is the first prospective study that extends this finding to a HCV-viremic population. In the light of our results, the treatment of hepatitis C in patients coinfected with HIV and HCV could not only potentially eradicate HCV, but it could also reduce the possible interference of hepatitis C in a patient’s response to HAART. Moreover, among coinfected persons for whom antiretroviral therapy may be safely deferred, treatment for HCV infection should be considered appropriate regardless of the extent of HCV-associated hepatic damage and may precede initiation of HAART.

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