Coinfection With Hepatitis Viruses and Outcome of Initial Antiretroviral Regimens in Previously Naive HIV-Infected Subjects

Andrea De Luca, MD; Roberto Bugarini, BStat; Alessandro Cozzi Lepri, PhD; Massimo Puoti, MD; Enrico Girardi, MD; Andrea Antinori, MD; Antonio Poggio, MD; Gabriella Pagano, MD; Giulia Tositti, MD; Gianpiero Cadeo, MD; Antonio Macor, MD; Mario Toti, MD; Antonella d’Arminio Monforte, MD; for the Italian Cohort Naive Antiretrovirals Study Group

Background: The effect of chronic coinfection with hepatitis viruses on the response to therapy against human immunodeficiency virus 1 (HIV-1) remains debated.

Methods: In a prospective cohort study, the effect of hepatitis B virus (HBV) and hepatitis C virus (HCV) serostatus on the outcome of potent HIV-1 therapy was analyzed in HIV-1–infected patients previously naive to antiretroviral therapy. Changes from baseline CD4+ cell counts and HIV RNA levels over time were analyzed by linear regression models. Time to clinical progression and time to reach virologic and immunologic response were analyzed by multivariate Cox proportional hazards regression models.

Results: We studied 1320 patients, among whom 600 were HCV antibody–positive and 90 were HBV surface antigen–positive. During a median follow-up of 37 months (range, 1-48 months), clinical progression was observed in 99 patients (56 new acquired immunodeficiency syndrome–defining events and 43 deaths). In multivariate models, HCV-positive HBV-negative patients showed a shorter time to clinical progression (hazard ratio, 1.55; 95% confidence interval, 1.00-2.41). Patients who were HCV-positive also showed mean CD4+ recoveries over time that were at least 30 cells/µL fewer than those of seronegative patients. Hepatitis virus serostatus did not affect the virologic response to HIV-1 therapy.

Conclusions: Clinical progression of HIV-1 disease after starting potent antiretroviral therapy is accelerated by concomitant infection with HCV. Compared with patients without coinfection, coinfected patients showed impaired CD4+ cell recovery, despite similar virologic response to HIV-1 therapy. These findings may have important implications for the treatment of HCV and for the timing of initiation of HIV-1 therapy in coinfected individuals.

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Potent combination antiretroviral therapies have changed the natural history of human immunodeficiency virus 1 (HIV-1) infection. However, longer patient survival leads to the emergence of hepatic comorbidity due to coinfections with hepatitis viruses, particularly hepatitis C virus (HCV). Significant proportions of HIV-1–seropositive patients, particularly injecting drug users, are coinfected with HCV, and others are chronically infected with hepatitis B virus (HBV). There is substantial evidence that HIV-1 infection and the related immunodeficiency negatively affect the natural history of chronic HCV and HBV infections, leading to increased replication of the viruses and more rapid evolution of liver fibrosis. It is still debated whether HCV coinfection might accelerate the natural history of HIV-1 disease or negatively affect the efficacy of antiretroviral therapy. Recent results from a cohort study have shown that, among patients beginning potent antiretroviral therapy, clinical progression of HIV and impaired recovery of CD4+ cells were associated with HCV seropositivity, independent of suppression of HIV-1 replication. Nevertheless, analyses of other cohorts did not confirm this observation. Therefore, this question needs to be further investigated in other large cohort studies of patients beginning potent antiretroviral therapies, preferably eliminating the bias of prior drug experience. It also remains to be analyzed in more depth whether HCV seropositivity is simply a marker of a patient group characterized by lower medication adherence or by a higher rate of toxicity associated with antiretroviral therapy, and whether observations made in HIV-1–seropositive subjects coinfected with HCV can be extended to those coinfected with HBV.

The objective of this study was to identify whether HBV and HCV serostatus are associated with immunologic, virologic,
and clinical responses in a cohort of antiretroviral-naïve patients initiating potent antiretroviral therapy. We estimated (1) the probability of clinical progression, (2) the mean change in CD4+ cell count and HIV RNA level over time, and (3) the probability of good immunologic and virologic responses.

### PATIENTS AND METHODS

#### ITALIAN COHORT NAIVE ANTIRETROVIRALS

The Italian Cohort Naive Antiretrovirals is a multicenter prospective observational study, started April 1, 1997, of HIV-1–positive persons who were antiretroviral-drug–naïve at the time of enrollment. Informed consent was obtained from all patients before enrollment. Together with the patient, the clinician independently chooses a therapeutic approach, without outside influence from the cohort study group. Demographic, clinical, and laboratory data and information on the specific therapy are collected for all participants and recorded in the cohort database via the Internet. All data relative to the occurrence of any clinical event are registered, or, in the absence of any event, patient data are registered at least every 6 months. All CD4+ cell counts and plasma HIV RNA measurements are recorded. Antiretroviral drugs are assumed to be given at the recommended dosages. Reasons for discontinuing therapy are also collected, as described elsewhere. As of May 31, 2001, 4870 patients had been enrolled.

#### STUDY POPULATION AND METHODS

To be included in the present study, patients in the Italian Cohort Naive Antiretrovirals had to meet the following criteria: (1) started a potent antiretroviral regimen, defined as the combination of at least 3 antiretroviral agents, without previous treatment for HIV-1 infection; (2) been tested for HCV antibodies and hepatitis B surface antigen (HBsAg); (3) have at least 2 measurements of CD4+ cell counts and HIV RNA levels during treatment start, and (4) had no treatment with interferon or other immunomodulating agents before baseline or during follow-up.

Other information used in this study included sex, age at enrollment, risk factors for the transmission of HIV-1 infection, stage, date of HIV treatment initiation, specific antiretroviral regimen, dates of changes in regimens and reasons for these changes, CD4+ cell counts, plasma HIV RNA levels, and alanine aminotransferase levels at initiation of antiretroviral therapy and every 3 months thereafter.

Plasma HIV RNA level was measured using quantitative reverse transcription–polymerase chain reaction (Amplicor; Roche Molecular Systems, Basel, Switzerland), signal amplification branched DNA assay (Quantiplex; Chiron Therapeutics, Emeryville, Calif), or nucleic acid sequence–based amplification (Organon Teknika, Marcy L’Étoile, France). The lower limit of detection of these assays was 500 copies/mL. Ultrasensitive versions (with a lower limit of detection of 50 copies/mL) were used, when appropriate, beginning in May 1998. For values below the limit of detection, we used the logarithm of the lower detection limit, divided by 2. CD4+ cell counts were performed using standard flow cytometry techniques.

#### STATISTICAL ANALYSIS

Descriptive statistical analyses were used to define the characteristics of the study population at the beginning of potent antiretroviral therapy. We then evaluated the trend over time of CD4+ cell counts and HIV RNA levels after initiation of potent antiretroviral therapy. The mean changes per month from baseline CD4+ cell counts and HIV RNA levels were estimated using a regression analysis that takes into account the correlation among repeated measurements at different times in the same patient. Random effect for slope was used, because there was substantial intrapatient and interpatient variation in the timing and number of measurements.

Standard survival analysis techniques by Cox proportional hazards regression were performed, using the time to reach a virologic or an immunologic response or clinical progression as end points. Virologic response was defined as the achievement of plasma HIV RNA levels less than 500 copies/mL, confirmed by at least 2 consecutive determinations. Immunologic response was defined as an increase of at least 100 CD4+ cells/µL or achievement of 500 cells/µL (for this analysis, 33 patients with a baseline CD4+ cell count of >500 cells/µL were excluded). Clinical progression was defined as the occurrence of a new acquired immunodeficiency syndrome (AIDS)–defining opportunistic disorder or death.

Mean effects and hazard ratios, obtained by multivariate mixed linear regression analysis and Cox proportional hazards regression models, respectively, were performed to evaluate whether there were factors associated with the mean changes in CD4+ cell counts and HIV RNA levels over time and with the time to immunologic or virologic response or to clinical progression. The factors analyzed were sex, age, CD4+ cell count, plasma HIV RNA concentration (on a log10 scale), AIDS stage at antiretroviral therapy initiation, HBsAg and HCV antibody serostatus, type of antiretroviral drug included in the treatment regimen, and treatment changes because of laboratory or clinical toxicity. When analyzing clinical progression as an end point, HIV RNA levels and CD4+ cell counts were evaluated as baseline or as time-dependent covariates in 2 separate Cox proportional hazards regression models. All the analyses were performed using an intention-to-treat approach.

#### RESULTS

### BASELINE PATIENT CHARACTERISTICS AND TREATMENT

Of 4870 patients enrolled in the Italian Cohort Naive Antiretrovirals, 1320 met the inclusion criteria and were eligible for analysis. There was no significant difference in the baseline characteristics between the enrolled patients and the other patients starting potent therapy (not shown). Baseline patient characteristics, hepatitis virus serostatus, and antiretroviral regimens given are summarized in Table 1.

Hepatitis C virus antibodies were detected in 600 individuals (45.5%), and HBsAg was detected in 90 (6.8%). As expected, there was a strong association between HIV-1 transmission risk group and positivity for HBV and HCV markers. In particular, 93.3% of the injecting drug users were HCV-coinfected, whereas the frequency of HCV infection among men who have sex with men and persons infected through heterosexual contacts or other routes was much lower (11.7% and 16.4%, respectively) (both χ2, P<.001). Positivity for HBsAg was evenly distributed among persons infected through heterosexual contacts or other routes (6.3%) and injecting drug users (7.1%), and gay men (8.1%) (P>0.1 for all).

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PATIENT FOLLOW-UP AND CLINICAL EVENTS

During a median follow-up of 36.8 months (range, 1-48 months), 335 patients changed their initial regimen because of toxicity or intolerance (6 for hepatotoxicity), 56 developed a new AIDS-defining event, and an additional 43 died. Therefore, a clinical progression end point was reached in 99 patients. New AIDS-defining events were pulmonary or extrapulmonary tuberculosis (n=9), Kaposi sarcoma (n=8), disseminated Mycobacterium avium complex infection (n=7), Pneumocystis carinii pneumonia (n=7), toxoplasmosic encephalitis (n=6), AIDS dementia (n=4), recurrent bacterial pneumonia (n=4), Candida esophagitis (n=4), progressive multifocal leukoencephalopathy (n=3), wasting syndrome (n=3), cytomegalovirus retinitis (n=2), cervical cancer (n=2), disseminated lymphoma (n=1), brain lymphoma (n=1), herpes simplex perianal ulcerations (n=1), and intestinal cryptosporidiosis (n=1). Seven patients showed 2 events at the same time. There was no significant difference in the type of clinical events among the different hepatitis virus serogroups.

Among the patients developing a new AIDS-defining event, 7 subsequently died. These cases were defined as clinical progression at the time of the new AIDS event only. Cause of death among 43 patients included end-stage liver disease (n=3); HIV-related diseases (n=24); non–HIV, non–liver-related diseases (n=12); and unknown (n=4).

DETERMINANTS OF CLINICAL PROGRESSION

Figure 1 shows the cumulative proportion of patients who developed clinical progression to a new AIDS-defining illness or died, by hepatitis virus serostatus. Two Cox proportional hazards regression models, which used viral load and CD4+ cell counts as baseline or as time-dependent variables, were used to analyze independent predictors of clinical progression (Table 2). Both models showed that HBsAg-negative HCV antibody-positive patients had an independent increased hazard of clinical progression (55%-57% higher) compared with subjects without hepatitis virus markers. Also, HBsAg-positive subjects showed an increased hazard ratio of clinical progression, but this was not statistically significant (P=.20), perhaps because of the small number of infected individuals. Individuals with higher CD4+ cell counts at baseline had a lower risk of clinical progression (P<.001), and those with AIDS at baseline were at higher risk of new AIDS-defining events or death (P=.02). Younger age was associated with lower risk of progression only in the model with CD4+ cell count and viral load as baseline covariates (P=.048) (Table 2). Higher ongoing HIV RNA levels showed a trend toward a higher risk of clinical progression (P=.07). Sex (P=.45), active injecting drug use (P=.85), baseline HIV RNA levels (P=.85), type of antiretroviral agents used in the initial combination therapy (nucleoside reverse transcriptase inhibitors, P=.10; hard-gel saquinavir mesylate, P=.45), and treatment change because of toxicity (P=.78) did not significantly affect the hazard of clinical progression.

IMMUNOLOGIC RESPONSES AND THEIR DETERMINANTS

For linear regression analyses, a median of 4 (range, 2-30) follow-up determinations of CD4+ cell counts and HIV RNA levels was used. The association of variables with the mean changes in CD4+ cell counts over time by linear regression analysis is shown in Table 3. The effect of HBV and HCV serostatus on the CD4+ counts over time
Table 2. Adjusted Hazard Ratios of Clinical Progression in 1320 Naive Subjects Starting Potent Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>1.22 (0.71-2.07)</td>
<td>1.19 (0.62-2.13)</td>
</tr>
<tr>
<td>Active injecting drug use</td>
<td>1.07 (0.53-2.12)</td>
<td>1.11 (0.45-2.32)</td>
</tr>
<tr>
<td>Hard-gel saquinavir mesylate–based regimen</td>
<td>0.80 (0.44-1.42)</td>
<td>0.85 (0.34-2.25)</td>
</tr>
<tr>
<td>Nonnucleoside reverse transcriptase inhibitor–based regimen</td>
<td>0.61 (0.27-1.22)</td>
<td>0.72 (0.24-1.34)</td>
</tr>
<tr>
<td>Age &lt;35 y</td>
<td>0.68 (0.48-0.99)†</td>
<td>0.75 (0.54-1.22)</td>
</tr>
<tr>
<td>Baseline HIV RNA (every log10 copies/mL higher)</td>
<td>0.98 (0.77-1.24)</td>
<td>NA</td>
</tr>
<tr>
<td>Baseline CD4* (every 100 cells/µL more)</td>
<td>0.65 (0.54-0.78)‡</td>
<td>NA</td>
</tr>
<tr>
<td>HIV RNA time–dependent (every log10 copies/mL higher)</td>
<td>NA</td>
<td>1.56 (0.97-2.03)</td>
</tr>
<tr>
<td>CD4* time–dependent (every 100 cells/µL more)</td>
<td>NA</td>
<td>0.72 (0.43-1.12)</td>
</tr>
<tr>
<td>Acquired immunodeficiency syndrome diagnosis</td>
<td>1.68 (1.07-2.67)§</td>
<td>1.79 (1.12-3.34)§</td>
</tr>
<tr>
<td>Treatment change for toxicity</td>
<td>1.06 (0.68-1.66)</td>
<td>1.06 (0.56-1.74)</td>
</tr>
<tr>
<td>HBSAg* and HCV Ab*</td>
<td>1.83 (0.72-4.65)</td>
<td>1.89 (0.77-4.98)</td>
</tr>
<tr>
<td>HBSAg and HCV Ab*</td>
<td>1.55 (1.00-2.41)¶</td>
<td>1.57 (1.01-2.61)#</td>
</tr>
<tr>
<td>HBSAg* and HCV Ab*</td>
<td>1.68 (0.66-4.28)</td>
<td>1.62 (0.64-4.48)</td>
</tr>
</tbody>
</table>

Data are given as hazard ratio (95% confidence interval). NA indicates not applicable; HIV, human immunodeficiency virus; HBSAg, hepatitis B surface antigen; HCV, hepatitis C virus antibody; plus sign, positive; and minus sign, negative.

*P = .048.
†P = 0.001.
‡P = .02.
§P = .034.
¶P = .05.
#P = .04.

Table 3. Multivariate Linear Regression Analysis Indicating the Differences in Mean Changes From Baseline CD4+ Cell Counts and Human Immunodeficiency Virus (HIV) RNA Levels According to Different Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>CD4+ Changes</th>
<th>HIV RNA Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Cells/µL</td>
<td>Mean Log10 Copies/mL</td>
</tr>
<tr>
<td>Month (for each month increase)</td>
<td>6.73</td>
<td>-0.03</td>
</tr>
<tr>
<td>Male sex</td>
<td>-19.3</td>
<td>-0.07</td>
</tr>
<tr>
<td>Active injecting drug use</td>
<td>1.1</td>
<td>0.21</td>
</tr>
<tr>
<td>Hard-gel saquinavir mesylate–based regimen</td>
<td>-7.2</td>
<td>0.32</td>
</tr>
<tr>
<td>Nonnucleoside reverse transcriptase inhibitor–based regimen</td>
<td>5.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Age &lt;35 y</td>
<td>3.9</td>
<td>-0.04</td>
</tr>
<tr>
<td>Baseline HIV RNA (every log10 copies/mL higher)</td>
<td>-8.6</td>
<td>-0.59</td>
</tr>
<tr>
<td>Baseline CD4* (every 100 cells/µL more)</td>
<td>4.4</td>
<td>-0.14</td>
</tr>
<tr>
<td>HIV RNA ongoing (every log10 copies/mL higher)</td>
<td>-42.8</td>
<td>NA</td>
</tr>
<tr>
<td>CD4* ongoing (every 100 cells/µL more)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Acquired immunodeficiency syndrome diagnosis at baseline</td>
<td>-6.3</td>
<td>0.15</td>
</tr>
<tr>
<td>HBSAg* and HCV Ab*</td>
<td>-19.3</td>
<td>0.03</td>
</tr>
<tr>
<td>HBSAg and HCV Ab*</td>
<td>-34.9</td>
<td>-0.008</td>
</tr>
<tr>
<td>HBSAg* and HCV Ab*</td>
<td>-31.6</td>
<td>-0.003</td>
</tr>
</tbody>
</table>

Value Mean Log 10 Copies/mL Value

*NA indicates not applicable; HBSAg, hepatitis B surface antigen; HCV Ab, hepatitis C virus antibody; plus sign, positive; and minus sign, negative.

is illustrated in Figure 2. After adjusting for all the significant variables, including active injecting drug use and ongoing viral load, HBSAg-negative HCV antibody–positive subjects and HBSAg-positive HCV antibody–positive subjects independently showed less increase in CD4+ cell counts over time compared with individuals who were seronegative for both hepatitis virus markers (by −34.9 and −31.6 cells/µL, respectively). Hepatitis B surface antigen–positive HCV-seronegative subjects showed a nonstatistically significant reduced CD4+ count increase compared with those who were seronegative for HBV and HCV. Analyses were repeated and confirmed with similar slopes after exclusion of the active injecting drug users from the analyses (data not shown). The simple analyses grouping the patients by single hepatitis virus serostatus indicated that HCV antibody–positive individuals had significantly worse mean CD4+ cell count changes compared with HCV antibody–negative individuals (by −47.1 cells/µL, P < .001), while HBSAg-positive subjects showed less increase compared with HBSAg-negative subjects (by −15.5 cells/µL), but this difference was nonsignificant (P = .29). Alanine aminotransferase levels at baseline and during follow-up did not have any significant effect on the mean changes in CD4+ cell counts over time on univariate analysis (data not shown) and were not included in the multivariate model.

In the multivariate Cox proportional hazards model, HBSAg-seronegative HCV-seropositive patients showed a 28% reduced probability of reaching the immunologic end point compared with HBSAg-negative HCV-negative patients (Table 4). Hepatitis B virus serostatus
did not show any appreciable association with this immunologic end point.

**Virologic Responses and Their Determinants**

Hepatitis B virus and HCV serostatus did not affect the virologic response to potent antiretroviral therapy, as shown by linear regression analysis in Table 3. Subjects showing significantly worse virologic responses were active injecting drug users, subjects treated with hard-gel saquinavir as a single protease inhibitor, and subjects with a previous AIDS diagnosis. A better virologic response was obtained in patients with higher HIV RNA levels and higher CD4+ cell counts at baseline. Cox proportional hazards regression analysis confirmed that HBV and HCV serostatus did not affect the virologic response (Table 4). The only independent predictor of a shorter time to reach HIV RNA levels less than 500 copies/mL was discontinuation of the initial regimen for toxicity, while therapy with nonnucleoside reverse transcriptase inhibitors, instead of protease inhibitors, and protease inhibitor therapy with hard-gel saquinavir were associated with worse virologic outcomes.

**Comment**

Our analysis of a cohort of antiretroviral-naive individuals beginning potent combination therapy for HIV infection showed that subjects who were HCV antibody-positive had an increased risk of new AIDS-defining clinical events or death. The risk was increased by a mean of 55% to 57% in HCV antibody-positive and HBsAg-negative patients and was independent of previous AIDS diagnosis, CD4+ cell counts and plasma HIV-1 loads at baseline and during follow-up, type of medication, and treatment changes for toxicity, sex, age, and active injecting drug use. Hepatitis B surface antigen-positive patients without HCV antibodies also showed an increased hazard of clinical progression after beginning antiretroviral therapy, but this was not statistically significant (P = .20), perhaps because of the small numbers observed. During a median follow-up of 3 years, HCV-seropositive HIV-1–infected patients showed an impaired immune reconstitution after beginning potent HIV therapy, with a mean CD4+ recovery from baseline that was at least 30 cells/µL fewer than that of HCV-seronegative patients, which was independent of viral suppression. In contrast, multivariate analysis showed that serostatus for HBV or HCV did not affect the HIV RNA changes from baseline over time or the time to reach HIV RNA levels less than 500 copies/mL.

These findings confirm and reinforce those of a previous Swiss cohort study showing similar increased risks of progression to new AIDS-defining events or death in HCV-seropositive patients. Hepatitis C virus–positive individuals had hazard ratios of clinical progression of 1.7 in the Swiss cohort and approximately 1.6 in our cohort, while the hazard ratios for the time to immunologic response were 0.77 and 0.72, respectively. The high reproducibility of the findings in 2 large cohorts supports the strength of this association.

To test whether HCV seropositivity was a marker of antiretroviral drug–related hepatotoxicity or lower medication adherence in this subgroup of individuals, we used several adjunctive strategies. First, the use of linear regression allowed us to analyze changes in CD4+ cell counts and HIV RNA levels from the baseline levels during the entire follow-up. This had several advantages, because it allowed a more complete analysis of all the determinants and it avoided the need for an arbitrary selection of an immunologic or virologic end point and the bias due to different numbers of determinants per patient. Second, in different models, we adjusted for the risk of clinical progression and the CD4+ changes by the ongoing viral load and alanine aminotransferase determinants.
minants (data not shown). These gave us a more direct measure of the ongoing patient adherence and treatment toxicity, respectively. Third, we adjusted for the effect of hepatitis virus serostatus by treatment discontinuation or changes because of toxicity, assuming that HCV seropositivity might have led to a more generalized increase in all kinds of treatment toxicity, beyond liver toxicity, due to reduced drug metabolism.22 Although treatment change because of toxicity increased the probability of virologic and immunologic success, the effect of HCV serostatus remained the same. Fourth, we adjusted the analysis for active injecting drug use, assuming a lower medication adherence in this subset of patients,23 and the effect of HCV seropositivity on CD4+ reconstitution and clinical progression remained independent. Fifth, we analyzed only patients starting potent antiretroviral therapy without prior use of suboptimal therapies and adjusted for the effect of hepatitis virus serostatus by the type of antiretroviral medication used. To prevent treatment toxicity, coinfected patients might have been prescribed suboptimal regimens before potent therapy or less aggressive regimens of potent treatment combinations.24 Therefore, our patient selection avoided this potential confounder. In contrast to findings from the present study and from the Swiss cohort, other cohorts did not detect any significant effect of HCV serostatus on clinical progression and immune recovery that was independent of the use and effectiveness of potent antiretroviral therapy.53,54 Potential confounders in different patient populations, such as those with a higher proportion with incomplete medication adherence and more severe underlying liver disease, might reduce the sensitivity of detection of an independent effect of HCV serostatus on these outcomes.

The mechanisms by which HCV-positive serostatus might lead to increased AIDS-related morbidity and mortality and to impaired CD4+ recovery after starting potent antiretroviral therapy are not well understood. Our findings suggest that increased drug toxicity and reduced medication adherence should not be major determinants of this phenomenon. Nevertheless, because there was no direct measurement of patient adherence in this study, this issue deserves further investigation. As indicated by alanine aminotransferase levels during the follow-up, necroinflammatory activity due to hepatitis viruses was not related to the described clinical and immunologic effect of HCV coinfection. Furthermore, the effect of HBV infection was not significant or, at best, was less than that of HCV seropositivity. Nevertheless, we cannot rule out that the effect of HBV coinfection might have been underestimated because of the small proportion of individuals who were HBsAg-positive in this cohort.

A possible explanation is that chronic HCV infection might be associated with persistent immune activation. Activation of immune cells has been shown to correlate with CD4+ T-cell apoptosis and is a stronger marker of HIV-1 disease progression than HIV RNA levels.25 Furthermore, there is evidence of active HCV replication in lymphoid tissue26 and in peripheral blood CD4+ cells in HIV-1–infected patients,27 in CD34+ progenitor cells,28 and in lymphoblastoid cells.29 Correlation of infection of peripheral blood mononuclear cells with HCV with Fas-mediated apoptosis has been shown30 and might explain the reduced CD4+ recovery and enhanced clinical progression after inhibition of HIV-1 replication by antiretroviral therapy.

In agreement with our findings and this hypothesis is the evidence from other studies that HCV coinfection might lead to faster clinical progression of HIV-1 disease12,13 and that higher HCV levels and specific genotypes have been associated with accelerated HIV-1 disease progression with suboptimal or absent antiretroviral medication.31,32 These latter findings are worthy of further investigation to identify whether enhanced HCV replication, specific genotypes, or quasispecies33 are related to clinical progression or reduced immune recovery with potent therapeutic inhibition of HIV-1.

A major limitation of this study was the fact that HCV infection has been analyzed by serologic examination only. Nevertheless, more than 90% of HCV antibody–positive HIV-infected individuals have HCV RNA in their serum.34 Moreover, defining these patients by serostatus only might have diluted and underestimated the effect of HCV on CD4+ recovery and clinical progression. Therefore, we expect that, with a direct measure of HCV infection, the observed effect of coinfection might have been larger. Another limitation is the evaluation of HBV by serum surface antigen only. We cannot exclude that occult HBV infection (ie, presence of HBV DNA in serum or liver tissue in the absence of serum HBsAg positivity) or co-infections with other parenterally transmitted viruses associated with HCV (hepatitis G virus, transfusion-transmitted virus, and SEN virus) might have been implicated in the impaired CD4+ recovery after potent HIV-1 therapy. An association of these 3 viruses with any human pathologic condition has yet to be demonstrated. However, recent reports35,36 indicate that active infection with hepatitis G virus is associated with reduced HIV replication and improved survival of HIV-infected patients. Despite the similarity between hepatitis G virus and HCV, the former is more easily sexually transmitted, so that among HIV-seropositive individuals the prevalence is similar between injecting drug users and other risk groups.37 It will be interesting to analyze the effect of HCV and hepatitis G virus infections on survival and treatment response of HIV-infected patients.

In conclusion, HCV seropositivity was associated with an increased risk of progression to new AIDS-defining events or death in treatment-naive HIV-1–positive patients after beginning potent antiretroviral therapy. Hepatitis C virus–positive serostatus was also associated with a consistently reduced recovery of CD4+ cells over time, without affecting the antiviral activity of HIV therapy. These effects appeared to be independent of surrogate measures of patient adherence and medication toxicity and were not associated with liver necroinflammatory activity. Direct effects of HCV on the immune cells and their function in association with HIV-1 infection can be hypothesized but need further investigation. Our findings have important implications regarding the decision to treat HCV in patients coinfected with HIV-1 and the timing of initiation of HIV therapy in coinfected individuals.
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From the Institute of Clinical Infectious Diseases, Catholic University of the Sacred Heart (Dr De Luca), Centro Operativo AIDS, Italian Institute of Health (Dr Bugarini), National Institute of Infectious Diseases “L Spallanzani” (Drs Girardi and Antonini), Rome; Institute of Infectious and Tropical Diseases, University of Brescia (Dr Puoti), and Department of Infectious Diseases, “Spedali Civili” (Dr Cadeo), Brescia; Departments of Infectious Diseases “Ospedale Civile” Pallanza, Verbania (Dr Poggio), Hospital “S Martino,” Genova (Dr Pagano), Hospital of Vicenza, Vicenza (Dr Tositti), “Amedeo di Savoia” Hospital, Torino (Dr Macor), Hospital of Grosseto, Grosseto (Dr Toti); and Institute of Infectious and Tropical Diseases, University of Milano, Milano (Dr d’Arminio Monforte), Italy; and Royal Free Centre for HIV Medicine and Department of Primary Care and Population Sciences, Royal Free and University College Medical School, London, England (Dr Cozzi Lepri).

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Corresponding author and reprints: Andrea De Luca, MD, Istituto di Clinica delle Malattie Infettive, Università Cattolica del S Cuore, L.go F Vito 1, 00168 Roma, Italy (e-mail: andrea.deluca@rm.unicatt.it).

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