Liver Injury and Changes in Hepatitis C Virus (HCV) RNA Load Associated with Protease Inhibitor–Based Antiretroviral Therapy for Treatment-Naive HCV-HIV–Coinfected Patients: Lopinavir-Ritonavir versus Nelfinavir

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Background. Highly active antiretroviral therapy (HAART) initiation in patients coinfected with human immunodeficiency virus type 1 (HIV-1) and hepatitis C virus (HCV) has been associated with transaminase and HCV viral load flares. Previous studies have included highly variable antiretroviral regimens. We compared effects of 2 protease inhibitor–based regimens on alanine aminotransferase (ALT) levels and HCV loads in HCV-HIV–coinfected patients initiating HAART.

Methods. Seventy HIV-infected patients with positive baseline results of HCV enzyme-linked immunosorbent assay from a treatment trial comparing lopinavir-ritonavir with nelfinavir were evaluated during a 48-week period. HCV and HIV titers were analyzed at baseline, at weeks 24 and 48 of treatment, and during flares in the ALT level of >5 times the upper limit of normal.

Results. A total of 57 of 70 patients tested positive for HCV RNA at baseline. HCV titers for patients in lopinavir-ritonavir and nelfinavir groups, respectively, were as follows: baseline, 6.07 and 6.22 log IU/mL; week 24 of treatment, 6.68 and 6.48 log IU/mL; and week 48 of treatment, 6.32 and 6.44 log IU/mL. Of patients with a CD4+ cell count of <100 cells/mm³ at baseline, 5 of 11 in the nelfinavir group and 0 of 10 in the lopinavir-ritonavir group had an increase in the HCV load of >0.5 log IU/mL from baseline to week 48. The mean ALT level increased by 45 U/L at 24 weeks and 18 U/L at 48 weeks in the nelfinavir group but decreased by 18 U/L at 24 weeks and 7 U/L at 48 weeks in the lopinavir-ritonavir group. Eight patients in the nelfinavir group and 2 patients in the lopinavir-ritonavir group had grade 3 or 4 flares in the ALT level.

Conclusions. HAART initiation is associated with increased HCV loads and ALT levels. A low baseline CD4+ cell count is associated with persistent increases in the HCV RNA load in nelfinavir-treated patients. These results warrant careful interpretation of abnormalities in the ALT load after HAART initiation in HCV-HIV–coinfected patients to prevent premature discontinuation of treatment.

Hepatitis C virus (HCV) and HIV share common modes of transmission via parenteral exposure, blood transfusion, and sexual contact. It is not surprising, therefore, that HCV-HIV coinfection is frequently observed among cohorts with shared risk factors. In the United States, >20% of HIV-infected patients are also chronically infected with HCV [1]. Coinfection with these agents leads to increased liver-associated morbidity and mortality [2]. Furthermore, concerns regarding use of potentially hepatotoxic antiretroviral agents may limit appropriate drug intervention in HIV-positive individuals with HCV infection [3].

Several published reports suggest that initiation of HAART is associated with a paradoxical increase in HCV RNA titers [4–6]. These increases have been described as transient in some cohorts but as more persistent in others. Efforts to identify subpopulations with the highest risk of HCV load increase have yielded con-
flicting results, as well. Chung et al. [4] reported that subjects with a baseline CD4+ cell count of <350 cells/mL were most likely to demonstrate increased viral titers during a 48-week period. Cooper et al. [7] noted this outcome only in subjects drinking >50 g of alcohol per day.

Discrepancies in the reported literature may be due to variability in the study designs and cohorts under evaluation. Failure to control for the multitude of available antiretroviral drug combinations limits interpretation of the data. Given the hypothesis that HAART initiation may be associated with transaminase flares and increased HCV titers, we sought to evaluate the impact of 2 specific protease inhibitor–based HAART regimens on transaminase levels and HCV loads in HCV–HIV–coinfected, antiretroviral treatment–naive patients enrolled in a prospective, randomized treatment trial.

SUBJECTS AND METHODS

Subjects. The parent study enrolled 653 patients recruited from 93 centers in 13 countries in North America, South America, Europe, Africa, and Australia [8]. Inclusion criteria were age of ≥12 years, HIV RNA load of at least 400 copies/mL (as measured by the Amplicor HIV-1 Monitor [Roche]), a Karnofsky score of >70, and no previous treatment with stavudine or lamivudine or with any other antiretroviral therapy for >14 consecutive days. There was no restriction on the CD4+ cell count. Exclusion criteria included treatment for an opportunistic infection within 30 days before screening, pregnancy, and alanine aminotransferase (ALT) or aspartate aminotransferase levels >3 times the upper limit of normal.

All subjects were screened for HCV by means of an HCV ELISA (Abbott Laboratories, Diagnostics Division). This assay has high sensitivity in HIV-infected populations and is unlikely to yield false-negative reactions [1]. Testing for HCV RNA in patients with positive results of HCV ELISA (as described below) was used to identify the relevant subset of interest. Subjects were screened for coinfection with hepatitis B virus by the Auszyme monoclonal ELA kit (Abbott Laboratories, Diagnostics Division) and the HBsAg Confirmatory assay (Abbott Laboratories, Diagnostics Division). All subjects provided informed consent for study participation, and protocols were approved by institutional review boards at all active sites. The parent study conformed to CONSORT guidelines for randomized clinical trials [9].

Treatment regimens. Patients in the parent cohort were

| Table 1. Summary of demographic characteristics of HIV-infected subjects with or without hepatitis C virus (HCV) coinfection. |
|--------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Variable                                         | HCV-HIV–coinfected group LPV-RTV (n = 29) | LPV-RTV (n = 326) | Nelfinavir (n = 41) | Nelfinavir (n = 327) |
| Sex                                              | 23 (79) | 31 (76) | 260 (80) | 264 (81) |
| Male                                             | 6 (21) | 10 (24) | 66 (20) | 63 (19) |
| Female                                           | 41.9 (23–84) | 37.8 (22–68) | 38.4 (19–84) | 37.3 (20–68) |
| Age, median years (range)                        | White | 15 (52) | 26 (63) | 184 (45) | 190 (58) |
| Race                                             | Black | 11 (38) | 9 (22) | 81 (25) | 83 (25) |
| Hispanic                                         | 2 (7) | 5 (12) | 48 (15) | 37 (11) |
| Other                                            | 1 (3) | 1 (2) | 5 (2) | 5 (2) |
| Alcohol abuse                                    | No | 5 (17) | 13 (32) | 88 (27) | 92 (28) |
| Yes                                              | Current | 14 (48) | 17 (41) | 179 (55) | 187 (57) |
| Past                                             | 9 (31) | 10 (24) | 58 (18) | 45 (14) |
| Unknown                                          | 1 (3) | 1 (2) | 1 (<1) | 3 (1) |
| Risk factora                                    | Injection drug use | 16 (55) | 23 (56) | 26 (8) | 27 (8) |
| Gay or bisexual man                              | 6 (21) | 8 (20) | 183 (56) | 182 (56) |
| HIV-positive sex partner                         | 4 (14) | 11 (27) | 91 (28) | 102 (31) |
| NOTE. Data are no. (%) of subjects, unless otherwise indicated. HCV-HIV–coinfected subjects are a subpopulation of the HIV-infected subjects, who were participating in a parent study [8]. No significant differences were found in any demographic characteristic (P > .05). lopinavir/ritonavir; N, nelfinavir. |
| a Subjects may have >1 risk factor.             |
Table 2. Baseline disease characteristics in the hepatitis C virus (HCV) substudy and Abbott 863.

| Variable                      | HCV-HIV–coinfected group | HIV-infected group |
|-------------------------------|--------------------------|--------------------|
|                               | LPV-RTV (n = 29)         | Nelfinavir (n = 41) |
|                               |                          |                    |
| Baseline log HCV load, IU/mL  | 6.07                     | 6.22               |
| Mean                          | Not applicable           | Not applicable     |
| Median (range)                | 6.28 (1.70–7.32)         | 6.45 (2.95–7.36)   |
| Baseline log HIV load, copies/mL | 4.94                     | 4.93               |
| Mean                          | 4.89                     | 4.92               |
| Median (range)                | 5.12 (3.02–6.28)         | 5.02 (2.98–6.72)   |
| Baseline CD4+ cell count, cells/mL | 252                      | 253                |
| Mean                          | 250                      | 258                |
| Median (range)                | 205 (2.5–868)            | 186 (15–818)       |
| Baseline CD8+ cell count, cells/mL | 754                      | 801                |
| Mean                          | 745                      | 812                |
| Median (range)                | 578 (171–2357)           | 803 (257–1927)     |
| Baseline ALT concentration, U/L | 44 (16–265)              | 39 (14–100)        |
| Mean                          | 55                       | 38                 |
| Median (range)                | 55 (16–265)              | 39 (14–100)        |

NOTE. HCV-HIV–coinfected subjects are a subpopulation of the HIV-infected subjects, who were participating in a parent study [8]. ALT, alanine aminotransferase; LPV-RTV, lopinavir-ritonavir.

a A total of 22 LPV-RTV recipients and 35 nelfinavir recipients had baseline data on their HCV load.

randomized in a phase III multicenter registration trial to receive either 400 mg of lopinavir and 100 mg of ritonavir (Kaletra; Abbott Laboratories) twice daily plus nelfinavir placebo 3 times daily (326 patients) or to receive nelfinavir (Viracept; Agouron) at a dosage of 750 mg 3 times daily plus lopinavir-ritonavir placebo twice daily (327 patients) [8]. All patients also received open-label lamivudine (150 mg twice daily [Epivir; GlaxoSmithKline]) and stavudine (40 mg twice daily [Zerit; Bristol-Myers Squibb]; patients weighing <60 kg received 30 mg). If adverse events related to stavudine or lamivudine occurred, the drug could be discontinued and replaced with another nucleoside reverse-transcriptase inhibitor at the discretion of the investigator.

Sample collection. Patients in the parent study were eval-

Table 3. Reasons for study discontinuation at or before week 48.

| Reason for discontinuation                      | HCV-HIV–coinfected group, no. (%) of subjects | HIV-infected group, no. (%) of subjects |
|-------------------------------------------------|-----------------------------------------------|----------------------------------------|
|                                                 | LPV-RTV (n = 29) | Nelfinavir (n = 41) | LPV-RTV (n = 326) | Nelfinavir (n = 327) |
| Study drug–related adverse event                | 1 (3)a          | 0                   | 11 (3.4)          | 12 (3.7)           |
| Other adverse or HIV-related event              | 1 (3)b          | 0                   | 5 (1.5)           | 2 (0.6)            |
| Lost to follow-up                               | 1 (3)           | 4 (10)              | 13 (4.0)          | 16 (4.9)           |
| Personal reasons                                | 1 (3)           | 0                   | 14 (4.3)          | 10 (3.1)           |
| Death                                           | 1 (3)b          | 1 (2)               | 5 (1.5)           | 3 (0.9)            |
| Required medication prohibited by study protocol| 1 (3)           | 0                   | 1 (0.3)           | 0                  |
| Virologic failure                               | 0               | 1 (2)               | 2 (0.6)           | 30 (9.2)           |
| Noncompliance with treatment                    | 0               | 0                   | 7 (2.1)           | 6 (1.8)            |
| Other                                           | 1 (3)           | 0                   | 0                 | 0                  |
| Totala                                          | 6 (21)          | 6 (15)              | 56 (17.2)         | 77 (23.5)          |

NOTE. HCV-HIV–coinfected subjects are a subpopulation of the HIV-infected subjects, who were participating in a parent study [8]. LPV-RTV, lopinavir-ritonavir; NFV, nelfinavir.

a Subject experienced anorexia that was probably related to study drug, according to the investigator.
b One subject experienced pancreatitis and pneumonia not related to study drug. The episode of pneumonia led to death.
c For a comparison between the treatment arms of the parent study. All patients who discontinued the study with an investigator-specified reason of virologic failure had reached a protocol-specific end point.
d One patient in the LPV-RTV arm of the parent study indicated >1 reason for discontinuation.
Figure 1. Kaplan-Meier estimates of time in weeks to undetectable HIV load of either <400 copies/mL (Roche Amplicor Monitor assay; A) or <50 copies/mL (Roche Ultrasensitive HIV RNA assay, beginning at week 24 of treatment; B) for patients who tested positive for hepatitis C virus by EIA at baseline. A total of 29 patients received lopinavir-ritonavir (LPV-RTV), and 41 patients received nelfinavir (NFV). By week 48 of therapy, 100% of patients treated with LPV-RTV and 87% of patients randomized to receive NFV achieved an HIV RNA load of <400 copies/mL (P = .274, by the log-rank test). Similar results were observed between groups when a decrease to 50 HIV RNA copies/mL was used as an end point; 100% of LPV-RTV–treated subjects and 73% of NFV–treated subjects reached this end point by week 48 (P = .308, by the log-rank test).

Figure 2. Changes in CD4⁺ cell count over time in lopinavir-ritonavir (LPV-RTV)–treated patients and nelfinavir (NFV)–treated patients from baseline (week 0) through week 48 of treatment.

HIV RNA detection, quantitation, and genotyping. Samples were coded and tested in batches at the University of Cincinnati. Personnel were trained and certified in the assay procedures, and the laboratory is Clinical Laboratory Improvement Amendments–certified for HCV RNA testing and analysis. All HCV ELISA-reactive samples were initially evaluated using the Amplicor Monitor assay, which has a linear range of 600–500,000 IU/mL for detection of HCV RNA. Aliquots in which HCV RNA was not detected were retested using the Amplicor Qualitative HCV RNA assay (Roche), which has a sensitivity of 50 IU/mL. HCV load was measured at baseline, at weeks 24 and 48, and when the ALT level was >5 times the upper limit of normal (170 U/L for women and 215 U/L for men, specified as grade 3+ elevations in the Division of AIDS table for grading adult adverse experiences [10]). HCV RNA genotypes were determined at baseline using the InnoLipa reverse hybridization assay (Bayer), in accordance with the manufacturer’s instructions.

HIV RNA detection and quantitation. HIV RNA viral load was evaluated using the Amplicor Monitor assay in accordance with the manufacturer’s instructions at baseline and every 4 weeks through week 24 of treatment. Testing frequency was reduced to 8-week intervals between weeks 24 and 48. The Roche Amplicor Ultrasensitive (<50 copies/mL) was not performed until week 24.

Statistical evaluation. Fisher’s exact test was used to eval-
Figure 3. Mean changes in hepatitis C virus (HCV) load for all HCV RNA–positive patients (A) or <100 cells/mm³ (B), by treatment group. LPV-RTV, lopinavir-ritonavir; NFV, nelfinavir.

Figure 4. Changes from baseline to week 48 in mean alanine aminotransferase (ALT) levels for patients who tested positive for hepatitis C virus RNA at baseline. Statistically significant differences in ALT levels were observed between treatment groups at week 24 after HAART initiation. At week 24, a mean increase in the ALT level of 45 U/L was observed in the nelfinavir (NFV) arm, and a mean decrease of 18 U/L was noted in patients receiving lopinavir-ritonavir (LPV-RTV). After 48 weeks of therapy, the mean ALT levels in both groups did not differ significantly from baseline levels.

RESULTS

Demographic characteristics. Seventy (11%) of 653 subjects enrolled in the parent clinical trial were HCV-antibody reactive upon HCV ELISA testing. Of this group, 57 subjects (81%) had HCV RNA detectable by either the quantitative or the qualitative assay. Whereas the majority of patients (56 [98%] of 57) had a viral titer sufficiently large enough to be detected by the less sensitive quantitative methodology, 1 subject (2%) had very low viral titer identifiable only by the qualitative PCR assay. No patient tested positive for hepatitis B virus. Table 1 displays the characteristics of the HCV substudy group relative to the parent study group classified by treatment arms. There were no statistically significant differences between the HCV RNA–positive subjects after randomization.

Table 2 demonstrates the baseline HCV and HIV disease characteristics observed after randomization among patients in the HCV subgroup and patients in the parent cohort. No statistically significant differences were observed in baseline HCV RNA levels, HIV RNA levels, CD4+ cell counts, or CD8+ cell counts between the treatment groups. A total of 6 patients in each treatment group of the HCV substudy withdrew after therapy was initiated. Reasons for dropout among patients in the substudy and patients in the parent study are displayed in table 3. In the HCV substudy, there were no statistically significant differences between treatment arms regarding the rea-
Figure 5. Alanine aminotransferase (ALT) levels from baseline to week 48 in patients with grade 3 or 4 flares in the ALT level (2 of 22 patients who received lopinavir-ritonavir [dashed line]; and 8 of 35 patients who received nelfinavir [solid lines]; $P = .18$). See Results for additional statistical analysis.

Figure 6. Data for individual patients who received lopinavir-ritonavir, showing alanine aminotransferase (ALT) levels and hepatitis C virus (HCV) RNA loads from baseline to week 48 of treatment in patients with grade 3 or 4 flares in the ALT level.

Effect of HAART on HIV load, CD4+ cell count, and HCV load. Patients in each treatment arm of the HCV substudy experienced dramatic decreases in HIV loads. By week 48 of therapy, 100% of subjects treated with lopinavir-ritonavir and 87% of subjects randomized to receive nelfinavir achieved HIV RNA loads of <400 copies/mL ($P = .274$). Similar results were observed between groups when a decrease to 50 copies/mL was used as an end point; 100% of lopinavir-ritonavir–treated subjects and 73% of nelfinavir–treated subjects reached this end point by week 48 ($P = .308$). Figures 1A and 1B demonstrate the HIV response among HCV-infected subjects by means of Kaplan-Meier estimates of time to the designated end point. As expected, HIV suppression was associated with a concomitant increase in CD4+ cell counts. A comparison of HCV-infected patients with HCV-uninfected patients in the parent cohort revealed no significant differences in virologic or immunologic response. In contrast, among subjects infected with HCV who were treated with lopinavir-ritonavir, the mean increase in the CD4+ cell count was 234 cells/mm$^3$ at 48 weeks, compared with 184 cell/mm$^3$ for those treated with nelfinavir. This difference was not statistically significant. However, among subjects with a CD4+ cell count of <100 cells/mm$^3$ at baseline, the mean increase in the CD4+ cell count from baseline to week 48 was 221 cells/mL in the lopinavir-ritonavir group versus 147 cells/mL in the nelfinavir group ($P = .049$). The overall change in the CD4+ cell count for the 2 treatment groups is shown in figure 2.

The mean HCV load for HCV-positive subjects in both treatment groups increased after initiation of HAART (figure 3B). By week 24, HCV titers had increased to 6.68 and 6.48 log IU/mL in the lopinavir-ritonavir and nelfinavir groups, respectively (6.1% and 9.6% increases from baseline among patients with measurements at both time points). By week 48, these levels were 6.32 and 6.44 log_{10} IU/mL, respectively (1.1% and 8.0% increases, respectively, from baseline). In the subset of patients with a low CD4+ cell count, HAART initiation was associated with larger increases in HCV load (figure 3B). The mean viral load for patients with a low CD4+ cell count who were receiving lopinavir-ritonavir increased by 6.4% from 5.72 log IU/mL at baseline to 6.75 log IU/mL at week 24 and was 5.95 log IU/mL (5.2% decrease from baseline levels among patients with measurements at both time points) at week 48. In the nelfinavir group, the mean levels were 5.57 log IU/mL at baseline, 6.28 log IU/mL at week 24 (23.3% increase from baseline), and 6.49 log IU/mL at week 48 (26.5% increase from baseline). Among patients with a baseline CD4+ cell count of <100 cells/mL, 5 of 11 nelfinavir-treated patients experienced an increase in the
HCV load from baseline to week 48 of >0.5 log IU/mL, compared with 0 of 10 lopinavir-ritonavir–treated patients ($P = .035$).

Liver injury. Hepatocellular injury was evaluated by assessment of serum ALT levels before, during, and after HAART initiation in all 70 subjects with positive ELISA results. The mean ALT at baseline was 55 U/L for the lopinavir-ritonavir group and 47 U/L for the nelfinavir group ($P = $ not significant). Of the 57 patients with detectable HCV RNA loads at baseline, the mean ALT level at baseline was 61 U/L in the lopinavir-ritonavir arm and 51 U/L in the nelfinavir arm ($P = $ not significant). Statistically significant differences in ALT concentrations were observed between treatment groups at week 24 after HAART initiation (figure 4). At week 24, a mean increase in

Figure 7. Data for individual patients who received nelfinavir, showing alanine aminotransferase (ALT) levels and hepatitis C virus (HCV) RNA loads from baseline to week 48 of treatment in patients with grade 3 or 4 flares in the ALT level.
ALT level of 45 U/L (a 111.4% increase from baseline) was observed in the nelfinavir arm, and a mean decrease of 18 U/L (a 5.5% decrease from baseline) was noted for patients receiving lopinavir-ritonavir. After 48 weeks of therapy, the mean ALT levels in both groups did not differ significantly from baseline levels.

Among 7 patients in the lopinavir-ritonavir group and 11 patients in the nelfinavir group with a CD4+ cell count of <100 cells/mm³, the mean ALT level decreased by 26 U/L (40.2%) and 15.1 U/L (48.3%), respectively, between baseline and week 24 (P = .002). Similar to the findings for all patients in the substudy, mean ALT levels among HCV-infected patients with a CD4+ cell count of <100 cells/mm³ were comparable at 48 weeks.

Use of the Division of AIDS table for grading adult adverse experiences revealed that 8 subjects (19.5%) who were treated with nelfinavir and 2 subjects (6.9%) who were treated with lopinavir-ritonavir had grade 3 or 4 ALT-related adverse events (P = .18) [8]. The pattern of increases in the ALT levels among patients with grade 3 or 4 adverse event scores is shown in figure 5. Flares in ALT levels tended to occur later among the lopinavir-ritonavir–treated subjects than among nelfinavir-treated subjects (hazard ratio, 2.93; 95% CI, 0.62–13.8; P = .18).

We also reviewed the association between increases in the ALT level and changes in the HCV RNA load. For the 2 lopinavir-ritonavir–treated subjects with grade 3 or 4 flares in the ALT level, there appeared to be a concomitant increase of >0.5 log IU/mL in the HCV load (figure 6). One of these patients, however, had a very low HCV titer at baseline (<2.7 log IU/mL) and experienced a dramatic increase in HCV load, whereas the other patient had a baseline HCV load of 6.6 log IU/mL that increased to 7.4 log IU/mL. In the nelfinavir-treated group, 5 of 8 patients with grade 3 or 4 flares in ALT levels either had no change or a slight decrease in HCV load, whereas 3 of 8 patients had clear increases (figure 7). In subjects without grade 3 or 4 flares in the ALT level, 2 (7%) of 27 lopinavir-ritonavir–treated patients and 5 (15%) of 33 nelfinavir-treated patients had an increase of >0.5 log IU/mL in the HCV load at week 48.

**DISCUSSION**

Although there is little argument that HAART has changed the spectrum of liver disease among persons infected with HIV, the relationship between HAART, HCV, and HIV remains controversial. HAART appears to decrease the liver-associated mortality rate among persons coinfected with HCV and HIV [11]. However, concern about additive hepatotoxicity in HCV–HIV–coinfected patients has resulted in reluctance by some health care professionals to initiate HAART in patients with HCV infection. Furthermore, observations that HCV–HIV–coinfected patients are more likely to exhibit higher grades of toxicity may lead to premature discontinuation of antiretroviral therapy [12].

Several series suggest that HCV loads may increase with HAART initiation, but these observations have been limited by variability in treatment regimens, small sample sizes, and post hoc analysis. In the analysis described herein, the study cohort was uniquely suited to address several of these issues. Treatment-naive patients were randomized to 1 of 2 treatment arms that differed only in the protease inhibitor component and used a stable nucleoside reverse-transcriptase inhibitor backbone, thus allowing a direct comparison between protease inhibitors regarding their effect on HCV. Samples were collected in an organized manner on a predefined schedule. Finally, all HCV loads and ALT levels were determined in a single laboratory, thus reducing risk of interlaboratory and interbatch bias.

The results demonstrate several important points. The prevalence of HCV coinfecion in this HIV-infected cohort was 11%. This is somewhat lower than that described by Sherman et al. [1] in the AIDS Clinical Trial Group (16.1%) and significantly lower than prevalences observed in high-risk inner-city cohorts (76.9%) [13]. Nearly 80% of subjects with HCV antibodies had evidence of active viral replication detected by sensitive PCR-based assays. Although it is possible that some HCV RNA–negative subjects had very low titers below the level of detectability, this observation more likely represents spontaneous clearance. Messick et al. [14] reported similar levels of spontaneous clearance among coinfected hemophiliacs.

Increases in mean HCV load after HAART initiation were clearly demonstrated in this analysis. Despite relatively small patient numbers, the observed differential in response between the 2 protease inhibitor regimens, particularly among patients with low CD4+ cell counts, may be of interest. Chung et al. [4] previously reported that patients with CD4+ cell counts <350 cells/mL demonstrated increased HCV loads after week 24 of HAART initiation, but that this effect was not observed in patients who began HAART with a CD4+ cell count of >350 cell/mm³. These observations may help explain the observation that HCV RNA levels among subjects with very low baseline CD4+ cell count (<100 cells/mL) demonstrated a drug-specific differential response (i.e., flares in HCV RNA loads were more prolonged in the nelfinavir arm than in the lopinavir-ritonavir arm). HIV responses and associated CD4+ cell count increases were somewhat blunted in the nelfinavir arm, compared with the lopinavir-ritonavir arm. This suggests that the increase in the HCV RNA load might be tied to relative effects on HIV suppression or immunologic recovery. The mechanism of this increase is unclear.

One hypothesis for an increase in the HCV RNA load after HAART initiation is viral quasispecies evolution. During immune restoration, as evidenced by an increased CD4+ cell count,
there may be selection of HCV quasispecies with greater replicative capability, thus paradoxically increasing the HCV load. Alternatively, impaired clearance of HCV could result in increased numbers of circulating HCV virions. However, it is difficult to conceptualize impaired clearance in persons with improved immune function. It is also possible that HIV gene products provide a regulatory brake to HCV replication, either directly or through the action of stimulated chemokines. In this regard, subjects with the CCR5Δ32 mutation have decreased HIV replication potential and increased serum levels of HCV RNA [15].

Some authors have argued that mild or moderate increases in HCV loads are not clinically relevant, particularly considering the variability of commercially available assays for measuring the HCV load [16]. However, our analysis clearly demonstrates changes in HCV load over time, and HCV load has been identified as the second most important factor, after HCV genotype, affecting the response to HCV treatment [17]. Furthermore, viral kinetics modeling suggests that even an increase of 0.5 log IU/mL significantly alters the predicted time to viral clearance [18].

It is also possible that ALT increases after initiation of HAART may lead to antiretroviral drug discontinuation or to dose modification [19]. Formal recommendations regarding evaluation and management of hepatotoxicity have been promulgated by expert panels in the field and have been widely distributed to practicing clinicians. These recommendations suggest that patients with new antiretroviral therapy regimens undergo ALT and/or aspartate aminotransferase testing 4 weeks after drug initiation. If grade 3 toxicity is present, drug should be stopped if any symptoms are evident or retested weekly if no symptoms are discernible. If grade 4 toxicity is present, the drug should be stopped, and expert consultation should be sought [20]. In our cohort, application of these rules might have significantly altered treatment regimens. Although clinical outcomes were not significantly different between these 2 regimens after 48 weeks, clinicians seeing flares in ALT levels and/or HCV loads might have altered their choice of treatment regimen at the time of the flare, resulting in suboptimal therapeutic efficacy. The choice of an initial antiretroviral regimen is generally based on a combination of availability, tolerability, resistance profiles, cost, and ease of administration [21]. The data presented herein suggest that choice of a protease inhibitor may lead to downstream laboratory findings with the potential to result in treatment modification.

There are limitations to this study that should be acknowledged. The HCV-HIV—coinfected patients were a subset of an HIV treatment trial and therefore included a higher proportional of gay or bisexual men relative to the general HCV-HIV—coinfected population. The rate of coinfection is lower than that seen in other cohorts with a greater proportion of injection drug users. HCV load was measured at 3 predetermined time points during the study (at baseline and at weeks 24 and 48 after treatment), unless a flare in the ALT level was noted. This limited the ability to correlate HCV titer with ALT level and CD4+ cell counts over time. It is also possible that patients with flares in the ALT level experienced confounding events that may have contributed to the flares, although this is unlikely, because subjects were not active alcohol users and because only 1 subject was taking corticosteroids at the time of the flare.

In summary, this analysis confirms that HCV loads increase after HAART initiation and that this increase is associated with appropriate immune reconstitution. These increases may be accompanied by flares in the ALT level. The observation that such flares occur after HAART initiation provides a strong rationale for mandatory screening for HCV in all HIV-infected patients infected with HIV before starting treatment. Differential HCV loads and ALT responses between protease inhibitor—treatment groups are noted, especially in patients with low baseline CD4+ cell counts. Future studies should include histologic evaluation at the time of flare, so that the level of liver injury in this setting can be assessed. These observations clearly warrant further evaluation of mechanisms that underlie these observations.

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