

Hepatitis C Virus Prevalence among Patients Infected with Human Immunodeficiency Virus: A Cross-Sectional Analysis of the US Adult AIDS Clinical Trials Group

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Hepatitis C virus (HCV) has emerged as an important etiologic agent of liver injury and failure in patients infected with human immunodeficiency virus (HIV). The prevalence and characteristics of HCV in a representative cohort of HIV-infected patients have not been described. Therefore, a representative sample of 1687 HIV-infected patients was studied; a 213-sample subcohort was selected by use of risk-based sampling from 2 large prospective US Adult AIDS Clinical Trials Group clinical trials. HCV prevalence, HCV RNA level, and genotype were determined. The weighted overall estimate of HCV prevalence in the study cohort was 16.1% (95% weighted confidence interval, 14.3%–17.8%), with significant variability depending on risk factors and HIV RNA levels. Among patients defined as being “at risk,” 72.7% were HCV positive, whereas, among low-risk patients, the positivity rate was 3.5%. Genotype 1 was found in 83.3% of infected patients. Median HCV RNA level was 6.08×10^6 IU/mL. High virus loads and genotype 1 prevalence may be important to interferon-based antiviral response rates among coinfecting patients.

With the successful implementation of highly active antiretroviral therapy (HAART) for patients with HIV infection, a rapidly fatal illness has been converted to an illness maintained as a chronic disease. With dramatic reductions in the prevalence of opportunistic infections, other diseases have become important health

problems in the HIV-infected population. Hepatitis C virus (HCV) coinfection has emerged as a major source of morbidity and mortality. Patients with HCV-HIV coinfection appear to have accelerated progression to symptomatic liver disease and cirrhosis, and successful initiation of HAART may be limited by either HCV-related liver disease or hepatotoxicity of medications in concert with viral liver disease [1, 2]. Furthermore, some evidence exists that presence of HCV may negatively influence the course of HIV infection [3]. Despite these emerging trends, screening for HCV in HIV-infected patients has not been routinely performed, because HCV has been perceived to be a slowly progressive disease, which would be unlikely to alter the natural history of HIV and associated opportunistic infections.

Data regarding the prevalence of coinfection have been compiled largely for individual risk groups and homogenous sample cohorts. These data demonstrate

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anti-HCV ELISA reactivity in HIV-infected patients at rates ranging from 6.45%, among pregnant HIV-positive women in Kinshasa (Democratic Republic of Congo), to >90% in some cohorts of patients with hemophilia [4–6]. Prevalence levels have been described in other discrete populations, including military populations [7, 8] and homosexual men [9]. Patients with HIV infection who have concurrent hemophilia and who received factor concentrates before 1987 or who were injection drug users [10] typically demonstrate the highest prevalence of HCV infection. To our knowledge, a comprehensive cross-sectional analysis of HCV prevalence in a nationally distributed HIV-infected cohort representing a mix of HCV risk groups in the United States has not been reported.

Important characteristics of HCV infection with respect to disease progression and treatment response to interferon-based regimens include viral factors, such as HCV genotype and RNA levels, while important host factors include age and duration of infection. This study was designed to evaluate these characteristics in the cohort in preparation for upcoming therapeutic intervention trials. Furthermore, identification of subsets of HIV-infected population with higher-than-average risk for HCV would facilitate screening efforts by health care providers. To this end, we endeavored to develop a predictive model of HCV risk in the HIV-infected population that included additional factors besides only suspected risk for disease transmission, which independently seems to define high- and low-risk groups.

The US Adult AIDS Clinical Trials Group (AACTG), under the auspices of the National Institutes of Health, has been a leading source of patient data and samples for a geographically diverse cohort of HIV-infected patients. More than 57,000 adult patient registrations are recorded, which give a broad depiction of the infected population, which is thought to approach 1 million persons in the United States. A representative sample from the AACTG cohort gives a snapshot of the coinfecting population.

PATIENTS AND METHODS

Patient samples. Stored plasma specimens obtained from patients enrolled in 2 AACTG trials were used. All samples were obtained in acid citrate dextrose (ACD) collection tubes and were stored in accordance with principles of viral RNA preservation, including rapid separation from cells, followed by rapid freezing and storage at -70°C or lower. Samples were from AACTG trials 320 and 343. Both were primary treatment intervention trials that used HAART; they were selected for this study because they included diverse and geographically representative patient populations with all stages of HIV-associated disease. AACTG 320 included HIV-infected subjects with CD4^{+} lymphocyte counts of ≤ 200 cells/ μL and a history of treatment with zidovudine of ≥ 3 months. AACTG 343 included HIV-

infected subjects with HIV RNA levels of >1000 copies/mL and CD4^{+} lymphocyte counts of >200 cells/ μL who had not previously received protease inhibitor therapy. Samples used were those obtained before the patients received their assigned therapy in the respective protocols. All subjects provided informed consent, and the studies were approved by the institutional review boards at the individual sites. HIV RNA testing by use of Roche Amplicor (Roche Diagnostics) was performed as part of the AACTG study protocols by Johns Hopkins HIV Specialty Laboratories (Baltimore, Maryland).

HCV testing. Serologic evaluation for HCV antibodies was performed by use of the Abbott HCV EIA 2.0 assay (Abbott). Samples were tested in accordance with manufacturer's specifications in duplicate to determine the percentage that was repeatedly reactive.

HCV RNA was assessed by a combination of qualitative and quantitative methods. All anti-HCV EIA reactive specimens were tested for HCV RNA levels by use of the Roche COBAS Amplicor HCV Monitor 2.0 assay (Roche Diagnostics). Sample results that were greater than the linear range of the assay (i.e., $>1,000,000$ copies/mL) were diluted 1:100 in HCV-negative human plasma and retested; we used a multiplier to determine the reported virus load. Qualitative testing was performed on all samples for which the results were less than the linear range of the assay (i.e., <1000 copies/mL) with the Roche COBAS Amplicor HCV version 2.0 assay, which has a reported sensitivity of 100 copies/mL (Roche Diagnostics). In addition, qualitative testing was also performed on all anti-HCV EIA non-reactive samples so that we could determine the rate of false-negative results in this population.

HCV RNA genotype was determined by means of a reverse hybridization technique that used type-specific nucleic acid probes, in accordance with manufacturer's instructions (INNO-LiPA HCV II; Innogenetics).

Study size and statistical analysis. To preserve samples and resources, a subsampling design was implemented. A power analysis was performed to determine the sample size necessary to estimate the prevalence, associated demographic characteristics, and viral characterization of HCV in the sample cohort. It was estimated that testing a total of 200 patients, encompassing 2 strata on the basis of risk likelihood (low or high) would be required to adequately represent the sample cohort. High-risk patients (i.e., "at risk" patients) were defined as those who reported risk behaviors previously associated with $>50\%$ disease association. This included all self-identified drug users and persons with hemophilia from the 2 studies. The low-risk category included all other patients. Prevalence estimates and 95% CIs were calculated by computing the weighted mean of the prevalence estimates from the 2 risk groups and the corresponding weighted variance.

Group comparisons were performed by use of parametric

and nonparametric techniques, as appropriate for the specific analysis. Testing procedures used included the χ^2 test, Fisher's exact test, Wilcoxon rank-sum test on median values, analysis of variance (ANOVA), and weighted logistic regression analysis, as noted in Results. A 2-tailed $P < .05$ α level was used.

RESULTS

A total of 213 representative patient samples derived from the desired cohort were studied. The demographic characteristics of the study cohort are shown in table 1. For comparison, characteristics of the entire Adult AIDS Clinical Treatment Group registration (as of 10 April 2000) and the estimated distributions of the HIV Cost and Services Utilization Study (HCSUS) are shown. An analysis was performed to compare the tested subcohort (213 patients) with the entire sample population (1687 patients). The risk-weighted sample was representative of the population of 1178 patients enrolled in AACTG 320 and the 509 patients enrolled in AACTG 343, except for the following: 59% of the at-risk patients were white and non-Hispanic, as compared with 36% of those in the nonsampled group; and patients with HIV RNA levels of $>100,000$ copies/

mL were slightly underrepresented in both risk groups, relative to the unsampled cohort.

Anti-HCV EIA testing revealed that 76 (35.7%) of 213 patients in the tested subcohort were repeatedly reactive. At-risk subjects demonstrated a 72.7% rate of HCV positivity, whereas, among low-risk subjects, 3.5% were coinfectd. From this data, a weighted overall prevalence estimate was calculated on the basis of the population of 1687 patients from which the sample was drawn. HCV prevalence was estimated to be 16.1% (95% weighted CI, 14.3–17.8). The demographic characteristics of the study cohort associated with anti-HCV EIA reactivity were analyzed, including risk category, sex, race, age, CD4⁺ lymphocyte count, and HIV load. Peak prevalence was noted in the 40–49-year-old age bracket. Weighted overall prevalence of those who tested HCV positive in this age group was 30.5%. Observed prevalence rates in other age groups were 7.7% in persons aged <30 years, 9.7% in those aged 30–39 years, and 13.3% in those aged ≥ 50 years. No association with the sex of the subject was observed. There was no evidence of increased risk observed among different ethnic groups.

CD4⁺ lymphocyte counts had a range of 0–1218 cells/ μ L (median, 411 cells/ μ L). CD4⁺ lymphocyte counts were signif-

Table 1. Demographic characteristics of the study population and comparison populations.

Characteristic	Study cohort (n = 1687)	AACTG population (n = 57,064)	HCSUS population (n = 231,400)
Age, years			
<30	13.8	—	34 ^a
30–39	46.7	—	54 ^b
40–49	29.8	—	—
≥ 50	9.7	—	11
Sex			
Male	82.9	83	77
Female	17.1	17	23
Race or ethnicity			
White, non-Hispanic	54	61	49
Black, non-Hispanic	28	23	33
Hispanic	16	15	15
Asian or Pacific Islander	1.5	1	3 ^c
American Indian or Inuit	1	<1	—
Risk factors			
Injection drug use or hemophilia	18.2	14	24
Other ^d	81.8	86	76

NOTE. Data are percentage of patients, unless otherwise indicated. AACTG, Adult AIDS Clinical Trial Group Registry (10 April 2000); HCSUS, HIV Cost and Services Utilization Study; published risk factors permit classification of only injection drug use versus "other."

^a This study used the age range of 18–34 years.

^b This study used the age range of 35–49 years.

^c Listed as "other."

^d For example, exposure via sexual contact, health care work, or tattooing.

icantly associated with anti-HCV EIA reactivity: patients who were positive for HCV antibody had a median CD4⁺ lymphocyte count of 400 cells/ μ L, whereas persons who were negative for HCV antibody had a median CD4⁺ lymphocyte count of 420 cells/ μ L ($P = .039$). An inverse relationship between a high CD4⁺ lymphocyte count and positive HCV test results was observed. Among at-risk subjects, 100% of the persons with CD4⁺ lymphocyte counts of ≤ 100 cells/ μ L were HCV positive, but only 68.6% of those with a CD4⁺ lymphocyte count of >100 cells/ μ L were positive ($P = .023$). Greater HIV RNA level was also associated with HCV EIA reactivity. The overall median HIV RNA level was 10,306 copies/mL (range, 7–750,000 copies/mL). HCV-positive patients had a median HIV RNA level of 19,319 copies/mL versus 7879 copies/mL among those found to be nonreactive ($P = .005$).

HCV RNA levels were evaluated in all patient samples and were found to be detectable in 91% of patients who had repeatedly reactive anti-HCV EIA serologic findings. Among anti-HCV EIA nonreactive subjects, 2 were found to be HCV RNA positive. The use of HCV RNA levels as the reference standard for evaluation of the EIA test revealed a sensitivity of 97.2% (95% CI, 90.18–99.7) and a specificity of 95% (95% CI, 90.1–97.99). The median HCV RNA level among patients with detectable virus was 6.1×10^6 copies/mL or 3.02×10^6 IU/mL (range, 1000– 8.02×10^7 copies/mL). Two patient samples that had HCV RNA levels of <1000 copies/mL were excluded from the quantitative comparisons. More than 65% of samples had levels of $>1,000,000$ copies/mL, making additional testing with specimen dilution necessary. No association was observed between HCV RNA level and risk factors for HCV acquisition or CD4⁺ lymphocyte count.

HCV genotype was determined in 66 patients (figure 1). The remainder of HCV RNA-positive patients did not have reverse

hybridization with the type-specific probes sufficiently to permit genotype determination. Most patients were infected with genotype 1 (83.3%), either alone or mixed with another type. Mixed genotypes were observed in 10.6% overall. Unmixed non-1 genotypes were found in 16.7% of patients. There was no observed relationship between genotype and HCV RNA level. There was no evidence of altered distribution on the basis of CD4⁺ lymphocyte count strata or by risk category.

Univariate analysis of factors associated with HCV coinfection was performed, including age, race, sex, CD4⁺ lymphocyte count, and log HIV RNA level. Only CD4⁺ lymphocyte count ($P = .043$) and log HIV RNA level ($P = .005$) were found to be statistically significant. For each unit of increase in log HIV RNA level, the odds of having a positive HCV RNA increased 86%. A multivariate model suggested that CD4⁺ lymphocyte count was not a significant independent contributor to the observed outcome and that risk category and log HIV RNA level within each category best predicted individual risk. The graphical representation of this relationship is shown in figure 2.

DISCUSSION

Although it is widely recognized that patients infected with HIV have increased risk of HCV coinfection, to our knowledge, the prevalence of coinfection in a geographically diverse, nationally representative sample has not been determined previously. Assessments of health policy, research priorities, and patient screening modalities require broad-based data to facilitate the decision-making process. To this end, we have described the prevalence and viral characteristics of HCV in HIV-infected patients who participated in the AACTG. A representative sample designed to mirror the study cohort was analyzed. The comparison of the study cohort with the cohort of 57,064 registered adults (as of

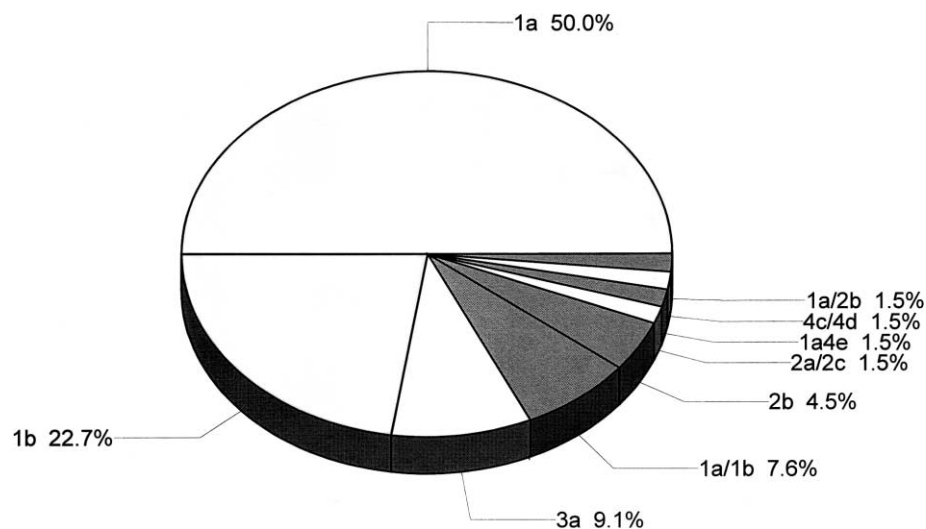


Figure 1. Hepatitis C virus genotype distribution. Genotype was determined by use of a reverse hybridization assay.

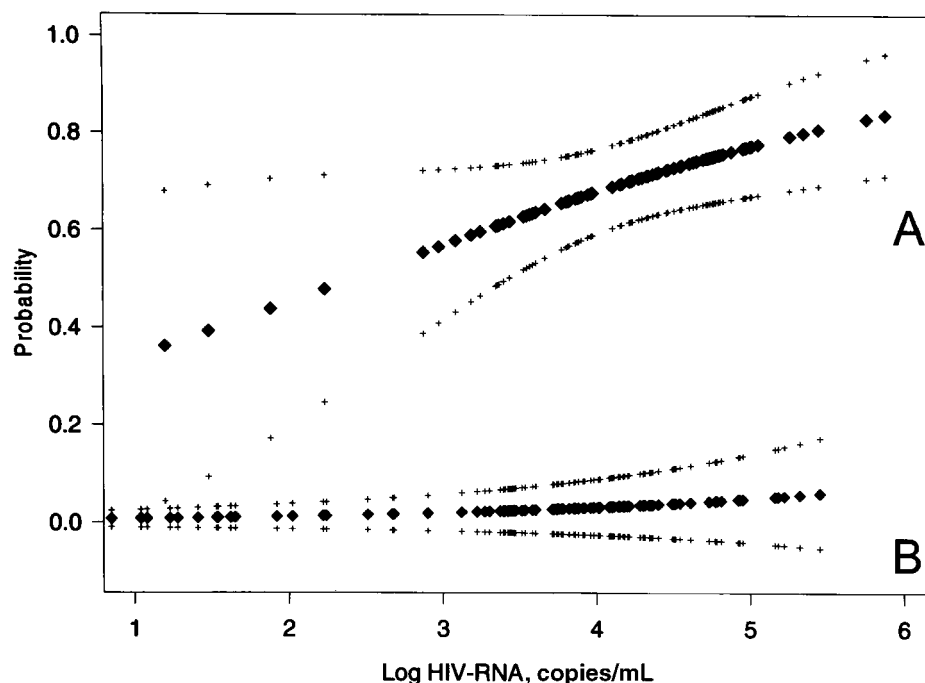


Figure 2. Predictive model of hepatitis C virus in HIV-infected subjects. Multivariate logistic model identified HIV RNA level as a key risk factor in at-risk subjects (*A*) and those not at risk (*B*). Subjects at risk include persons with hemophilia and injection drug users. The category “not at risk” includes all other subjects. Standardized 95% CIs are shown.

10 April 2000) is provided. The proportion of patients reporting history of injection drug use in the study cohort is slightly higher than that reported in the AACTG as a whole (18.2% vs. 14%, respectively). The HCSUS studied representative patients with HIV infection and provides an alternative comparative representation of HIV in the United States [11]. That study suggests a higher percentage of patients who report injection drug use (24%). Therefore, our estimate of this important risk factor for HCV falls between the estimates of injection drug use for 2 large cohorts purported to represent the HIV epidemic in the United States. Our study cohort appears to underrepresent women (17%), but sex was not found to be a factor associated with HCV RNA level or disease prevalence.

The Centers for Disease Control and Prevention’s estimates of HIV prevalence in the United States, which were derived from the National Health and Nutrition Examination Survey (NHANES) III survey, suggest that there are a total of 650,000–900,000 HIV-infected persons in the United States at present [12]. The NHANES III survey also determined that the HCV prevalence was 1.8%, or an estimated 3.9 million residents of the United States [13]. Sixty-five percent of HCV-infected persons were 30–49 years old, a finding similar to that of our study. The overall prevalence of HCV in our study was estimated to be 16.1% (95% CI, 14.3–17.8). Thus, we observed a significantly higher rate of HCV prevalence in coinfecting patients than that observed in the general population represented

by NHANES III data. The high prevalence of risk factors common for both HCV and HIV seems to account for the increased overall prevalence.

Risk factors for parenteral exposure to both viruses clearly influence risk of coinfection. Hemophilia and injection drug use are the highest risk categories. Among patients with lower risk in the 2 studies sampled, which include men who have sex with men, persons with heterosexual exposure, and health care workers with exposure, the overall prevalence of coinfection was 3.5%. This figure is comparable to that observed among adults in the NHANES III data set, with 3.9% prevalence observed in the 30–39-year-old age group, but it is higher than that observed in the 20–29-year-old age group (1.6%) and the 40–49-year-old age group (3%). However, 95% CIs reported for the NHANES III data set seem to overlap with levels observed in this study. Therefore, among low-risk subjects with HIV infection, epidemiologic data do not necessarily support HCV screening on the basis of increased risk relative to the general population. However, current guidelines from the Centers for Disease Control and Prevention suggest that HIV-infected patients may benefit from HCV screening [14]. Because the risk of liver toxicity may be mildly increased in coinfecting patients treated with HAART, universal testing of HIV-infected patients before initiation of antiviral therapy for HIV might be indicated [15].

HCV screening methodology for HIV-infected patients has

been controversial. Several investigators have reported false-negative reactions using anti-HCV EIA. Ragni et al. [16] described a cohort of coinfecting patients with hemophilia who lost serologic reactivity to the first-generation anti-HCV EIA. This group also had decrement in HCV recombinant immunoblot assay positivity and an incremental (12%) decrease in anti-HCV EIA. These patients generally remained HCV RNA positive. By using HCV RNA level as the reference standard, we identified false-negative anti-HCV EIA 2.0 results in 2.8% (95% CI, 0.36–9.7) of the tested cohort, suggesting that false-negative serologic results occur less frequently than has been previously reported. Subjects with false-negative results of assays had CD4⁺ lymphocyte counts of >200 cells/mL, suggesting that severe concomitant immunodeficiency, usually defined as CD4⁺ lymphocyte counts of <200 cells/mL, was not a prerequisite for false-negative reactions. The overall rate of HCV viremia among patients with serologic reactivity was 91%. This is higher than the rate of 79% reported in the NHANES III survey [13]. Higher overall rates of RNA detection may reflect a decreased likelihood of spontaneous viral clearance. Alternatively, it may reflect the shift to higher virus loads, which decreases the chance of nondetection near the limits of the assay's sensitivity.

High serum HCV RNA levels were noted in this study and have been described previously in HIV-infected patients [17–19]. Thus, use of test technologies with a relatively low ceiling for virus load may require selection of alternative assays with a wider linear range or a change in initial approach to HCV RNA level testing, which should include sample dilution to obtain accurate quantitation.

The relationship between HIV RNA and HCV reactivity, which was observed in the multivariate analysis, is intriguing and raises the possibility that HCV coinfection has an adverse effect on HIV disease progression, either directly or indirectly (by limiting successful antiretroviral therapy or by association with limited compliance or adherence). Alternatively, the possibility remains that these persons have had HIV disease of a longer duration with increased overall HCV exposure. Before these possibilities can be distinguished, longitudinal analysis of coinfecting cohorts needs to be performed.

HCV load has been well described as a marker of response to interferon-based treatment regimens [20], and the high levels observed in this and other studies have negative prognostic implications for the likelihood of obtaining a significant long-term response to interferon treatment in this group. This premise must be tested in prospective treatment trials in coinfecting patients.

Patients with hemophilia who have HCV-HIV coinfection have been shown to have distributions of HCV genotypes that do not mirror those seen in the population infected with HCV alone. Furthermore, errors in genotype classification and emer-

gence of previously unidentified genotypes have been described previously [21]. It is not known whether these observations are applicable to HIV-infected populations with low proportions of patients with hemophilia. The cohort described here appears to have genotype distributions that reflect those described for immunocompetent populations without coinfection. Although the overall percentage of samples that contained genotype 1 (83.3%) is higher than that described in the NHANES III survey of 250 samples (73.7%), this difference was not found to be statistically significant. However, the importance of genotype 1 and its associated poor response to interferon-based therapy cannot be overemphasized. Even for patients who received the latest generation of treatment, pegylated interferon plus ribavirin, the sustained viral response rate for patients infected with genotype 1 was 42%, as compared with ~80% for subjects infected with genotype 2 or 3 [22].

The relationship between HCV RNA level and genotype is also controversial. In the past, significant mean load differences between genotypes were partially attributable to test methodologies that favored a single detection of one genotype versus another [23]. One report from Germany suggested that the high HCV RNA levels seen in HIV-infected patients are a function of genotype, with genotype 1 having significantly higher loads than do other types [24]. This finding may also be related to the specific test technology used. By use of a version of the Roche Amplicor assay that has been modified to detect all genotypes equally, we did not demonstrate a genotype-specific difference in virus loads among the coinfecting patients.

In summary, hepatitis C infection is highly prevalent in HIV-infected patients and is related to risk exposures. The titer of HIV RNA was found to be an important factor in calculating the probability of HCV infection in patients before initiation of HAART. Although false-negative reactions are uncommon when standard serologic assays for HCV are used, negative test results for patients with evidence of liver disease (as demonstrated by elevated serum transaminase levels) or a history of high-risk behaviors should be followed up with HCV RNA testing. High virus loads are common in coinfecting patients, and quantitative HCV RNA testing in this population may require altered testing strategies.

Large longitudinal studies are urgently needed to determine the effect of protease inhibitor therapy on HCV RNA; the relationship of these findings to immune reconstitution, as measured by CD4⁺ lymphocyte counts; and the association with hepatic injury. Reports involving small populations have suggested that HCV RNA levels increase with initiation of protease inhibitors, although this has not been observed in all studies. Furthermore, the relationship of HAART to serum alanine aminotransferase level is unclear, according to the current data [25–27]. Attribution of drug-associated hepatotoxicity is often confounded by the presence of HCV [15], and prospective trials

are needed to further explore whether the observed hepatotoxicity is due to exacerbation of HCV or primarily to direct drug-related injury. Finally, conflicting data exist regarding the role of HCV in the alteration of response of HIV to HAART. At least 1 study suggests that HCV may blunt the T cell response to effective antiretroviral treatment [28]. Ultimately, clinical correlation with histopathology will be necessary to define these relationships.

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