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Liver Enzymes Elevation and Immune Reconstitution Among Treatment-Naïve HIV-Infected Patients Instituting Antiretroviral Therapy

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Abstract

Objectives—Because liver enzymes elevation (LEE) complicates antiretroviral (ARV) therapy, and because the strongest risk factor for ARV-related LEE is HBV/HCV coinfection, it is speculated that ARV-related LEE may be a form of immune reconstitution disease. This study summarizes the relation between immune reconstitution, ARV-induced LEE, and HBV/HCV coinfection.

Methods—Medical records of ARV-naïve HIV-infected patients initiating ARV were reviewed for hepatitis coinfection, LEE (grade ≥ 2 AST/ALT) and changes in CD4 T-cell counts over time in an urban HIV clinic. Risk factors for LEE were statistically evaluated, and changes in CD4 T-cell counts were estimated by a mixed-effects linear model.

Results—Predictors of LEE included HBV/HCV coinfection (OR = 6.44) and stavudine use (OR = 2.33). Nelfinavir use was protective (OR = 0.45). The mean rate of change in CD4 T-cell counts was higher in HBV/HCV coinfecting subjects who developed LEE (99 cells/ μ L per month) compared with non-coinfecting subjects who did not develop LEE (59 cells/ μ L per month, $P = 0.03$), non-coinfecting subjects who developed LEE (36 cells/ μ L per month, $P = 0.01$), and coinfecting subjects who did not develop LEE, 38% higher (62 cells/ μ L per month; $P = 0.11$)

Conclusions—A more robust immune restoration was observed among HBV/HCV coinfecting subjects who developed liver enzyme elevation after antiretroviral initiation compared with other groups. This finding suggests that ARV-related liver enzyme elevation may be related in part to immune reconstitution, as measured by changes in CD4 T-cell counts.

KEY INDEXING TERMS

Hepatotoxicity; Liver enzymes elevation; Antiretroviral drugs; Immune reconstitution; HIV/AIDS

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Liver enzymes elevations (LEE) of varying degree have been reported with all classes of antiretroviral (ARV) drugs approved by the Food and Drug Administration for the treatment of HIV infection.^{1–12} Severe cases of hepatotoxicity with fatal outcomes have been reported with ARV therapy and LEE is a common reason for highly active antiretroviral therapy (HAART) discontinuation in clinical practice.

The mechanisms of ARV induced hepatic injury are still poorly understood. Mitochondrial toxicity resulting from nucleoside reverse transcriptase inhibitors (NRTIs) use and hypersensitivity reactions to non nucleoside reverse transcriptase inhibitors (NNRTIs) are speculated to be partly responsible. It is however unclear whether the protease inhibitors (PIs) directly induce liver injury. Although higher plasma concentrations for PIs have been reported among HIV infected subjects with hepatic impairment (often due to HBV/HCV coinfection),^{13–15} there are no published data linking elevated serum PI levels to the development of LEE.

In studies addressing ARV-associated liver injury, 30–50% of subjects were coinfecting with either HBV and/or HCV, and the strongest independent risk factor for ARV-associated hepatotoxicity was coinfection with HBV and/or HCV.^{16–19} Given this association, it is speculated that hepatic injury after ARV therapy in the presence of chronic viral hepatitis may represent immune reconstitution against cells expressing viral antigens rather than direct effects of medication.^{2,17} Other known risk factors for HAART-related liver injury include ARV-naïve patients undergoing their first HAART regimen, recent start of nevirapine, high-dose ritonavir, higher baseline levels of alanine aminotransferase, and female gender.

The aims of this study were to identify risk factors for ARV-induced LEE in a patient population without significant LEE at baseline and to examine the relation between immune reconstitution, ARV-induced LEE, and HBV/HCV coinfection. We hypothesized that ARV-associated rise in CD4 T-cell counts (a measure of immune reconstitution) in the presence of HBV/HCV coinfection increases the risk of grade ≥ 2 LEE.

Materials and Methods

The medical records of all ARV-naïve, HIV-infected patients ages 18 years or older who initiated ARV therapy at the Grady Infectious Diseases Program outpatient center (The Ponce Center) between January 1996 and December 2002 were reviewed. Subjects were excluded if they had history of ARV use, if they were pregnant, or serum creatinine levels were ≥ 2 mg/dL. It is a standard practice at the Ponce Center for ARV to be initiated in treatment-naïve patients 6 to 8 weeks after starting prophylactic treatment for opportunistic infections. Therefore, to reduce the confounding effect of concomitant drugs on the occurrence of LEE, subjects were also excluded if they had preexisting elevation (grade ≥ 2) in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT). AST/ALT were graded according to the AIDS Clinical Trials Group grading scale (grade 0 = 0 to 31 mg/dL; grade 1 = 38.75 to 77.5 mg/dL; grade 2 = 77.6 to 155 mg/dL; grade 3 = 156 to 310 mg/dL; and grade 4 > 310 mg/dL). However, cirrhotic subjects were not excluded unless they had grade ≥ 2 AST/ALT elevation. Demographic information (age, race/ethnicity, sex) and clinical variables including HIV risk factor, recreational drug use, weight, alcohol use, history of opportunistic infections, and ARV history were extracted from the medical record. Subjects were identified as active recreational drug users if there was a clinical documentation of recreational drug use at anytime during the evaluation period. Results of testing for Hepatitis B surface antigen (HbsAg) and Hepatitis C IgG antibody (HCV Ab) obtained before ARV initiation were recorded. Other laboratory test results including CD4 T-cell counts, plasma HIV-1 RNA PCR (viral load), ALT, and AST just before (within 90

days) ARV initiation and after ARV therapy up to 96 weeks were collected. This study was designed according to the ethical guidelines for human studies and approved by the Emory University Institutional Review Board and Grady Health System Research Oversight Committee.

Statistical Analyses

The primary outcome of interest in the baseline analyses was development of LEE after ARV initiation. Liver enzymes were graded according to the AIDS Clinical Trials Group (ACTG) grading scale. Because all subjects in the studied cohort by design had baseline AST/ALT of grade ≤ 1 , LEE was defined as grade ≥ 2 AST and/or ALT. The primary predictor variable was HBV and/or HCV coinfection. A subject was considered to be hepatitis virus-infected if HBsAg and/or HCV AB were positive. The potential association of each risk factor in Table 1 with LEE prevalence was evaluated by using a χ^2 or Fisher's exact test. Factors significant to at least a value of $P \leq 0.05$ were used in a stepwise backward logistic regression analysis. The OR and its 95% confidence interval were calculated for each factor in the presence of the others in the final model. The cumulative incidence rates for LEE were obtained by the Kaplan-Meier method.

To examine the relation between immune reconstitution, baseline HBV/HCV infection status, and the development of LEE after ARV initiation, a mixed-effects linear model was fit to the data. Rates of increase of CD4 T-cell counts were obtained by using a mixed-effects linear model specifying that CD4 T-cell counts follow a linear regression over time, with a random intercept for each patient.²⁰ The mean slope or the mean increase in CD4 T-cell counts was estimated and compared for the 4 subgroups (HBV/HCV coinfecting who progressed to LEE or did not progress to LEE and HBV/HCV uninfected who progressed to LEE or did not progress to LEE). The mean rate in CD4 T-cell counts increase was also compared between patients who received NFV and those patients who did not receive NFV. While the length of follow-up was 96 weeks, a significantly large proportion of the cases of LEE (60 of the 81 cases) occurred during the first 8 weeks of observation; therefore, this analysis included CD4 T-cell counts data obtained between the start of ARV therapy and 2 months of follow-up and excluded CD4 T-cell counts obtained after the diagnosis of LEE.

Results

Patient Characteristics

A total of 352 subjects (261 men and 91 women) met the inclusion criteria. Selected patient characteristics are summarized in Table 2.

Clinical Features

The median baseline CD4 T-cell counts was $60/\mu\text{L}$ with 25 and 75 percentiles of 20 and 170, respectively, reflecting the severity of HIV disease among patients at the Ponce Clinic. The median baseline viral load was 168, 295 copies/mL. Of the 352 patients, 84 (23.9%) were coinfecting with HBV and/or HCV. Fifty-two subjects (14.7%) were infected with HCV, whereas 35 (9.9%) were infected with HBV. Three subjects (0.85%) were infected with both HBV and HCV. The baseline AST and/or ALT were normal (grade 0) in 249 (70.7%), and grade 1 in 103 (29.3%) of subjects as shown in Table 2.

Antiretroviral Use

The 2 most commonly used nucleoside reverse transcriptase inhibitors in this cohort were lamivudine (3TC) (90.9%) and zidovudine (AZT) (77%). Most (69.9%) of the subjects who were treated with AZT and 3TC received this drug as a combination pill (Combivir). Stavudine (d4T) was used by 18.2%. Efavirenz (EFV) was used among 23.3% of the study

population, whereas nevirapine (NVP) was used by 15 (4.3%) of patients. Among the protease inhibitors, NFV was part of the ARV combination in 54.8% of subjects and was by far the most commonly utilized PI, followed by ritonavir (RTV) in 11.4% and indinavir (IDV) in 9.7%.

Incidence of LEE

Eighty-one subjects developed LEE over the 96-week follow-up period, representing a LEE prevalence of 23%. Of the 84 patients who were coinfecting with HBV and/or HCV, 51% developed LEE (43 of 84). On the other hand, among subjects who were uninfected with HBV and/or HCV, 14% (38 of 268) developed LEE. The cumulative incidence of LEE were 5.7% (standard error [SE] = 1.2) at 1 month, 9.2% (SE = 1.5) at 2 months, 11.5% (SE = 1.7) at 3 months, 17.3% (SE = 2.1) at 6 months, and 19.0% (SE = 2.1) at 9 months.

Risk Factors for LEE by Univariate Analysis

Several potential risk factors associated with the development of LEE were tested in the univariate analysis as summarized in Table 1. The presence of HBsAg and/or HCV Ab were the most significant risk factors for LEE (OR = 6.45, CI = 3.67 to 10.99, $P < 0.0001$). Active recreational drug use was associated with increased risk of LEE (OR = 3.09; CI = 1.52–6.29, $P = 0.001$). ARV drugs associated with increased risk of LEE included d4T (OR = 2.03, CI = 1.13–3.67, $P = 0.02$), RTV (OR = 2.86, CI = 1.45 to 5.68, $P = 0.02$), and LPV/RTV (OR = 3.53, CI = 1.11 to 11.3, $P = 0.04$). The use of NFV and AZT were associated with reduced risk of LEE with (OR = 0.45, CI = 0.27 to 0.74, $P = 0.0016$) and (OR = 0.5, CI = 0.29 to 0.86, $P = 0.01$), respectively. The risk of LEE was not significantly affected by subjects' sex, age, or race. The use of NNRTIs was also not a significant risk factor for ARV-associated LEE in this cohort. Because there were introduction of a number of new ARV agents during the observation period and therefore changes in the choice of available ARV regimens, we assessed the risk of LEE among subjects who initiated ARV therapy before the year 2000 as compared with those who initiated therapy thereafter. About two-thirds of the subjects in our cohort initiated HAART therapy after 2000, and there was no significant difference in the occurrence of LEE among subjects treated before 2000 when compared with subject treated thereafter.

Multivariate Analysis

After adjusting for HBV and/or HCV sero status, other predictor variables associated with significant change in the risk of LEE were the use of NFV and d4T, as shown in Table 3. AZT and LPV/RTV use did not significantly change the risk of LEE (not shown in table). HBV and/or HCV coinfection status increased the risk of LEE by 6.44 fold (CI = 3.66 to 11.35, $P < 0.0001$), whereas d4T use was associated with 2.89-fold increase in the risk of LEE (CI = 1.21 to 4.48, $P = 0.01$). The odds of LEE were reduced by 55% for patients treated with NFV containing ARV regimen (OR = 0.45, CI = 0.26 to 0.78, $P = 0.004$).

Two additional logistic regression models similar to the one represented in Table 3 were developed. In these models, the risks of LEE among subjects coinfecting with HBV and HCV were independently assessed. The odds of LEE among subjects coinfecting with HBV was 5.99 (95% CI = 2.82 to 12.74, $P < 0.0001$). Among HCV coinfecting subjects, the odds of LEE was 4.31 (95% CI = 2.38 to 8.14, $P < 0.0001$). In these 2 models, the use of d4T was significantly associated with increased risk of LEE (OR = 2.28, 95% CI = 1.23 to 4.24, $P = 0.009$ for HCV infected subjects and OR = 2.09, 95% CI = 1.11 to 3.93, $P = 0.02$ for HBV infected subjects). Additionally, NFV use was associated with significant reduction in the risk of LEE (OR = 0.42, 95% CI = 0.25 to 0.72, $P = 0.001$ for HCV infected subjects and OR = 0.27, 95% CI = 0.28 to 0.80, $P = 0.006$ for HBV infected subjects).

Relation Between Immune Reconstitution, HBV/HCV Sero Status, and LEE

The mean rate of increase in CD4 T-cell counts in the first 2 months of follow-up among HBV and/or HCV coinfecting subjects who subsequently developed LEE (99 cells/ μ L per month) was significantly higher compared with the rate of CD4 T-cell counts increase among HBV and/or HCV uninfected subjects who developed LEE (36 cells/ μ L per month; $P = 0.01$), and the rate of increase among subjects HBV/HCV uninfected who did not develop LEE (59 cells/ μ L per month; $P = 0.03$; Table 4 and Figure 1). Although the mean rate of increase in CD4 cells count among subjects with positive HBV and/or HCV sero status who subsequently developed LEE was 38% higher compared with that among subjects with positive HBV/HCV sero status who did not develop LEE, this difference was not statistically significant (99 cells/ μ L per month vs 62 cells/ μ L per month; $P = 0.11$). The mean rate of CD4 cell count increase was similar for subjects treated with NFV when compared with subjects not treated with NFV (mean slope = 62 cells/ μ L per month for both groups, $P = 0.99$, data not shown).

Discussion

Antiretroviral-induced liver injuries are common, and fatal cases have been reported in the medical literature.²¹ Liver enzyme elevation after ARV initiation is a common reason for HAART modification in clinical practice. The pathogenesis underlying this ARV-induced liver injury is, however, poorly understood. The role of inflammatory response to dormant HBV/HCV antigens resulting from immune reconstitution in the pathogenesis of ARV-induced liver injury, though speculated, remains to be confirmed. The primary objective of this study, therefore, was to describe the relation between chronic viral hepatitis infection, ARV-associated liver injury, and immune reconstitution among ARV naïve HIV-infected subjects with no significant liver function abnormalities at the time of HAART initiation. In one of the few studies that have examined this relation, a cohort of 42 HBV/HCV coinfecting HIV-subjects initiating ARV therapy was evaluated.²² No significant association between ARV-related liver injury and immune reconstitution (defined as increase in CD4 T-cell counts over time) was observed. In another study, Stone et al²³ examined the relation between ARV-related LEE and pathogen-specific immune reconstitution among 16 HCV coinfecting HIV subjects who responded to ARV treatment. Contrary to the findings of Martin-Carbonero et al, these investigators observed that HCV core-specific IgG antibody was increased in 10 (91%) patients who had LEE after HAART compared with 1 (20%) patient who did not.

In the current study, immune reconstitution during the first 8 weeks of ARV therapy, defined as the mean rate in changes in CD4 T-cell counts after ARV initiation, was significantly more robust among subjects who were HBV and/or HCV coinfecting and subsequently developed LEE (99 cells/ μ L per month) compared with subjects who were HBV and/or HCV uninfected who did not develop LEE (59 cells/ μ L per month, $P = 0.03$) or subjects who were HBV- and/or HCV-uninfected who developed LEE (36 cells/ μ L per month, $P = 0.01$) (Figure 1). Although the mean rate of increase in CD4 T-cell counts among subjects with HBV and/or HCV coinfection who subsequently developed LEE was 38% higher compared with that among subjects with HBV and/or HCV coinfection who did not develop LEE, this difference was not statistically significant (99 cells/ μ L per month vs 62 cells/ μ L per month; $P = 0.11$). We speculate that a larger sample size with more CD4 T-cell counts and AST/ALT measurements would have provided better statistical power to detect a difference between the mean rates of change in CD4 T-cell counts in these 2 groups. Nevertheless, taken together, this finding of greater immune response among HBV and/or HCV coinfecting subjects who subsequently developed LEE after ARV initiation compared with the other three groups is interesting. It raises the possibility that ARV associated LEE

may in part be related to inflammatory response to viral specific antigens as a result of immune restoration after response to ARV therapy.

It should be noted, however, that ARV-related liver injury were also observed in subjects without evidence of HBV or HCV coinfection. This observation suggest that the etiology of hepatotoxicity after ARV initiation is likely to be multifactorial and may not be explainable by immune reconstitution to HBV or HCV antigens alone, other mechanisms may also be at play. Such mechanisms may include direct drug induced hepatocytes injury, NRTI related mitochondrial toxicity, hypersensitivity reaction, and other immune mediated phenomenon that are known to mediate liver damage with the use of other classes of drug.^{24–27} However, should our finding be confirmed and ARV-associated LEE is shown to be mediated partly by immune reconstitution to dormant pathogenic antigens in a large, prospective clinical studies, it could have clinical significance. Argument could be made for therapeutic trials of anti-inflammatory agents for the treatment of severe cases of ARV-related hepatotoxicity that are suspected to be immune reconstitution related.

In addition, a relatively high rate of ARV associated LEE was observed in this cohort of patients with normal or close to normal (grade 1) baseline AST/ALT. The overall ARV associated LEE (grade ≥ 2) prevalence rate was 23%, grade ≥ 3 LEE prevalence rate was 7.9%, and the 9-month LEE cumulative incidence was 19.0%. In comparison, the incidence of LEE (>200 IU/L) in the ICONA cohort (HCV coinfection of 46.2%, and HBV coinfection of 7.2%) was 4.5%, in the CHORUS cohort (HCV coinfection of 11.5%, and HBV coinfection of 33%) LEE (grade ≥ 3) incidence was 5.5%, and in the Amsterdam cohort (HCV coinfection 10.7%, and HBV coinfection was 8.8%) LEE (grade 4) incidence was 6.5%.^{28–31} Contrary to the current study where there was no significant AST/ALT elevation at baseline, in the Amsterdam and CHORUS cohorts, there were no AST/ALT limitation at entry, and the baseline AST/ALT levels were <200 IU/L in the ICONA cohort. This observation of relatively high rate of LEE in our cohort, where all patients had normal to near normal hepatic and renal functions before ARV initiation, suggests that LEE in this setting is unlikely to be the result of direct drug toxicity due to ARV accumulation from impaired hepatic metabolism or renal clearance. Alternative explanations such as immune reconstitution mediated inflammatory response to chronic hepatitis viral specific antigens or differences in ARV regimens in our study compared with the earlier cohorts appear more plausible.

In consistence with the results of previous reports where the risk of ARV associated LEE was 2- to 10-fold higher among HIV patients with HBV and/or HCV coinfection,^{32–34} the strongest risk factor for ARV associated LEE in our study was HBV and/or HCV coinfection status in both the univariate and multivariate analyses. The odds of ARV associated LEE was 6.44 higher for patients with HBV and/or HCV infection. Antiretroviral medications associated with a significant change in the risk of developing LEE in the univariate analysis included AZT, d4T, RTV, LPV, and NFV. However, after controlling for HBV and/or HCV coinfection status and other risk factors in the multivariate analysis, only d4T was significantly associated with increased risk of LEE, with OR of 2.33. The use of NFV was protective, and was associated with a 2-fold lower risk of LEE when compared with non-NFV-containing regimens. The reason for the lower risk of LEE associated with NFV use in our findings is unclear. The mean rate of change in CD4 T-cell counts among subjects treated with NFV was comparable to that among subjects who did not receive NFV (62 cells/ μ L per month vs 62 cells/ μ L per month, $P = 0.99$), therefore, the lower risk of LEE associated with NFV is unrelated to weaker immune response. However, this finding of reduced LEE risk with NFV containing regimen if corroborated by other studies may be of therapeutic importance, particularly in the management of HBV and/or HCV coinfecting HIV-infected patients who are often at increased risk of ARV induced liver disease. Also,

we observed that HBV and HCV infection status were independent predictors of ARV associated LEE. However, contrary to previous reports,^{35,36} NVP use was not associated with increased risk of developing LEE in this study population. This is probably because of the small number of patients treated with NVP and the low baseline CD4 T-cell counts in our study cohort. In the FTC 302 study,³⁷ female gender was reported as a risk factor for the development of ARV associated liver injury with a relative risk of 2.0. However, in our study, neither sex, nor race nor the age of subjects was associated with increased risk of development of ARV associated LEE.

Our study is limited by its retrospective design because several potentially confounding variables, such as other concomitantly used drugs, may have affected the progression to LEE. The small subgroup sample sizes and the limited number of longitudinal laboratory test measurements (particularly AST, ALT, and CD4 T-cell counts) available for analysis were inadequate to fully evaluate the relationship between ARV induced LEE and CD4 T-cell count changes among HBV and/or HCV coinfecting subjects. Confirmation of an association between the CD4 T-cell count response and the development of LEE by HBV/HCV sero status in a larger prospective cohort study using newer medications may affect medical practice. Patient HBV/HCV misclassification is another potential study limitation. By limiting our definition of HBV/HCV to presence of HBsAg and/or HCV Ab, coinfecting subjects that could have been detected by HBV DNA or HCV RNA PCR may have been misclassified. The incidence of ARV-related LEE may have been underestimated because several patients with chronic active viral hepatitis and abnormal baseline AST and ALT were excluded by the study design. Weekly follow-up would have been necessary to precisely estimate LEE incidence and the rate of CD4 T-cell counts increase since both progression to LEE and the CD4 T-cell counts rise occurs within 2 months of the start of ARV therapy.

In summary, taking into consideration these limitations, in this cohort of ARV-naïve HIV-infected subjects with no significant AST/ALT abnormalities at baseline, the risk of ARV induced liver injury was higher in the presence of HBV/HCV coinfection and with the use of d4T. NVP use was associated with a two fold reduction in the risk of LEE. A more robust immune restoration was observed among HBV and/or HCV infected subjects who developed LEE compared with other groups, suggesting that ARV induced LEE occurring early during ARV therapy may in part be related to immune reconstitution-induced inflammatory response to viral hepatitis specific antigens.

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Figure 1.

Mean rate of change in CD4 T-cell counts (cells/mL) in the first 8 weeks after antiretroviral initiation for HBV/HCV-infected subjects with LEE (LEE+ and Hepatitis+), HBV/HCV-infected subjects without LEE (LEE- and Hepatitis+), HBV/HCV-uninfected subjects with LEE (LEE+ and Hepatitis-), and HBV/HCV-uninfected subjects without LEE (LEE- and Hepatitis-).

Prevalence of Liver Enzymes Elevation After Antiretroviral Initiation Among 352 HIV-Infected Subjects According to Clinical Characteristics

Table 1

Risk Factors	LEE Prevalence and Risk Factor (+)		LEE Prevalence and Risk Factor (-)		P Value
	%	(s/y)	%	(s/y)	
Age >40 (years)	26.5	(39/147)	20.5	(42/205)	0.18
Male sex	24.1	(63/261)	19.8	(18/91)	0.40
Weight >150 pounds	22.2	(44/198)	24.0	(37/154)	0.69
African American	24.4	(64/262)	18.9	(17/90)	0.28
Caucasian	15.9	(7/44)	24.0	(74/308)	0.23
Hispanic	20.0	(5/25)	23.2	(76/327)	0.71
Alcohol use 4 drinks/day	40.0	(8/20)	22.0	(73/332)	0.096*
Active recreational drug use	44.4	(16/36)	20.6	(65/316)	0.001
Positive HBsAg and/or HCV Ab	51.2	(43/84)	14.2	(38/268)	<0.0001
Positive CMV IgG	21.9	(37/169)	23.5	(42/179)	0.73
History of MAC	33.3	(11/33)	21.6	(68/315)	0.13
Zidovudine (AZT)	19.9	(54/271)	33.3	(27/81)	0.01
Lamivudine (3TC)	23.13	(74/320)	21.9	(7/32)	0.87
Stavudine (d4T)	34.4	(22/64)	20.5	(59/288)	0.02
Didanosine (ddI)	9.1	(2/22)	23.9	(79/330)	0.12
Abacavir (ABC)	33.3	(6/18)	22.46	(75/334)	0.13
Tenofovir (TDF)	40.0	(4/10)	22.5	(77/342)	0.25*
Nevirapine (NVP)	20.0	(3/15)	23.2	(78/337)	1.00*
Efavirenz (EVF)	28.1	(23/82)	21.5	(58/270)	0.22
Ritonavir (RTV)	42.5	(6/12)	20.5	(75/340)	0.02
Indinavir (IDV)	29.4	(32/193)	22.3	(49/159)	0.35
Nelfinavir (NFV)	16.6	(10/34)	30.8	(71/318)	0.0016
Lopinavir/ritonavir (LPV)	50.0	(17/40)	22.1	(64/312)	0.04*
ARV therapy before year 2000	24	(16/67)	23%	(65/3285)	0.85

LEE, Liver enzymes elevation; s/y, (number with LEE/total number); HCV Ab, Hepatitis C antibody; HbsAg, Hepatitis B surface antigen; MAC, Mycobacterium avium complex; CMV, Cytomegalovirus; ARV, antiretroviral therapy.

* Based on two-sided Fisher's exact test.

Table 2**Demographic and Clinical Characteristics of 352 ARV-Naïve HIV-Infected Patients**

	n (percent)
Demographic	
Male	261 (74.2%)
African Americans	262 (74.4%)
Caucasians	44 (12.5%)
Hispanics	25 (7.1%)
Other race/ethnicity	21 (6.0%)
Self-reported risk for HIV infection	
Heterosexual	187 (53.1%)
Homosexual	93 (26.4%)
Bisexual	57 (16.2%)
Transfusion	37 (10.5%)
Intravenous drug use	33 (9.4%)
Social behavior	
Active recreational drug use	36 (10.2%)
Alcohol use (4 drinks/day)	20 (5.7%)
Clinical features	
HCV Ab positive	52 (14.7%)
HBsAg positive	35 (9.9%)
HCV Ab and HBsAg positive	3 (0.85%)
HBV and/or HCV infected	84 (23.9%)
Grade 2 LEE after ARV	81 (23.0%)
Grade ≥ 3 LEE after ARV	26 (7.39%)
Subjects with baseline grade 0 AST/ALT	249 (70.7%)
Subjects with baseline grade 1 AST/ALT	103 (29.3%)

	Median	(P25	P75)
Age (years)	39	(33	44)
Weight (kg)	71.4	(63.6	81.8)
Baseline AST ^a	30	(23	40)
Baseline ALT ^b	27	(18	38)
Baseline CD4 cell count (cells/ μ L)	60	(20	170)
Baseline HIV-1 viral load (copies/mL)	1.6×10^5	$(5.4 \times 10^4 - 4.3 \times 10^5)$	

LEE, Liver enzymes elevation; HCV Ab, hepatitis C IgG antibody; HBsAg, hepatitis B surface antigen; HBV and/or HCV, HBsAb and/or HCV Ab; ARV, antiretroviral drugs; P25, 25% percentile; P75, 75% percentile; AST, amino transferase; ALT, alanine transferase;

^aLaboratory normal range = 0 to 31 mg/dL;

^bLaboratory normal range = 0 to 31 mg/dL.

Table 3

Multivariable Analysis of Factors Associated With Liver Enzyme Elevation in Antiretroviral-Naïve HIV-infected Patients (n = 352)

Variables	Point Estimate	SE	OR	95% CI	P Value
Positive HbsAg and/or HCV Ab	1.8632	0.2890	6.44	3.7–11.4	<0.0001
Stavudine (d4T)	0.8463	0.3328	2.33	1.2–4.5	0.01
Nelfinavir (NFV)	−0.8029	0.2819	0.45	0.26–0.78	0.0044

SE, Standard error; OR, odds ratio; CI, confidence interval; HCV Ab, Hepatitis C antibody; HbsAg, Hepatitis B surface antigen.

Table 4

Relation of LEE to Hepatitis Status and CD4+ T-Cell Count Changes

Progression to LEE	HBV and/or HCV Status	Number of Patients	Number of Measurements	Baseline Median HIV RNA PCR	CD4 Intercept (SE)	Mean CD4 Slope (SE)	Mean CD4 at 2 Months (95% CI)	P Value
Yes	Infected	36	53	161,105	98 (19)	99 (17)	295 (230,361)	–
No	Infected	34	60	135,660	136 (20)	62 (16)	260 (197,321)	0.11
Yes	Uninfected	24	37	152,080	100 (23)	36 (19)	171 (92,250)	0.01
No	Uninfected	183	283	173,390	100 (9)	59 (7)	217 (191,244)	0.03

Mean CD4 T-cell counts (cells/ μ L) in ARV-naïve HIV-infected patients are given. Mean rate (mean slope) of increase of CD4 T-cell counts in the first 2 months of follow-up and the mean CD4 cells count at 2 months for HIV-infected subjects with HBV/HCV infected status who developed LEE or did not develop LEE and HIV-uninfected subjects with HBV/HCV uninfected status who developed LEE or did not develop LEE. CD4 T-cell counts were excluded after the diagnosis of LEE. Analyses included 277 patients (433 CD4 T-cell measurements) and 60 developed LEE subsequent to initiation of ARV therapy (median time until LEE diagnosed = 83 days).