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Risk Factors for Hepatotoxicity in HIV-1–Infected Patients Receiving Ritonavir and Saquinavir with or without Stavudine

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Liver enzyme elevation (LEE) is commonly observed after combination antiretroviral therapy (ARVT) for HIV infection is begun. Potential risk factors for LEE after treatment with ritonavir and saquinavir with or without stavudine were investigated in 208 HIV-infected patients, by use of the Cox proportional hazard model. Eighteen patients (9%) developed LEE during the 48-week follow-up. Multivariate analysis, adjusted for baseline levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), showed that hepatitis B surface antigen (HBsAg) positivity (relative risk [RR], 8.8; 95% confidence interval [CI], 3.3–23.1) and the use of stavudine (RR, 4.9; 95% CI, 1.5–16.0) were the only significant risk factors for developing LEE. After LEE occurred, ALT and AST concentrations decreased by >50% in 13 of 14 patients who continued ARVT during LEE. In this study, it appeared safe to continue ARVT during LEE; however, more data from larger studies are required to confirm this finding.

Liver enzyme elevation (LEE) has been reported to be a potential side effect of most antiretroviral agents used for the treatment of HIV infection [1]. Since the introduction of highly active antiretroviral therapy with triple-drug combination regimens, severe LEE has been observed more frequently. LEE may be drug-induced; however, it seems to occur more often in HIV-infected patients who are coinfected with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) [2–9].

Coinfections of HIV and HBV and/or HCV are common. Up to 84% of injection drug users with HIV infection and 83% of homosexuals with HIV infection have markers of past or current HBV infection, and 81% and 14%, respectively, have markers of past or current HCV infection [10]. There are many unanswered questions related to the clinical management of patients who develop LEE while using antiretroviral agents. First, the risk of hepatotoxicity developing has not been properly quantified. Second, it is unknown whether certain antiretroviral drugs, classes of antiretroviral drugs, or combinations of antiretroviral drugs are more prone to predispose patients for development of LEE. Finally, there are no guidelines for deciding whether to continue or discontinue highly active antiretroviral therapy once LEE has occurred.

The aim of this study was to describe hepatotoxicity in HIV-infected patients treated with ritonavir and saquinavir with or without stavudine. We searched for risk factors for LEE in this study population and described the clinical management of the patients and the patients' outcome.

Patients and Methods

Patients and data collection. The Prometheus Study was an open-label, randomized, controlled multicenter trial in 208 HIV-1–infected patients in The Netherlands and Belgium. From January 1997 through January 1998, patients were randomized to receive oral ritonavir and saquinavir (400 mg each b.i.d.) with or without stavudine (40 mg b.i.d.; 30 mg b.i.d. if body weight was <60 kg). Participants had to be protease inhibitor–naive and stavudine-naive at study entry, and they had to have an indication for initiation of antiretroviral treatment or change of current treatment. Participants were ⩾18 years of age and had a Karnofsky score ⩾60. Antiretroviral drugs used before the study had to be discontinued before starting study medication. The only exclusion criterion for

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study entry was the presence of a clinical condition or laboratory abnormality that was, in the investigator's opinion, incompatible with the use of study medication. Patients were allowed to intensify their treatment with 2 new reverse transcriptase inhibitors (RTIs), primarily stavudine and lamivudine, (a) if their serum HIV RNA concentrations did not drop to <400 copies/mL at week 12 and if they remained at that level at week 18 or (b) if serum HIV RNA became detectable again after dropping to undetectable levels.

The following baseline characteristics were determined for each patient: sex, age, weight, height, prior antiretroviral drug use, Centers for Disease Control and Prevention (CDC) AIDS classification, transmission risk group, $CD4^+$ and $CD8^+$ lymphocyte counts, serum levels of HIV-1 RNA, and the presence of hepatitis B surface antigen (HBsAg) and anti-hepatitis C antibody (anti-HCV) in serum. During the study, patients were evaluated at weeks 0, 2, 4, 8, 12, 18, 24, 36, and 48. After week 48, follow-up on the clinical outcome of LEE was continued for patients who consented to extended follow-up. The following data were recorded at every visit: occurrence of HIV-related events as classified according to the CDC 1993 guidelines [11], occurrence of other clinical events, use of antiretroviral medication, use of comedication, laboratory safety parameters (including levels of alanine aminotransferase [AST], aspartase aminotransferase [ALT], alkaline phosphatase, and γ-glutamyl transferase), and laboratory efficacy parameters (levels of serum HIV-1 RNA [Amplicor HIV monitor test; Roche Diagnostic Systems, Branchburg, NJ], $CD4^+$ and $CD8^+$ lymphocyte counts).

Definition of HBV and HCV serologic categories. Previous studies reported that HCV infection has a very high rate of persistence [12]. Therefore, when antibodies against HCV were present at baseline, patients were considered to have a chronic HCV infection. The following 2 categories subsequently were distinguished: chronic hepatitis B or C (for patients with positive HBsAg [13] or anti-HCV serology, respectively); and no chronic hepatitis (for patients without serologic markers for chronic HBV and HCV infection).

Definition of LEE. A clinically relevant LEE was defined, according to AIDS Clinical Trials Group (ACTG) criteria, as having transaminase (ALT and/or AST) levels elevated ⩾5 times the upper limit of normal (grade 3 or 4) [14]. In addition, the absolute increase had to be ⩾100 U/L, compared with an individual's baseline value, to avoid misclassification of patients with high baseline transaminase values and only minor transaminase elevation. Patients were regarded as having LEE if they had experienced ⩾1 episode of LEE while they were using study medication. If LEE was based on elevated ALT, improvement in transaminase elevation was defined as a decrease in ALT to <50% of the ALT concentration at the time LEE first was observed; AST improvement was determined in a similar manner.

Statistical analyses. Potential risk factors for LEE were explored by use of univariate Cox proportional hazard analysis, with the time to LEE considered a dependent variable. Patients in whom LEE did not occur were censored at the last study visit. Parameters considered as potential predictors of LEE were age, sex, weight, pretreatment with RTIs, HIV transmission category, stage of HIV disease (CDC classification), baseline levels of AST and ALT, HIV-1 RNA, $CD4^+$ and $CD8^+$ cell counts, change in $CD4^+$ and $CD8^+$ cell counts between weeks 0 and 12, and results of HBsAg and anti-HCV tests. In addition to variables with $P < .10$ in the univariate model, baseline AST and ALT levels were entered a priori in the multivariate model, because the study end point LEE was based on ALT and/or AST levels. Differences between groups were considered significant at $P < .05$, and all reported P values are 2-sided. Analyses were performed using SAS software, version 6.12 (SAS Institute, Cary, NC).

Results

Patient characteristics. A total of 208 HIV-1–infected subjects participated in this study. The participants were predominantly homosexual men with a median serum HIV-1 RNA level of 4.47 $\log_{10}$ copies/mL and a median $CD4^+$ cell count of 255 cells/mm^3 (table 1).

Patients were considered to have chronic hepatitis B if they had tested positive for HBsAg, and they were considered to have chronic hepatitis C if they had tested positive for anti-HCV at baseline. Results of the HBsAg test at baseline (week

Table 1. Baseline characteristics of 208 HIV-infected patients.

Characteristic	HIV-infected patients: With chronic hepatitis[a] (n = 40)	HIV-infected patients: Without chronic hepatitis[b] (n = 168)	P
Treatment			
Rtv/Sqv/d4T	18 (45)	86 (51)	.60
Rtv/Sqv	22 (55)	82 (49)	
ALT, median U/L (IQR)	36 (25–55)	28 (21–42)	.01
AST, median U/L (IQR)	32 (27–45)	25 (20–34)	.002
Sex			
Male	35 (88)	142 (85)	.81
Female	5 (12)	26 (15)	
Prior antiretroviral therapy			
Pretreated	27 (68)	71 (42)	.005
Naive	13 (32)	97 (58)	
HIV transmission risk group			
Homosexual contacts	20 (50)	114 (68)	.04
Heterosexual contacts and/or former residence in endemic area	5 (13)	38 (22)	.20
Injection drug use	11 (28)	0 (0)	<.001
Other	3 (8)	13 (8)	1.0
Unknown	1 (3)	3 (2)	
Time since first positive HIV test, median y (IQR)	3.4 (1.3–7.8)	2.4 (0.5–6.0)	.04
CDC classification			
A	15 (37)	78 (47)	.38
B	17 (43)	51 (30)	.19
C	8 (20)	39 (23)	.83
Age, median y (IQR)	36 (31–46)	37 (32–45)	.57
Weight, median kg (IQR)	72 (66–81)	72 (64–80)	.51
Serum HIV-1 RNA, median $\log_{10}$ copies/mL (IQR)	4.3 (3.8–4.7)	4.5 (4.0–5.0)	.12
$CD4^+$ count, median cells/mm^3 (IQR)	275 (190–355)	250 (115–390)	.22
$CD8^+$ count, median cells/mm^3 (IQR)	815 (625–1140)	835 (655–1150)	.80

NOTE. Data are no. (%) of patients, unless otherwise specified. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CDC, Centers for Disease Control and Prevention; d4T, stavudine; HIV-1, HIV type 1; IQR, interquartile range; Rtv, ritonavir; Sqv, saquinavir.

[a] Patients who were positive for serum hepatitis B surface antigen (HBsAg) or anti-hepatitis C antibody (anti-HCV).

[b] Patients negative (or with missing serology) for HBsAg and anti-HCV.

0 or week −2) were available for 195 subjects (94%), and results of HCV serology were available for 201 subjects (97%): 25 patients (12%) were HBsAg positive, and 17 (8%) were anti-HCV positive (2 of these patients were positive for both HBsAg and anti-HCV). Patients with missing data were classified as having no chronic hepatitis. Since some patients with missing data may have been positive for HBsAg or anti-HCV, this assumption will give a conservative approach when patients who have chronic hepatitis are compared with those who do not have chronic hepatitis.

Patients with chronic hepatitis were more likely to have higher baseline levels of ALT or AST and were more likely to have acquired HIV by injection drug use and to have used antiretroviral medication before participation in the study (table 1). Patients assigned to treatment with ritonavir/saquinavir/stavudine were equally distributed between the 2 groups (i.e., the group with no chronic hepatitis and the group with chronic hepatitis B or C), reflecting the randomization in this study.

LEE. Eighteen patients (9%) developed LEE at a median of 12 weeks (range, 2–48 weeks) after the study began. LEE was observed earlier in the ritonavir/saquinavir treatment arm than in the ritonavir/saquinavir/stavudine treatment arm (median time, 9 weeks and 14 weeks, respectively; $P = .01$). The median ALT level was 358 U/L (range, 150–1890 U/L) at the time LEE was first observed. Ten patients experienced grade 3 ALT or AST toxicity, and 8 patients experienced grade 4 ALT or AST toxicity (according to ACTG criteria [14]) at that time point. The median highest ALT level measured during LEE was 574 U/L (range, 150–1890 U/L). Seven patients experienced grade 3 toxicity, and 11 patients experienced grade 4 toxicity (figure 1).

During the study, the highest ALT levels per patient were significantly higher in the group receiving ritonavir/saquinavir/stavudine (104 patients), which had a median ALT level of 69 U/L, compared with the group receiving ritonavir/saquinavir group (104 patients) ($P = .03$), which had a median ALT level of 51 U/L. These highest levels occurred later in the group receiving ritonavir/saquinavir/stavudine (median, 18 weeks; mean, 19 weeks) than in the group receiving ritonavir/saquinavir (median, 4 weeks; mean, 13 weeks; $P = .002$).

Patients with chronic hepatitis who were treated with ritonavir/saquinavir/stavudine had a 45% chance of developing LEE during the study period; patients with chronic hepatitis B who were treated with ritonavir/saquinavir alone had a 21% chance of developing LEE. In patients without chronic hepatitis B, LEE was observed in 9% and 2% of patients treated with ritonavir/saquinavir/stavudine or ritonavir/saquinavir, respectively.

Patients were allowed to intensify their initial treatment with RTIs (a) if their serum HIV RNA concentration did not drop to <400 copies/mL at week 12 and if it remained at that level at week 18 or (b) if it became detectable again after dropping to an undetectable level. Thirty-one patients, 28 (27%) of those receiving ritonavir/saquinavir and 3 (3%) of those receiving ritonavir/saquinavir/stavudine, intensified study medication as stated in the protocol. Median follow-up after intensification was 26 weeks. Most patients (21/31) added stavudine plus lamivudine to their initial regimen. LEE was not observed after intensification of study medication.

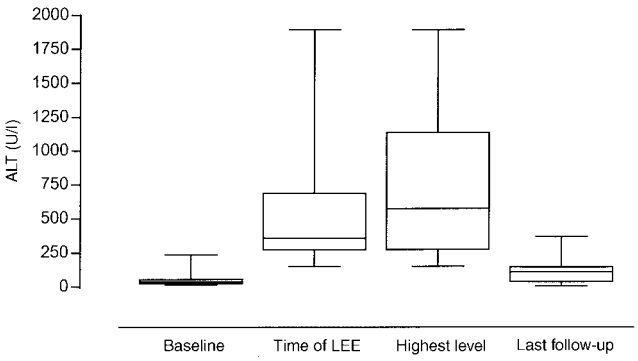

Figure 1. Course of alanine aminotransferase (ALT) levels in patients with liver enzyme elevation (LEE). Box and whisker plot of ALT levels in 18 patients with LEE at baseline (initiation of therapy), at the time LEE first occurred, at the highest level during LEE, and at the last follow-up visit. LEE occurred a median of 12 weeks (range, 2–48 weeks) after initiation of therapy. The last follow-up was done at a median of 39 weeks (range, 0–130 weeks) after LEE occurred. The solid line across the box indicates the median. Values in the box are values within the 2d and 3d quartiles; minimal and maximal values are connected by whiskers. LEE was defined, according to AIDS Clinical Trials Group criteria [14], as having elevated (toxicity, grade 3 or 4) ALT or aspartate aminotransferase levels that were ⩾5 times the upper limit of normal.

Risk factors for LEE. In univariate Cox regression analyses, HBsAg positivity (OR, 7.3; 95% CI, 2.9–18.7; $P = .0001$) and a higher baseline ALT concentration (RR, 1.1; 95% CI, 1.0–1.2; $P = .03$) were significant risk factors for development of LEE. The use of stavudine (RR, 2.7; 95% CI, 1.0–7.7) showed a trend ($P = .06$). Anti-HCV positivity, sex, age, weight, CDC HIV classification status, HIV transmission risk group, prior antiretroviral treatment, baseline AST concentrations, $CD4^+$ and $CD8^+$ cell counts at baseline, $CD4^+$ or $CD8^+$ increases from week 0 to week 12, and baseline HIV-1 RNA levels were not predictive for the development of LEE in univariate analyses (table 2).

Multivariate analysis, adjusted for baseline ALT and AST levels, showed that HBsAg positivity (RR, 8.8; 95% CI, 3.3–23.1) and randomization to the stavudine-containing regimen (RR, 4.9; 95% CI, 1.5–16.0) were the only 2 significant risk factors for development of LEE (table 2).

Follow-up and clinical management after LEE. The median follow-up after development of LEE was 40 weeks (range, 0–130 weeks). In 1 patient, no follow-up was available from the time of LEE, and another patient was followed for only 1.5 weeks after LEE occurred, at which time ALT had already

Table 2. Cox proportional hazard ratios for baseline characteristics of patients with liver enzyme elevation during treatment with ritonavir and saquinavir (Rtv/Sqv) with or without stavudine (d4T).

Risk factor	Univariate analysis hazard ratio (95% CI)	*P*	Multivariate analysis hazard ratio (95% CI)	*P*
HBsAg positive	7.3 (2.9–18.7)	.0001	8.8 (3.3–23.1)	.0001
Rtv/Sqv/d4T treatment arm	2.7 (1.0–7.7)	.06	4.8 (1.5–16.0)	.01
ALT concentration[a]	1.1 (1.0–1.2)	.03	1.2 (1.0–1.5)	.11
AST concentration[a]	1.1 (1.0–1.3)	.09	0.8 (0.5–1.3)	.47
Anti-HCV positive	1.8 (0.4–8.0)	.42		
Sex, male	0.9 (0.2–3.9)	.87		
Prior antiretroviral therapy	0.7 (0.3–1.7)	.40		
HIV transmission risk group				
Homosexual	0.8 (0.3–2.0)	.59		
Heterosexual	0.5 (0.1–2.1)	.32		
Injection drug use	1.3 (0.2–10.1)	.77		
Other	0.9 (0.1–6.5)	.89		
CDC classification				
A	0.9 (0.4–2.4)	.91		
B	1.4 (0.6–3.7)	.46		
C	0.7 (0.2–2.3)	.50		
Age[b]	1.0 (0.9–1.0)	.73		
Weight[c]	1.0 (1.0–1.0)	.58		
HIV-1 RNA, per $\log_{10}$ copies/mL	1.2 (0.6–2.2)	.66		
$CD4^+$ lymphocyte count[d]	1.0 (0.8–1.3)	.88		
$CD8^+$ lymphocyte count[d]	1.1 (1.0–1.2)	.19		
$CD4^+$ increase $\geq 50/mm^3$[e]	1.2 (0.4–3.5)	.80		
$CD8^+$ increase $\geq 100/mm^3$[e]	0.7 (0.3–1.9)	.54		

NOTE. ALT, alanine aminotransferase; anti-HCV, anti-hepatitis C antibody; AST, aspartate aminotransferase; CDC, Centers for Disease Control and Prevention; HBsAg, hepatitis B surface antigen; HIV-1, HIV type 1.

[a] Per 10 U/L increase in baseline AST or ALT concentrations.

[b] Per year increase in baseline age.

[c] Per kilogram increase in baseline weight.

[d] Per 100 cells/mm^3 increase in baseline $CD4^+$ or $CD8^+$ lymphocyte counts.

[e] Change in absolute $CD4^+$ or $CD8^+$ lymphocyte counts from week 0 to week 12.

decreased by 50%. In 14 of 16 patients with ⩾14 weeks of follow-up since LEE occurred, ALT and/or AST concentrations decreased to levels <50% of those measured when LEE was first observed. In 1 anti-HCV–positive patient, ALT levels remained high up to 23 months after LEE, although antiretroviral medication was discontinued 3 weeks after LEE occurred. In 1 patient who continued study medication, ALT levels had decreased from 151 U/L to 100 U/L after 36 weeks. The median ALT concentration at the last follow-up visit was 110 U/L (range, 6–368 U/L) (figure 1). Of 14 patients with improved LEE, only 3 (21%) interrupted study medication for 3–8 weeks after experiencing LEE.

Discussion

In this study, we showed that chronic hepatitis B coinfection and the use of stavudine were independent risk factors for the development of clinically relevant LEE in HIV-1–infected patients who started antiretroviral treatment with ritonavir/saquinavir with or without stavudine. LEE developed in 32% of HBsAg-positive patients and in 14% of patients randomized to the stavudine-containing regimen.

The definitions that we used for chronic hepatitis B and C infection were based on serologic markers; no liver biopsies were done to confirm the diagnosis of chronic hepatitis in participants of this randomized trial of antiretroviral therapy. Anti-HCV–positive patients may not have had chronic hepatitis: The positive results may have been due to clearance of HCV or a false-positive test result [15]. This phenomenon may have led to a conservative estimate of the risk for LEE in patients with chronic hepatitis C. On the other hand, positive HCV RNA, as determined by PCR, has been reported in a low percentage of anti-HCV–negative patients at high risk for HCV infection [16, 17]. Because this patient population was not at high risk for HCV infection, we believe that this did not significantly influence our results.

Asymptomatic carriers of hepatitis B at study entry may have had a reactivation of hepatitis B during antiretroviral treatment. We included these asymptomatic carriers, who were positive for anti-HBsAg and/or anti-HBV core antigen in the group with "no chronic hepatitis." These elements may have caused an underestimation of the true risk for LEE in patients with chronic hepatitis B.

Compared with patients without chronic hepatitis, patients with chronic hepatitis had higher baseline ALT or AST concentrations, reflecting their underlying liver disease. In addition,

they were more likely to have acquired HIV by injection drug use, as reflected by the high prevalence of hepatitis C in this risk group. Compared with other study participants, more patients with chronic hepatitis had received treatment before entering the study.

Our data confirm the results of cohort studies [2, 3] and anecdotal reports [4–8]. These studies suggest that LEE during antiretroviral treatment is more common in HIV-infected patients who are coinfected with hepatitis B. However, we did not find an association between anti-HCV positivity and occurrence of LEE.

Recently published papers on the incidence of hepatotoxicity in cohort studies reported comparable incidences of LEE [18, 19], although the observed median time to LEE was longer in these studies. Patients in this randomized trial were evaluated intensively in the first 6 months, which could have led to earlier recognition of LEE.

Sulkowski et al. [18] found a high incidence (30%) of LEE in patients treated with ritonavir. This was much higher than the incidence (9%) in our study population, all of whom were treated with ritonavir. An explanation for this difference can be found in the different study population. Moreover, a bias in the choice of antiretroviral therapy could have occurred because the analyses by Sulkowski et al. were done in a nonrandomized cohort. In other studies, the association between ritonavir use and a high incidence of LEE was not confirmed [2, 3, 19].

Hepatotoxicity is a well-known side effect of antiretroviral therapy. Immune reconstitution induced by antiretroviral therapy can cause disease activation of chronic or previous latent infections, such as hepatitis B or C [4, 20]. In this study, LEE was highly associated with the presence of HBsAg. LEE occurred most frequently in the first 3 months of treatment, and none was observed after intensification of therapy with stavudine and lamivudine. Patients who intensified treatment during the study were not different from other patients with respect to baseline ALT or AST levels, serologic markers for hepatitis, or pretreatment status. These observations support the hypothesis that hepatotoxicity is caused by immune restoration. However, the difference between the 2 treatment arms in this study cannot be explained by a difference in immune restoration. The treatment groups did not differ in their $CD4^+$ and $CD8^+$ lymphocyte response to therapy [21]; moreover, the change in $CD4^+$ or $CD8^+$ lymphocyte counts was not associated with the occurrence of LEE.

Direct toxic effects of antiretroviral drugs can also cause LEE. Nucleoside analogue RTIs cause mitochondrial toxicity [1]. Although the nucleoside analogue RTI stavudine is seldom described as a hepatotoxic drug at the currently prescribed dose [22, 23], we found that stavudine was an independent risk factor for development of LEE in this study. Of note, in the current study, is that the highest ALT levels per patient occurred later (at approximately week 18) among patients receiving ritonavir/saquinavir/stavudine than among patients receiving ritonavir/saquinavir only (week 12).

In all but 1 of the patients who continued receiving antiretroviral medication, ALT and AST concentrations decreased to <50% of the level that was measured at the time LEE was first observed. This suggests that antiretroviral medication can be continued safely during LEE; however, more data from larger studies are required to confirm this finding.

In conclusion, clinically relevant LEE during antiretroviral combination therapy is more frequently observed among HIV-infected patients with concurrent chronic hepatitis B. We also found that the use of stavudine in combination with ritonavir and saquinavir was an independent risk factor for LEE.

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