Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection

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Objective: To investigate the risk of hepatotoxicity after initiation of protease inhibitor-containing highly active antiretroviral therapy (HAART) for HIV-1 infected patients with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) co-infection.

Design: Retrospective study with 394 HIV-1-infected patients initiating HAART at a single university clinic.

Methods: Liver enzyme elevation (LEE) was defined as alanine aminotransferase or aspartate aminotransferase at least five times the upper limit of normal and an absolute increase of > 100 U/l. Relative risks for time to LEE were estimated using Cox proportional hazards models.

Results: Of 394 patients 7% were hepatitis B surface antigen (HBsAg)-positive and 14% were anti-HCV-positive. Patients with chronic hepatitis had a higher risk for LEE compared with patients without co-infection: 37% versus 12% respectively. After adjustment for higher baseline transaminases, the presence of HBsAg or anti-HCV remained associated with an increased risk of LEE – relative risk 2.78 (95% confidence interval, 1.50–5.16) and 2.46 (95% confidence interval, 1.43–4.24) respectively. In patients with LEE, transaminases declined whether HAART was continued or modified. Of patients with chronic HBV infection 38% lost HBeAg or developed anti-HBe after initiation of HAART, and one seroconverted from HBsAg-positive to anti-HBs-positive. However, there was no clear relationship with LEE.

Conclusions: HIV-1-infected patients co-infected with HBV or HCV were at considerably higher risk of developing LEE when HAART was initiated compared with patients without co-infection, but it is usually not necessary to modify antiretroviral therapy.

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Keywords: HIV-1, hepatitis B virus, hepatitis C virus, highly active antiretroviral therapy, hepatotoxicity, liver enzyme elevation

Introduction

Liver enzyme elevation (LEE) has been reported to be a potential side-effect of most antiviral agents used for the treatment of HIV-1 infection [1]. Since the introduction of highly active antiretroviral therapy (HAART) with triple drug combination regimens, severe elevations in liver enzyme levels are being...
observed frequently. Anecdotal reports and data from two clinical cohorts suggest that such antiretroviral-therapy-related LEE may appear more often in HIV-1 infected patients who are co-infected with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) than in HIV-1 infected patients without such a co-infection [2–8].

HIV-1, HBV and HCV share similar potential routes of transmission. Not surprisingly, co-infections of HIV-1 and HBV and/or HCV are common. Up to 82% of injecting drug users (IDU) with HIV-1 infection, and up to 77% of homosexual men with HIV-1 infection have markers of past or chronic HBV infection; 72% and 7%, respectively, have markers of past or chronic HCV infection [9].

Many issues related to the clinical management of patients who develop LEE following the start of HAART are uncertain: the risk of developing hepatotoxicity varies among cohorts, as does the relative contribution of individual antiretroviral agents [7,8], and guidelines for deciding whether to continue or modify antiretroviral treatment are lacking.

The primary aim of this retrospective study was to investigate whether a chronic HBV or HCV infection is a risk factor for LEE when initiating HAART. Secondly, to estimate the risk of LEE following the initiation of HAART, and to identify other potential risk factors which might enhance this risk. Thirdly, to describe the effect of continuation or modification of antiretroviral therapy on the course of LEE.

Materials and methods

Patients and data collection
An observational database was used in which data were entered from HIV-1-infected adults followed in the outpatient clinic of the Academic Medical Centre, University of Amsterdam. These patients started treatment with antiretroviral combination therapy containing at least one protease inhibitor (PI) between 1 July 1996 and 10 February 1998. To be included, patients could be either antiretroviral therapy-naïve or -experienced, but had to be PI-naïve before starting HAART. Patients participating in clinical trials with antiretroviral drugs were excluded from this analysis. As described elsewhere [10], data collected from patients’ medical records were: age, sex, risk group for HIV-1 transmission, previous use of antiretroviral drugs, prescribed antiretroviral medication at the start of this observational study (baseline), and the occurrence of HIV-1-related events as classified according to the Centers for Disease Control and Prevention (CDC) 1993 guidelines [11].

The following serologic parameters regarding HBV and HCV infection status were collected at baseline: hepatitis B virus surface antigen (HBsAg) and antibodies against hepatitis C virus (anti-HCV). Data on the following additional laboratory measurements were collected at the start of HAART, and 4, 8, and 12 weeks thereafter, and at least every 3 months during further follow-up: peripheral blood CD4 and CD8 cell counts, plasma HIV-1 RNA, alanine aminotransferase (ALT), asparate aminotransferase (AST), g-glutamyl transferase (g-GT) and alkaline phosphatase (AF). Baseline values for these laboratory parameters were obtained within 26 weeks prior to the initiation of HAART. In the majority of the patients (>95%) results were obtained at the initiation of HAART. Three patients had no results available at or before this time point, therefore results obtained 4, 5, and 14 days after the initiation of treatment were used as baseline values. Results of laboratory tests were retrieved from the hospital information system electronically. All other data were collected on standardized case record forms. Source document and data entry verification were performed in a randomly selected group of patients, who comprised approximately 25% of the total population.

Plasma HIV-1 RNA was determined by the following techniques: NASBA HIV-1 RNA QT (Organon Teknika, Boxtel, The Netherlands), NASBA Nuclisens (Organon Teknika) and Roche Amplicor (Roche Diagnostic Systems, Branchburg, New Jersey, USA). The lower limits of these assays were set at 1000 copies/ml, as described elsewhere [10], matching the highest of the three, the NASBA HIV-1 RNA QT technique. Values below this level obtained with different assays were considered to be <1000 copies/ml. Patients’ HBV and HCV serological status was determined by the AxSYM immunoassay (Abbott GmhH Diagnostika, Wiesbaden, Germany).

Definition of HBV and HCV serologic categories
Patients were considered to have chronic HBV infection when HBsAg could be detected in plasma on two occasions at least 6 months apart [12]. As reported previously, HCV infection has a very high rate of persistence [13] and so patients were considered to have a chronic HCV infection when anti-HCV was present. Patients without HBsAg and without anti-HCV were considered not to have chronic viral hepatitis.

Definition of LEE
In accordance with AIDS Clinical Trials Group criteria [14], severe LEE – toxicity grade 3 – was defined as a transaminase elevation (ALT and/or AST) ≥ 5 times the upper limit of normal. The upper limit of normal used in this hospital are 37 U/l for ALT and 47 U/l for AST. In addition, the absolute increase needed to be more than 100 U/l compared with an
individual’s baseline value in order to avoid misclassification of patients as a consequence of a high baseline transaminase level. Patients were regarded as having LEE if they had experienced the above definition of transaminase elevation at least once since the start of HAART. Elevations of g-GT and AF were not considered as primary parameters of interest, as these do not reflect liver cell damage.

As a means of confirmation, the maximum increase of transaminase observed in the first 6 months for each participant was compared between the above mentioned groups also.

**Clinical management of patients with LEE**

To study the effect on liver enzymes of continued or modified use of antiretroviral medication after LEE was observed, patients were evaluated for a period of 90 days following LEE regarding changes in the use of antiretroviral medication. ALT and AST were followed up for 48 weeks after the occurrence of LEE. For the evaluation of continued or modified use of antiretroviral medication, data were collected on ALT, AST, g-GT, and AF values, CD4 and CD8 cell counts, plasma HIV-1 RNA copy number, and names of the treating physicians at the time LEE was observed.

Furthermore, it was determined whether or not patients with a chronic HBV infection seroconverted from HBsAg-positive to anti-HBs-positive and whether their HBeAg and anti-HBe status changed 1 year after the initiation of HAART.

**Prognostic factors for LEE following HAART**

To study potential risk factors for the occurrence of LEE following the start of HAART, Cox proportional hazards analyses were performed. Baseline parameters considered as possible predictors of LEE were: age, sex, hepatitis serological status, risk group for HIV-1 transmission, stage of HIV-1 disease (CDC classification), CD4 and CD8 cell count, plasma HIV-1 RNA copy number, previous antiretroviral drug use, the use of a specific PI, the concomitantly used nucleoside analogue reverse transcriptase inhibitors (NRTI), and ALT, AST, γ-GT, and AF values.

**Statistical analyses**

Group comparisons were made using student’s t test or ANOVA for normally distributed continuous data, or Wilcoxon or Kruskal–Wallis tests for data that were not normally distributed. Chi-square test or Fisher’s exact test, where appropriate, were used for categorical data. Differences between groups were considered to be significant at a P value < 0.05. All reported P values are two-sided. Variables with a P value ≤ 0.10 in the univariate Cox regression analysis were entered in a multivariate model, performing a stepwise analysis.

Survival analysis for LEE-free survival was performed and Kaplan–Meier curves were obtained.

**Results**

**Patients characteristics**

A total of 409 HIV-1-infected subjects started HAART within the 18 month inclusion period. Of these 409 patients, results of HBV and HCV serology were available for 394 (96%) (Fig. 1). These 394 patients had a median follow-up of 16 months [inter quartile range (IQR), 8–21 months]. Of these 394 HIV-1-seropositive patients with known HBV/HCV serology, 29 (7%) were HBsAg positive, 57 (14%) were anti-HCV positive, two (1%) were both HBsAg and anti-HCV positive (not listed in Table 1, but included in the Cox proportional hazard analysis), and 306 (78%) patients were both HBsAg and anti-HCV negative.

Baseline characteristics of the 394 patients did not differ significantly between the three hepatitis serological subgroups, except for sex, risk group for HIV-1 transmission, and ALT, AST, γ-GT, and AF values (Table 1).

**LEE**

Seventy (18%) out of the 394 patients developed LEE; 13 out of 29 (45%) and 19 out of 57 (33%) of the patients who were HBsAg positive or anti-HCV positive, respectively, compared with 38 out of 306 (12%) among subjects without these serological markers. The two patients who tested positive for both HBsAg and anti-HCV did not develop LEE. The 70 cases of LEE were seen after a median of 25 weeks following the initiation of HAART (IQR, 12–42 weeks). More rapid occurrence of LEE was observed in HBsAg-positive as well as anti-HCV-positive patients compared with patients without these parameters \( P = 0.0001 \), (Fig. 2).

The maximal increase in ALT observed during the first 6 months of HAART was median 35 U/l (IQR, 11–192 U/l) in HBsAg-positive patients, 22 U/l (IQR, 2–116 U/l) in anti-HCV-positive patients and 11 U/l in neither HBsAg nor anti-HCV-positive patients.

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Among the patients with unknown HBV and HCV serology status, LEE was seen only once (7%).

### Predictors for LEE

In Table 2, the results of the univariate Cox proportional hazard model are shown for all patients. The presence of HBsAg or anti-HCV appeared to be a risk factor for developing LEE during HAART, with relative risks (RR) of 3.10 [95% confidence interval (CI), 1.69–5.67] and 2.71 (95%CI, 1.59–4.59), respectively. The level of ALT, g-GT, and IDU as a risk group for HIV-1 infection were predictive as well, with RR of 1.07 (95% CI, 1.03–1.10) and 1.01 (95% CI, 1.00–1.03) per 10 U/l increase and 2.25 (95% CI, 1.12–4.53) respectively. In the multivariate analysis the presence of HBsAg or anti-HCV remained predictive, with RR of 2.78 (95% CI, 1.50–5.16) and 2.46 (95% CI, 1.43–4.24) both with P values of 0.001. Beside these predictors, only baseline ALT remained predictive: 1.05 (95% CI, 1.01–1.08) per 10 U/l increase (P = 0.01).
Clinical management of LEE

Of 70 patients, one died 12 days after developing LEE (due to a late stage Kaposi’s sarcoma with pneumonia, cardiac failure and sepsis) and one subject was lost to follow-up. At the time of this analysis, three of the remaining 68 patients had less than 90 days follow-up (56, 77 and 84 days) but were still included in the analysis.

In 25 out of 68 (37%) of the patients with LEE, antiretroviral treatment was modified during the 90 days after LEE was observed. Patients who continued or modified treatment were compared at the time LEE was observed in terms of the following parameters: liver enzyme levels, CD4 and CD8 cell counts, plasma HIV-RNA copy number, NRTI backbone and PI component of HAART, and the names of the treating physicians. None of these parameters differed significantly among these two groups. At borderline significance, only g-GT was higher in patients who modified antiretroviral treatment \([\text{median (IQR) of 246 (108–304) U/l, compared with patients who did not [149 (92–238) U/l]}.\]

Transaminase levels of patients who continued treatment were compared with those of patients who ceased treatment at the time LEE was observed, 90 days and 48 weeks later (Table 3 and Fig. 3). As LEE was defined post hoc, ALT and AST at the first LEE did not differ significantly as expected, except for HBsAg-positive patients. Most ALT and AST values normalized 90 days after LEE when patients modified treatment, except for anti-HCV-positive patients. Although in this latter group the ALT and AST values did not normalize, they did not differ significantly between the two treatment policy groups. Forty-eight weeks after the occurrence of LEE the median AST and ALT had returned to baseline levels in the patients who modified treatment (median AST, 35 U/l; IQR, 27–48 U/l; Wilcoxon \(P\) value, 0.61; median ALT, 45 U/l; IQR, 27–63 U/l; Wilcoxon \(P\) value, 0.53). The median AST and ALT in the patients who continued treatment declined to values just above baseline (median AST, 1.01 (0.97–1.05) U/l, compared with patients who did not.

Table 2. Univariate Cox regression analyses: relative risks for liver enzyme elevation after the institution of highly active antiretroviral therapy (HAART) for all patients.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Relative risk (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.98 (0.95–1.01)</td>
<td>0.20</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.25 (0.71–2.22)</td>
<td>0.44</td>
</tr>
<tr>
<td>Hepatitis serological status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg – and anti-HCV –</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HBsAg +</td>
<td>3.10 (1.69–5.67)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Anti-HCV +</td>
<td>2.71 (1.59–4.39)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Risk group for HIV-1 infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homosexual</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Injecting drugs use</td>
<td>2.25 (1.12–4.53)</td>
<td>0.02</td>
</tr>
<tr>
<td>Other</td>
<td>1.17 (0.58–2.36)</td>
<td>0.65</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>1.11 (0.58–2.12)</td>
<td>0.76</td>
</tr>
<tr>
<td>CDC C Class</td>
<td>0.99 (0.62–1.59)</td>
<td>0.96</td>
</tr>
<tr>
<td>CD4 cell count (per square root (10^6)cells/l)</td>
<td>0.97 (0.93–1.01)</td>
<td>0.12</td>
</tr>
<tr>
<td>CD8 cell count (per square root (10^6)cells/l)</td>
<td>0.99 (0.96–1.01)</td>
<td>0.34</td>
</tr>
<tr>
<td>HIV-1 RNA copies (per log(_{10}))</td>
<td>1.17 (0.89–1.53)</td>
<td>0.26</td>
</tr>
<tr>
<td>HIV-1-RNA undetectable prior to start HAART (&lt;1000 copies/ml)</td>
<td>0.64 (0.32–1.29)</td>
<td>0.21</td>
</tr>
<tr>
<td>Naive to antiretroviral therapy prior to the start of HAART</td>
<td>0.92 (0.55–1.56)</td>
<td>0.76</td>
</tr>
<tr>
<td>NRTI backbone of HAART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine/lamivudine</td>
<td>1.44 (0.70–2.97)</td>
<td>0.33</td>
</tr>
<tr>
<td>Didanosine/stavudine</td>
<td>1.12 (0.58–2.15)</td>
<td>0.75</td>
</tr>
<tr>
<td>Stavudine/lamivudine</td>
<td>0.96 (0.53–1.74)</td>
<td>0.90</td>
</tr>
<tr>
<td>Protease inhibitor component of HAART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td>1.70 (0.88–3.29)</td>
<td>0.11</td>
</tr>
<tr>
<td>Saquinavir/ritonavir</td>
<td>1.32 (0.62–2.80)</td>
<td>0.47</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>1.30 (0.72–2.33)</td>
<td>0.39</td>
</tr>
<tr>
<td>Liver enzymes (per 10 U/l increase)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>1.07 (1.03–1.10)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Asparate aminotransferase</td>
<td>1.03 (0.98–1.07)</td>
<td>0.29</td>
</tr>
<tr>
<td>g-Glutamyl transferase</td>
<td>1.01 (1.00–1.03)</td>
<td>0.04</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>1.01 (0.97–1.05)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

CI, Confidence interval; NRTI, nucleoside analogue reverse transcriptase inhibitor.
these, 10 had experienced LEE. Of these 21 patients seven (33%) lost HBeAg and three out of 21 (14%) developed anti-HBe. Of patients who experienced LEE four out of 10 (40%) lost HBeAg, compared to three out of 11 (27%) patients without LEE; one out of 10 (10%) patients with LEE developed anti-HBe, compared to two out of 11 (18%) patients without LEE. One patient, who experienced LEE, lost HBeAg and developed anti-HBe, and seroconverted from HBsAg positive to anti-HBs positive.

### Discussion

These results confirm earlier reports that suggested that patients with chronic HBV or HCV infection are at increased risk for developing LEE following the initiation of HAART. Increased risks of developing LEE of approximately 2.78 times for patients with a chronic HBV infection, and 2.46 times for patients with a chronic HCV infection were found in the multivariate analysis. Patients had an increased risk of developing LEE of 1.05 times per 10 U/l increase of baseline ALT. However, age, sex, baseline AST, γ-GT, baseline CD4 and CD8 cell counts, baseline HIV-1 RNA load, and stage of HIV-1 disease at baseline were not predictive. The use of specific antiretroviral therapies was not predictive, in contrast with a recent publication where use of ritonavir was associated with an increased risk of hepatotoxicity [8].

According to the literature, using anti-HCV as a marker for chronic HCV infection may give an overestimation of 10±15% [15,16]. However, this misclassification will only dilute the real differences between patients with or without chronic HCV infection. Therefore, our conclusion that chronic HCV infection is a risk factor for developing LEE after the initiation of HAART is not undermined by this misclassification bias. In this observational study, the patients were not assigned randomly to receive a particular regimen.

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### Table 3. Transaminases of patients with liver enzyme elevations (LEE), at the time LEE was observed and 90 days thereafter, broken down into patients who continued antiretroviral treatment and who did not.

<table>
<thead>
<tr>
<th>Continuation of treatment</th>
<th>Transaminases at the time of LEE</th>
<th>Transaminases 90 days after LEE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients (n) ALT median (IQR)</td>
<td>Patients (n) ALT median (IQR)</td>
</tr>
<tr>
<td></td>
<td>All 43 242 (201–398) 172 (106–291)</td>
<td>All 25 224 (206–455) 209 (141–326)</td>
</tr>
<tr>
<td>HbsAg – and anti-HCV–</td>
<td>23 210 (199–296) 146 (94–278)</td>
<td>14 215 (197–292) 207 (141–286)</td>
</tr>
<tr>
<td>HbsAg+ and anti-HCV–</td>
<td>5 205 (193–319) 106 (103–113)</td>
<td>7 533 (211–750) 351 (151–1000)</td>
</tr>
<tr>
<td>HbsAg – and anti-HCV–</td>
<td>14 215 (197–292) 207 (141–286)</td>
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</tr>
</tbody>
</table>

*LEE was defined as: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 times the upper limit of normal and an increase of ≧ 100 U/l compared with baseline. IQR, Interquartile range.
Patient adherence to the antiretroviral drug regimen might be related to the development of LEE. However, adherence data were not collected in this study and so could not be included in the analysis. In this retrospective study no liver biopsies were performed before the start of HAART or after the development of LEE. In future studies liver biopsies might provide information on how LEE develops. Another limitation is that no information on alcohol use and possible hepatitis A virus (HAV) infection was available. However, we do not expect HAV infection to be an important factor for the development of the LEE observed, as the incidence of HAV infection is low in the western world and it is highly unlikely that many patients would experience an HAV infection shortly after the initiation of HAART.

Several mechanisms can be postulated to play a role in the increased risk for LEE. First, there could be enhanced toxicity of the antiretroviral drugs in the presence of pre-existing HCV or HBV infection. Secondly, HAART may be associated with recovery of cell-mediated immunity, leading to immune-mediated HBV- and HCV-specific liver cell damage and transaminase elevation [5,17]. A similar mechanism has been postulated to explain the unusual course of cytomegalovirus retinitis and atypical mycobacterial infections shortly after commencing antiretroviral therapy [18,19]. Cell-mediated immunity is considered to play a central role in the pathogenesis of HBV [20,21]. This is compatible with the reverse observation that when immunosuppression from HIV-1 infection occurs in an HBV carrier, HBV replication increases, but HBV related liver inflammation in fact lessens and transaminase values decrease [2,22,23]. Of note, in accordance with earlier case histories [2,24], quite a few of our patients lost HBeAg or developed anti-HBe and one lost HbsAg after initiation of HAART. There was, however, no clear relationship with LEE.

HIV-1-induced immunodeficiency may not reduce hepatic inflammation that is caused by HCV whereas replication of HCV may be enhanced [25]. Epidemiological evidence indeed suggests a more rapid progression of chronic HCV infection in HIV-1 infected patients [26].

An increase in the number of CD4 cells is a crude measure of the improvement of the immune system of a person. Although the patients who experienced LEE had slightly lower increases in their CD4 cell counts, these increases might still reflect an increased immune response against HBV or HCV-infected hepatocytes (data not shown).

It was observed that the likelihood of improvement in LEE was similar when HAART was continued or modified. This might allow the clinician to follow a expectative course in cases of HAART-associated LEE, and does not call for an immediate treatment modification. On the other hand these results apply only to PI-containing HAART regimens. Acute lethal hepatic toxicity has been documented in a few cases of nevirapine-containing HAART regimens [27], and one should also always remain alert to the possibility of potentially lethal mitochondrial toxicity, associated with the use of NRTI [28].

References


14. AIDS Clinical Trials Group criteria, division of AIDS. Table for grading severity of adult adverse experiences, August 1992.


