Grade 3-4 Liver Enzyme Elevation during HAART in HIV and Hepatitis C Co-infected Adults

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ABSTRACT

Aim: to evaluate the incidence of grade 3-4 LEE in HIV/HCV co-infected patients after the introduction of HAART, the clinical significance to the patients and to determine any factors that could predict its development.

Methods: a retrospective cohort study of HIV/HCV co-infected adults in Pokdisus AIDS Clinic Cipto Mangunkusumo Hospital was conducted. All patients were antiretroviral naïve and had never had interferon therapy before. Patients who started taking first line combination therapy in Indonesia (NNRTI based regimen) from January 2004 to August 2006 and who were followed up for at least 6 months later were included in this study.

Results: a total of 59 grade 3-4 LEE (any ALT increase by ≥ 5 times ULN or any increase of 100 U/L from baseline) developed in 284 patients during the follow up (20.8%). The median onset of grade 3-4 LEE was 20 weeks (min-max 2-80). Only 27.1% accompanied with symptoms. Two patients developed decompensated liver diseases, one of them ended with death. In 5 patients, grade 3-4 LEE coincided with nevirapine or efavirenz-related rashes. Fifty-two patients (88.1%) continued their antiretroviral regimen throughout the entire episode of grade 3-4 LEE. The median peak level of ALT was 2311 IU/L (IQR, 174–327).

Conclusion: lower baseline ALT was the only factor significantly correlated with grade 3-4 LEE in this study.

Key words: liver enzyme elevation, highly active antiretroviral therapy, HIV/HCV.

INTRODUCTION

The use of highly active antiretroviral treatment (HAART) has dramatically reduced human immunodeficiency virus (HIV)-related morbidity and mortality. However, antiretroviral therapy is associated with significant increases in serum liver enzymes. Severe liver enzyme elevations (LEE) are frequently observed, ranging from 6% to 36.9%. The majority of the patients with liver enzyme elevation were asymptomatic, but fatal condition was also reported.

Data from numerous clinical studies 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.

HIV-1 and HCV share similar potential routes of transmission. Not surprisingly, co-infections of HIV-1 and HCV are common. Our previous report showed that up to 80% of HIV-infected adults in Jakarta have markers of past or chronic HCV infection, thereby antiretroviral management of these patients is uniquely challenging.

However, incidence of liver enzyme elevation and additional risk factors that may enhance liver enzyme elevations in large cohorts of HCV/HIV co-infected patients are lacking.

The objective of this study was to evaluate the incidence of grade 3-4 liver enzyme elevation (LEE) in HIV/HCV co-infected patients after the introduction of HAART, the clinical significance to the patients and to determine if there were any factors that could predict its development.

METHODS

A retrospective cohort study of HIV/HCV co-infected adults in Pokdisus AIDS Clinic Cipto
Mangunkusumo Hospital was conducted. All patients were antiretroviral naïve and had never had interferon therapy before. Patients who started taking first line combination therapy in Indonesia (NNRTI based regimen) from January 2004 to August 2006 and who were followed for at least 6 months later were included in this study. Hepatitis B co-infection, and age less than 17 years were excluded. Treatment changes, therapy withdrawal, or any other decision regarding therapy were made by the physician in charge.

Data collected from patients at baseline included age, sex, risk factors for HIV and HCV infection, present treatment of opportunistic infection, and CD4+ cell count.

**Definition of HCV Serologic Category**
Patients are considered to have HCV infection when anti-HCV can be detected in plasma in the baseline.

**Outcomes**
The primary outcome was the development of grade 3-4 liver enzyme elevation in this population. Liver enzyme elevation was defined in accordance with modified version of the AIDS Clinical Trial Group. For patients with normal baseline ALT level, grade 3 LEE was defined as an increase of 5.1 to 10 times the upper normal limit, whereas grade 4 LEE was defined as an increase of more than 10 times the upper normal limit. In those patients with elevated baseline enzyme levels, liver enzyme elevation was defined as an elevation of at least 3 times above baseline level.

Secondary outcomes measured were the continuation of antiretroviral regimen, decompensated liver disease or liver related death.

Furthermore, medical files of all patients experiencing grade 3-4 LEE were reviewed with the aim to identify the onset of grade 3-4 LEE, coincidence with NNRTI-associated rash, and non-antiretroviral drug related liver enzyme elevation.

**Statistical Analysis**
The following factors assessed at baseline for the possible correlation with grade 3-4 LEE: gender, age, baseline absolute CD4+ cell count, baseline serum ALT level, and baseline body mass index (BMI). We analyzed the different variables with chi-square and independent t-test or Mann-Whitney test to check if there was a statistically significant association. A P-value of < 0.05 was considered to indicate statistical significance. All variables with a P-value lower than 0.25 at univariate analysis were included in multivariate logistic regression model, if clinically meaningful. All the studies were conducted using SPSS software version using SPSS version 10.0.

**RESULTS**

**Patient Characteristics**
A total of 284 HIV/HCV co-infected patients were identified and matched with the study criteria. Baseline characteristics of the patients are summarized in table 1. The majority of the patients were male and former intravenous drug user. All patients were started antiretroviral for their first regimen. First line antiretroviral regimen according to Indonesian guideline was a combination of either zidovudine or stavudine plus lamivudine plus either nevirapine or efavirenz. None of the patients has been treated with interferon and ribavirine treatment before taking antiretroviral.

No difference was detected in pre-treatment of serum ALT level between those prescribed nevirapine and efavirenz (mean ALT 43 U/L and 37.7 U/L, respectively).

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (N=284)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>271</td>
<td>96.1%</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>3.9%</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30 years</td>
<td>252</td>
<td>88.7%</td>
</tr>
<tr>
<td>&gt; 30 years</td>
<td>32</td>
<td>11.3%</td>
</tr>
<tr>
<td>Risk of transmission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDU</td>
<td>221</td>
<td>77.8%</td>
</tr>
<tr>
<td>Sexual transmission</td>
<td>9</td>
<td>3.2%</td>
</tr>
<tr>
<td>IDU and sexual transmission</td>
<td>54</td>
<td>19%</td>
</tr>
<tr>
<td>NRTI backbone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>zidovudine/lamivudine</td>
<td>232</td>
<td>81.7%</td>
</tr>
<tr>
<td>stavudine/lamivudine</td>
<td>52</td>
<td>18.3%</td>
</tr>
<tr>
<td>NNRTI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nevirapine</td>
<td>253</td>
<td>89.1%</td>
</tr>
<tr>
<td>efavirenz</td>
<td>31</td>
<td>10.9%</td>
</tr>
<tr>
<td>Median baseline CD4 + cell count/μL (min-max)</td>
<td>85.9</td>
<td>2-588</td>
</tr>
<tr>
<td>Median baseline ALT (min-max)</td>
<td>34</td>
<td>7-180</td>
</tr>
</tbody>
</table>

**Incidence of Grade 3-4 LEE**
Fifty nine of the cases developed grade 3-4 liver enzyme elevation during the follow up period. The cumulative incidence was 20.8% of the entire study. An elevation of ALT 5.1 to 10 times the upper normal limit (grade 3 LEE) was observed in 22 patients, and an elevation above 10 times the upper normal limit (grade 4 LEE) was observed in 11 patients (3.9%). Fifteen patients with elevated baseline enzyme levels had ALT raised 3 times above their baseline levels.
The highest incidence of grade 3-4 LEE was observed during the first three months after starting HAART (45.6%) as seen in figure 1. Twenty five percent of grade 3-4 LEE occurred in second semester. However, grade 3-4 LEE could also be observed even after one year of therapy. The median duration of treatment before the detection of grade 3-4 liver enzyme elevation was 20 weeks (minimum-maximum 2-80 weeks).

Grade 3-4 liver enzyme elevations were detected in 20.6% patients who started with nevirapine regimen (52 of 253 patients), and 22.6% of patients who started with efavirenz containing regimen (7 of 31 patients). The difference was not statistically significant (p= 0.79).

Outcome of Grade 3-4 LEE
Overall, sixteen (27.1%) of 59 grade 3-4 liver enzyme elevated patients were symptomatic. The most frequently occurring symptoms were nausea only (12 patients), followed by jaundice in 2 patients, and decompensated liver disease in 2 patients.

In 5 patients, grade 3-4 LEEs coincided with nevirapine or efavirenz-related rashes. Fifty-two patients (88.1%) continued their antiretroviral regimen throughout the entire episode of grade 3-4 LEE. Seven patients (11.9%) discontinued or interrupted the therapy, five of them were caused by grade 3-4 LEE while others were caused by other reasons. One patient died during the episode of decompensated liver disease.

The median peak level of ALT in patients who developed grade 3-4 LEE was 231.1 IU/L (IQR, 174 – 327).

Factors Associated with Grade 3-4 LEE
There were no significant differences between the patients who had a grade 3 – 4 ALT during follow-up relative to those who did not in baseline demographic variables. In univariate analysis, baseline ALT was found to be the only factor significantly associated with a grade 3–4 elevation in ALT levels.

DISCUSSION
HCV has consistently been suggested as a risk factor for development of liver enzyme elevation during HAART.4,7,11-13 Rodriguez, et al reported that chronic HCV infection is associated with 2.8-fold greater risk for hepatotoxicity with the use of HAART.14 Den Brinker, et al demonstrated the data from their cohort that patient with HCV had a relative risk of developing LEE 2.46 times higher than other population.7 This study is the first study carried out in Asian population, which included only HIV co-infected with HCV patients.

We found the cumulative incidence grade 3-4 LEE of 20.8%. This cumulative incidence is in the range of those previously reported studies among HIV patients (6-36.9%),2-4 and other studies among HIV/HCV co-infected patients. Servin-Abad, et al reported the incidence of grade 3-4 LEE in HIV and HCV population was 10.6%, Torti, et al reported 20 of 155 naive HIV and HCV patients (12.9%), Chihrin, et al reported the incidence of 17%, Nunez, et al reported incidence of 22%.15-18

Table 2. Factors associated with grade 3-4 LEE

<table>
<thead>
<tr>
<th></th>
<th>With gr 3-4 LEE (n=59)</th>
<th>Without gr 3-4 LEE (n=225)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26.4 (SD 2.73)</td>
<td>26.1 (SD 3.61)</td>
<td>0.372</td>
</tr>
<tr>
<td>Male (%)</td>
<td>58 (21.2%)</td>
<td>215 (78.8%)</td>
<td>0.469</td>
</tr>
<tr>
<td>Risk factors for transmission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDU (%)</td>
<td>46 (20.8%)</td>
<td>175 (79.2%)</td>
<td>0.729</td>
</tr>
<tr>
<td>Sexual contact (%)</td>
<td>1 (11.1%)</td>
<td>8 (88.9%)</td>
<td>0.915</td>
</tr>
<tr>
<td>IDU and sexual contact (%)</td>
<td></td>
<td>12 (22.2%)</td>
<td>0.917</td>
</tr>
<tr>
<td>CD4+ before HAART (cells/µL)</td>
<td>85.1 (SD 101.24)</td>
<td>86.2 (SD 117.96)</td>
<td>0.491</td>
</tr>
<tr>
<td>ALT before HAART (U/L)</td>
<td>36.6 (SD 27.43)</td>
<td>44.0 (SD 28.72)</td>
<td>0.024</td>
</tr>
<tr>
<td>BMI before HAART</td>
<td>18.8 (SD 3.51)</td>
<td>19.1 (SD 3.2)</td>
<td>0.329</td>
</tr>
<tr>
<td>Concomitant drugs:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antituberculosis (%)</td>
<td>25 (25%)</td>
<td>75 (75%)</td>
<td>0.196</td>
</tr>
<tr>
<td>Cotrimoxazole (%)</td>
<td>49 (20.9%)</td>
<td>185 (79.1%)</td>
<td>0.882</td>
</tr>
</tbody>
</table>
The percentage of antiretroviral treatment modification after grade 3-4 LEE in our population is lower than observed in other studies (11.9% vs 19%-37%). All antiretroviral drugs were part of the government free drug program and changing treatment was not easy due to logistic limitation. Protease inhibitor is strictly used only for second line regimen. Therefore, we could not include ritonavir-based regimen in this study.

The percentage of symptomatic grade 3-4 LEE in this study (27.1%) is higher than previously reported. Indeed, one patient died during the episode of decompensated liver disease in our study. Servin-Abad, et al, who did a retrospective study of 85 HIV-HCV coinfected patients, did not identify any clinical manifestations associated with grade 3-4 LEE. It is suggestive that the overall conditions of the patients when starting antiretroviral may influence the symptoms. Our patients had a much lower median baseline CD4+ cell counts (85.9 cells/mL) compared to patients in numerous studies, due to late HIV diagnosis. Patients in Servin-Abad, et al had started antiretroviral therapy when their CD4+ cell counts were 255.2 cells/mL (SD 199.3). Puoti, et al showed that severe hepatotoxicity was related to preexisting chronic viral hepatitis followed by irreversible liver failure in a few patients, all with severe CD4+ T-cell depletion (i.e., <200 CD4+ T cells/mm3) before starting ART.

Several mechanisms had been postulated to play a role in the development of LEE during antiretroviral treatment in HIV co-infected with HCV patients. It is probable that multiple-pathogenic pathways simultaneously concur in some patients, being difficult to identify the exact mechanisms involved in the development of LEE. First, there could be enhanced direct toxicity of the antiretroviral drugs in the presence of pre-existing HCV infection. Since many of the antiretrovirals are metabolized in the liver through the cytochrome pathways, some drugs may potentiate the activation of death receptors and/or intracellular stress pathways. Second mechanism was hypersensitivity reaction-related LEE. Drug-related hypersensitivity syndrome should be suspected if liver enzymes are elevated within the first 4 to 6 weeks of therapy along with fever, rash, malaise, and peripheral eosinophilia. This reaction was common in patients using NNRTI (nevirapine or efavirenz). Other mechanisms were mitochondrial toxicity related to nucleoside analog treatment and metabolic abnormalities. The last possible mechanism was immune reconstitution. In some patients liver enzyme elevations may be a manifestation of immune reconstitution that follows ART. After immune recovery, CD4+ cell counts rise and the ability of immunocytes to identify and lyse HCV-infected hepatocytes may be increased.

Baseline ALT level was the only baseline variable associated with grade 3-4 LEE. Other groups have reported high initial transaminases (mainly ALT) as predictive of LEE, but only this study shows that patients with grade 3-4 LEE had lower ALT level than those without. A possible explanation was the recovery of cell-mediated immunity after starting HAART, leading to immune-mediated HCV-specific liver cell damage and transaminase elevation. Unfortunately, we do not have additional immunologic data, such as CD8 lymphocyte counts, to expand our analysis in this area.

We did not observe a higher incidence of grade 3-4 LEE among NVP users compared to EFV users. It is possible that the observed lack of association is related to the small number of patients receiving EFV. Others have recommended that NVP not routinely be used in coinfected patients, because most studies shown that that patients treated with NVP were significantly more likely to experience a grade 3-4 LEE than patients treated with EFV. Palmon et al also showed that there were no difference in the incidence of grade 3-4 LEE in patients treated with nevirapine, efavirenz or another type of NNRTI –delavirdine. In conclusion, there is still a need for further studies involving more patients with EFV in our population to describe the relationship between HCV infection and these NNRTIs.

A study by Aranzabal et al in HIV and HCV coinfected patients shown that patients with more advanced liver fibrosis had a 3-fold increase in the risk of liver toxicity compared to patients with mild or moderate liver fibrosis. In this retrospective study, no liver biopsies were performed before starting HAART or after developing LEE to differentiate the grade of liver fibrosis of these patients and the correlation with grade 3-4 LEE.

Our study has several limitations, including its retrospective nature and lack of control group. Moreover, the fact that liver enzyme measurements were not performed at fixed time points during HAART, the uncertainties regarding adherence to HAART, might have altered the results. Another limitation is that no information on alcohol use and possible hepatitis A virus (HAV) infection. However, we do not expect alcohol use as an important factor for the development of LEE, as the use of alcohol in Indonesia is lower than in the western world. The laboratory data for hepatitis A virus, which are common in Indonesia, were only available in one patient after starting HAART. We did not have any
data of HIV-RNA level, HCV-RNA level, nor HCV genotype. These are not routine laboratory examinations in our situation due to limited resources.

CONCLUSION

It is important to keep in mind that the HIV-HCV co-infected patients are more prone to develop severe liver enzyme elevation. This population requires a closer follow up of their liver enzymes after they start HAART. The high incidence of grade 3-4 LEE in our population indirectly underline the need for early treatment before severe immune depletion occurs. Given the importance of ascertaining which co-infected patients may be at highest risk for liver enzyme elevation following the initiation of HAART and how it develops, further data addressing these questions are needed. We believe that larger and prospective studies are warranted.

REFERENCES