Prevalence of liver injury among patients with acquired immunodeficiency syndrome treated with highly active antiretroviral therapy in China

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Abstract

OBJECTIVE: To estimate the prevalence of liver injury among patients with acquired immunodeficiency syndrome (AIDS) who received highly active antiretroviral therapy (HAART) in rural Henan Province in China, and to explore whether Traditional Chinese Medicine (TCM) treatment based on HAART would increase this risk.

METHODS: This was a retrospective cross-sectional study. We collected medical information on patients with AIDS from two treatment databases in 2014. Criteria established by the AIDS Clinical Trials Group in 1996 were used for grading liver injury, classified based on the limit of normal (ULN) for alanine transaminase and aspartate aminotransferase: grade 1 (1.25-2.5 × ULN); grade 2 (2.6-5 × ULN); grade 3 (5.1-10 × ULN); and grade 4 (> 10 × ULN). Factors associated with liver injury were evaluated using a logistic regression model.

RESULTS: A total 6953 patients with AIDS (3324 male and 3629 female patients) were enrolled into this study. The prevalence of liver injury was 22.0% (18.0% grade 1, 3.1% grade 2, 0.9% grade 3). In multivariate analysis, patients aged 34-45 years were more likely to have liver injury than patients in other age groups [adjusted odds ratio (AOR), 1.39; 95% CI, 1.01-1.91]. Other factors associated with liver injury included male sex (AOR, 1.64; 95% CI, 1.46-1.85), HIV infection via blood (AOR, 1.47; 95% CI, 1.19-1.82), hepatitis B virus antibody positive (AOR, 1.07; 95% CI, 0.85-1.36), and hepatitis C virus (HCV) antibody positive (AOR, 2.76; 95% CI, 2.28-3.34).

CONCLUSION: The prevalence of liver injury was relatively high among HAART-experienced patients. Several factors associated with liver injury included male sex, age 35-45 years old, HIV infection through blood, and concurrent HCV infection. TCM had no relationship with liver injury in patients receiving HAART.

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Keywords: Acquired immunodeficiency syndrome; Chemical and drug induced liver injury; Prevalence; Antiretroviral therapy, highly active; Medicine, Chinese traditional

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is
caused by human immunodeficiency virus (HIV) and decreases the immune function in infected patients. The mortality and morbidity of patients with AIDS was initially high because of various opportunistic infections and cancer. Since highly active antiretroviral therapy (HAART) was introduced in 1996, the death rate from AIDS-related causes has decreased significantly. Unfortunately, HAART can only inhibit HIV replication in infected patients; it cannot completely eliminate the HIV virus. Additionally, patients with AIDS must take HAART for the rest of their life, and many side effects can emerge, such as liver injury. The symptoms of liver injury among patients with AIDS varies from no symptoms to generalized signs such as nausea, fatigue, and abdominal pain. Life-threatening symptoms occur at a rate of 2.6/100 person-years. The mechanism of liver injury among patients with AIDS is complex and may include mitochondrial toxicity, immune reconstitution, allergic reaction, hepatotoxicity caused by HAART, and concurrent infection with hepatitis C virus (HCV) or hepatitis B virus (HBV). The rate of HAART hepatotoxicity in patients with AIDS varies by geographic region. One HAART hepatotoxicity study in Nigeria showed that the incidence of HAART hepatotoxicity was 17.9%, and over 80.0% of patients with AIDS who had hepatotoxicity were asymptomatic. In that study, mild-to-moderate liver injury occurred in 7.1% of patients whereas severe hepatotoxicity occurred in 10.7% of patients. As has been reported, with an extended HAART administration time, there is an increasing trend of death caused by liver injury. However, there are few studies to date in China on liver injury among patients with AIDS in the HAART era. In the present study, we investigated patients with AIDS who were receiving HAART and had liver injury, in a rural area of Henan Province in China, to estimate the prevalence of liver injury and explore whether Traditional Chinese Medicine (TCM) treatment based on HAART would increase this risk.

METHODS

Study setting
This study was carried out in Henan Province, which is located in mid-central China, where the prevalence of HIV infection is relatively high because of paid blood donation during the mid-1990s. Residents of Henan are mainly engaged in agricultural activities, and there are high levels of poverty in rural areas. To control the prevalence of HIV infection in these areas, the Chinese government established the National Free Antiretroviral Treatment Program (NFATP) in 2004, and formulated the Handbook of China’s free Anti-Retroviral Treatment (ART) program to guide therapy. The State Administration of Traditional Chinese Medicine of China initiated a national TCM HIV treatment trial program (NTCMTP) to treat patients with AIDS. These patients participated in the NTCMTP voluntarily and were treated with yaikang capsules, a Chinese medicine that is especially intended for the treatment of individuals with AIDS, at no charge until they withdrew from the NTCMTP.

Information on patients with AIDS in the NFATP and NTCMTP was captured using a case report form, which included epidemiological information, laboratory results (i.e., CD4 + T-cell count, whole blood cell count, urinalysis, liver and renal function, and HIV viral load), details of therapy, clinical symptoms, and vital status. Laboratory tests were conducted every 6 months and data of patients with AIDS in the NFATP and NTCMTP were recorded by the Chinese Center for Disease Control and Prevention (CDC) and the administrative offices of the NTCMTP respectively. The data used in the present study were obtained from these two databases.

Study population and data collection
This was a retrospective cross-sectional study using information in databases that was collected from patients with AIDS in 2014. All individuals in this study lived in Henan Province, were confirmed to be positive for HIV antibody by western blot, were older than 18 years of age and younger than 65 years of age, and were receiving HAART in 2014. Individuals without recorded alanine transaminase (ALT) and aspartate aminotransferase (AST) values were excluded from this analysis.

The following data were collected in this study: sex, age, ethnicity, education, marital status, profession, route of HIV transmission, date identified as HIV positive, concurrent HBV or HCV infection, HAART start date and regimen, TCM start date and regimen, AST value, ALT value, and CD4 cell counts. The values of AST, ALT, and CD4 cell counts used in this study were mean values from the above two databases in 2014.

Study definitions
Liver injury in patients with AIDS was defined in terms of AST or ALT. The level of liver injury was classified based on changes relative to the upper limit of normal (ULN) for AST or ALT. Liver injury was classified as follows: grade 1 (1.25-2.5 × ULN), grade 2 (2.6-5 × ULN), grade 3 (5.1-10 × ULN), and grade 4 (> 10 × ULN). The normal range of serum AST and ALT was < 40 U/L. The patient was considered to have no liver injury with < 1.25 × ULN. If AST and ALT levels (and thus, the resulting grades) were inconsistent, the higher of the two results was used for grade classification.

Data analysis
Data are presented as mean ± standard deviation (x ± s) or frequency (%). The differences between groups
were tested using the χ² test and a multivariate logistic regression model. All analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA). P value < 0.05 was set as the statistical significance level.

**Ethical considerations**

This study was approved by the institutional review board of the first hospital affiliated with the Henan University of Traditional Chinese Medicine (2013HL017-01). Individual informed consent was not obtained because this analysis used currently existing data collected during the course of routine treatment, and the data were reported in aggregate without use of individual identifying information.

**RESULTS**

**General characteristics of patients with AIDS**

A total of 6953 patients with AIDS, including 3324 male and 3629 female patients, met the inclusion criteria for this study. Participants’ mean age was (48 ± 9) years, and 73.4% were 35–55 years old. Other demographic parameters included the following: 99.3% of patients were Han ethnicity; 58.3% had ≤ 6 years of education; 73.6% were married; and 94.1% were farmers. Additionally, 84.8% of participants were infected with HIV through blood, 6.3% were HBV antibody positive, and 38.4% were HCV antibody positive. There were 82.8% of patients who were identified as being HIV positive for > 6 years and 76.3% who were receiving HAART > 4 years. Overall, 28.4% of patients were receiving TCM therapy. Laboratory test results were as follows: 59.4% of patients had CD4 cell counts > 350 cells/mL, and the mean count was (464 ± 235) cells/mL.

A comparison of these characteristics between the liver injury group and the non-liver injury group is presented in Table 1. The distributions of sex, age, marital status, education level, HIV transmission route, duration of HIV-positive status, duration of HAART, HBV antibody positive status, and HCV antibody positive status between the two groups were significantly different (P < 0.05).

There were 1531 patients who had liver injury, with a prevalence of 22.0%. Among them, 1254 patients (18.0%) had grade 1 liver injury, 216 (3.1%) had grade 2 liver injury, and 61 (0.9%) had grade 3 liver injury.

**Factors associated with liver injury in patients with AIDS**

Variables with statistically significant differences (sex, age, marital status, education level, HIV transmission route, duration of HIV-positive status, duration of HAART, HBV antibody positive, and HCV antibody positive) were further evaluated using a multivariate logistic regression model to determine those factors that were independently associated with liver injury (Table 2).

In the multivariate analysis, patients aged 34-45 years were more likely to have liver injury than patients of other ages [adjusted odds ratio (AOR), 1.39; 95% CI, 1.01-1.91]. Other factors associated with liver injury included male sex (AOR, 1.64; 95% CI, 1.46-1.85), infected with HIV through blood (AOR, 1.47; 95% CI, 1.19-1.82), HBV antibody positive (AOR, 1.07; 95% CI, 0.85-1.36), and HCV antibody positive (AOR, 2.76; 95% CI, 2.28-3.34). Signal analysis showed that the factors associated with liver injury were, education, duration of HIV-positive status, and duration of HAART (P < 0.05), but there was no association in the multivariate analysis (P > 0.05).

**DISCUSSION**

In this study, the prevalence of liver injury among patients with AIDS receiving HAART was 22%. Among them, 1254 patients (18.0%) had grade 1 liver injury, 216 (3.1%) had grade 2, and 61 (0.9%) had grade 3 liver injury. These results were similar to the findings of studies from other countries. A study in the United States showed that the incidence of severe hepatotoxicity was 1.1%, which is consistent with our results. Another study from Spain reported an overall incidence of liver damage of 31%, with severe liver injury accounting for 9% of patients. Several studies have reported that the incidence of severe liver injury in patients receiving HAART ranges from 2%-18%. The incidence rate in our study was lower than this range.

Many potential risk factors could influence the incidence of liver injury among patients with AIDS taking HAART, such as sex, age, education, marital status, HIV transmission route, duration of HAART, and CD4 cell counts. The influence of sex on the prevalence of liver injury among patients with AIDS has been inconsistent among different studies. Some studies have found no differences in the prevalence of liver injury between women and men, but one cohort study from the United States showed that female patients with AIDS may be more likely to have liver injury than male patients. In the present study, we found that liver injury was more prevalent among male patients. Older age, especially older than 40 years, is reportedly associated with an increased prevalence of liver injury. The results of our study demonstrated that the risk of liver injury was higher among patients with AIDS aged between 35 and 45 years. The prevalence of liver injury was higher among patients with AIDS who were infected with HIV through the blood; these patients had a 1.47 times higher risk of liver injury than other transmission routes. Patients can be infected with many diseases via the blood, such as HBV and HCV. After receiving HAART, patients have a greater risk of liver injury if they are coinfected with HBV or HCV. Our results showed that the risk
of liver injury was 2.76 times higher among patients with AIDS who also had HCV than in patients who had AIDS but not HCV. However, there was no association between liver injury and patients with AIDS who had HBV. Some studies have found that HIV and HCV have a combined effect on liver injury, which could accelerate the progress of liver fibrosis. The risk of increased liver enzymes is up to 10-fold higher in response to HBV and 2- to 5-fold higher in response to HCV.\textsuperscript{18,19} Some studies have reported that patients with lower CD4 cell counts are more likely to have a higher liver injury prevalence, especially patients with AIDS who have a CD4 cell count less than 200 cells/mL.\textsuperscript{1} However, our results showed that liver injury was not associated with CD4.

A 10-year cohort study in Europe showed that liver injury was increased with longer duration of therapy in patients with AIDS who were taking HAART, among patients with similar CD4 cell counts.\textsuperscript{20} The results of multivariable analysis showed that there was no relationship between the duration of HAART and liver injury.

### Notes:
AIDS: acquired immunodeficiency syndrome; HIV: human immunodeficiency virus; HAART: highly active antiretroviral therapy; HBV: hepatitis B virus; HCV: hepatitis C virus; TCM: Traditional Chinese Medicine.

### Table 1 Characteristics of patients with AIDS between groups with and without liver injury [n (%)]

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients No.</th>
<th>Liver injury (n = 1531)</th>
<th>Non-liver injury (n = 5422)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>3324 (47.8)</td>
<td>873 (57.0)</td>
<td>2451 (45.2)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>3629 (52.2)</td>
<td>658 (43.0)</td>
<td>2971 (54.8)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>&lt;35</td>
<td>381 (5.5)</td>
<td>54 (3.5)</td>
<td>327 (6.0)</td>
</tr>
<tr>
<td></td>
<td>35-45</td>
<td>2440 (35.1)</td>
<td>570 (37.2)</td>
<td>1870 (34.5)</td>
</tr>
<tr>
<td></td>
<td>46-55</td>
<td>2666 (38.3)</td>
<td>609 (39.8)</td>
<td>2057 (37.9)</td>
</tr>
<tr>
<td></td>
<td>&gt;55</td>
<td>1466 (21.1)</td>
<td>298 (19.5)</td>
<td>1168 (21.5)</td>
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<td>Marital status</td>
<td>Married</td>
<td>5117 (73.6)</td>
<td>1171 (76.5)</td>
<td>3946 (72.8)</td>
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<tr>
<td></td>
<td>Others</td>
<td>1836 (26.4)</td>
<td>360 (23.5)</td>
<td>1476 (27.2)</td>
</tr>
<tr>
<td>Education level (years)</td>
<td>≤6</td>
<td>4054 (58.3)</td>
<td>846 (55.3)</td>
<td>3208 (59.2)</td>
</tr>
<tr>
<td></td>
<td>&gt;6</td>
<td>2899 (41.7)</td>
<td>685 (44.7)</td>
<td>2214 (40.8)</td>
</tr>
<tr>
<td>HIV transmission route</td>
<td>Blood</td>
<td>5893 (85.0)</td>
<td>1386 (90.8)</td>
<td>4507 (83.3)</td>
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<tr>
<td></td>
<td>Others</td>
<td>1942 (15.0)</td>
<td>140 (9.2)</td>
<td>902 (16.7)</td>
</tr>
<tr>
<td>Duration of HIV positive (years)</td>
<td>&lt;6</td>
<td>1195 (17.2)</td>
<td>214 (14.0)</td>
<td>981 (18.1)</td>
</tr>
<tr>
<td></td>
<td>6-9</td>
<td>3370 (48.5)</td>
<td>694 (45.3)</td>
<td>2676 (49.4)</td>
</tr>
<tr>
<td></td>
<td>&gt;9</td>
<td>2388 (34.3)</td>
<td>623 (40.7)</td>
<td>1765 (32.6)</td>
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<tr>
<td>Duration of HAART (years)</td>
<td>&lt;4</td>
<td>1648 (23.7)</td>
<td>328 (21.4)</td>
<td>1320 (24.3)</td>
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<tr>
<td></td>
<td>4-8</td>
<td>2995 (43.1)</td>
<td>637 (41.6)</td>
<td>2358 (43.5)</td>
</tr>
<tr>
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<td>&gt;8</td>
<td>2310 (33.2)</td>
<td>566 (37.0)</td>
<td>1744 (32.2)</td>
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<tr>
<td>HBV antibody test</td>
<td>Positive</td>
<td>438 (6.3)</td>
<td>113 (7.4)</td>
<td>325 (6.0)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>3634 (52.3)</td>
<td>812 (53.0)</td>
<td>2822 (52.0)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>2881 (41.4)</td>
<td>606 (39.6)</td>
<td>2273 (40.0)</td>
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<tr>
<td>HCV antibody test</td>
<td>Positive</td>
<td>2671 (38.4)</td>
<td>784 (51.2)</td>
<td>1887 (34.8)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>1416 (20.4)</td>
<td>164 (10.7)</td>
<td>1252 (23.1)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>2866 (41.2)</td>
<td>583 (38.1)</td>
<td>2283 (42.1)</td>
</tr>
<tr>
<td>TCM therapy</td>
<td>Yes</td>
<td>1917 (28.4)</td>
<td>449 (29.3)</td>
<td>1528 (28.2)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>4976 (71.6)</td>
<td>1082 (70.7)</td>
<td>3894 (71.8)</td>
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<tr>
<td>CD4 cell count (cells/mL)</td>
<td>&lt;200</td>
<td>685 (9.9)</td>
<td>158 (10.3)</td>
<td>527 (9.7)</td>
</tr>
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<td>200-350</td>
<td>1692 (24.4)</td>
<td>355 (23.2)</td>
<td>1337 (24.7)</td>
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<tr>
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<td>351-500</td>
<td>1896 (27.3)</td>
<td>422 (27.6)</td>
<td>1474 (27.2)</td>
</tr>
<tr>
<td></td>
<td>&gt;500</td>
<td>2669 (38.4)</td>
<td>592 (38.8)</td>
<td>2077 (38.4)</td>
</tr>
</tbody>
</table>

Notes: AIDS: acquired immunodeficiency syndrome; HIV: human immunodeficiency virus; HAART: highly active antiretroviral therapy; HBV: hepatitis B virus; HCV: hepatitis C virus; TCM: Traditional Chinese Medicine.
The therapeutic effect of TCM treatment in patients with AIDS is remarkable because TCM can alleviate symptoms, improve quality of life, and prolong the life of these patients.2-23 In this study, TCM had no relationship with liver injury.

This study had some limitations. The study population was a convenience sample and selection bias was present. Additionally, this study had a retrospective design and some important variables, such as alcohol consumption, could not be evaluated.

In conclusion, we found that the prevalence of liver injury was relatively high among HAART-experienced patients in rural Henan province of China. Several factors associated with liver injury included male sex, age 35-45 years old, HIV infection via blood, and concurrent HCV infection. TCM had no relationship with liver injury in patients taking HAART.

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