Hepatitis Delta Is a Major Determinant of Liver Decompensation Events and Death in HIV-Infected Patients

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Background. Coinfection with hepatitis viruses is common in individuals infected with human immunodeficiency virus (HIV) and has become a leading cause of complications and death in those receiving antiretroviral therapy (ART).

Methods. We retrospectively examined the effect of coinfection with hepatitis B, C, and/or D viruses (HBV, HCV, HDV, respectively) on liver decompensation events (ascites, variceal bleeding, encephalopathy, and/or hepatocellular carcinoma) and liver-related mortality in HIV-positive patients on regular follow-up since the year 2004 at a reference HIV clinic in Madrid, Spain.

Results. A total of 1147 HIV-infected patients (mean age, 42 years; 81% males; 46% intravenous drug users, 85.4% on ART) were analyzed. Mean follow-up was 81.2 ± 17.8 months. At baseline, 521 patients (45.4%) were HCV-antibody positive, 85 (7.4%) were hepatitis B surface antigen positive, and 17 (1.5%) were anti-HDV positive. A total of 233 HIV/HCV-coinfected patients received antiviral therapy for HCV, of whom 106 (45%) achieved sustained virologic response (SVR). Overall, 15 patients died of liver-related complications and 26 developed hepatic decompensation events. Taking as controls the 524 HIV-monoinfected patients, HDV coinfection (adjusted hazard ratio [AHR], 7.5; 95% confidence interval [CI], 1.84–30.8; P = .005) and baseline liver stiffness (AHR, 1.1; 95% CI, 1.07–1.13; P < .0001) were associated with a higher rate of liver-related morbidity and mortality. In contrast, SVR following hepatitis C therapy in HIV/HCV-coinfected patients was protective (AHR, 0.11; 95% CI, .01–.86; P = .03).

Conclusions. Hepatitis delta is associated with a high rate of death and liver decompensation events in HIV-infected patients on ART.

Keywords. HIV; hepatitis (HBV, HCV, and HDV); cirrhosis; death.

Hepatitis delta virus (HDV) was first discovered in 1977 [1]. HDV is the smallest human RNA virus with a single-stranded negative sense genome of approximately 1700 nucleotides forming a covalently closed circle [2]. The RNA encodes a protein called the delta antigen, which is subsequently encased in an envelope embedded with the hepatitis B surface antigen (HBsAg).

HDV replication only takes place in the presence of HBV infection. Hepatitis delta causes the most severe form of viral hepatitis in humans, including fulminant liver failure, rapid progression to cirrhosis and hepatic decompensation, and increased risk of hepatocellular carcinoma (HCC) [3, 4].

Because shared routes of transmission, infection with hepatitis viruses B, C, and D (HBV, HCV, and HDV, respectively) is common in individuals infected with human immunodeficiency virus (HIV) [5]. Not surprisingly, the success and wide use of antiretroviral therapy has unveiled liver disease as a major cause of clinical complications and death in HIV-positive individuals coinfected with hepatitis viruses [6]. Efforts to minimize the impact of hepatitis B and C using antiviral therapy
are being applied with increasing success in this population [7, 8]. Unfortunately, there is no efficacious antiviral treatment for HDV infection [9, 10], and most HIV-positive patients with chronic hepatitis delta will go on to develop hepatic decompensation and death [11].

Herein, we report the hepatic clinical outcomes in a large cohort of HIV-positive patients followed for nearly a decade, focusing on those coinfected with distinct hepatitis viruses and specifically on the subset with HIV/HDV coinfection.

PATIENTS AND METHODS

Study Design
This was a retrospective, observational study in which clinical and laboratory data, as well as life status, were examined in all HIV-infected individuals recruited in a study of hepatic damage conducted at our institution that began in 2004. Other characteristics of this cohort have been reported elsewhere [12, 13]. In brief, all consecutive HIV-infected individuals seen at our clinic were invited to participate in a longitudinal assessment of liver disease, including characterization of potential hepatotoxic medications and coinfection with hepatitis viruses, as well as periodic measurement of liver fibrosis using transient elastometry [14].

Study Variables
Main demographics (age, sex, alcohol abuse [defined as an alcohol intake >60 g/day], and body mass index), hematologic variables (hemoglobin, leukocyte, and platelet counts), biochemistry (glucose, aspartate aminotransferase [AST], alanine aminotransferase [ALT], γ-glutamyl transpeptidase, alkaline phosphatase, total bilirubin, total cholesterol, low-density lipoprotein cholesterol, triglycerides, and creatinine), HIV parameters (CD4 count and CD4 nadir, plasma HIV RNA, current and prior antiretroviral drug regimens), and viral hepatitis status were examined.

Clinical charts were reviewed, and the incidence of liver decompensation events or death was recorded. Hepatic decompensation endpoints were defined as the first episode of ascites, encephalopathy, variceal bleeding, or HCC.

Study Population
All HIV-infected individuals enrolled in the study were grouped into 7 categories based on their hepatitis virus profile, as follows: (1) spontaneous HCV clearance (n = 21), (2) untreated HCV patients (n = 258), (3) HIV/HCV-coinfected patients who achieved sustained virologic response (SVR) with antiviral therapy (n = 106), (4) HIV/HCV-coinfected patients for whom treatment failed (n = 127), (5) HIV/HBV-coinfected patients (n = 85), (6) HIV/HDV-coinfected patients (n = 17), and (7) controls, represented by HIV-monoinfected individuals (n = 524). For this analysis, we excluded from the HBsAg-positive group all individuals with HDV antibodies (which obligatorily were also HBsAg positive).

Outcomes
Patients had been followed regularly at around 4-month intervals on average. They were assessed at each visit for clinical manifestations potentially associated with either HIV or hepatitis viruses, along with routine hematological, immunological, virological, and biochemical examinations. Prescription of antiretroviral therapy was made following international guidelines [15–17].

The baseline timepoint was defined as the date of the first transient elastometry examination, whereas the follow-up period corresponded to the months lapsed until the development of liver-related events, death, or the censoring date (8 May 2013), whichever occurred first. Information on vital status or development of liver decompensation was obtained from clinical records.

Endpoints
A composite endpoint of development of first decompensation event (ascites, encephalopathy, variceal bleeding, and liver cancer) or liver-related death was used. The event-free survival was compared between the aforementioned groups. The association between the endpoint and other variables, such as age, sex, body mass index, alcohol abuse, baseline liver stiffness, CD4 cell count, glucose, total cholesterol, ALT, plasma HIV RNA, and viral hepatitis markers was assessed using logistic regression.
Statistical Analysis
Continuous variables are expressed as mean and standard deviation (SD), and categorical variables are presented as percentages and 95% confidence intervals. The liver event-free survival was defined as the cumulative proportion of patients who did not develop neither liver decompensation events nor liver-related deaths at the end of follow-up, and was represented by Kaplan-Meier curves. Univariate and multivariate analyses were calculated using Cox regression.

The Student t test was used for comparing continuous variables, and comparisons of categorical variables were tested using the χ2 test. Univariate and multivariate analysis were performed using logistic regression. Variables with P values <.25 in the univariate analysis were included in the multivariate analysis. SPSS version 20.0 software was used for calculations.

RESULTS
Data from a total of 1147 HIV-infected patients were analyzed. The main baseline characteristics of the study population are recorded in Table 1. Mean age was 42 years, 80.6% were male, 46.1% had prior history of injection drug use, and 6.9% of alcohol abuse. Mean body mass index was 24.1 kg/m2, and mean CD4 count was 566 cells/µL. At baseline, 85.4% of patients were on antiretroviral therapy.

Overall, 521 patients (45.4%) were HCV antibody positive, 85 (7.4%) were HBsAg positive, and another 17 (1.5%) were anti-HDV positive. The mean liver stiffness value was 8.5 ± 7.6 kPa. However, 20.8% of patients had baseline liver fibrosis stages F3–F4.

All anti-HDV reactive patients had detectable HDV RNA. Serum HBV DNA was detectable at baseline in 42 (49.7%) of HBsAg-positive patients. Of 521 individuals with HCV antibodies, 21 had cleared HCV spontaneously and 233 received interferon-based therapy during the study period, of whom 106 achieved SVR.

During the study period (mean follow-up 81.2 ± 17.8 months), 15 patients died of liver-related conditions (6 due to cirrhosis, 5 due to HCC, 3 due to variceal bleeding, and 1 due to hepatorenal syndrome) and 26 developed a first episode of liver decompensation (16 ascites, 6 variceal bleeding and 5 HCC). Table 2 records the study outcomes for each study group. Although the incidence of death or liver decompensation for the overall cohort was 3.6%, specific groups such as HIV/HDV-coinfected patients or HIV/HCV-coinfected individuals who did not respond to antiviral therapy experienced significantly higher incidence rates (14% and 8.6%, respectively).

The mean event-free survival was 101.3 ± 0.3 months for HIV-monoinfected individuals. As expected (see Figure 1), it was shorter in untreated HIV/HCV-coinfected patients (98.8 ± 0.9 months, P < .0001), those who failed HCV therapy (98.8 ± 1.23 months, P = .002), and in HIV/HDV-coinfected patients (86.7 ± 7.2 months, P < .0001). In contrast, patients who achieved HCV clearance, either spontaneously (99.4 ± 2.55 months, P = .09) or following antiviral therapy (101.1 ± 0.9 months, P = .9), and HIV/HBV-coinfected patients (100.1 ± 0.3 months, P = .5) exhibited event-free survival rates that did not differ from those in HIV-monoinfected controls.

Variables associated with the development of hepatic decompensation events or death in the study population were as follows: baseline positive HCV antibodies, HDV coinfection, baseline liver stiffness, and baseline ALT. However, in the multivariate analysis only, hepatitis delta and baseline liver stiffness remained as significant predictors of developing hepatic endpoints, whereas achievement of SVR with antiviral therapy in HIV/HCV-coinfected patients was protective (Table 3).

DISCUSSION
Approximately 15 million people are infected with HDV worldwide, with higher prevalence rates in the Mediterranean basin, Eastern Europe, Middle East, Central Asia, Central Africa, and the Amazonian basin. Due to shared transmission routes, hepatitis delta is relatively common among HIV-infected

### Table 1. Main Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (1147)</th>
<th>HIV Monoinfection (524)</th>
<th>Hepatitis B (85)</th>
<th>Hepatitis C (521)</th>
<th>Hepatitis D (17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>42.1 ± 7.1</td>
<td>42.6 ± 8.5</td>
<td>41.2 ± 8.1</td>
<td>41.8 ± 5.1</td>
<td>40.5 ± 4.5</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>81</td>
<td>86</td>
<td>94.5</td>
<td>73.7</td>
<td>83.8</td>
</tr>
<tr>
<td>Intravenous drug use, %</td>
<td>46.1</td>
<td>16.7</td>
<td>10.9</td>
<td>82.3</td>
<td>81.3</td>
</tr>
<tr>
<td>Mean body mass index, kg/m², mean ± SD</td>
<td>24.1 ± 4.2</td>
<td>24.7 ± 4.1</td>
<td>25.1 ± 4.2</td>
<td>23.3 ± 4.1</td>
<td>23.8 ± 4</td>
</tr>
<tr>
<td>Alcohol intake &gt;60 g/day, %</td>
<td>6.9</td>
<td>4.1</td>
<td>7.3</td>
<td>9.8</td>
<td>25</td>
</tr>
<tr>
<td>Baseline advanced liver fibrosis, %</td>
<td>20.8</td>
<td>8.3</td>
<td>16.4</td>
<td>34.7</td>
<td>62.5</td>
</tr>
<tr>
<td>Mean baseline CD4 count, cells/µL, mean ± SD</td>
<td>566 ± 310</td>
<td>574 ± 323</td>
<td>698 ± 302</td>
<td>543 ± 291</td>
<td>476 ± 146</td>
</tr>
<tr>
<td>Mean baseline ALT, IU/mL, mean ± SD</td>
<td>53.6 ± 56.2</td>
<td>37.5 ± 49</td>
<td>61.3 ± 82</td>
<td>70.1 ± 55.1</td>
<td>93.2 ± 71</td>
</tr>
<tr>
<td>Antiretroviral therapy, %</td>
<td>85.4</td>
<td>86.4</td>
<td>85.5</td>
<td>84.3</td>
<td>87.5</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; HIV, human immunodeficiency virus; SD, standard deviation.
individuals. In this setting, about 15% of HIV-infected individuals with chronic hepatitis B in Europe are superinfected with HDV [11], the greatest prevalence rates being seen among intravenous drug users [11, 18, 19].

Chronic hepatitis delta has already been associated with a disproportionate rate of cirrhosis [20] and poor clinical outcomes [21] in HIV-infected patients. In a case-control study, 26 HIV/HDV-coinfected patients experienced significantly higher rates of hepatitis flares, liver cirrhosis, liver decompensation, and death over a median follow-up of 55 months than matched HIV-monoinfected controls [22]. To our knowledge, our study has the longest follow-up period of HIV-positive patients with chronic hepatitis delta, and provides a long-term perspective of its complications, using as reference HIV-monoinfected as well as individuals coinfected with other hepatitis viruses. The results provide a unique insight about the natural history of patients with HIV/HDV coinfection. This population died or developed end-stage liver disease more frequently than did HIV-monoinfected individuals (adjusted hazard ratio, 7.5), although it should be acknowledged that they were more likely male, injection drug users, and alcohol abusers, features known to result in a worse outcome regardless of HDV coinfection.

In our study, HIV-positive patients with chronic hepatitis B and C who were successfully treated with antivirals displayed similar rates of hepatic decompensation events or death as HIV-monoinfected patients. These results are consistent with prior reports [23, 24] and support that treatment of HBV and/or HCV should be prioritized in all HIV-coinfected patients. On the other hand, our study provides additional evidence for untreated HIV/HCV-coinfected patients and those who failed therapy. Both groups experienced significantly higher rates of hepatic events than HIV-monoinfected patients, although the biggest impact was for hepatitis delta.

Treatment of hepatitis delta has remained elusive up to date [25, 26]. Only interferon given at high doses and for long periods seems to provide some benefit, although only a low proportion of treated patients sustain permanently complete viral suppression upon drug discontinuation [27, 28]. Oral nucleoside analogues active against HBV, such as lamivudine or ade- fovir, have not demonstrated any significant benefit [29, 30]. However, long-term exposure to tenofovir may reduce HDV replication and ameliorate HDV-related liver damage [31, 32]. If confirmed, tenofovir treatment might represent a unique alternative for HIV/HCV-coinfected patients in whom we demonstrated a 7.5-fold increase in liver decompensation events and death compared with HIV-monoinfected individuals.

This study provides a long-term perspective of liver-related complications and death in HIV-positive individuals with and without coinfection with hepatitis viruses. For most patients experiencing the benefit of antiretroviral therapy and those with HBV or HCV coinfection coupled with the corresponding success of specific antiviral therapies, only hepatitis delta seems to remain out of any benefit. The highest rates of hepatic events and death were seen in HIV-infected patients with hepatitis delta. In the absence of effective specific treatment for hepatitis delta, HBV vaccination of all susceptible individuals, screening of anti-HDV in all HBsAg-positive patients, and prescription of
antiretrovirals with anti-HBV activity such as tenofovir should be encouraged.

Notes

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References