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Epidemiology and Social Science

Risk of Hepatitis-Related Mortality Increased Among Hepatitis C Virus/HIV-Coinfected Drug Users Compared With Drug Users Infected Only With Hepatitis C Virus
A 20-Year Prospective Study

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Background: Progression of liver-related disease is accelerated in individuals coinfected with HIV and hepatitis C virus (HCV). Because the life expectancy of HIV-infected drug users (DUs) improved after the widespread use of highly active antiretroviral therapy (HAART), HCV-related death is likely to become more important. To disentangle the effects of HIV and HCV, we compared the overall and cause-specific mortality between HIV/HCV-infected DUs and HCV-infected DUs and DUs without HCV or HIV, followed up between 1985 and 2006.

Methods: A total of 1295 participants in the Amsterdam Cohort Study were included. Cause-specific hazard ratios (CHR) were estimated for the eras before (<1997) and since HAART (≥1997) within and among serologic groups.

Results: The risk of dying decreased for most causes of death ≥1997; this decrease was not the same for the different serologic groups. Among HCV/HIV-coinfected DUs, the risk of hepatitis/liver-related death did not substantially change over time (CHR = 0.87, 95% confidence interval [CI]: 0.21 to 3.58), whereas the risk of AIDS-related mortality decreased. Compared with DUs solely infected with HCV, HCV/HIV-coinfected DUs were at increased risk of dying from hepatitis/liver-related disease (CHR = 7.15, 95% CI: 1.98 to 25.8), other natural causes (CHR = 3.09, 95% CI: 1.41 to 6.79), and non-natural causes (CHR = 2.30, 95% CI: 1.07 to 4.95) in the HAART era.

Conclusions: HCV/HIV-coinfected DUs remain at increased risk of dying from hepatitis/liver-related death in the HAART era compared with HCV-monoinfected DUs. This risk did not change in HCV/HIV-coinfected DUs after HAART was introduced, suggesting that in the HAART era, HIV continues to accelerate HCV disease progression. Efforts should be made to establish effective treatment for HCV infection in HCV/HIV-coinfected individuals.

Key Words: cause-specific mortality, disease progression, hepatitis C virus coinfection

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The progression of liver disease associated with hepatitis C virus (HCV) is known to be accelerated in HIV-infected persons.1 In the mid-1990s, highly active antiretroviral therapy (HAART) became available and improved their survival. In the HAART era, mortality from HCV is therefore likely to take on a greater significance among these individuals,2 and several studies have indeed shown an increase in liver-related deaths.3–6 Drug users (DUs) with HIV also benefit from HAART at the population level, although their improvement is less than that observed for heterosexual and homosexual individuals.7,8 Because HIV-infected DUs are almost universally coinfected with HCV, HCV/HIV coinfection has a major impact on their mortality.9 Indeed, an earlier study showed that the risk of dying from hepatitis- and liver-related disease among HIV-infected DUs is increased in the HAART era compared with the pre-HAART era.10

The Amsterdam Cohort Study (ACS) among DUs includes non–HIV-infected DUs and HIV-infected DUs, with or without HCV coinfection; information on causes of death is available, providing the unique opportunity to disentangle the effects of HIV and HCV on cause-specific mortality in DUs with 1 or both viruses. In addition, their mortality can be compared with that of uninfected DUs who are nevertheless at increased risk of dying compared with the general population.

In the present study, we therefore compared the cause-specific mortality between HIV/HCV-coinfected DUs, HCV-monoinfected DUs, and DUs without HCV or HIV. They were followed between 1985 and 2006 to compare the pre-HAART and HAART eras.

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METHODS

Study Population

The prospective ACS among DUs began in December 1985 and is still ongoing,11 with 1640 DUs included as of January 1, 2006. Recruitment is by means of local methadone outposts, sexually transmitted diseases clinics, and word of mouth. Injecting and noninjecting DUs using hard drugs (ie, heroin, cocaine, methadone) at least 3 times per week are invited to participate.

DUs return for their ACS follow-up visit every 4 to 6 months at the Health Service of Amsterdam. At each visit, a standardized questionnaire is administrated by trained nurses and blood is drawn for laboratory testing and storage. HIV-positive DUs undergo a clinical examination by a physician.

The ACS has been conducted in accordance with the ethical principles set out in the declaration of Helsinki, and written informed consent is obtained before data collection.

Serologic Testing

After each ACS visit, blood samples are prospectively tested for HIV antibodies by enzyme-linked immunosorbent assay (ELISA), and positive results are confirmed using Western blot analysis (since 1995: HIV Blot version 2.2; Genelab diagnostics, Singapore). For HIV-infected DUs, CD4 cell counts and HIV RNA plasma levels are determined. In the present study, stored samples from DUs with at least 2 cohort visits were retrospectively tested for HCV antibodies, starting with the blood samples collected at the first cohort visit in each case. A third-generation ELISA assay was used to detect HCV antibodies (Axsym HCV version 3.0; Abbott, Wiesbaden, Germany). DUs who were HCV-negative at their first cohort visit were tested for HCV antibodies at their last cohort visit. If this blood sample was HCV-positive, samples taken in between the first and last visits were tested to identify the approximate moment of seroconversion. All blood samples collected at the first visit were retrospectively tested for hepatitis B core antigen (HBc) antibodies.

Specific Causes of Death

Information about vital status was obtained by matching the ACS data against the local and national registries. To obtain information on the cause of death (COD), we reviewed medical records from the hospitals, methadone clinics, and general practitioners.

Causes were grouped into 5 categories: AIDS/HIV-related causes of death, liver-related causes of death (including HCV- and hepatitis B-related death and liver disease), nonnatural causes of death (including overdose, accidents, suicide, and homicide), other natural causes of death, and unknown. When more than 1 cause of death was recorded, the most likely cause was scored according to the following hierarchy: nonnatural as most likely, followed by AIDS/HIV related, HCV/liver related, and natural.

Statistical Analyses

Of the 1640 DUs participating in the ACS, 1295 had at least 2 cohort visits and were included in this study. Follow-up was calculated from ACS entry until the earliest of the following: death, 1 year after the last visit, or the censoring date of January 1, 2006. Using calendar time as a proxy for the introduction and widespread use of HAART, we defined 2 calendar periods, before 1997 and 1997 onward, to reflect the pre-HAART and HAART eras, respectively.

Four serologic groups were defined: (1) HCV-positive/HIV-positive, (2) HCV-positive/HIV-negative, (3) HCV-negative/HIV-negative, and (4) HCV-negative/HIV-positive. Individuals could switch between groups (time updated covariate) when they acquired an infection during follow-up. The date of HIV or HCV seroconversion was estimated as the midpoint between the last seronegative result and first seropositive result at an ACS visit.

Using the Kaplan-Meier method, we estimated the time from ACS entry to death by any cause for each serologic group. Cause-specific hazard ratios (CHRs) were estimated within and between serologic groups using a Cox proportional hazards model. All analyses were adjusted for age, gender, hepatitis B status at ACS entry, and duration of injecting. The confounding effect of current injecting, alcohol intake, and homelessness was also evaluated. All variables subject to change, such as age, alcohol intake, duration of injection, and current injecting, were treated as time-updated variables. The number of individuals (n = 17) and deaths (n = 5) for the HCV-negative/HIV-positive serologic group was too small to estimate any CHR. Also in the HCV-negative/HIV-negative group, the number of deaths for some specific CODs was too small to estimate the CHR for these CODs. Finally, a sensitivity analysis was conducted by excluding those DUs who had never injected drugs.

RESULTS

Baseline characteristics of the DUs are presented in Table 1. The median age of the 1295 DUs with at least 2 cohort visits was 30 years, and 64% were male. At baseline, 621 DUs (72%) had ever injected drugs and 31 noninjecting DUs started to inject during follow-up. At ACS entry, 20% had an HCV/HIV coinfection, 44% were monoinfecting with HCV, 36% of the DUs were not infected with HIV or HCV, and 1% were solely infected with HIV. During follow-up, 95 HIV and 59 HCV seroconversions occurred, and 272 DUs died. A specific COD was available for 252 deaths.

HCV/HIV-coinfected DUs and HCV-monoinfected DUs were more often of Dutch origin, had higher anti-HBc prevalence rates, and more often had a history of injecting drugs. Less than 1% of the HCV-infected patients received HCV treatment.

Overall Mortality

The all-cause mortality was highest among DUs infected with HCV and HIV: after 10 years of follow-up, 49% (95% confidence interval [CI]: 42 to 54) had died (Fig. 1). HIV-monoinfected DUs show a slightly lower death rate: 10 years after ACS entry, 43% (95% CI: 2 to 66) had died. All-cause mortality was lowest among DUs without HIV or HCV infections, and among those with mono-HCV infection, 7% (95% CI: 3 to 11) and 13% (95% CI: 10 to 16) had died, respectively, after 10 years of follow-up.
Risk of Dying

We compared the risk of dying from each specific COD in the pre-HAART era with the HAART era. Overall, the risk of dying decreased in the HAART era for almost all CODs, but the effect of calendar time was not the same for each serologic group. Therefore, the CHRs and their 95% CIs are shown for the serologic groups separately in Table 2. Within each group, the risk of dying in the HAART era is compared with that in the pre-HAART era. Because we wanted to know the impact of HCV infection on mortality, we likewise compared separately the risk of dying from specific causes among the coinfected and uninfected DUs (HCV-positive/HIV-positive and HCV-negative/HIV-negative) with the risk among HCV-monoinfected DUs (reference) for the pre-HAART era.

Changes in the Risk of Death Within Serologic Groups

In the HAART era compared with the pre-HAART era, in DUs infected with HIV and HCV, we observed a significant reduction in the risk of dying from AIDS-related death (CHR = 0.37 adjusted for age, gender, hepatitis B status at ACS entry, and duration of injection, 95% CI: 0.19 to 0.72). In this group, the risk of dying from liver-related death did not significantly change (CHR = 0.87, 95% CI: 0.21 to 3.58).

No significant reductions in the risk of dying for all CODs were observed in HCV-monoinfected and uninfected serologic groups. The risk of dying specifically from hepatitis- or liver-related death could not be estimated for DUs solely infected with HCV because no hepatitis/liver-related deaths were observed in the pre-HAART era.

Comparison of the Risk of Death Among Serologic Groups

When comparing the risk of dying in HCV/HIV-coinfected DUs with the risk of dying among HCV-monoinfected DUs, those coinfected had a significantly higher risk of dying from nonnatural CODs (CHR = 3.03, 95% CI: 1.22 to 7.58) in the pre-HAART era. The same was true for the HAART era (CHR = 2.30, 95% CI: 1.07 to 4.95).

In the HAART era, the coinfected DUs had a significantly higher risk of dying from hepatitis/liver-related death than HCV-monoinfected DUs (CHR = 7.15, 95% CI: 1.98 to 25.8) and from natural CODs (CHR = 3.09, 95% CI: 1.41 to 6.79). No major differences were seen between DUs without infections and HCV-monoinfected DUs, except that in the pre-HAART era, the noninfected DUs had a nonsignificantly lower risk of dying from natural CODs (CHR = 0.58, 95% CI: 0.13 to 2.60).
Adjustment for homelessness, alcohol intake, and current injecting did not affect the results. When including ever-injectors only (n = 952) in a sensitivity analysis, we found that the risk of dying from hepatitis/liver-related disease within the HCV/HIV-coinfected group was somewhat higher in the HAART era than in the pre-HAART era (CHR = 1.23, 95% CI: 0.18 to 8.26) and that the effect was opposite when compared with the CHR in the total study population. The effect remained nonsignificant, however. In the HAART era, the increased risk of dying from hepatitis/liver-related disease was smaller than observed in the total population for coinfected DUs compared with HCV-monoinfected DUs (CHR = 3.94, 95% CI: 0.59 to 26.22). The other CHRs were comparable to the results in the total population.

**DISCUSSION**

This study describes the cause-specific mortality in a large group of DUs over a 20-year period. The risk of dying was highest among DUs solely infected with HIV or coinfected with HCV/HIV. Although the risk of dying substantially decreased for almost all causes in the HAART era, the decrease was not the same for all serologic groups. The risk of dying from hepatitis/liver-related disease did not change significantly over time among HCV/HIV-coinfected DUs, but this study demonstrates a strongly increased risk of their dying from hepatitis/liver-related disease compared with DUs solely infected with HCV in the era of HAART. This suggests that in the HAART era, HIV coinfection continues to accelerate HCV disease progression.

One might argue that DUs have not benefited from HAART; however, comparing the risk of dying among DUs infected with HCV and HIV between the pre-HAART and HAART eras shows that the risk of dying from AIDS-related causes decreased over time. This is in line with other studies and indicates that DUs indeed benefit from HAART, although

**TABLE 2. Adjusted* CHRs and Their 95% CIs for Each COD**

<table>
<thead>
<tr>
<th>Within serologic groups (HAART era vs. pre-HAART era)</th>
<th>AIDS/HIV-Related Causes</th>
<th>Hepatitis/Liver-Related Causes</th>
<th>Nonnatural Causes</th>
<th>Natural Causes</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV+HIV−</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-HAART</td>
<td>†</td>
<td>1</td>
<td>1</td>
<td>†</td>
<td></td>
</tr>
<tr>
<td>HAART era</td>
<td></td>
<td>0.77 (0.37 to 1.63)</td>
<td>0.55 (0.15 to 1.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV+HIV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-HAART</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HAART era</td>
<td>0.37 (0.19 to 0.72)</td>
<td>0.87 (0.21 to 3.58)</td>
<td>0.57 (0.22 to 1.47)</td>
<td>0.90 (0.31 to 2.67)</td>
<td>5.65 (1.42 to 22.5)</td>
</tr>
<tr>
<td>Pre-HAART</td>
<td>†</td>
<td>1</td>
<td>†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAART era</td>
<td></td>
<td>0.33 (0.03 to 3.85)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between serologic groups in the pre-HAART era</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV/’HIV+HIV−</td>
<td>†</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HCV+HIV</td>
<td></td>
<td>3.03 (1.22 to 7.58)</td>
<td>1.33 (0.75 to 2.37)</td>
<td>1.38 (0.27 to 6.91)</td>
<td></td>
</tr>
<tr>
<td>HCV+/HIV−</td>
<td>0.58 (0.13 to 2.60)</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between serologic groups in the HAART era</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV+HIV</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HCV+HIV</td>
<td>7.15 (1.98 to 25.8)</td>
<td>3.09 (1.41 to 6.79)</td>
<td>2.30 (1.07 to 4.95)</td>
<td>8.70 (2.89 to 26.42)</td>
<td></td>
</tr>
<tr>
<td>HCV+HIV</td>
<td>1.11 (0.34 to 3.61)</td>
<td>0.92 (0.25 to 3.43)</td>
<td>1.22 (0.12 to 11.68)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CHRs are estimated within each serologic group and in the pre-HAART and HAART eras separately, compared with the risk of dying among HCV+HIV− infected DUs.

*Adjusted for age, gender, hepatitis B status at ACS entry, and duration of injecting.

†Results not presented because of small numbers.
their uptake of HAART is lower than that seen in other HIV risk groups.\textsuperscript{2,10}

Although several studies have shown an increase in liver-related mortality among HIV-infected individuals in the HAART era,\textsuperscript{11–14} the impact of HCV coinfection on HIV disease progression remains contradictory.\textsuperscript{15–17} When mortality was compared between DUs infected with HCV and/or HIV and DUs without an infection, a study found higher overall mortality rates among HCV/HIV-coinfected DUs versus non–HCV/HIV-infected DUs\textsuperscript{12} but did not compare cause-specific mortality. In an earlier study, no liver-related deaths occurred among HCV-monoinfected individuals,\textsuperscript{16} whereas 10% of the HCV/HIV-coinfected DUs developed liver decomposition. This study was analyzed cross-sectionally, however. In the present longitudinal ACS study, we had the unique opportunity to evaluate the effect of the time-updated HIV and HCV status of all DUs on cause-specific mortality. In addition, we were able to correct for duration of injecting drugs, which served as a proxy for duration of HCV infection, because most DUs get infected with HCV within 2 years after they start injecting.\textsuperscript{20}

The results of this study show an increased risk of dying from hepatitis- and liver-related causes in the era of HAART among those infected with both HIV and HCV compared with those solely infected with HCV. Theoretically, the increase could be explained by HBV infection, which was highest among those DUs who were coinfected with HCV/HIV. We adjusted for anti-HBc status at study entry, however. This adjustment may be a limitation of the study, because an anti-HBc–positive test result is a marker for past HBV infection but not for chronic HBV infection. In the general population, 3% to 10% of the HBV infections become chronic, whereas a higher percentage become chronic in HIV-infected individuals.\textsuperscript{21} Therefore, we might have overestimated the effect of anti-HBc, but this overestimation would be smaller for those DUs infected with HIV.

In this study, HCV treatment was not taken into account, but it occurred sporadically and only recently in our cohort (1%), and would therefore only marginally affect our results.

The risk of dying from nonnatural causes (ie, overdose, suicide, homicide, accidents) was increased in HCV/HIV-coinfected DUs compared with HCV-monoinfected DUs in the pre-HAART and HAART eras, whereas no differences were seen between HCV-monoinfected DUs and DUs without HCV and HIV. This finding suggests that HCV/HIV-coinfected DUs had been taking more risk in general with respect to drug use. Although the impact of HCV coinfection on HIV disease progression is still debated, this study shows higher all-cause mortality among HCV/HIV-coinfected DUs than in the other serologic groups. When they are compared with HCV-monoinfected DUs, their risk of hepatitis- and liver-related death remains higher in the HAART era, suggesting that HIV continues to alter HCV disease progression. Although HCV treatment among HCV/HIV-coinfected individuals is complicated, our results highlight its importance and the need to establish effective treatment for HCV in HCV/HIV-coinfected individuals. We believe that, next to reducing risk behavior related to drug use, daily observed therapy for DUs with HIV and/or HCV is likely to increase their uptake, adherence, and therapy success.