HAART attenuates liver fibrosis in patients with HIV/HCV co-infection: fact or fiction?

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Since highly active antiretroviral therapy (HAART) has significantly improved survival in patients with HIV, liver disease from hepatitis C virus (HCV) infection is now an important cause of morbidity and mortality in such a cohort. Studies assessing liver fibrosis in an H/HCV cohort are beset with methodological flaws and heterogeneity of the study population, precluding definite conclusions. Nonetheless, recent data (albeit from retrospective studies) do suggest that HAART can attenuate liver fibrosis in the co-infected cohort with fibrosis progression rates comparable to the mono-infected patients. This is especially true for those patients whose HIV was diagnosed after 1996 and for whom HAART is associated with successful viral suppression. The mechanism(s) underlying this favourable course of events however remain speculative but could be related to immune restoration-induced changes in inflammatory and fibrogenic cytokines or to a direct effect of HAART on hepatic fibrosis. Therefore with the current available evidence it seems unjustifiable to defer HAART in those that need it because of concerns regarding potential hepatotoxicity as the benefits (both from the HIV and HCV viewpoint) probably outweigh any potential risks. Nonetheless, this issue can only be unequivocally resolved by better designed prospective studies.

Introduction

Because of their similar routes of transmission ~15–30% (150,000–300,000) of those infected with HIV in the United States are also co-infected with the hepatitis C virus (HCV). Similar rates of co-infection have been reported in Western Europe. The prevalence of anti-HCV antibodies depends on the risk factors for HCV infection, being <10% in homosexual men to >80% in those with history of injection drug use (IDU). In immunocompetent subjects, chronic HCV infection takes an indolent course with ~20% eventually developing cirrhosis after 20 years of infection. The immunosuppression induced by HIV accelerates the natural history of HCV-related liver disease, and co-infected patients are 2- to 3-fold more likely to develop cirrhosis. Liver disease from chronic hepatitis C is therefore increasingly being recognized as an important cause of morbidity and mortality in the co-infected cohort. This is especially true in the post-highly active antiretroviral therapy (HAART) era because of improved survival of HIV-infected individuals. However, the effects of HAART on the liver are complex. On the one hand, 6–30% of those prescribed HAART can develop hepatotoxicity and co-infection with HCV does increase the risk of HAART hepatotoxicity 2-fold. On the other hand, recent data do suggest that HAART is associated with a reduction in liver-related mortality in the co-infected cohort, though effects on hepatic fibrosis remain controversial (Table 1).

Impact of HAART on liver fibrosis in HIV/HCV patients

There are a number of potential pitfalls in analysing studies designed to assess liver fibrosis in HIV/HCV co-infected subjects. One of the main shortcomings of biopsy-based studies is that patients who do not undergo biopsy are excluded from further analysis thereby introducing a selection bias. Second, nearly all of these studies (Table 1) have been retrospective, thereby making it difficult to accurately document alcohol consumption history and time of HCV acquisition. Third, since serial biopsies are not available, the observed stage of hepatic fibrosis may in fact have been reached many years before the single point assessment. Hence we may actually underestimate the fibrosis progression rate (FPR) (which is calculated by dividing fibrosis stage by HCV disease duration). Furthermore, this calculation assumes that fibrosis progression is linear which is a flawed assumption, since the FPR increases with age and the severity of the underlying fibrosis. This means that an individual will take longer to progress from stage 1 to stage 2 fibrosis than to advance from stage 3 to stage 4 fibrosis. In those with HIV/HCV co-infection this issue is more complicated as these patients are likely to have different FPRs depending on when they acquired the HCV in relation to the HIV and when HAART was initiated. Co-infected subjects with a history of IDU (which is the most common risk factor) probably acquired HCV years before HIV. Following

Keywords: HAART hepatotoxicity, hepatic necroinflammation, hepatic fibrosis, CD4 count, HIV VL
<table>
<thead>
<tr>
<th>Type of study</th>
<th>Benhamou et al.\textsuperscript{8} 2001</th>
<th>Tural et al.\textsuperscript{9} 2003</th>
<th>Macias et al.\textsuperscript{10} 2004</th>
<th>Martin-Carbonero et al.\textsuperscript{11} 2004</th>
<th>Marine-Barjoan et al.\textsuperscript{12} 2004</th>
<th>Sterling et al.\textsuperscript{13} 2004</th>
<th>Mehta et al.\textsuperscript{14} 2005</th>
<th>Brau et al.\textsuperscript{15} 2006</th>
<th>Verma et al.\textsuperscript{16} 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>182</td>
<td>126</td>
<td>152</td>
<td>914</td>
<td>116</td>
<td>101</td>
<td>210</td>
<td>274</td>
<td>85</td>
</tr>
<tr>
<td>Age at biopsy (years)</td>
<td>37.7 versus 36.3</td>
<td>36.6</td>
<td>38 versus 30*</td>
<td>37*</td>
<td>38*</td>
<td>43</td>
<td>44.5*</td>
<td>44.9</td>
<td>44.1</td>
</tr>
<tr>
<td>Male</td>
<td>63%</td>
<td>77.8%</td>
<td>86%</td>
<td>75%</td>
<td>67%</td>
<td>75%</td>
<td>67%</td>
<td>80%</td>
<td>81%</td>
</tr>
<tr>
<td>IDU</td>
<td>91%</td>
<td>82.8%</td>
<td>95%</td>
<td>83%</td>
<td>72%</td>
<td>N/A</td>
<td>76.7%</td>
<td>71.9%</td>
<td>69%</td>
</tr>
<tr>
<td>CD4 count (cells/mm(^3))</td>
<td>286 versus 399**</td>
<td>531</td>
<td>494 versus 460</td>
<td>480</td>
<td>440 versus 369</td>
<td>503</td>
<td>366</td>
<td>433**</td>
<td>241 versus 306 versus 329</td>
</tr>
<tr>
<td>Undetectable HIV VL</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>54%</td>
<td>N/A</td>
<td>48%</td>
<td>N/A</td>
<td>51.5%</td>
<td>N/A</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>28%</td>
<td>54%</td>
<td>28%</td>
<td>25%</td>
<td>14%</td>
<td>N/A</td>
<td>39.5%</td>
<td>17.2%</td>
<td>39%</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>predominantly French</td>
<td>predominantly Spanish</td>
<td>predominantly Spanish</td>
<td>N/A</td>
<td>predominantly French</td>
<td>N/A</td>
<td>82% African American</td>
<td>N/A</td>
<td>66% Hispanics (predominantly Mexican)</td>
</tr>
<tr>
<td>BMI</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>22</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>23.5*</td>
</tr>
<tr>
<td>HCV disease duration (years)</td>
<td>16.2 versus 14.0</td>
<td>N/A</td>
<td>15.5 versus 9*</td>
<td>16*</td>
<td>15*</td>
<td>N/A</td>
<td>23.5*</td>
<td>N/A</td>
<td>25.5</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>14%</td>
<td>5.6%</td>
<td>17%</td>
<td>13%</td>
<td>26% (stage 3, 4, Metavir)</td>
<td>13%</td>
<td>17%</td>
<td>24.8%</td>
<td>55%</td>
</tr>
<tr>
<td>Conclusions</td>
<td>PI attenuate liver fibrosis time on ART independent predictors of hepatic fibrosis</td>
<td>PI attenuate but NVP accentuates fibrosis</td>
<td>HAART does not impact hepatic fibrosis</td>
<td>HAART has no impact on NI or hepatic fibrosis</td>
<td>HAART has no impact on NI or hepatic fibrosis</td>
<td>HAART associated with less NI, but no impact on fibrosis</td>
<td>successful HAART (HIV VL &lt;400) attenuates fibrosis</td>
<td>HAART only group have attenuated liver fibrosis</td>
<td></td>
</tr>
<tr>
<td>Independent predictors of fibrosis</td>
<td>CD4 count, alcohol, no PI therapy, age at HCV</td>
<td>CD4 count, alcohol, time on ART, age at HCV</td>
<td>CD4 count, no PI therapy, NVP therapy, age at HCV</td>
<td>CD4 count, age, alcohol</td>
<td>CD4 count, age, alcohol</td>
<td>CD4 count, age, alcohol</td>
<td>CD4 count, age, alcohol</td>
<td>CD4 count, age, alcohol</td>
<td>CD4 count, age, alcohol</td>
</tr>
</tbody>
</table>

Data given as mean unless indicated by *' (median).
CD4 counts given as median unless indicated by **' (mean).
BMI, body mass index; NI, necroinflammation; NVP, nevirapine; PI, protease inhibitor; N/A, not available; UD, undetectable.
Alcohol use: in most studies this was defined as >40–50 g/day.
HIV acquisition they will undoubtedly have a faster FPR until immune restoration is achieved with antiretroviral therapy (ART). Fourth, HIV/HCV co-infected subjects are a very heterogeneous group as regards age, alcohol consumption, ethnicity, CD4 counts and HIV viral load (VL) (all of which can impact fibrosis), so studies are not necessarily comparable (Table 1). Furthermore, very few studies have actually assessed FPR by stratifying according to CD4 counts and HIV VL. Finally, in prior studies it was unclear whether those who received HAART did so at onset as a sole form of therapy or initially received nucleoside reverse transcriptase inhibitors (NRTIs) and subsequently switched to HAART after 1996. It therefore comes as no surprise that these studies have reported such discordant results (Table 1).

Two recently published studies have tried to address some of these issues, though both were retrospective and did not include patients with serial liver biopsies. The first one from our unit compared 85 HIV/HCV co-infected subjects with 296 HCV mono-infected patients (Group 1) over a 10 year period (1994–2004). We were therefore able to stratify the co-infected subjects (depending on availability or not of drugs) into three groups: Group 2 received either no therapy or only NRTIs, Group 3 received only HAART as their HIV infections were diagnosed after 1996 (HAART only group) and Group 4 initially received NRTIs and were subsequently switched to HAART after 1996 (sequential therapy group). In Group 2, nine patients had received no ART, of whom two were long-term non-progressors. Groups 2–4 were well matched as regards age, HCV disease duration, alcohol consumption, body mass index (BMI) and HIV parameters. The time from HIV diagnosis to HAART initiation was significantly shorter in Group 3 compared with Group 4 (9.1 versus 34.1 months, \( P < 0.0001 \)). As is evident from Table 2, those in the HAART only group had similar HCV-related disease severity compared with HCV mono-infected subjects. However Groups 2 and 4 had significantly more advanced disease as regards fibrosis stage (\( P < 0.0009 \)), FPR (\( P < 0.0001 \)), necroinflammation (NI) (\( P < 0.0001 \)) and prevalence of cirrhosis (\( P < 0.006 \)). Figure 1 shows the probability of developing cirrhosis in the four groups. After 25 years of HCV infection, the probability of developing cirrhosis in Groups 1 and 3 were again similar (16% versus 24%) though Groups 2 and 4 had a significantly higher probability (72% and 38%, \( P < 0.0001 \)). The probability of developing cirrhosis was also lower in Group 3 compared with Group 2 (\( P = 0.01 \)). Group 4 subjects had also received HAART (for a mean of 3.9 years versus 3.3 years for

### Table 2. Histological parameters depending on type of antiretroviral therapy received (data obtained from Verma et al.)

<table>
<thead>
<tr>
<th></th>
<th>HCV mono-infected (Group 1) n = 296</th>
<th>No therapy/NRTIs (Group 2) n = 25</th>
<th>HAART only (Group 3) n = 22</th>
<th>Sequential therapy (Group 4) n = 38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis stage</td>
<td>3.1 ± 2</td>
<td>4.6 ± 1.8</td>
<td>3.4 ± 2.4</td>
<td>4.3 ± 2.0</td>
</tr>
<tr>
<td>Necroinflammation (grade)</td>
<td>6.1 ± 1.8</td>
<td>7.8 ± 1.9</td>
<td>6.1 ± 2.0</td>
<td>6.5 ± 1.9</td>
</tr>
<tr>
<td>Fibrosis progression rate (FPR)</td>
<td>0.13 ± 0.09</td>
<td>0.24 ± 0.11</td>
<td>0.16 ± 0.11</td>
<td>0.20 ± 0.10</td>
</tr>
<tr>
<td>Cirrhosis (%)</td>
<td>32</td>
<td>68</td>
<td>41</td>
<td>55</td>
</tr>
</tbody>
</table>

Fibrosis stage (0–6) and grade of necroinflammation (0–18) were assessed by the Ishak scoring system.35
Group 3), but because of the delay between HIV diagnosis and HAART initiation, Group 3 had better immune reconstitution compared with Group 4, which may have contributed to the slower FPR in Group 3. However, neither the CD4 count nor the HIV VL were independent predictors of advanced hepatic fibrosis in this study.

The second and one of the largest studies to date was the multicentre study by Brau and colleagues. They recruited 274 co-infected subjects from two centres (Puerto Rico and New York). To assess FPR they stratified patients depending on CD4 counts and HIV VL at biopsy (Figure 2). They observed that co-infected subjects with HIV VL < 400 copies/mL had similar FPR to HCV mono-infected subjects (0.122 per year versus 0.122 per year) whereas those with any detectable HIV RNA had more rapid FPR compared with HIV-negative patients (0.151 per year versus 0.128 per year, P = 0.013). Similarly FPR was dependent on CD4 count (Figure 2). However, in those with CD4 counts > 500 cells/mm³ HIV VL did not impact fibrosis. Furthermore, in this study HIV VL but not CD4 count was an independent predictor of hepatic fibrosis.

So the conclusions that can be drawn from these two recent studies are that it is not just the presence or absence of HAART that results in attenuated hepatic fibrosis in HIV/HCV co-infected patients. Rather what is more important is when HAART was initiated in relation to HIV acquisition and whether it was successful. This means that patients who received HAART (rather than sequential therapy) as soon as possible after HIV diagnosis (i.e. those whose HIV was diagnosed after 1996) and who showed successful VL suppression were more likely to have slower fibrosis progression compared with those in whom HAART was either delayed or (even if it was initiated appropriately) the therapy was ineffective. Failure of prior studies to stratify patients by nature of HIV therapy and severity of HIV disease might explain the observed lack of benefit of HAART on liver fibrosis.

Only one study has reported accentuated hepatic fibrosis with HAART. Macias et al. observed that nevirapine (median duration 527 days) use was associated with more advanced hepatic fibrosis. However the sample size was small (n = 25), and it was unclear whether those receiving versus those not receiving nevirapine were matched for other determinants that impact hepatic fibrosis. Furthermore, we were unable to corroborate these findings in a subsequent study.

Mechanism/s by which HAART attenuates liver fibrosis in HIV/HCV patients

The mechanism/s underlying slower fibrosis progression with HAART remain contentious. Multiple studies have now shown that a low CD4 count is associated with accelerated hepatic fibrosis in co-infected patients. Immunosuppression may result in changes in intrahepatic cytokine profile, producing a proinflammatory and profibrogenic milieu (due to a predominance of Th2 T cell responses). Animal studies have demonstrated that a predominant Th2 response is associated with accentuated hepatic fibrosis. In addition, individuals with HIV/HCV co-infection have significantly less intrahepatic CD4+ T cell HCV-specific interleukin-10 (IL-10) production compared with HCV mono-infected patients. Hepatic NI has been associated with anti-inflammatory effect. Hepatic NI may be more applicable to immunocompetent patients, and in HIV/HCV co-infected populations. At least two recent studies have reported lower necroinflammatory grades after HAART initiation. Therefore it is conceivable that immune reconstitution induced by HAART could result in attenuation of hepatic NI, which in the long-term could slow fibrosis progression. Furthermore, HAART may also lead to better control of HCV replication thereby attenuating hepatic fibrosis.

Nonetheless, it does seem paradoxical that immune reconstitution improves rather than worsens liver injury in HCV infection, as in this disease the injury is largely immune mediated via HCV-specific CD4+ T cells. However immune-mediated injury may be more applicable to immunocompetent patients, and in those with immunosuppression a direct cytopathic effect of HCV may be possible. In HIV/HCV co-infection there is evidence (rarely) of such a cytopathic injury, producing the fatal condition fibrosing cholestatic hepatitis. This is associated with high

Figure 2. Fibrosis progression rates (FPR) stratified by HIV parameters. Reproduced from Brau et al. with kind permission from the European Association for the Study of the Liver.
therapy.6,7,15,16,30 With the currently available evidence it is could attenuate hepatic fibrosis, reduce liver-related mortality overall improvement in mortality. In addition immune restoration CD4 counts, reduced morbidity from opportunistic infection and successful therapy will result in reduction of HIV VL, increased

**Recommendations**

In an ideal situation recommendations should be made on the basis of prospective randomized studies with paired liver biopsies before and after introduction of different antiretroviral drugs, so that the effects of individual therapy on hepatic fibrosis and cytokine profile can be studied. Since in the real world such studies may not only be impractical but also unethical to perform, the recommendations are based on existing current literature. Initiating HAART in HIV/HCV co-infected patients just to attenuate hepatic fibrosis (rather than for immunological benefits) is a tempting proposition though this needs to be weighed against the side effects of therapy, compliance and development of drug resistance. Certainly in those with immunosuppression (CD4+ < 350 cells/mm³) HAART should be a priority, as successful therapy will result in reduction of HIV VL, increased CD4 counts, reduced morbidity from opportunistic infection and overall improvement in mortality. In addition immune restoration could attenuate hepatic fibrosis, reduce liver-related mortality and may improve subsequent response rates to interferon therapy.8,14,15,30 With the currently available evidence it is unjustifiable to withhold HAART in such a cohort because of concerns related to potential hepatotoxicity. In those at high risk of developing HAART hepatotoxicity (because of older age, excess alcohol consumption, prior elevations of liver enzymes), less hepatotoxic regimens can be considered (lamivudine, tenofovir, atazanavir). In the presence of well-preserved immune function (CD4+ > 500 cells/mm³) it may be preferable to treat the HCV first, if possible (Table 3). Since co-infected patients are more likely to develop an abnormal liver panel after HAART initiation compared with those with HIV alone, eradicating HCV may reduce this risk. In a parallel situation, HIV/HCV co-infected subjects treated with antitubercular therapy (ATT) are 14-fold more likely to develop hepatotoxicity than if both viruses are absent, and successful treatment of HCV is associated with a reduced risk of subsequent ATT hepatotoxicity.34 Finally, for those whose CD4 counts fall in between (350–500 cells/mm³), treatment needs to be individualized depending on which disease is perceived to be more life threatening. In such patients if HCV therapy is unsuccessful or not tolerated, HAART could be considered with an aim to reduce fibrosis progression.

**Conclusions**

In summary, the effects of HAART on liver fibrosis remain controversial, and the lack of consensus on this important issue underscores the need for better designed prospective studies. Nonetheless, recent available data do suggest that HAART attenuates hepatic fibrosis in HIV/HCV co-infected patients, though the underlying mechanism/s remain speculative. The patients most likely to benefit are those who receive HAART at onset, i.e. those whose HIV was diagnosed after 1996, rather than those who were switched to HAART after initially receiving NRTIs. It is not sufficient just to initiate HAART, it has to be successful and associated with suppression of HIV viraemia (and/or increased CD4 counts?). Thus patient compliance and avoidance of drug resistance is of paramount importance. It seems clear that HAART has reduced liver-related mortality in the co-infected cohort and so the inference must be that it has impacted liver fibrosis first. The long-term hepatic safety profile of some drugs (nevirapine) needs further study, but at present for certain patients the benefits of HAART (both from the HIV and HCV perspective) probably outweigh the potential risks. Nonetheless, in those with well-preserved immune function (CD4+ > 500 cells/mm³) it would be preferable to treat the HCV first.

**Acknowledgements**

S. V. is grateful to Dr Maurizio Bonacini for his excellent critique of the manuscript. One of the studies discussed in this article (Verma *et al.*16) was partly funded by a research grant from the Liver Research and Education Foundation (LREF) at Rancho Los Amigos Center, Downey, California. This research grant was made available to S. V. by a donation from the late Dr Telfer Reynolds.

**Transparency declarations**

None to declare.

**References**


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**Table 3.** Potential reasons for treating hepatitis C virus (HCV) first in those with HIV/HCV co-infection and well-preserved immune function

HCV is regarded as an opportunistic infection in those with HIV HCV may impair immune response to HAART Eliminating HCV may reduce the risk of developing subsequent HAART-induced hepatotoxicity Treating HCV first could reduce additive toxicity (neuropsychiatric, lactic acidosis, anaemia) associated with HAART and interferon/ribavirin Recent studies have documented the safety and efficacy of pegylated interferon and ribavirin in HIV/HCV co-infected patients In the RIBAVIC study,53 those with non-1 HCV genotype were less likely to respond to interferon-based therapy if they were concomitantly receiving a PI

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